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Human Biomonitoring of Phthalates and Bisphenol A Exposure in Austria

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ABBREVIATIONS

AC	Abdominal circumference
ADI	Acceptable Daily Intake
AGD	Anogenital distance
AGI	Anogenital Index
AL	Acceptable Level of Exposure
AMDE	Absorption, Metabolism, Distribution and Elimination
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
AR	Androgen receptor
ASNS	Austrian Study on Nutritional Status
ATSDR	Agency for Toxic Substances and Disease Registry
BBzP	Butyl benzyl phthalate
BCS	Bureau of Chemical Safety
BMI	Body Mass Index
BPA	Bisphenol A
bw	bodyweight
CAS	Chemical Abstract Service
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CERHR	Center For The Evaluation Of Risks To Human Reproduction
CI-PP95	Confidence interval of the 95th population percentile
CMR	carcinogenic, mutagenic, or toxic for reproduction
crea	creatinine
CVD	Cardiovascular disease
d	day(s)
Danish EPA	Danish Environmental Protection Agency
DCHP	Di-cyclohexyl phthalate
DEHP	Di-2-ethylhexyl phthalate
DEP	Diethyl phthalate
Dgr	Danger
DiBP	Di-isobutyl phthalate
DiDP	Di-isodecyl phthalate
DiNP	Di-isononyl phthalate

DIUP	Di-isoundecyl phthalate
DNA	deoxyribonucleic acid
DnBP	Di-n-butyl phthalate
DnOP	Di-n-octyl phthalate
DnPeP	Di-n-pentyl phthalate
DOTP	Dioctyl tere-phthalate
DPHP	Bis(2-propylheptyl) phthalate
DR	detection rate
DTDP	Ditridecyl phthalate
EAA	Environment Agency Austria
EAG	Environment Agency Germany
EC	European Commission
ECB	European Chemicals Bureau
ECHA	European Chemicals Agency
ECPI	European Council for Plasticisers and Intermediates
ED	Endocrine disruption
EDC	Endocrine disrupting chemical
EFSA	European Food Safety Authority
EINECS	Inventory of Existing Commercial Chemical Substances
EL	Effect Level
ELFE	Étude Longitudinale Francaise depuis l'Enfance
ER	Estrogen receptor
EU	European Union
FDA	Food and Drug Administration
FFQ	Food Frequency Questionnaire
fl	femtolitre
FSH	Follicle-stimulating hormone
GerES IV	German Environmental Survey for Children IV
GIT	Gastrointestinal Tract
GLP	Good Laboratory Practice
GnRH	Gonadotrophin-releasing hormone
GR	Glucocorticoid receptor
HBM	Human Biomonitoring
HC	Hip circumference

HHS	U.S. Department of Health and Human Services
HI	Hazard Index
HQ	Hazard Quotient
HSDB	Hazardous Substance Data Bank
IfEW	Department of Nutritional Sciences of the University of Vienna
IgE	Immunoglobulin E
IHCP	Institute for Health and Consumer Protection
IOELV	Indicative Occupational Exposure Limit Value
IUPAC	International Union of Pure and Applied Chemistry
LH	Luteinising hormone
LOAEL	Lowest observed adverse effect level
LOD	Limit of detection
LOQ	Limit of quantitation
MBzP	Mono-benzyl phthalate
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCHP	Mono-cyclohexyl phthalate
MCV	Mean corpuscular volume
MEHP	Mono-2-ethylhexyl phthalate
MEP	Mono-ethyl phthalate
METI	Ministry of Economy, Trade and Industry Japan
MiBP	Mono-isobutyl phthalate
MiDP	Mono-isodecyl phthalate
MiNP	Mono-isononyl phthalate
MnBP	Mono-n-butyl phthalate
MnOP	Mono-n-octyl phthalate
MnPeP	Mono-n-pentyl phthalate
mRNA	Messenger ribonucleic acid
MW	molecular weight
n.d.	not detected
n.r.	not reported
NCBI	National Center for Biotechnology Information
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart Lung and Blood Institute

NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NLM	U.S. National Library of Medicine
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
NUTS	Nomenclature des unités territoriales statistiques
OEHHA	Office of Environmental Health Hazard Assessment
PBT	persistent, bioaccumulative and toxic for reproduction
PC	Polycarbonate
PET	Polyethylenterephthalate
PPAR	Peroxisome proliferator-activated receptor
PVC	Poly Vinyl Chloride
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfD	Reference Dose
RfD AA	Reference Dose for Anti-Androgenicity
SML	Specific Migration Limit
STOT RE	Specific target organ toxicity – repeated exposure
STOT SE	Specific target organ toxicity – single exposure
SVHC	Substance Of Very High Concern
T3	Triiodothyronine
T4	Thyroxine
TDI	Tolerable Daily Intake
TDI_{cum}	Relative Cumulative Tolerable Daily Intake
TR	Thyroid receptor
U.S. EPA	United States Environmental Protection Agency
UDP	Uridine 5’-diphosphate
UDPGA	Uridine 5’-diphospho-glucuronic acid
UGT	Uridine 5’-diphosphoglucuronyl transferase
VKM	Norwegian Scientific Committee for Food Safety
vol	volume
vPvB	very persistent and very bioaccumulative
w/w	Weight by weight
WC	Waist circumference
WHO	World Health Organisation
WHR	Waist-Hip Ratio

Wng	Warning
3cx-MPP	3-carboxy-mono-propyl phthalate
5cx-MEPP	Mono-5-carboxy-2-ethylpentyl phthalate
5OH-MEHP	Mono-(2-ethylhydroxyhexyl) phthalate
5oxo-MEHP	Mono-2-ethyl-5-oxohexyl phthalate

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ABSTRACT

There is a multitude of industrial chemicals produced and used in a variety of common consumer products, to which humans and the environment are exposed. For several of these chemicals, associations between exposure and adverse health effects on animals and humans have been identified in scientific studies. Some chemicals, the so-called endocrine disruptors, present a specific problem as they may affect the hormone system.

Amongst such substances and substance groups, phthalates and bisphenol A are of particular interest. Phthalates are used as plasticisers and additives in an immense variety of products and applications, and bisphenol A is used as monomer for the production of polycarbonates, polyvinyl chloride, epoxy resins and thermal paper. Due to their presence in common consumer products as well as their chemical structure, they can migrate from these products into food, beverages, water, air, dust and soil, leading to human exposure by a variety of routes. Human Biomonitoring for these compounds is therefore a crucial method for the analysis of chemicals and their corresponding metabolites in various body fluids to determine the extent of exposure in both a qualitative and quantitative manner.

At present, only a few Human Biomonitoring studies have been carried out in Austria. The main aim of the present study, conducted at the Environment Agency Austria, was therefore the investigation of the exposure to phthalates and bisphenol A of a large sample of the Austrian population. Samples and data were collected by the Department of Nutritional Sciences of the University of Vienna within the context of the Austrian Study on Nutritional Status 2010/2012. In total, the study population consisted of 595 male and female participants from almost all Austrian federal states, who were each assigned to one of the following groups: Children I (6-8 years), Children II (7-15 years), Adults (18-65 years), and Elderly People (64-81 years). In total, 14 urinary phthalate metabolites[1] of 10 parent compounds were analysed by HPLC-MS/MS. Generally, phthalate metabolites were detected in almost all of the investigated samples, with low molecular weight phthalates as well as the high molecular weight phthalate metabolites of di-2-ethylhexyl phthalate (DEHP) being found in the majority of the urine samples. In

[1] *Low molecular weight phthalate metabolites:* monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-cyclohexyl phthalate (MCHP), mono-n-pentyl phthalate (MnPeP) and mono-benzyl phthalate (MBzP). *High molecular weight phthalate metabolites:* mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-oxohexyl phthalate (5oxo-MEHP), mono-2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP), mono-5-carboxy-2-ethylpentyl phthalate (5cx-MEPP), mono-n-octyl phthalate (MnOP), 3-carboxy-mono-propyl phthalate (3cx-MPP), mono-isononyl phthalate (MiNP) and mono-isodecyl phthalate (MiDP).

agreement with other scientific studies, children were found to be more highly exposed to the majority of the investigated phthalate metabolites when compared to adults and elderly people, except in the case of the metabolite MEP, where results were inversely. Additionally, similar to findings from previous studies, females showed exhibited higher exposures to several phthalate metabolites than males. The analysis of urinary total BPA (free and conjugated) was performed with on-line SPE-HPLC-MS/MS. BPA was detected in only a marginal number of samples, with a minimum detection rate of 11% in adults and elderly people, and a maximum detection rate of 50% in children aged 6-8 years (Children I group). Thus, similar to the case of phthalate metabolite exposure, children were also more highly exposed to BPA compared than older participants, and a decrease of exposure with increasing age was also exhibited. The highest exposure level for creatinine-unadjusted BPA was 17 µg/l in an adult, and for creatinine-adjusted BPA, 21 µg/g in a child. The exposure to BPA was generally low within the present study population. In addition to the data from Human Biomonitoring, daily intakes were estimated based on urinary volume excretion and urinary creatinine excretion, respectively, and were then compared to various acceptable exposure levels. Exceedances of acceptable levels were primarily observed among children, and, although the overall number of exceedances was low, their presence should be considered a potential cause of concern. Additionally, the trend of decreasing daily intakes with increasing age was shown similar to analysed urinary exposure. The estimations of daily BPA intake also followed two different calculation models, similar to those of daily phthalate intakes. In general, the calculated daily BPA intakes were low. Again, similar to trends related to phthalate exposure, a decrease with increasing age was also identified. Regarding acceptable exposure levels, and especially the new temporary TDI of 5 µg/kg bw/d, no exceedances existed. For the investigation of cumulative phthalate exposure, a cumulative risk assessment was performed under consideration of the dose-addition concept of the Hazard Index (HI) based on TDIs and RfD AAs. Exceedances were identified only for HI values based on TDIs especially among children, where the maximum rate of exceedance of 13% was determined in the group of Children I. Associations between exposure and selected parameters were also investigated and identified, thereby exhibiting interesting discoveries which could constitute the subject of further investigations. Overall, the present study provided new exposure data for a large sample of the Austrian population and contributes to national and international exposure and risk assessment.

KURZFASSUNG

Heutzutage wird weltweit eine Vielzahl an Industriechemikalien hergestellt, die unter anderem in einer Reihe von sehr unterschiedlichen Konsumprodukten ihren Einsatz finden. Der Kontakt mit diesen Produkten kann zu einer Belastung des Menschen sowie der Umwelt führen, wobei etliche dieser Stoffe im Zusammenhang mit negativen Effekten auf die Gesundheit stehen. Dabei handelt es sich unter anderem um sogenannte endokrin wirksame Substanzen, die schädigende Effekte auf das Hormonsystem haben können.

Zu den endokrin wirksamen Substanzen, die in hohen Mengen hergestellt und verwendet werden, gehören die Phthalate sowie Bisphenol A. Phthalate werden als Kunststoffweichmacher und Additive in einer Vielzahl von unterschiedlichen Produkten eingesetzt, während Bisphenol A als Monomer in der Herstellung von Polykarbonaten, Polyvinylchlorid, Kunstharzen und Thermopaper seine Verwendung findet. Durch ihr Vorkommen in diesen Produkten sowie aufgrund ihrer chemischen Struktur können sowohl Phthalate als auch Bisphenol A in Lebensmittel, Getränke, Wasser, Luft, Staub und Böden migrieren und so über unterschiedliche Wege vom Menschen aufgenommen werden. Im Körper werden sie schnell verstoffwechselt und über den Harn wieder ausgeschieden, wo sie in weiterer Folge nachgewiesen werden können. Durch das sogenannte Human-Biomonitoring kann dieser Nachweis der Substanzen bzw. ihrer Metaboliten in unterschiedlichen Körperflüssigkeiten erfolgen, um die Belastung sowohl qualitativ als auch quantitativ zu bestimmen.

Bisher wurden in den vergangenen Jahren nur wenige Human-Biomonitoring-Studien in Österreich durchgeführt. Das Hauptziel der vorliegenden Studie, durchgeführt am Umweltbundesamt Wien, war die Untersuchung der Phthalat- und Bisphenol A-Belastung im Harn in einer großen Stichprobe der österreichischen Bevölkerung. Das Probenmaterial und die Daten wurden vom Institut der Ernährungswissenschaften der Universität Wien im Rahmen der Österreichischen Studie zum Ernährungsstatus 2010/2012 gesammelt. Insgesamt bestand die untersuchte Studienpopulation aus 595 männlichen und weiblichen ProbandInnen aus nahezu allen österreichischen Bundesländern. Die Einteilung der Studienpopulation erfolgte in die Kategorien Kinder I (6-8 Jahre), Kinder II (7-15 Jahre), Erwachsene (18-65 Jahre) und SeniorInnen (64-81 Jahre).

Insgesamt wurden 14 Metaboliten[2] von 10 Phthalaten in den Harnproben mittels HPLC-MS/MS analysiert. In nahezu allen Proben konnten diverse Phthalatmetaboliten detektiert werden, wobei der Nachweis der niedermolekularen Metaboliten sowie der Metaboliten des hochmolekularen Di-2-ethylhexylphthalat (DEHP) in einem Großteil der Proben erfolgte. Wie bereits in mehreren wissenschaftlichen Studien gezeigt, gehören Kinder zur der am höchsten belasteten Populationsgruppe. Eine Ausnahme stellt die Belastung mit MEP dar, die bei Erwachsenen und SeniorInnen im Vergleich zu jüngeren StudienteilnehmerInnen wesentlich höher lag. Ebenfalls in Übereinstimmung mit anderen internationalen Studien konnten in weiblichen Teilnehmerinnen höhere Belastungen mit diversen Phthalatmetaboliten verglichen mit männlichen Teilnehmern festgestellt werden. Die Untersuchung der Konzentrationen an Gesamt-BPA (freies und konjugiertes BPA) in den Harnproben erfolgte mittels on-line SPE-HPLC-MS/MS, wobei BPA nur in einer verhältnismäßig geringen Probenanzahl nachgewiesen werden konnte. Die Anteile der positiven Proben variierten je nach Studiengruppe zwischen 11% bei Erwachsenen und SeniorInnen, und 50% bei Kindern im Alter von 6-8 Jahren (Gruppe Kinder I). Auch hier waren Kinder höher exponiert als ältere StudienteilnehmerInnen und es lag eine Abnahme der Belastung mit steigendem Alter vor. Die maximale nachgewiesene BPA-Konzentration lag bei 17 µg/l Harn bei einem Erwachsenen, sowie nach Kreatinin-Adjustierung bei 21 µg/g Kreatinin bei einem Kind der Gruppe Kinder I, wobei generell die Belastung in der untersuchten Studienpopulation gering ausfiel. Anhand der im Harn bestimmten Substanzkonzentrationen wurde die Bestimmung der täglichen Aufnahmemenge von Diethylphthalat (DEP), Di-n-butylphthalat (DnBP), Di-isobutylphthalat (DiBP), Butylbenzylphthalat (BBzP) und Di-2-ethylhexylphthalat (DEHP) nach zwei unterschiedlichen Berechnungsmodellen basierend auf dem ausgeschiedenen Harnvolumen sowie der ausgeschiedenen Kreatininkonzentration durchgeführt. Die berechneten Aufnahmemengen wurden mit tolerierbaren Aufnahmemengen verglichen, um mögliche Überschreitungen feststellen zu können. In erster Linie wurden diese bei Kindern festgestellt. Obwohl die Anzahl der Überschreitungen generell gering ausfiel, weist deren Auftreten auf ein mögliches Gesundheitsrisiko hin. Außerdem konnte eine Abnahme der täglichen Aufnahmemengen mit steigendem Alter identifiziert werden. Zur Erhebung der täglichen BPA-Aufnahmemengen erfolgten ebenfalls Berechnungen

[2] *Niedermolekulare Phthalatmetaboliten:* Monoethylphthalat (MEP), Mono-n-butylphthalat (MnBP), Mono-isobutylphthalat (MiBP), Mono-cyclohexylphthalat (MCHP), Mono-n-pentylphthalat (MnPeP) und Mono-benzylphthalat (MBzP). *Hochmolekulare Phthalatmetaboliten:* Mono-2-ethylhexylphthalat (MEHP), Mono-2-ethyl-5-oxohexylphthalat (5oxo-MEHP), Mono-2-ethyl-5-hydroxyhexyl)phthalat (5OH-MEHP), Mono-5-carboxy-2-ethylpentylphthalat (5cx-MEPP), Mono-n-octylphthalat (MnOP), 3-carboxy-mono-propylphthalat (3cx-MPP), Mono-isononylphthalat (MiNP) und Mono-isodecylphthalat (MiDP).

basierend auf zwei unterschiedlichen Modellen, die ähnlich wie bei den Phthalaten durchgeführt wurden. Die kalkulierten täglichen Aufnahmemengen erwiesen sich als generell gering, wobei ebenfalls eine Abnahme mit zunehmendem Alter identifiziert werden konnte. Im Vergleich mit tolerierbaren Aufnahmemengen, speziell mit der neuen temporären tolerierbaren täglichen Aufnahmemenge (Tolerable Daily Intake, TDI) von 5 µg/kg Körpergewicht/d, existierten keine Überschreitungen. Für die Phthalate wurde zur Untersuchung der kombinierten Belastung eine kumulative Risikobewertung unter Berücksichtigung des Konzepts des „Hazard Index“ (HI) basierend auf den entsprechenden TDIs und RfD AAs (Referenzdosis für Anti-Androgenität) durchgeführt, wobei die Überschreitung eines HI-Wertes von 1 ein mögliches Gesundheitsrisiko darstellt. Die berechneten HIs nahmen mit steigendem Alter von Kindern zu Erwachsenen ab. Bei SeniorInnen wurde ein erneuter Anstieg beobachtet. Überschreitungen existierten alleinig bei Kindern bezogen auf den von den TDIs abgeleiteten HI-Werten, wobei 13% der StudienteilnehmerInnen der Gruppe Kinder I den HI überschritten. Bei der Untersuchung von möglichen Assoziationen zwischen den Phthalat- bzw. BPA-Belastungen und ausgewählten erhobenen Parametern zeigten sich einige statistisch signifikante Zusammenhänge, deren weitere Untersuchung von Interesse wäre. Die vorliegende Studie bietet damit neue Daten zur Exposition für eine große Stichprobe der österreichischen Bevölkerung und trägt damit zur nationalen und internationalen Expositionsabschätzung und Risikobewertung bei.

1 INTRODUCTION

1.1 BACKGROUND

The production and usage of chemical substances in various food and non-food consumer products can lead to chemical exposure in humans as well as in the environment.

In a multitude of scientific studies, associations have been shown between exposure to certain chemicals and adverse health effects in animals and humans. Generally, some of the substances show effects on the hormone system and are therefore suspected to contribute to various diseases such as fertility disorders, genital malformations or cancer and may be able to contribute to other health effects such as obesity, insulin resistance and diabetes. These chemicals are, or are suspected to be, so-called endocrine-disrupting chemicals, because of their disrupting effects on the endocrine system of humans and animals.

Amongst other substances and substance groups, phthalates and bisphenol A (BPA) show endocrine-disrupting effects and are therefore of particular interest. Phthalates are the most frequently manufactured plasticisers and additives worldwide, and BPA is used as a monomer in polymer production. Because of their wide range of production and usage in many common consumer products, humans are exposed to these substances through various routes. Exposure to phthalates and BPA can occur via oral ingestion, dermal contact or inhalation. They are rapidly metabolised by the human body and eliminated mainly via urine, where they can be detected. A common method for measuring analytes in a qualitative and quantitative manner is so-called Human Biomonitoring (HBM). Measurements can be performed in various matrices such as urine, blood and other body fluids, tissues and organs. Thus, the determination of exposure to various substances in the general population as well as in individuals, the comparison of exposure levels with reference values and the definition of exposure limits, as well as the investigation of potential associations with the occurrence of diseases are possible.

As part of the Austrian Study on Nutritional Status conducted by the Institute of Nutritional Sciences of the University of Vienna, a Human Biomonitoring study was undertaken in order to investigate the phthalate and BPA exposure of the Austrian population.

1.2 OBJECTIVES

Presently, only few Human Biomonitoring studies have been carried out in Austria.

In the context of the Austrian Study on Nutritional Status (ASNS) performed by the Department of Nutritional Sciences (IfEW) of the University of Vienna (published as Austrian Nutrition Report 2012), this thesis aims to determine:

(i) the phthalate and BPA exposure of a representative sample of the Austrian population (children, adults and elderly people) through analysis of urine samples with HPLC-MS/MS (phthalate metabolites) and on-line SPE-HPLC-MS/MS (bisphenol A),
(ii) reference values for the Austrian population,
(iii) possible associations between exposure levels and several parameters such as age, sex and regional differences,
(iv) possible associations between exposure and collected data concerning diet, environment and lifestyle, and
(v) possible relationships of exposure and parameters such as bodyweight, body mass index, waist/hip/abdominal circumference or nutritional diseases.

Additionally, several analyses were performed:

(vi) Daily Intake estimations,
(vii) Cumulative risk assessment estimations,
(viii) Scenario calculations, and
(ix) Meta-analyses.

The design of this study makes a detailed investigation at national level possible. Because of the large sample size and the availability of comprehensive data, a valuable contribution to the international risk research is possible. Further, the investigations could be a highly useful contribution to the Austrian Nutrition Survey.

1.3 PHTHALATES

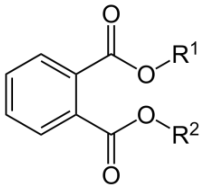
1.3.1 Introduction

Phthalates are the di-esters of 1,2-benzenedicarboxylic acid (phthalic acid), a group of not naturally occurring but man-made chemical substances used primarily as plasticisers in polyvinyl chloride (PVC) production, which can be found in many consumer products such as toys, food packaging materials, household products, care products and pharmaceuticals, as well as in coatings, insecticides, lacquers, varnishes, floorings, adhesives, sealants, synthetic leather and medical devices. (Hauser and Calafat, 2005) For many years, great attention was paid on phthalates, because of their suspected adverse effects on human health, especially relating to endocrine-disrupting effects and their toxicity to reproduction. However, it must be recognised that the group of phthalates contains many different types and that it is indicated that they do not all have the same effects on health. (EC, 2011f; Danish EPA, 2013; Kortenkamp et al., 2011)

Generally, phthalates can be divided into 2 groups:

- *Low molecular weight phthalates,* which include ester side-chain lengths of one to four carbon atoms (NRC, 2008). These are primarily used in personal care products such as cosmetics, perfumes and lotions, as well as in lacquers, coatings and varnishes, as plasticisers in cellulose acetate, and in pharmaceuticals (Hauser and Calafat, 2005).

- *High molecular weight phthalates,* including ester side-chain lengths of five or more carbon atoms (NRC, 2008). Because of the number of carbon atoms, they have an increased durability and permanency (ECPI, 2010b). High molecular weight phthalates are mainly used as plasticisers in vinyl products such as flooring, wall covering, medical devices and food contact materials (Hauser and Calafat, 2005).



(R^1 and $R^2 = C_nH_{2n+1}$)

Figure 1. General chemical structure of phthalates (BCERC, 2011)

Low and high molecular weight phthalates are listed in Table 1. Phthalates in bold are the parent compounds of phthalate metabolites investigated in this study.

Table 1. List of phthalates (EAG, 2011; ECPI, 2010a; Hauser and Calafat, 2005; Swedish Chemical Agency, 2012)

Phthalate name	Molecular formula	CAS No.	Molecular weight type
DMP (Dimethyl phthalate)	$C_{10}H_{10}O_4$	131-11-3	very low
DEP (Diethyl phthalate)	**$C_{12}H_{14}O_4$**	**84-66-2**	**very low**
DAP (Diallyl phthalate)	$C_{14}H_{14}O_4$	131-17-9	low
DPP (Di-n-propyl phthalate)	$C_{14}H_{18}O_4$	131-16-8	low
DnBP (Di-n-butyl phthalate)	**$C_{16}H_{22}O_4$**	**84-74-2**	**low**
DiBP (Di-isobutyl phthalate)	**$C_{16}H_{22}O_4$**	**84-69-5**	**low**
BCP (Butyl cyclohexyl phthalate)	$C_{18}H_{24}O_4$	84-64-0	low
DnPeP (Di-n-pentyl phthalate)	**$C_{18}H_{26}O_4$**	**131-18-0**	**low**
DCHP (Di-cyclohexyl phthalate)	**$C_{20}H_{26}O_4$**	**84-61-7**	**low**
BBzP (Butyl benzyl phthalate)	**$C_{19}H_{20}O_4$**	**85-68-7**	**low**
DnHP (Di-n-hexyl phthalate)	$C_{20}H_{30}O_4$	84-75-3	low
DiHP (Di-isohexyl phthalate)[1]	$C_{20}H_{30}O_4$	68515-50-4	low
DiHpP (Di-isoheptyl phthalate)	$C_{22}H_{34}O_4$	41451-28-9	low
BDP (Butyl decyl phthalate)	$C_{22}H_{34}O_4$	89-19-0	low
DEHP (Di(2-ethylhexyl) phthalate)	**$C_{24}H_{38}O_4$**	**117-81-7**	**high**
DnOP (Di-n-octyl phthalate)	**$C_{24}H_{38}O_4$**	**117-84-0**	**high**
DiOP (Di-isooctyl phthalate)	$C_{24}H_{38}O_4$	27554-26-3	high
ODP (n-octyl n-decyl phthalate)	$C_{26}H_{42}O_4$	119-07-3	high
DiNP (Di-isononyl phthalate)	**$C_{26}H_{42}O_4$**	**28553-12-0**	**high**
DPHP (Di(2-propylheptyl) phthalate)	$C_{28}H_{46}O_4$	53306-54-0	high
DiDP (Di-isodecyl phthalate)	**$C_{28}H_{46}O_4$**	**26761-40-0**	**high**
DUP (Diundecyl phthalate)	$C_{30}H_{50}O_4$	3648-20-2	high
DIUP (Di-isoundecyl phthalate)	$C_{30}H_{50}O_4$	85507-79-5	high
DTDP (Di-tridecyl phthalate)	$C_{34}H_{58}O_4$	119-06-2	high
DIDTP (Di-isotridecyl phthalate)	$C_{34}H_{58}O_4$	68515-47-9	high

Comments: Phthalates which include 1-2 carbon atoms in their molecular backbone are used as solvents in non-PVC applications. Low molecular weight phthalates include 4-6 carbon atoms in their backbone, and high molecular weight phthalates include 6-13 carbon atoms in their backbone. Phthalates with 11-13 carbon atoms are used for requirements of high temperature performance or low fogging, and are used in car interiors and automotive cables. (ECPI, 2010a)

1.3.2 Production and usage

Generally, plasticisers are grouped into phthalates, aliphatics (mainly adipated and hydrogenated phthalates), epoxy, terephthalates, trimellitates, polymerics, phosphates and others, whereby phthalates are the predominant plasticisers among these groups. 80-90% of the plasticisers are used for PVC products worldwide. (IHS, 2012)

In 2008, about 6 million tonnes of plasticisers were produced worldwide, of which phthalates are the most important group with a production rate of 87% (more than five million tonnes) per year. 50% of global phthalate usage occurs in Asia, 20% in Western Europe and 16% in North America. Compared with the amount of one million tonnes of phthalates produced in Western Europe in 1998, 906,000 tonnes were produced in 2008. In recent years, the production of phthalates has changed in Europe due to toxicity classifications, mandatory labelling, as well as because of restrictions and bans on several members of this group. For example, in 1998 DEHP usage accounted for 47% of all phthalates, which fell to 23% in 2008, because of its replacement by DiNP and DiDP. However, on a global level, DEHP was still the most important phthalate in 2008. (EAG, 2011) In 2012, 78% of worldwide plasticiser consumption comprised phthalates. As shown in Figure 2, the largest plasticiser market in the world is China (38% of world consumption 2012), followed by Western Europe (16%) and North America (13%). It is assumed that the market in Western Europe will grow at a rate of 1% annually. The global consumption of phthalates is forecast to increase 2.4% annually during 2011 and 2018, whereby the consumption of low molecular weight phthalates is forecast to decrease due to replacement mainly by non-phthalates. (IHS, 2012) Detailed information on the production and use of phthalates investigated in this study is provided in 1.3.7.

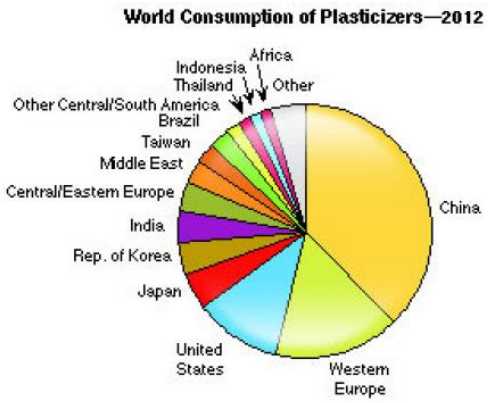


Figure 2. Worldwide consumption of plasticisers in 2012 (IHS, 2012)

1.3.3 Toxicokinetics

1.3.3.1 Routes of exposure

Humans are exposed to phthalates through various routes. They are contained in a multitude of common consumer products such as food packaging materials, building

materials, clothing, cosmetics, pharmaceuticals, furnishings, medical devices, toys, cleaning products and pesticides, to name a few. This exposure occurs through direct contact and use, or indirectly via leaching into other products or general environmental contamination (e.g. via indoor air and food). Phthalates are a group of substances with varying chemical structures, and therefore with varying physico-chemical characteristics which influence their behaviour in the environment as well as in organisms. (Schettler, 2006) Because of their characteristics, phthalates contained in consumer products are not chemically bound to polymers and are able to migrate from product surfaces into food and beverages, water, indoor and outdoor air, house dust and soil (Wormuth et al., 2006; Navarro et al., 2010).

Routes of phthalate exposure include:

- *Oral route:* uptake via food, nutritional formulas, pharmaceuticals, nutritional supplements, medical devices, toys placed into mouth, as well as other mouthing objects.
- *Inhalation route:* uptake via house dust, indoor air, or medical devices (e.g. for respiratory therapy).
- *Dermal route:* uptake via skin contact (e.g. with clothing, cosmetics, personal care products, sunscreens, modelling clay, toys, cleaning products, soil or dust).
- *Intravenous route:* uptake via medical devices. (Schettler, 2006)

1.3.3.2 Metabolism and elimination

For risk assessment, it is very important to understand the metabolism of substances such as phthalates. In many cases, biotransformation and metabolism of chemical substances result in detoxification and make the excretion easier. In the case of the group of phthalates, this does not occur. DEHP and DnBP, for example, are metabolised to their respective monoesters MEHP and MnBP, which are bioactive and are excreted via urine. (Silva et al., 2003)

The metabolism and the excretion via urine and faeces of phthalates occur rapidly. Low molecular weight phthalates are metabolised into their corresponding hydrolytic monoesters by hydrolysis during the phase I biotransformation. On the contrary, phthalates with high molecular weights are metabolised to their corresponding hydrolytic monoesters, followed by an enzymatic oxidation of the alkyl chain and are finally metabolised to oxidative, more hydrophilic metabolites. (Hauser and Calafat,

2005) The general phthalate metabolism is shown in Figure 3 and Figure 4. Further, the monoesters and the oxidative metabolites can be excreted via urine and faeces, or are able to undergo the phase II biotransformation catalysed by the enzyme uridine 5'-diphosphoglucuronyl transferase (UGT). During this process, phthalate metabolites react with glucuronic acid and form glucuronide conjugates, which result in a higher water solubility and in an increased excretion via urine. Additionally, because of the glucuronidation of the metabolites, the biological activity may be reduced. Investigations suggest that the phase II biotransformation may be the main way of detoxification for the phthalates DBP, BBzP and DEHP, but not for DEP. The percentages of the excretion of free monoester phthalates or monoester glucuronides depend on their aqueous solubility. MEP, the main metabolite of DEP, has been found in human urine samples predominantly as free MEP, whereas the metabolites MBP, MBzP and MEHP have been found predominantly as glucuronides, which suggests similar pathways for DBP and BBzP. (Silva et al., 2003)

The individual metabolisms of phthalates investigated in this study are discussed in Chapter 1.3.7.

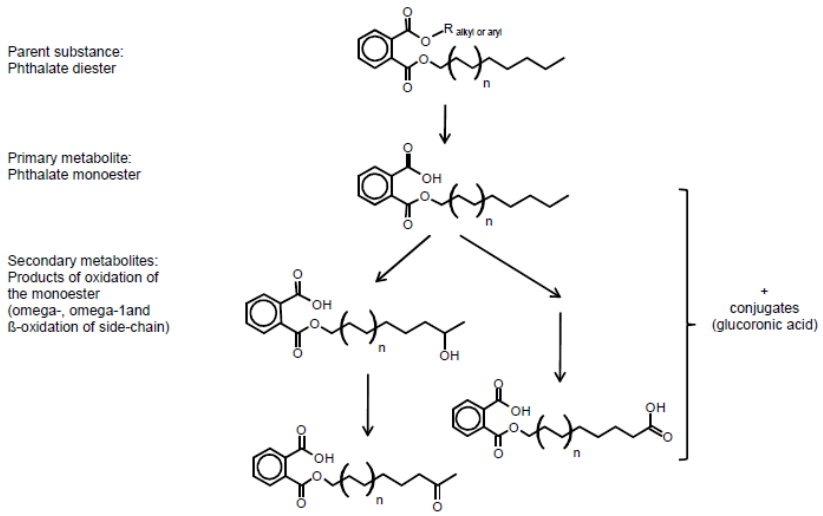


Figure 3. General scheme of phthalate metabolism (EAG, 2011)

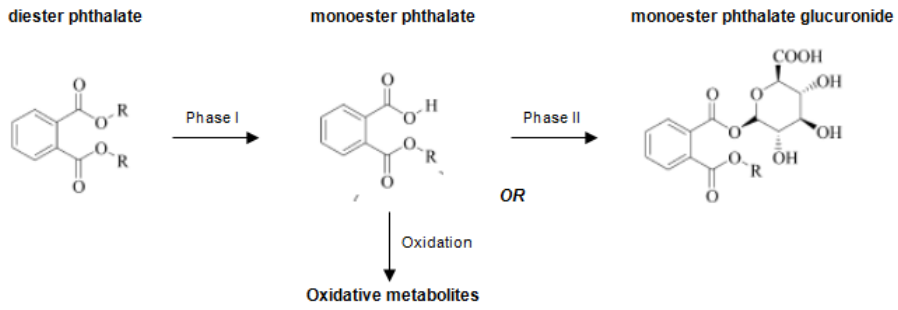


Figure 4. Metabolism pathways of phthalates (modified according Silva et al., 2003)

1.3.3.3 Biomarkers

As described above, the knowledge of metabolism and elimination of substances such as phthalates is important for the conduction of valid exposure investigations, and thus for Human Biomonitoring. Depending on their chemical structure, phthalates are metabolised only in their hydrolytic monoesters, such as DnBP for example, or are further transformed to the corresponding oxidative metabolites like DiNP. (Koch and Angerer, 2012) Table 2 shows several phthalates and their metabolites used as biomarkers:

Table 2. Parent phthalates and their metabolites used as biomarkers in Human Biomonitoring (adapted from Koch and Angerer, 2012)

Parent phthalate	Hydrolytic monoester (primary metabolite)	Oxidised monoester(s) (secondary metabolite(s))
DMP (Dimethyl phthalate)	MMP (Monomethyl phthalate)	-
DEP (Diethyl phthalate)	**MEP (Monoethyl phthalate)**	-
DCHP (Di-cyclohexyl phthalate)	**MCHP (Mono-cyclohexyl phthalate)**	-
DnPeP (Di-n-pentyl phthalate)	**MnPeP (Mono-n-pentyl phthalate)**	-
DiBP (Di-isobutyl phthalate)	**MiBP (Mono-isobutyl phthalate)**	OH-MiBP (OH-Mono-methyl-propyl phthalate)
DnBP (Di-n-butyl phthalate)	**MnBP (Mono-n-butyl phthalate)**	OH-MnBP (OH-Mono-n-butyl phthalate), ***3cx-MPP (3-carboxy-mono-propyl phthalate)[1]***
DnOP (Di-n-octyl phthalate)	**MnOP (Mono-n-octyl phthalate)**	***3cx-MPP (3-carboxy-mono-propyl phthalate)[1]***
DEHP (Di-(2-ethylhexyl) phthalate)	**MEHP (Mono-(2-ethylhexyl) phthalate)**	**5OH-MEHP (5OH-mono(2-ethylhexyl) phthalate),** **5oxo-MEHP (5oxo-mono(2-ethylhexyl) phthalate),** **5cx-MEPP (5carboxy-mono(2-ethylhexyl) phthalate)**
DiNP (Di-isononyl phthalate)	**MiNP (Mono-isononyl phthalate)[2]**	OH-MiNP (7OH-mono-methyloctyl phthalate), oxo-MiNP (7oxo-mono-methyloctyl phthalate), cx-MiNP (7carboxy-momo-methylheptyl phthalate), ***3cx-MPP (3-carboxy-mono-propyl phthalate)[1]***
DiDP (Di-isodecyl phthalate)	**MiDP (Mono-isodecyl phthalate)[2]**	OH-MiDP (6OH-mono-propylheptyl phthalate), oxo-MiDP (6oxo-mono-propylheptyl phthalate), cx-MiDP (Mono(2,7-methyl-7-carboxy-heptyl) phthalate

Analysed phthalates and phthalate metabolites in this study are in bold.

[1] 3cx-MPP is the metabolite from several phthalates (DnBP, DnOP, and DiNP), and was analysed in this study, but no conclusion could be made relating to the parent compound.

[2] In this study, only primary metabolites were analysed. Only 2-7% of parent compounds are excreted via urine as the corresponding simple monoesters (Koch and Angerer, 2012). Thus, primary metabolites are not accurate biomarkers for investigating parent phthalate exposure.

1.3.3.4 Mechanisms of action

Endocrine disruption and sexual differentiation

Endocrine disrupting chemicals can interfere with sex determination (hormone-independent formation of testis or ovary) and sexual differentiation (hormone-dependent) (Sharpe, 2006). Recent studies in animals have shown endocrine disrupting effects of several phthalates. The primary DEHP metabolite MEHP is identified to affect Sertoli cells in testes, which lead for example to decreased sperm production. Under normal conditions, the development of these cells depends on stimulation by follicle stimulating hormone (FSH) which is produced in the pituitary gland. By interacting with FSH-receptors in the cell membranes of Sertoli cells, event cascades are triggered which are necessary for normal growth and development of the Sertoli cells. The metabolite MEHP, as well as other phthalates and their metabolites, are able to interfere with these cascades, resulting in toxicity to Sertoli cells. However, detailed mechanisms of actions of phthalates are not completely understood at the present time. Additionally, in ovaries, granulosa cells that are responsible for the production of estrogen are dependent on FSH as well. In animal tests and in in vitro cell culture studies, adverse effects of MEHP on these granulosa cells have been demonstrated, which lead to increased estrogen production and abnormal estrogen cycling in adult females. (Schettler, 2005)

Phthalates may influence the masculinisation of males. For testes formation, three hormones from fetal testes are important: the anti-Müllerian hormone (AMH), testosterone, and the insulin-like factor-3 (Insl3). AMH is secreted by Sertoli cells into the bloodstream as the first hormonal event of masculinisation and acts on Müllerian ducts which induce their regression. Testosterone secreted by fetal Leydig cells is the second and most important event that supports most body-wide processes of masculinisation. Low testosterone levels in the bloodstream activate a hormonal amplification achieved through the enzyme 5α-reductase in androgen target tissues to guarantee complete masculinisation. Thus, 5α-reductase converts testosterone into 5α-dihydrotestosterone (DHT). DHT has a 10-fold higher potency of activating the androgen receptor (AR) than testosterone and to genes which are regulated by activated AR. Alternatively, testosterone can also be converted into estradiol via the activation of the enzyme aromatase. Estradiol can bind to the estrogen receptors ERα and ERβ, which can induce biological effects. A potential target for endocrine disruption by environmental chemicals is 5α-reductase, although no such effects have been yet

reported. Insl3 is also produced by the fetal Leydig cells. (Sharpe, 2006) The hormonal processes that are involved in masculinisation are shown in Figure 5.

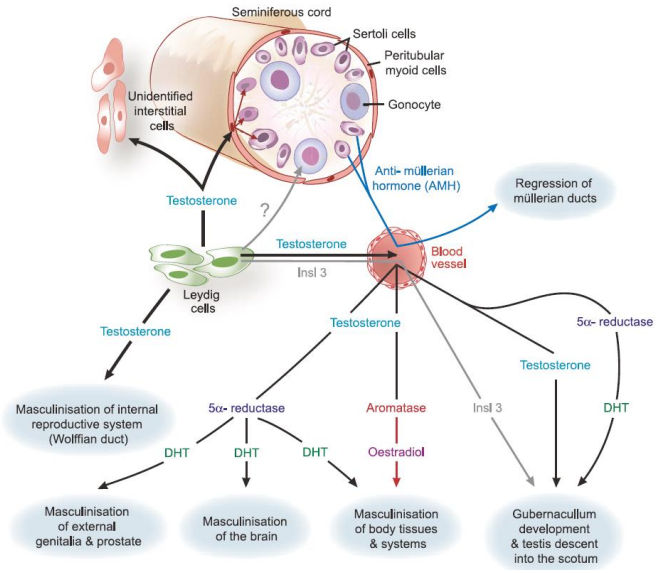


Figure 5. Hormonal processes involved in masculinisation (Sharpe, 2006)

Testicular Dysgenesis Syndrome

The most common birth defects in human males are cryptorchidism and hypospadias. Additionally, incidences of germ-cell cancers in males and decreased sperm quality are increasing. Such observations are comprised as “testicular dysgenesis syndrome” arising in fetuses during the development of the reproductive system caused by disruption of gene programming in critical stages of the development of fetal testes by genetic or environmental factors. Exposure to phthalates and their effects on the reproductive tract in male rodents exhibit with endpoints that are concerned in human males that lead to testicular dysgenesis syndrome. (NRC, 2008)

PPAR activation

Peroxisome proliferator-activated receptors (PPAR) are nuclear steroid hormone-like receptors which act as transcription factors. They play several important roles in the body, such as modulating signal molecules responsible for mediating changes in gene expression for maintaining lipid homeostasis, or activating transcription of specific target genes. Different PPAR isoforms (α, β/δ, γ) exist related to the specific organ or the individual cell type. In the liver, PPARα is primarily responsible for mediation of effects induced by peroxisome proliferators, and in all species expressed in their hepatocytes. Synthetic peroxisome proliferators such as DEHP metabolites act as

PPARα ligands, whereby MEHP is able to transactivate PPARα reporter constructs in transfected cells, for example. But it must be considered, however, that there are large differences between species, e.g. between rodents and humans (in rodents, the effect of transactivation by DEHP metabolites, MEHP in this case, occur at lower concentrations and with greater efficacy compared to humans). Additionally, MEHP is also able to transactivate PPARγ, and studies have reported the transactivation of PPARβ/δ as well. But compared to other specific PPARα ligands, the DEHP metabolite MEHP is a relatively weak agonist, and although MEHP is able to transactivate PPARα in vitro, there are species-specific differences. (Rusyn, Peters and Cunningham, 2006)

Peroxisome proliferation and peroxisomal protein induction

Peroxisomes are organelles in the cytoplasm of all cell types which contain hydrogen peroxide generating oxidases, catalase and an enzyme system for fatty acid β-oxidation. As described above, peroxisome proliferators are able to reduce the number and size of peroxisomes, lead to changes in morphology, and can induce peroxisomal enzyme activities. These effects are found in hepatocytes, whereas only minor effects have been found in other tissues. (ECB, 2008; Rusyn, Peters and Cunningham, 2006) The phthalate DEHP is a known peroxisome proliferator (PP). Hepatocytes, which are the main cell type in the liver, are responsive to exposure to PPs including DEHP. In general, PPs are substances that share many biological effects. They are characterised as non-genotoxic rodent carcinogens.

PPARα are transcription factors of several target genes, which are involved in the metabolism of fatty acids (e.g. PPARα affects expression of mitochondrial and peroxisomal fatty acid enzymes). In rodents, decreases in activity of those enzymes which are involved in β-oxidation in the liver have been shown after treatment with peroxisome proliferators. DEHP exhibits similar effects. Compared to results from rodents, humans are less responsive. (Rusyn, Peters and Cunningham, 2006)

Apoptosis suppression

Apoptosis, a process in the body which maintains the correct number of cells in body tissues and removes unwanted and damaged cells, is important for preventing cells from tumor progressing. In vivo studies in rodents have shown that PPARα agonists are able to supress apoptosis rates. In cell culture studies in rodents, MEHP leads to suppression of the spontaneous apoptosis of hepatocytes. In humans, there is currently no evidence of anti-apoptotic effects of MEHP. (Rusyn, Peters and Cunningham, 2006)

Reactive Oxygen Species production and oxidative stress

Imbalances between pro- and antioxidants lead to oxidative stress in an organism. Reactive oxygen species (ROS) are consequently increased, which can lead to oxidative DNA damage and lipid and protein damage. The most important intracellular defence systems in the body for the prevention of oxidative stress are antioxidant enzymes such as superoxide dismutases, glutathione peroxidases and catalases. A disruption of these systems leads to ROS accumulation and oxidative damage. In humans and in animal models, antioxidants and ROS are implicated in the regulation of follicle development, maturation of oocytes, fertilisation, embryo development and pregnancy. The accumulation of ROS has been shown in studies to be related with age-associated declines in follicle quality, endometriosis, infertility and low reproductive success. Additionally, they may influence the initiation of apoptosis in antral follicles. Studies in animals have shown that MEHP can inhibit the activity of glutathione peroxidase which may lead to toxic effects. (Wang et al., 2012b) MEHP, which is the primary metabolite of DEHP, has been shown to induce oxidative stress through other mechanisms compared than its parent compound DEHP by affecting different antioxidant enzymes (Wang et al., 2012b). DEHP can affect the expression and activity of superoxide dismutases, but not of glutathione peroxidase and catalase (Wang et al., 2012c).

1.3.4 Health Effects

During the last decades, exposure to various industrial chemicals among the general population increased. Sources include common consumer products as well as food and drinking water. In the same period of increasing use of these substances, the prevalence of chronic illnesses such as malformation of genitals, asthma and allergies, diabetes and obesity increased as well. These findings may be the result of diagnostic criteria changes, but environmental and genetic factors also play important roles. (Bornehag and Nanberg, 2010)

Phthalates as industrial chemicals have been identified to lead to various adverse health effects relating to reproduction and development, oxidative stress, inflammation, asthma and allergies, obesity or insulin resistance for some examples.

Several phthalates are endocrine disrupting chemicals (EDCs) which are able to act as anti-androgens, estrogens, anti-estrogens or inhibitors of steroidogenic enzymes and are able to act with thyroid hormones and their receptors through interaction, as well as

within the brain and the immune system. (Fisher, 2004) Various studies have shown that changes in testosterone levels in men can lead to several health effects. Testosterone administration has been shown to reduce total fat mass. In men undergoing an androgen deprivation therapy for prostate cancer, increases of total fat, serum glucose and of the prevalence of metabolic syndrome were shown. On the one hand, several epidemiologic studies support these findings, but on the other hand, some epidemiologic studies do not. Amongst other man-made chemicals, phthalates are able to reduce the production or function of androgens such as testosterone. (Stahlhut et al., 2007)

The exposure to anti-androgenic chemicals during sexual differentiation can lead to malformations of the reproductive tract in mammals. The perinatal administration of AR antagonists such as DEHP inhibits the testicular testosterone production in fetuses and demasculinises males. Thus, reduced anogenital distance (AGD), cleft phallus with hypospadias, retained nipples, undescended testes, vaginal pouch and epididymal agenesis were observed. DBP have also been shown to lead to anti-androgenic effects and is capable of inducing malformations in male rats. (Gray Jr. et al., 2000)

The endocrine system consists of many interacting and interconnecting axes. For the mature reproductive system, the main regulator is the hypothalamo-pituitary-gonadal axis, which works as a negative feedback system, that exist because of the existence of gonadotrophin-releasing hormone (GnRH) neurons located in the hypothalamus in the brain. These neurons release GnRH from the hypothalamus in the portal blood supply, which leads to the stimulation of the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the gonadotrophic cells into the pituitary gland. Via the systemic circulation, LH and FSH move to endocrine-active cells of the testis and ovary, and act. In the testis, testosterone and estradiol are secreted by the so-called Leydig cells, and inhibin B is secreted by the Sertoli cells. Thus, feedbacks to the pituitary and the hypothalamus are signalled for the regulation of the release of GnRH, LH, and FSH. EDCs are capable of acting at all levels of the hypothalamo-pituitary-gonadal axis. Thus, during the development of the axis during fetal life stages, this may be a strong vulnerability window for altering homeostatic mechanisms of the endocrine system. (Fisher, 2004)

In the following, various health effects caused by phthalate exposure are discussed.

1.3.4.1 Reproduction and development

Anti-androgen activity and sexual differentiation

The androgens testosterone and dihydrotesterone (DHT), which are produced during fetal and neonatal development by the testes, are one of the major factors for the development of the internal and external reproductive tract in males and therefore for masculinisation. Exogenous substances like some phthalates are able to interfere with androgen synthesis and/or action, which leads to adverse effects on the developing male genital tract. (Fisher, 2004) In rats, several phthalates have been shown to alter sexual differentiation, to exhibit anti-androgenic activity (Gray et al., 2000; Stroheker et al., 2005), to lead to reduced testosterone production, to the reduction of testicular and whole-body testosterone levels in fetuses and neonates, to reduced AGD in offspring, Leydig cell hyperplasia, to increased multinucleated gonocytes (Parks et al., 2000), decreased bulbocavernosus and levator ani muscles, prostate and seminal vesicles relative weights and to an increased relative weight of the liver (Strohecker et al., 2005). Studies in humans have shown that prenatal phthalate exposure and the anogenital index (AGI; AGI=AGD/weight [mm/kg]) in boys are inversely associated (Swan et al., 2005). Positive correlations were reported in a cohort-study investigating breast milk contaminations and possible influences of phthalates in male newborns between several phthalates and sex-hormone binding globulin, LH to free testosterone ratio, and LH, which suggests that development and function of Leydig cells may be vulnerable to perinatal phthalate exposure (Main et al., 2006).

Estrogenic activity

Estrogenic effects are ER-mediated and initiate a cascade of cell/tissue-specific effects similar to those caused by estradiol. Estrogen-like effects are defined as resembling effects of 17β-estroadiol, but are not ER-mediated. Overall, estrogenicity is a cumulative response in cells and/or tissues that are sensitive to estrogen resulting from ER-activation (directly or indirectly) and subsequent cellular/tissue responses. (Moore, 2000).

Similar to androgens, estrogens affect reproductive systems in males and females. Several studies in rodents have shown that prenatal phthalate exposure leads to the reduction of fetal Leydig cells and testosterone production, resulting in postnatal reproductive disorders in males. Prenatal DnBP exposure at low doses has been shown to lead to alterations of ERα and ERβ, and to alterations of AR on testicular Leydig cells in rats. Additionally, seminiferous tubule degeneration and atypical

hyperplasia of Leydig cells during the rat's adulthood was identified, which was related to increased ERα expression, and decreased ERβ and AR expression in the testes. (Wakui et al., 2014) DnBP was identified to bind ERα and to enhance the proliferation of a breast cancer cell line (MCF-7) expressing ERα (Nishihara et al., 2000; Wakui et al., 2014). Thus, some phthalates have the affinity to bind to ERβ, although the affinity is weak (Harris et al., 1997; Wakui et al., 2014). DEHP binds to ERβ and reduces the binding of 17β-estradiol to the ER (Jobling et al., 1995).

Fertility, sperm motility and sperm quality

Worldwide, reproductive health has been becoming increasingly impaired, and the fertility rates and sperm counts of average men have been declining. Because of the changes taking place over a short time period, they are more likely to be due to environmental than genetic factors. (Pant et al., 2010) In toxicological studies, several phthalates have been identified to be reproductive and developmental toxicants, whereby a multitude of these studies focused on exposure to phthalates and their effects during gestational exposure windows. However, there is also evidence that the exposure to some phthalates can lead to testicular toxicity in adolescents and adults, which includes impaired spermatogenesis. (Hauser et al., 2007) Recent studies have also shown that there are indications that phthalate exposure affects semen quality, but the results of these studies are not conclusive and further investigations are needed (Duty et al., 2004; Hauser et al., 2007; Jönsson et al., 2005; Liu et al., 2012).

Birth outcome and preterm birth

Preterm birth is defined as the birth of a child at <37 completed weeks or 259 days of gestation. It is a major cause of neonatal mortality and morbidity and leads to long-term adverse health effects such as cerebral palsy, sensory deficits, learning disabilities, and respiratory illnesses. In 2005, 9.6% of all births were preterm, whereby 85% of them occurred in Africa and Asia. In Europe, about 0.5 million preterm births occurred (6.2%). (Beck et al., 2010) In industrialised nations, preterm birth rates have increased in recent decades. Factors that contribute to the increase of preterm births remain largely unclear, but exposure to environmental pollutants may play a role. (Meeker et al., 2009) Several studies indicate possible relationships between phthalate exposure and preterm birth and/or influence on birth outcome, but the results of these studies are inconclusive. In newborns, several studies have observed that various phthalates were associated with shorter pregnancy durations and therefore with preterm births (Latini et al., 2003; Meeker et al., 2009; Wolff et al., 2008).

Neurobehaviour

Some epidemiologic studies have demonstrated that phthalate exposure may have an influence on neurobehaviour in infants. Associations were found between urinary DEHP metabolites and IQ scores in South Korean school children, as well as between DEHP and DnBP metabolites and vocabulary subscale scores. However, limitations in cross-sectional epidemiology exist. (Cho et al., 2010) Additionally, associations were found between prenatal DEHP exposure and non-optimal reflexes in males (Yolton et al., 2011), and between prenatal phthalate exposure and decreased mental and motor development, and increased internalising behaviours in children (Whyatt et al., 2012).

1.3.4.2 Thyroid hormone system

Thyroid hormones are important for many physiological processes in the body such as growth, brain development, energy balance, metabolism or various functions in the reproductive, nervous, cardiovascular and pulmonary systems of fetuses, children and adults (Meeker and Ferguson, 2011). In preterm infants, main reported factors affecting thyroid function are immaturity of the hypothalamic-pituitary-thyroid axis, immature synthesis and metabolism of thyroid hormones, and insufficient or excessive iodine exposure (Latini et al., 2014). Studies reported evidence that exposure to environmental chemicals such as phthalates and BPA can affect thyroid signalling through various mechanisms. (Meeker and Ferguson, 2011) Phthalates may interfere with thyroid homeostasis via several mechanisms: they are capable of interfering with various receptors and can thus influence the synthesis of thyroid hormones, they are able to bind competitively to the transport protein transthyretin, and can inhibit the uptake of red blood cells or the expression of the thyroid receptor beta gene. (Boas et al., 2006) In adults, significant inverse associations between DEHP metabolites and total and free T4, total T3, and thyroglobulin, as well as positive associations with TSH have been reported (Meeker and Ferguson, 2011). In children, studies have found negative associations between phthalate concentrations and thyroid hormones, insulin-like growth factor and childhood growth with gender differences (Boas et al., 2010), as well as possible alterations of serum TSH levels after high-dose exposure to phthalate-tainted food (Wu et al., 2013).

1.3.4.3 Oxidative stress and inflammation

Oxidative stress is an imbalance between the production of free radicals and antioxidant capacity in the organism which results in an excess of oxidative products

and is important for many pathological conditions such as insulin resistance. (Hong et al., 2009) Animal studies have shown increased oxidative stress and inflammation induced by phthalate exposure. These increases may lead to adverse health effects in humans. Some studies in humans have investigated possible relationships between exposure to phthalates and biomarkers of oxidative stress and inflammation. (Ferguson, Loch-Caruso and Meeker, 2011) In a study conducted on U.S. American males and females, positive associations were found between the marker for inflammation C-reactive protein and MBzP as well as MiBP, and between the marker for oxidative stress gamma glutamyltransferase and MEHP. However, inverse relationships were shown between the biomarkers and mainly oxidized metabolites. (Ferguson, Loch-Caruso and Meeker, 2012) Additionally, positive associations were identified between 5OH-MEHP concentrations in urine and fasting blood sugar levels, which may contribute to insulin resistance development, as well as significant dose-response relationships between urinary chemical exposure biomarkers and levels of oxidative stress (Hong et al., 2009).

1.3.4.4 Asthma, rhinitis, eczema, and allergies

In recent years, incidences of asthma and allergies have been increased and become one of the most common chronic diseases among children and adolescents. The main route of phthalate exposure is via food ingestion; however, studies have shown that children have higher total intakes than adults, which is expected to be due to sucking on plastic toys and other plastic products, and due to the ingestion of indoor dust. (Bornehag and Nanberg, 2010) Although the volatility of phthalates is low, they are able to off-gas and be present in indoor air and house dust (Jaakkola and Knight, 2008) The most commonly found phthalate in indoor dust has been DEHP, followed by BBzP, DnBP, DiBP, as well as DEP, whereby main sources are PVC floorings and coverings and furniture polishing products. (Bornehag and Nanberg, 2010) Many studies, including case reports, epidemiologic studies and toxicity studies, have observed that emissions of phthalates from PVC materials may lead to an increased risk of asthma and allergies (Tsai, Kuo and Ko, 2012).

Several studies in children have shown that significant associations exist between the occurrence of asthma and allergies, and/or symptoms of wheezing, rhinitis, eczema and/or bronchial obstruction and phthalate levels in relating house dust samples (Bornehag et al., 2004; Hsu et al., 2012; Jaakkola et al., 1999; Jaakkola and Knight, 2008; Kolarik et al., 2008). Phthalate exposure through indoor dust does not solely affect children. A study that investigated associations between bronchial asthma

among office employees and the state of indoor air as a result of the degradation of PVC floor coverings has shown that the indicator for DEHP degradation 2-ethyl-1hexanol indicated the PVC degradation.

Higher incidences of several respiratory, conjunctival and dermal symptoms were found. (Tuomainen, Seuri and Sieppi, 2004) In a meta-analysis and systematic review of the available literature between 1950 and 2007 on the effects of phthalate exposure via air and the occurrence of asthma and allergies, the findings of several studies supported the hypothesis that phthalates leaching from PVC materials increase the risk of allergies and asthma. High phthalate levels are able to modulate the murine immune response to a co-allergen. In adults, heated PVC fumes may contribute to the development of asthma. In children, associations between indicators of exposure to phthalates in homes and the risk of asthma and allergies were shown. (Jaakkola and Knight, 2008)

Investigations of the pathogenesis of asthma and allergies have identified exposure to environmental factors, especially pollutants in indoor air and dust, as contributors (Hsu et al., 2012). Phthalates, which are extensively used in daily life, contribute to the pathogenesis of asthma, allergies and related diseases. Much of the epidemiologic evidence addresses the associations between asthma and allergic diseases and phthalate exposure, and most of the experimental studies address the effects of phthalates on immune responses. Regarding to investigations of the detailed molecular signalling mechanisms of phthalate exposure, only a few studies exist. Therefore, further investigations are necessary, including in vivo and in vitro studies. (Tsai, Kuo and Ko, 2012)

1.3.4.5 Obesity, insulin resistance, diabetes mellitus

Worldwide, the prevalence of overweight and obesity, insulin resistance and diabetes mellitus is still increasing. In Austria, 24% of children between 7 and 14 years are obese. Among the adult population, the prevalence of obesity among males amounts 52%, and among females 28%, as well as 33% of the elderly people. (Elmadfa et al., 2012) Most presumable causes for the development of obesity are behavioural, genetic and environmental factors that interact in complex ways. In recent decades, the main interest has centred on the most common causes: the high caloric fatty diets in combination with sedentary lifestyle and genetic predisposition. But the exact aetiology of obesity is unknown. Endocrine disrupting chemicals may contribute to its prevalence. (Newbold, 2010) An exposure to endocrine disrupting chemicals during critical

developmental stages may contribute to adipogenesis and to the development of obesity (Hao et al., 2012).

Several phthalate metabolites are able to bind to and activate the PPARs in humans. PPARγ controls insulin sensitivity and plays an important role in fat storage by the promotion of adipocyte maturation and survival. Thus, phthalate metabolites can promote the differentiation from pre-adipocytes to adipocytes by PPAR activation. (Hao et al., 2012; Lind et al., 2012; Martinelli, Mocchiutti and Bernal, 2010; Schmidt et al., 2012) In an *in vitro* study in primary cultures of human subcutaneous adipocytes, the rapid stimulation of MEHP expression in genes involved in glyceroneogenesis, and enhancement of the cytosolic phosphoenolpyruvate carboxykinase expression, as well as a reduction of fatty acid release have been shown, which supports that MEHP is able to increase the glyceroneogenesis and fatty acid re-esterification in adipocytes in humans. Additionally, they reported that these and other findings indicate the promotion of the differentiation of human pre-adipocytes to adipocytes by MEHP. (Ellero-Simatos et al., 2011)

Additionally, a multitude of scientific epidemiological studies have been carried out in recent years. In children and/or adults, positive associations have been found between several urinary phthalate metabolite concentrations and abdominal obesity (Stahlhut et al., 2007), insulin resistance (Hong et al., 2009; Stahlhut et al., 2007), self-reported diabetes (Svennson et al., 2011), increased waist circumference (Hatch et al., 2008; Lind et al., 2012; Teitelbaum et al., 2012), increased BMI (Hatch et al., 2008; Teitelbaum et al., 2012; Wolff et al., 2008), as well as total fat mass, trunk fat mass, and subcutaneous adipose tissue in females (Lind et al., 2012).

1.3.5 Legislation in the EU

In the EU, phthalates are regulated in various ways. Generally, chemicals are regulated by the REACH regulation[3] and the CLP regulation[4]. Under REACH, the registration of substances produced or imported into the EU in amounts of ≥1 tonne/year are required, which includes the documentation of health effects and environmental

[3] Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (Regulation (EC) No 1907/2006); published in 2006 and entered into force in June 2007. REACH harmonises the European chemicals legislation. (EC, 2012)

[4] Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures; entered into force in January 2009. CLP harmonises and notificates classification and labelling of chemicals. (Schöning, 2010)

properties. The information requirements increase with the amounts of produced or imported substances, whereby the industry is responsible for submitting documentation. A substance is not allowed to be produced or be placed on the market if documentation is not provided. Several regulatory options exist under REACH, whereby the authorisation scheme, the harmonised classification and restrictions are the most important. (Danish EPA, 2013)

1.3.5.1 Classification

The classification and labelling of substances is conducted according to the CLP regulation (Regulation (EC) No 1272/2008) which entered into force in January 2009 and replaced the Directive 67/548/EEC (Dangerous Substances Directive), the Directive 199/45/EC (Dangerous Preparations Directive), and the REACH Title XI (Classification and Labelling). The main aim is the harmonisation and notification of the classification and labelling of chemicals, and to request the use of alternative names for chemicals in substances. (Schöning, 2010) CLP is based on the third revision of the Globally Harmonised System of Classification and Labelling of Chemicals of the United Nations (UN GHS), which was developed on a global level in order to minimise differences between several existing systems for classification, and provides an integrated system of hazard communication elements: hazard pictograms, signal words and hazard statements[5] as well as precautionary statements (ECHA, 2013e).

Concerning phthalates, some of them are classified as toxic to reproduction, whereby different categories exist:

- Repr. Cat. 1: known or presumed to be toxic to human reproduction (Cat. 1A: evidence of effects in humans; Cat. 1B: evidence of effects in animals)
- Repr. Cat. 2: suspected to be toxic to human reproduction.

Substances that are toxic to reproduction are further classified in relation to their adverse health effects:

- F/f: adverse effects on sexual function and fertility
- D/d: adverse effects on development of offspring (Danish EPA, 2013)

[5] Hazard statements determine different hazard classes and categories describing the type of hazards of a hazardous substance including the degree of hazard (United Nations, 2007).

Table 3 shows the harmonised classification of DEHP as an example for classification and labelling:

Table 3. Harmonised classification according to Annex VI of CLP Regulation for DEHP (ECHA, 2014b)

Classification		
Hazard Class and Category Code	Repr. 1B	Toxic for reproduction category 1B
Hazard Statement Code	H360FD	May damage fertility, may damage the unborn child
Labelling		
Pictogram	GHS08	"Health Hazard"
Signal Word	Dgr	"Danger"

No separate classifications for endocrine disrupting effects exist. Various endocrine disrupting chemicals meet the criteria for classification as "toxic to reproduction", but these effects on the endocrine system can also lead to other health effects which are not covered by classification rules yet. (Danish EPA, 2013)

Classification and labelling of individual phthalates investigated in this work are shown in the related sub-chapters of Chapter 1.3.7. For phthalates that are currently not classified and labelled according to harmonised CLP, self-classifications by industries are listed.

1.3.5.2 Registration

Substances manufactured or imported in quantities ≥1 ton/year must be registered under REACH regulation by the manufacturer or importer. (Danish EPA, 2013) Details on the registration regime and data requirements are provided at the dissemination website of the ECHA[6].

1.3.5.3 Authorisation

The authorisation under REACH ensures the control of risks of substances of very high concern (SVHC), and the successive replacement by alternatives. The authorisation procedure consists of two steps: first the selection of substances for authorisation (decision on substance inclusion in candidate list and further in authorisation list

[6] Dissemination website of ECHA is available at: http://echa.europa.eu/regulations/reach/substance-registration/substances-to-be-registered

(Annex XIV of REACH regulation)), and secondly the authorisation applications (by the industry) and decisions (by the EC). (Schöning, 2010)

A substance is identified as a SVHC when the substances is classified as CMR (carcinogenic, mutagenic and toxic for reproduction category 1A or 1B according CLP regulation), as PBT (persistent, bioaccumulative and toxic for reproduction) or as a vPvB (very persistent and very bioaccumulative) substance according to REACH regulation Annex XIII, or as a substance of equivalent concern identified case-by-case (e.g. endocrine disrupting chemicals). (EC, 2007; ECHA, 2013c) Substances which are identified as SVHC are included in the so-called Candidate List by member states or the European Chemicals Agency (ECHA). Included substances can be prioritised for inclusion in the so-called Authorisation List (Annex XIV of REACH regulation) by the EC. (EC, 2007; Schöning, 2010)

Candidate List

Currently (latest update at 20 June 2013), 144 substances are on the candidate list. Table 4 shows listed phthalates:

Table 4. Phthalates listed on REACH Candidate List (state: 06/2013) (ECHA, 2013b)

Substance (CAS No.)	Inclusion date	Reason for inclusion	Decision number
Di-pentyl phthalate (DPP) (131-18-0)	2013-06-20	Toxic for reproduction (Article 57c)	ED/69/2013
n-pentyl-isopentyl pthalate (776297-69-9)	2012-12-19	Toxic for reproduction (Article 57c)	ED/169/2012
Di-isopentyl phthalate (605-50-5)	2012-12-19	Toxic for reproduction (Article 57c)	ED/169/2012
Bis(2-methoxyethyl) phthalate (117-82-8)	2011-12-19	Toxic for reproduction (Article 57c)	ED/77/2011
DiBP (84-69-5)	2010-01-13	Toxic for reproduction (Article 57c)	ED/68/2009
BBzP (85-68-7)	2008-10-28	Toxic for reproduction (Article 57c)	ED/67/2008
DEHP (117-81-7)	2008-10-28	Toxic for reproduction (Article 57c)	ED/67/2008
DnBP (84-74-2)	2008-10-28	Toxic for reproduction (Article 57c)	ED/67/2008

Authorisation list

Currently, 22 substances are listed on the REACH authorisation list (status October 2013). Of the substance group of the phthalates, BBzP, DEHP, DnBP, and DiBP are listed (Table 5). (ECHA, 2013a)

Table 5. Phthalates listed on REACH Authorisation List (state: 10/2013) (ECHA, 2013a)

Substance (CAS No.)	Latest application date / sunset date[1]	Exempted uses
BBzP (85-68-7)	2013-08-21 / 2015-02-21	Use in immediate packaging of medical products (Regulation (EC) No 726/2004, Directive 2001/82/EC, and/or Directive 2001/83/EC
DEHP (117-81-7)	2013-08-21 / 2015-02-21	Use in immediate packaging of medical products (Regulation (EC) No 726/2004, Directive 2001/82/EC, and/or Directive 2001/83/EC
DnBP (84-74-2)	2013-08-21 / 2015-02-21	Use in immediate packaging of medical products (Regulation (EC) No 726/2004, Directive 2001/82/EC, and/or Directive 2001/83/EC
DiBP (84-69-5)	2013-08-21 / 2015-02-21	

[1] date at which a substance cannot be used or be placed on the market any longer unless the company is granted authorisation (ECHA, 2013c).

1.3.5.4 Restrictions

The REACH regulation provides the criteria for the CMR classification category 1 or 2 of substances in accordance with the Council Directive 67/548/EEC of 27 June 1967. With Regulation (EU) No 143/2011, the EC amended Annex XIV of the REACH regulation. Thus, DEHP, BBzP and DnBP fulfil the criteria for classification as toxic to reproduction category 1B, are included in the candidate list according to Article 59, and meet the criteria for inclusion in Annex XIV according to Article 57(c) of the REACH regulation. The use of DEHP, BBzP and DnBP in immediate packaging of medicinal products covered under Regulation (EC) No 726/2004, Directive 2001/82/EC and/or Directive 2001/83/EC is exempted. (EC, 2011c)

Toys and childcare articles

According to the EC Regulation 552/2009 of 22 June 2009, the use of DEHP, DnBP and BBzP as substances or in mixtures in toys and childcare articles[7] is not allowed at concentrations of more than 0.1% by weight of the plasticised material. It is prohibited to place toys or childcare articles on the market if these phthalates are contained in concentrations higher than 0.1%. The same regulations apply for the phthalates DiNP, DiDP and DnOP, but only for toys and childcare products that may be placed in the mouth by children. (EC, 2009c) The restrictions regarding the placement of phthalates on the market and their use in toys and childcare articles, which are included in the

[7] Childcare articles are any products that are intended to facilitate sleep, hygiene, relaxation, feeding or sucking of children (EC, 2009c).

entries 51 and 52 of Annex XVII of the REACH regulation, were introduced by Directive 2005/84/EC of 14 December 2005 (ECHA, 2010b).

Cosmetic products

Through Directive 76/768/EEC (amended by Directive 2003/15/EC) the European Parliament prohibits substances in cosmetic products that are classified as CMR (carcinogenic, mutagenic or toxic for reproduction) of categories 1, 2 and 3. The use of substances classified category 3 is allowed if they have been evaluated and approved by the Scientific Committee on Cosmetic Products and Non-Food Products. In 2004, the EC established Directive 2004/93/EC which amended Directive 76/768/EEC, and added CMR substances of the categories 1 and 2 that were not yet listed in Annex II. DnBP, DEHP, and bis(2-methoxyethyl) phthalate were added in Annex II. (EC, 2004) In 2009, the EU re-casted the regulation on cosmetic products, including significant recent and further amendments (Regulation (EC) No 1223/2009). In Annex II, which contains prohibited substances in cosmetic products, DnBP, DEHP, BBzP, and bis(2-methoxyethyl) phthalate are listed, as well as n-pentyl-isopentyl phthalate, di-n-pentyl phthalate, and di-isopentyl phthalate. (European Parliament, 2009)

Food contact materials

In the EU, the use of DEHP, DnBP, BBzP, DiNP, and DiBP in food contact materials for fatty foods and for non-repeated use, as well as in food contact materials for infant feeding is banned. However, as technical support agents, DEHP, BBzP, DiNP and DiDP are allowed to be present in the final product up to 0.1%, and DnBP up to 0.05%. (EC, 2011e) Table 6 summarises the EU legislation of phthalates in food contact materials:

Table 6. EU legislation (Commission Regulation (EU) No 10/2011) of several phthalates in food contact materials (EC, 2011e)

Phthalate (CAS No)	Allowed use as plasticiser in			(1)	SML [mg/kg]
	(a)	(b)	(c)		
DEHP (117-81-7)	x	x		0.1%	1.5
BBzP (85-68-7)	x		x	0.1%	30
DnBP (84-74-2)	x	x		0.05%	0.3
DiNP (68515-48-0 and 28553-12-0)	x		x	0.1%	
DiDP (68515-49-1 and 26761-40-0)	x		x	0.1%	

(a) repeated use materials and articles
(b) materials and articles containing non-fatty foods
(c) single-use materials and articles containing non-fatty food except for infant and follow-on formulae
(1) Allowed concentration in final product as technical support agent
Abbreviation: SML, specific migration limit [mg phthalate/kg food].

1.3.5.5 Endocrine regulations

Within the so-called Strategy for Endocrine Disruptors of the EU, a priority list was established, but not regarded as final, containing priority substances for further evaluation of their role as endocrine disruptors. The establishment of the priority list occurred in two phases: the first phase was an independent review of evidence of endocrine disrupting effects of chemicals and exposure, and the second was priority-setting by consultation of stakeholders and Commission Scientific Committees of the EU. The chemicals were classified in relation to the strength of evidence of endocrine disruption into Category 1 (evidence of endocrine activity in at least one species), Category 2 (some in vitro evidence of biological activity related to endocrine disruption) and Category 3 (no evidence of endocrine disruption, or no data available). Currently, 66 chemicals are classified into Category 1, 60 of which humans are considered to be exposed to, and 52 chemicals are classified into Category 2 (status: February 2014). (EC, 2014)

The following phthalates are listed at the updated priority list:

Table 7. Phthalates and phthalate metabolites listed in the priority list of the Strategy for Endocrine Disruptors (Petersen, Rasmussen and Gustavson, 2007)

Substance (CAS No)	*Category*		
	Human Health	**Wildlife**	**Overall categorisation**
DCHP (84-61-7)	1	3b	1
DnPeP (131-18-0)	1	3b	1
DnBP (84-74-2)	1	3	1
BBzP (85-68-7)	1	3	1
DEHP (117-81-7)	1	3	1
DiBP (84-69-5)	2	3b	2
Di-n-hexyl phthalate (DnHP) (84-75-3)	2	3b	2
Di-n-propyl phthalate (DprP) (131-16-8)	2	3b	2
DiNP (28553-12-0)	2	3	2
DiDP (26761-40-0	2	3	2
DnOP (117-84-0)	3b	3b	3b
Metabolites:			
MnBP (131-70-4)	1	3b	1
MEHP (4376-20-9)	1	3b	1

1.3.6 Acceptable Levels of exposure

In Europe and the USA, agencies have set out several acceptable levels of exposure (AL) for various phthalates. Generally, ALs are derived from different endpoints of

selected studies under consideration of uncertainty factors. In this study, the Tolerable Daily Intake (TDI), the Reference Dose (RfD) and the Reference Dose for Anti-Androgenicity (RfD AA) were used. Therefore, explanations and values are only given for these ALs.

Comparing the RfD set out by the U.S. EPA and the TDI set out by the EFSA, one determines that values for the same phthalates are vary up to 10-fold. The reason for these discrepancies is the use of different departure values based on different key studies, endpoints and exposure scenarios, as well as different No Observed Adverse Effect Levels (LOAEL)[8] and uncertainty factors. (Søeborg, Frederiksen and Andersson, 2012)

1.3.6.1 Definitions

Tolerable Daily Intake (TDI)

The TDI is the estimated concentration of a substance which can be ingested daily over a lifetime without significant risks to human health (EFSA, 2011). TDIs are set out by the EFSA and are based on selected studies.

Reference Dose (RfD)

The RfD set out by the U.S. EPA is defined as “an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.” (U.S. EPA, 2012a) For the RfD derivation, a NOAEL, a LOAEL or a benchmark dose can be used, whereby uncertainty factors are applied for reflection of limited data (U.S. EPA, 2012a).

Reference Dose for Anti-Androgenicity (RfD AA)

Certain phthalates show anti-androgenic effects. RfD and TDI values do not identify these effects as the most sensitive endpoints for phthalates. Therefore, they are not able to be used as ALs for anti-androgenic effects. RfD AA values for several phthalates have been established by Kortenkamp and Faust (2010) based on the

[8] LOAEL (Lowest Observed Adverse Effect Level): lowest level of exposure at which significant increasing in frequency or severity of adverse effects between an exposed population and its control group occur (U.S. EPA, 2012a).

specific effects on anti-androgenicity. (Kortenkamp and Faust, 2010; Søeborg, Frederiksen and Andersson, 2012)

1.3.6.2 Selected acceptable levels of exposure for several phthalates

DEP: For DEP, a TDI is currently not available. Based on decreased growth rates, food consumption and altered organ weights in rats, the U.S. EPA set out a RfD of 800 µg/kg bw/d (U.S. EPA, 2007b).

DnBP: The NOAEL for the male reproductive system of DnBP is 50 mg/kg bw/d. In rats, effects in male and female offspring were shown after feeding DBP to the corresponding mothers in late pregnancy and during lactation; however no NOAEL could be established. The EFSA TDI is set out at 10 µg/kg bw/d. (EC, 2013) The U.S. EPA set out a RfD of 100 µg/kg bw/d based on a feeding study in rats (HHS, 2001).

DiBP: The developmental and reproductive effects of DiBP are similar to those of DnBP and DEHP, but currently no NOAEL has been derived and no TDI set out. Therefore, further investigations are needed. (EC, 2013)

DEHP: The EFSA TDI is set out at 50 µg/kg bw/d based on the NOAEL for reproductive and developmental effects of 4.8 mg/kg bw/d (EC, 2013). The U.S. EPA set out a RfD for DEHP of 20 µg/kg bw/d based on increased relative liver weights in guinea pigs (U.S. EPA, 2007a).

BBzP: In rats, a NOAEL of 100 mg/kg bw/d for reproductive effects to organs was shown, as well as a NOAEL of 20 mg/kg bw/d and of 50 mg/kg bw/d for developmental effects in two studies, respectively. The EFSA set out a TDI of 500 µg/kg bw/d. (EC, 2013) The RfD for chronic oral exposure is set out by the U.S. EPA at 200 µg/kg bw/d based on increased liver-to-body weight and liver-to-brain ratios in adult humans (U.S. EPA, 2007b).

DnOP: For DnOP, there is no TDI available, because adverse effects on reproduction and development are unlikely at current knowledge (EC, 2013).

DiNP: The NOAEL for effects on reproduction ranges between 500 and 622 mg/kg bw/d. The NOAEL for changes in the liver, which are the main toxicological effects, is 15 mg/kg bw/d. The EFSA set out a TDI of 10 µg/kg bw/d. (EC, 2013)

DiDP: Currently, no effects of DiDP on reproductive organs have been shown. For effects on the liver, a NOAEL 15 mg/kg bw/d was derived from a study in dogs. A TDI for DiDP is not available, but 150 µg/kg bw/d may be a good safety margin. (EC, 2013)

Table 8. Tolerable Daily Intake (TDI), Reference Dose (RfD), and Reference Dose for Anti-Androgenicity (RfD AA) established by the EFSA and U.S. EPA respectively for several phthalates

Phthalate	TDI (EFSA)[1] [µg/kg bw/d]	RfD (U.S. EPA)[2] [µg/kg bw/d]	RfD AA[3] [µg/kg bw/d]
DEP (diethyl phthalate)	-	800	-
DnBP (di-n-butyl phthalate)	10	100	100
DiBP (di-isobutyl phthalate)	-	-	200
BBzP (butyl benzyl phthalate)	500	200	330
DEHP (di(2-ethylhexyl) phthalate)	50	20	30
DiNP (di-isononyl phthalate)	150	-	1500
DiDP (di-isodecyl phthalate)	150	-	-

Abbreviations: EFSA, European Food Safety Authority; RfD, Reference Dose; RfD AA, Reference Dose for Anti-Androgenicity; TDI, Tolerable Daily Intake; U.S. EPA, United States Environmental Protection Agency

[1] Sources: EC (2013), EFSA (2005a, 2005b, 2005c, 2005d, 2005e)

[2] Sources: HHS (2001), U.S. EPA (2007a, 2007b)

[3] Sources: Kortenkamp and Faust (2010), Søeborg, Frederiksen and Andersson (2012)

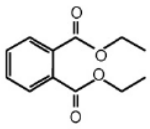
1.3.7 Overview of investigated phthalates

1.3.7.1 Diethyl phthalate (DEP)

1.3.7.1.1 General information

Table 9 provides the general information for DEP:

Table 9. General information on DEP (ECHA, 2013a; WHO, 2003; Zhao et al., 2010)

EC Number	201-550-6
CAS Number	84-66-2
IUPAC Name	diethyl benzene-1,2-dicarboxylate
Molecular formula	$C_{12}H_{14}O_4$
Molecular weight	222.3 g/mol
Physico-chemical properties	Colourless, slight aromatic odorous liquid; soluble in alcohol, acetone, ether, benzene, ketones, esters, aromatic hydrocarbons, aliphatic solvents, and vegetable oils; water solubility: 1 g/l at 25°C
Chemical structure	

1.3.7.1.2 Classification and labelling

DEP is not classified and labelled according to harmonised CLP, but self-classified by industry: 1026 notifiers have not classified it currently (2014-06-06), whereas 15 notifiers have classified it as acute toxic category 3 (H331: Toxic if inhaled). The strictest notification is acute toxic category 1 by one notifier. (ECHA, 2014f)

1.3.7.1.3 Legislation

In the EU, DEP is allowed to be used in various products without limitations. However, some countries in Europe (EU member states and non-EU member states) have banned all phthalates, including DEP, from several consumer products such as toys and childcare articles (Norway, Denmark and Sweden). (VKM, 2005)

1.3.7.1.4 Production and usage

DEP is produced by a reaction of phthalic anhydride with ethanol in the presence of sulphuric acid (WHO, 2003). Per year, 1,000-10,000 tonnes are manufactured (ECHA, 2013g). DEP is used as a plasticiser in many consumer products such as plastic packaging films, food packing materials, cosmetics, personal care products, medical treatment tubings (WHO, 2003), coatings of e.g. pharmaceuticals, dyes and insecticides (Hauser and Calafat, 2005). In detail, its use was identified in air care products, perfumes, washing and cleaning products, coatings and paints, modelling clay, polish and wax blends, biocide products (e.g. disinfectants), adhesives, sealants, anti-freeze and de-icing products, metal surface treatment products and textile dyes, as well as in finishing and impregnating products to name some examples (ECHA, 2013g).

1.3.7.1.5 Toxicokinetics

Routes of exposure

Humans can be exposed to phthalates through oral, dermal or inhalation routes (Silva et al., 2003).

Distribution, metabolism and elimination

After oral administration, DEP is absorbed and distributed throughout various tissues in the body, whereby the highest accumulation occurs in the kidneys and the liver. DEP is metabolised by partial hydrolysis catalysed by hydrolase to ethanol and its monoester

monoethyl phthalate (MEP). The hydrolysis can occur in the lumen of the GIT and in intestinal mucosal cells following oral administration, as well as in organs such as the liver, kidneys and lung after systemic absorption. MEP is excreted rapidly via urine, mostly in its free form. (ATSDR, 1995; Api, 2001)

Biomarker

The biomarker used for Human Biomonitoring of DEP is its primary metabolite mono-ethyl phthalate (MEP) (Koch and Angerer, 2012).

1.3.7.1.6 Health effects

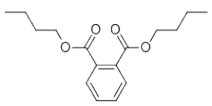
DEP is used in personal care products; therefore, potential dermal toxicity is of interest. In humans, no dermal irritation has been identified, and DEP is not a dermal sensitizer. However, some studies have reported dermal sensitisation, but mainly in persons with skin diseases. (Calafat and McKee, 2006) Additionally, the toxicity of DEP is low. Studies on sub-chronic toxicity and reproduction have not shown adverse effects, and DEP as well as MEP are not considered to be genotoxic. Furthermore, available studies do not provide sufficient evidence for associations to be determined between DEP exposure to humans and health effects. (VKM, 2005)

1.3.7.2 Di-n-butyl phthalate (DnBP)

1.3.7.2.1 General Information

In Table 10, general information on DnBP are summarised:

Table 10. General information on DnBP (ECHA, 2008c; ECHA, 2013b)

EC Number	201-557-4
CAS Number	84-74-2
IUPAC Name	1,2-Benzenedicarboxylic acid dibutyl ester
Molecular formula	$C_{16}H_{22}O_4$
Molecular weight	278.34 g/mol
Physico-chemical properties	Oily liquid; melting/freezing point at -69°C; boiling point at 340°C; water solubility of 10 mg/l at 20°C.
Chemical structure	

1.3.7.2.2 Classification and labelling

DnBP is classified according to CLP classification as Repr. 1B; H360Df (toxic to reproduction category 1B; May damage unborn child; Suspected of damaging fertility), and Aquatic Acute 1; H400 (Very toxic to aquatic life). It is labelled by the signal word “Danger” and by the pictograms “Environment” and “Health hazard”. (ECHA, 2013k)

1.3.7.2.3 Legislation

Amongst other phthalates, DnBP is listed in the REACH authorisation list (ECHA, 2013a). It is banned in immediate packaging of medical products (EC, 2011c), in toys and childcare articles at concentrations >0.1% by weight (EC, 2009c), and in cosmetic products (European Parliament, 2009). In food contact materials, DnBP is prohibited in single-use materials and articles and in materials and articles containing fatty foods. However, as a technical support agent it is allowed to be present in the final product at a concentration of 0.05%. The SML of DnBP is set out at 0.3 mg/kg food. (EC, 2011e)

1.3.7.2.4 Production and usage

The production of DnBP occurs by the reaction of phthalic anhydride with n-butanol in the presence of sulphuric acid. In the EU, about 26,000 tonnes of DnBP were manufactured in 1998, whereby 8,000 tonnes were exported outside the EU. DnBP is mainly used as a plasticiser in PVC products. Furthermore, it is used for adhesives, printing inks, film coatings and glass fibres. Before its ban in the EU, it was widely used in cosmetics. (ECB, 2003c)

1.3.7.2.5 Toxicokinetics

Routes of exposure

Routes of DnBP exposure through consumer products are oral and via inhalation. Dermal exposure is negligible. (ECB, 2003c)

Metabolism and elimination

Amongst others, MnBP and 3cx-MPP are metabolites of DnBP (Koch et al., n.r.). Figure 6 shows the metabolism of DnBP as postulated by Koch et al. (2012). The primary metabolite is MnBP, which is further metabolised to the secondary metabolites 3OH-MnBP, 4OH-MnBP, and 3cx-MPP (abbreviated in Figure 6 as MCPP). In a metabolism study of an individual male (aged 36 years, 87 kg bodyweight), two separate doses of DnBP and DiBP were administrated in respective concentrations of

60 µg/kg bodyweight, and the corresponding metabolites were measured in urine collected continuously until 48 hours after the administration. After 24 hours, 92.2% of DnBP was excreted, whereas the simple monoester MnBP was the major metabolite (84%). 8% of the excreted DnBP were the oxidized metabolites. The DnBP metabolites had elimination halftimes between 2.6 hours (MnBP) and the maximum 6.9 of hours (secondary oxidized metabolites). (Koch et al., 2012a)

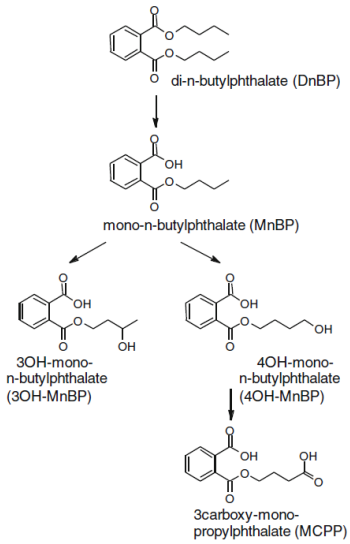


Figure 6. Postulated metabolism of DnBP in humans (Koch et al., 2012a)

Biomarkers

For DnBP, biomarkers for Human Biomonitoring are its hydrolytic metabolite mono-n-butyl phthalate (MnBP) and its oxidative metabolite OH-mono-n-butyl phthalate (OH-MnBP) (Koch and Angerer, 2012). However, most biomonitoring studies use only the primary metabolite as a biomarker.

3-carboxy-mono-propyl phthalate (3cx-MPP) is also a metabolite of DnBP, but is not usable as a biomarker for exposure, because it is a metabolite of several phthalates (DnBP, DnOP, and DiNP) (Koch and Angerer, 2012).

1.3.7.2.6 Health effects

DnBP is toxic to reproduction (category 1B according to CLP classification) and may harm the unborn child. Additionally, it is suspected to impair fertility. (ECHA, 2013k) Among workers (occupational exposure), concerns for systemic toxicity following repeated dermal exposure, and for adverse local effects in the respiratory tract following repeated inhalation exposure exist (ECB, 2003c).

DnBP has shown a weak estrogenic activity *in vitro* (ECB, 2003c). Further, anti-androgen activity has been shown (ECB, 2003c; Main et al., 2006). In some epidemiologic studies, associations were indicated between DnBP and the occurrence of eczema (Hsu et al., 2012), insulin resistance (Stahlhut et al., 2007) and BMI (Hatch et al., 2008; Wolff et al., 2008).

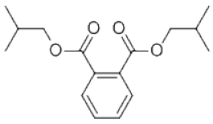
Some studies have shown that DnBP may eventually have an influence on several semen parameters (Duty et al., 2004) and sperm concentration (Liu et al., 2012). Additionally, study results have indicated that there may be possible associations between DnBP exposure and preterm birth (Meeker et al., 2009), but the results are not clear regarding both the influence of DnBP on semen quality and preterm birth.

1.3.7.3 Di-isobutyl phthalate (DiBP)

1.3.7.3.1 General Information

Table 11 includes general information on DiBP:

Table 11. General information on DiBP (Danish EPA, 2011; ECHA, 2009c)

EC Number	201-553-2
CAS Number	84-69-5
IUPAC Name	Bis(2-methylpropyl)benzene-1,2-dicarboxylate
Molecular formula	$C_{16}H_{22}O_4$
Molecular weight	278.34 g/mol
Physico-chemical properties	Colourless, odourless viscous liquid; melting/freezing point at -37°C; boiling point at 320°C; water solubility of 20 mg/l at 20°C.
Chemical structure	

1.3.7.3.2 Classification and labelling

According to Article 57(c) of the REACH regulation (Regulation (EC) No 1907/2006), DiBP is identified as a CMR substance. DiBP is categorized as Repr. 1B; H360Df (toxic to reproduction category 1B; May damage the unborn child; Suspected of damaging fertility) at a specific concentration limit of ≥25%, and as Repr. 2; H361f (toxic to reproduction category 2; Suspected of damaging fertility) at a specific concentration limit between 5% and <25% (ECHA, 2009c; ECHA, 2013d).

1.3.7.3.3 Legislation

Similar to DnBP, DiBP is listed in the REACH authorisation list (ECHA, 2013a). In the EU, its use is prohibited in immediate packaging of medical products (EC, 2011c), in toys and childcare articles at concentrations above 0.1% by weight (EC, 2009c), as well as in cosmetic products (European Parliament, 2009).

1.3.7.3.4 Production and usage

No specific information regarding DiBP content in articles is available. However, ECHA has calculated the amount of DiBP manufactured and used on the EU, which is specified at a range of 10,000-50,000 tonnes/year. DiBP is used for PVC floorings and wall coverings, and is also found in bags, suitcases, table cloths, curtains, footwear and lacquers for wooden furniture and flooring. (Danish EPA, 2011) Generally, DiBP is used for the same purposes as DnBP, but less commonly (Benson, 2009).

1.3.7.3.5 Toxicokinetics

Routes of exposure

Routes of DiBP exposure are similar to the exposure routes of DnBP, which are oral, dermal or through inhalation (ECB, 2003c).

Metabolism and elimination

DiBP is metabolised to its primary metabolite MiBP, and further to its secondary metabolites 3OH-MiBP and 2OH-MiBP (cf. Figure 7). According to a human metabolism study by Koch et al. (2012), DiBP is eliminated primarily through urine (90.3% after 24 h), whereby the major metabolite is MiBP (71%). Elimination halftimes of DiBP metabolites are between 3.9 h (MiBP) and 4.2 h (secondary oxidized metabolites). The primary metabolite MiBP has its maximum urinary concentration at 8.585 µg/g creatinine after 2.83 h. (Koch et al., 2012a)

Biomarkers

Primarily MnBP (mono-n-butyl phthalate), but also OH-MnBP (OH-mono-n-butyl phthalate) are used as biomarkers in Human Biomonitoring (Koch and Angerer, 2012).

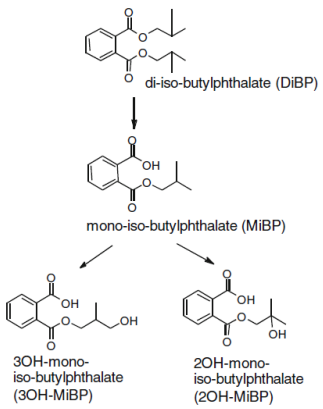


Figure 7. Postulated metabolism of DiBP in humans (Koch et al., 2012a)

1.3.7.3.6 Health effects

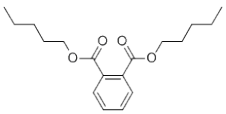
DiBP is toxic to reproduction (category 1B according to CLP), suspected to damage fertility and may harm the unborn child (ECHA, 2009c, 2013d).

Studies in animals reported adverse effects on the developing male reproductive system caused by DiBP similar to those caused by DnBP. It was shown that DiBP may lead to reduction of testosterone production in male rodent offspring, reduction in testicular histopathology, reduction in immunohistochemical staining for steriogenic acute regulated proteins in Leydig cells, reduction in anogenital distance in male offspring and increase in anogential distance in female offspring. (Benson, 2009) In general, health effects of DiBP are similar to effects of DnBP (cf. 1.3.7.2.6).

1.3.7.4 Di-n-pentyl phthalate (DnPeP)

1.3.7.4.1 General information

Table 12. General information on DnPeP (ECHA, 2013i; NCBI, 2013)

EC Number	205-017-9
CAS Number	131-18-0
IUPAC Name	dipentyl phthalate, 1,2-Benzendicarboxylic acid, 1,2-dipentyl ester
Molecular formula	$C_{18}H_{26}O_4$
Molecular weight	306.4 g/mol
Synonyms and abbreviations	diamyl phthalate, amyl phthalate, Amoil, dipentyl ester, di-n-pentyl phthalate, diamyl phthalate DNPP, DPP, DnPeP
Physico-chemical properties	Colourless oily liquid; melting/freezing point at -55°C; boiling point at 342°C; water solubility of 0.8 mg/l at 25°C.
Chemical structure	

1.3.7.4.2 Classification and labelling

DnPeP is a SVHC because of its CMR properties, and is classified according to CLP Regulation (Annex VI, part 3 Index Number: 607-426-00-1) as Repr. 1B; H360FD (toxic to reproduction category 1B; May damage fertility; May damage the unborn child), and Aquatic Acute 1; H400 (Very toxic to aquatic life), and is labelled by the pictograms "Environment" (GHS09) and "Health hazard" (GHS08), and by the signal word "Danger". (ECHA, 2013i, 2013j)

1.3.7.4.3 Legislation

DnPeP is banned in cosmetic products (Regulation (EC) No 1233/2009), and in toys or components of toys above a specific migration limit of 0.5% until May 2015 (Directive 1999/45/EC), and above a specific migration limit of 0.3% from June 2015 onward (Regulation (EC) No 1272/2008). (ECHA, n.r.)

1.3.7.4.4 Production and usage

In Europe, DnPeP is produced at low volumes (10-1000 tonnes/year), and its use is limited. Primarily, it is used as plasticiser in PVC (HSDB, 2009a), and in nitrocellulose (Silva et al., 2011).

1.3.7.4.5 Toxicokinetics

Routes of exposure

Humans can be exposed to DnPeP through dermal contact with consumer products. Occupationally, workers can be exposed via inhalation of aerosols and dermal contact. (ECHA, n.r.)

Metabolism and elimination

In a study of 9 adult female Sprague-Dawley rats, Silva et al. (2011) administrated a single oral DnPeP dose (500 mg/kg bw) and investigated DnPeP metabolites eliminated in urine 24h and 48h after administration. Similar to findings in other phthalate metabolisms, DnPeP forms metabolites after hydrolytic, ω-, ω-1 and β-oxidation, and dehydrogenation. Several urinary metabolites were identified as potential biomarkers for humans exposure (µg/ml 24h after administration): mono(4-hydroxylpropyl) phthalate (993), mono(4-carboxybutyl) phthalate (168), mono(3-carboxyethyl) phthalate (0.2), mono-n-pentyl phthalate (222), mono(4-oxopentyl) phthalate (47), mono-n-pentyl phthalate (16), phthalic acid (26), and mono(3-

carboxypropyl)phthalate (9), whereby mono(4-hydroxylpropyl) phthalate was the major metabolite in urine. The primary metabolite was mono-n-pentyl phthalate (MnPeP). Most of DnPeP administered was excreted within 24h. (Silva et al., 2011) The schematic DnPeP metabolism is shown in Figure 8.

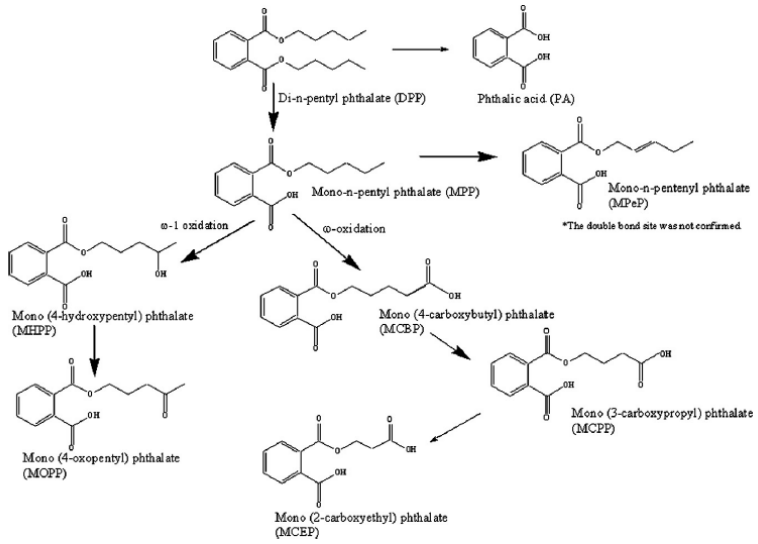


Figure 8. Metabolism of DnPeP in rats (Silva et al., 2011)

Biomarker

The hydrolytic monoester (primary metabolite) MnPeP is used as a biomarker for DnPeP exposure (Koch and Angerer, 2012).

1.3.7.4.6 Health effects

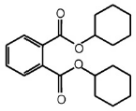
Amongst other phthalates (such as DEHP, DnBP, DiBP, BBzP and DiNP), DnPeP has been shown in rodent studies to be toxic to development and reproduction (Koch and Angerer, 2012). Studies in animals have indicated that DnPeP has greater potential to induce testicular toxicity than several other phthalates. DnPeP showed morphological changes in the testes, inhibition of testicular steroidogenic enzymes, and reduction of testicular T production in utero. Additionally, DnPeP is 2-fold more potent to reduce AGD and 4.5-fold more potent to induce male nipple retention than DEHP. (Hannas et al., 2011) Testicular atrophy and fertility impairing effects of DnPeP were shown in doses relevant for classification. Additionally, in rats, direct effects on cytochrome P450-dependent steroid production were shown and may be the reason for the toxic effects of DnPeP on testicular function and structure. (ECHA, 2013i)

1.3.7.5 Di-cyclohexyl phthalate (DCHP)

1.3.7.5.1 General Information

Table 13 includes the general information on DCHP:

Table 13. General information on DCHP (HSDB, 2009b; ECHA, 2013d; Zhao et al., 2010)

EC Number	201-545-9
CAS Number	84-61-7
IUPAC Name	1,2-Benzenedicarboxylic acid, dicyclohexyl ester
Molecular formula	$C_{20}H_{26}O_4$
Molecular weight	330.42 g/mol
Physico-chemical properties	White solid, mildly aromatic odorous substance; melting point at 66°C; boiling point at 224°C; soluble in most organic solvents; water solubility of 4 mg/l at 24°C.
Chemical structure	

1.3.7.5.2 Classification and labelling

There is currently no harmonised classification for DCHP. However, the industry's self-classification of this phthalate is currently (2014-06-06) "Toxic to Reproduction category 2" with the related hazard statement code H361 ("Suspected of damaging fertility or the unborn child") and "Aquatic Chronic category 3" with the related code H412 ("Harmful to aquatic life with long lasting effects"), as well as labelled with the pictogram GHS08 ("Health hazard") and the signal word "Warning" (32 notifiers). Additionally, one notifier classified DCHP as STOT SE 3 (H335, "May cause respiratory irritation") and Toxic to Reproduction category 1B (H360, "May damage fertility or the unborn child, which is the strictest classification for DEHP. (ECHA, 2014e)

1.3.7.5.3 Legislation

Currently, no EU legislation for DCHP exists. Because of its endocrine disrupting effects, DCHP is listed in the Danish list of potential endocrine disruptors (Danish EPA, 2013).

1.3.7.5.4 Production and usage

DCHP is used as a plasticiser for nitrocellulose, ethylcellulose, vinyl acetate and vinyl chloride resins (METI, 2003), and in PVC products, paints, inks and food packaging material (Hass et al., 2012).

1.3.7.5.5 Toxicokinetics

Routes of exposure

Workers can be exposed to DCHP through inhalation of aerosols and dermal contact. The general population may be exposed through inhalation of ambient air or dermal contact with DCHP-containing consumer products. (HSDB, 2009b)

Metabolism and elimination

Like other phthalates, after absorption, DCHP is rapidly metabolised to the hydrolytic monoester mono-cyclohexyl phthalate (MCHP) following absorption, whereby the hydrolysis rate is greater for low molecular weight phthalates such as DCHP. The elimination occurs also in a rapid fashion. (HSDB, 2009b)

Biomarker

The biomarker for Human Biomonitoring of DCHP exposure is its primary hydrolytic monoester mono-cyclohexyl phthalate (MCHP) (Koch and Angerer, 2012).

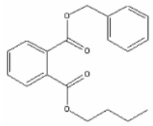
1.3.7.5.6 Health effects

For DCHP, no relevant studies in humans are currently available. Studies *in vitro* have shown that DCHP has estrogenic effects. (METI, 2003; Hass et al., 2012) Additionally, DCHP is an anti-androgen and causes impaired masculinisation of male rat offspring after perinatal exposure, reduced AGD in males, increased prevalence of nipple retention and delayed puberty in males. In adult rodents, decreased weights of reproductive organs, and altered testis histology and sperm quality were identified. Also in rats, it was shown that DCHP can increase thyroid weights. (Hass et al., 2012)

1.3.7.6 Butyl benzyl phthalate (BBzP)

1.3.7.6.1 General Information

Table 14. General information on BBzP (ECB, 2007; ECHA, 2013f)

EC Number	201-622-7
CAS Number	85-68-7
IUPAC Name	benzyl butyl phthalate
Molecular formula	$C_{19}H_{20}O_4$
Molecular weight	312.35 g/mol
Synonyms and abbreviations	BBP, 1-O-butyl 2-O-(phenylmethyl) benzene-1,2-dicarboxylate, benzyl butyl phthalate, 1,2-benzenedicarboxylic acid, butyl phenylmethyl ester, benzyl-n-butyl phthalate, phthalic acid, Santicizer 160, Sicol 160, Unimoll BB
Physico-chemical properties	Clear oily liquid, characteristic odour and bitter taste; boiling point at 370°C; melting point below -35°C; water solubility of 2.8 mg/l at 20-25°C.
Chemical structure	

1.3.7.6.2 Classification and labelling

According to Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation), BBzP is classified as Repr. 1B; H360Df (toxic to reproduction category 1B; May damage the unborn child; Suspected of damaging fertility), Aquatic Acute 1; H400 (very toxic to aquatic life), and Aquatic Chronic 1; H410 (very toxic to aquatic life with long lasting effects), and is labelled with the pictograms GHS09 Environment and GHS08 Health hazard (signal word: Danger) (ECHA, 2013f).

1.3.7.6.3 Legislation

According to Annex I of Directive 76/769/EEC and Annex XVII of the REACH Regulation, BBzP is classified as a substance toxic to reproduction and is not allowed to be placed on the market in concentrations greater than 0.1% by mass in plasticised materials, toys and childcare articles (EC, 2008; ECHA, 2009b), and is banned in cosmetics (European Parliament, 2009). BBzP is listed in the REACH authorisation list (ECHA, 2013a). In food contact materials, BBzP is banned in single-use materials containing fatty foods, and in contact materials for infant formulae and follow-on formulae. Allowed concentration as technical support agent is 0.1% in final products. A SML is set out for food contact materials at 30 mg/kg food. (EC, 2011e)

1.3.7.6.4 Production and usage

In 2007, BBzP was produced in volumes of 20,000 tonnes in the EU. Within recent years, the production has therefore decreased from the previous value of 45,000 tonnes/year in 1994-1997. The export of BBzP amounts to 12,000 tonnes/year, which leads to a BBzP use in the EU of approximately 8,000 tonnes/year. 70% BBzP is used as a plasticiser in polymer products, whereas the main use is for PVC floorings. Other uses for polymers include leather and textile coating (e.g. for upholstery, shoe uppers, wallets, bags, luggage), film calendaring (e.g. for packaging film, wall covering), medical products packaging and active substances. Additionally, it is used in printing inks, adhesives and paints.

As claimed above, the production volumes of BBzP have decreased during recent years. This reflects that BBzP is being replaced by alternatives for many applications. The main probable alternatives for BBzP are Dipropylene glycol dibenzoate (DGD; for flooring, spread coated fabric, adhesives, and sealants), Alkylsulphonic phenyl ester (ASE; for calendared film, spread coated fabric, adhesives, paints, lacquers, and sealants), Di-isononyl phthalate (DINP; for all polymer and non-polymer applications), Di(2-ethylhexyl) terephthalate (DEHT; for flooring, calendared film, and spread coated fabric), and Di-isononyl-cyclohexan-1,2-dicarboxylate (DINCH; for calipered film, spread coated fabric, adhesives, paints, and lacquers). (ECHA, 2009b)

1.3.7.6.5 Toxicokinetics

Routes of exposure

BBzP exposure can occur through orally route via food, baby equipment, or toys, and through inhalation via indoor air (ECB, 2007).

Metabolism and elimination

After absorption, BBzP is metabolised in the gut wall and/or liver to its primary metabolites mono-n-benzyl phthalate (MBzP) and mono-n-butyl phthalate (MnBP).

A study in female Wistar rats has shown that 29-34% of the recovered metabolites are MnBP, and 7-12% MBzP. 51-56% is represented by the secondary major metabolite hippuric acid, which is the main metabolite of benzoic acid. Overall, the following BBzP metabolites were identified: MBzP, MnBP, MnBP ω-oxidized, benzoic acid, hippuric acid and phthalic acid. (Nativelle et al., 1999) In humans, BBzP is metabolised mainly to MBzP, which is contrary to the metabolism in rats. Therefore, the MBzP excretion in

the urine reflects human exposure to BBzP. BBzP has a calculated halftime of <24h. After inhalation and oral exposure, 100% of BBzP is absorbed, whereas 5% of BBzP is absorbed after dermal exposure. (ECB, 2007)

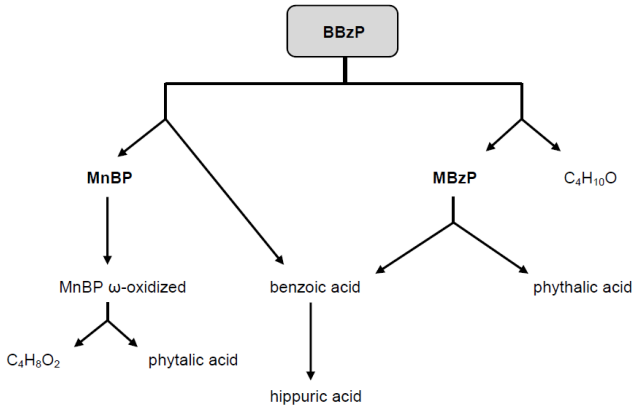


Figure 9. Metabolism routes of BBzP (modified according Nativelle et al., 1999)

Biomarker

For Human-Biomonitoring, the biomarker for BBzP exposure is its primary hydrolytic monoester mono-benzyl phthalate (MBzP) (Koch and Angerer, 2012).

1.3.7.6.6 Health effects

BBzP has a low acute toxicity (ECB, 2007). Repeated-dose toxicity studies in rats have shown decreased bodyweight gain, alteration in haematological parameters, and damages to testes, prostate, liver, kidney, spleen and pancreas, decreased sperm concentrations, and reduced fertility, as well as reduced AGD. (ECB, 2007) BBzP alters sexual differentiation in male rats (Gray Jr. et al., 2000). Studies in humans have also found associations between BBzP and sperm quality (Duty et al., 2004), and anogenital index (=AGD/weight) in male newborns and infants (Swan et al., 2005). Additionally, a study in humans has shown possible positive associations with preterm birth (Meeker et al., 2009), however, study results are generally not conclusive in this regard.

Relating to possible carcinogenic effects of BBzP, results of various studies differ, but there are some concerns: the ECB has claimed in their risk assessment report that BBzP is a “borderline case” between classification as carcinogenic category 3 and no classification. Nevertheless, there currently is no classification within the EU because of a lack of genotoxic effects of BBzP. (ECB, 2007)

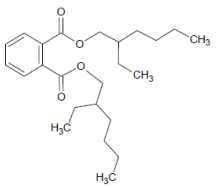
Epidemiologic studies have indicated that BBzP is associated with rhinitis and eczema in children (Bornehag et al., 2004; Hsu et al., 2012). Positive associations were also found for a biomarker of oxidative stress (Ferguson, Loch-Caruso and Meeker, 2012), insulin resistance (Stahlhut et al., 2007), and BMI and WC (Hatch et al., 2008; Wolff et al., 2008).

In vivo and *in vitro* studies have investigated the endocrine disrupting effects of BBzP and its major metabolites MBzP and MnBP. In *in vitro* studies, weak estrogenic activity was found at high BBzP concentrations. The metabolites did not exhibit any estrogenic activity. Weak estrogenic activity was also found in *in vivo* studies. (ECHA, 2008a) Anti-androgen activity of BBzP was shown in one *in vitro* study, and *in vivo* studies in rats indicated anti-androgen-like activity of BBzP and its major metabolites. (Gray Jr. et al., 2000; ECHA, 2008a)

1.3.7.7 Di-(2-ethylhexyl) phthalate (DEHP)

1.3.7.7.1 General Information

Table 15. General information on DEHP (ECB, 2008; ECHA, 2009a)

EC Number	204-211-0
CAS Number	117-81-7
IUPAC Name	Bis(2-ethylhexyl) phthalate
Molecular formula	$C_{24}H_{38}O_4$
Molecular weight	390.6 g/mol
Synonyms and abbreviations	1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester, Bis(2-ethylhexyl) 1,2-benzenedicarboxylate, Bis(2-ethylhexyl) o-phthalate, Dioctyl phthalate, DOP (pseudo-synonym), phthalic acid dioctyl ester
Physico-chemical properties	Colourless oily liquid; melting point between -50 and -55°C; boiling point at 385°C; water solubility widely ranging in literature from 0.003 to 1.3 mg/l at 20-25°C.
Chemical structure	

1.3.7.7.2 Classification and labelling

According to Article 57(c) of REACH, DEHP has been identified as a Substance of Very High Concern (SVHC). It is toxic to reproduction (Category 2), and thus included in the candidate list for authorisation. (ECHA, 2008b, 2009a) According to CLP, DEHP

is classified as Repr. 1B; H360FD (toxic for reproduction category 1B; may damage fertility, may damage the unborn child), and labelled with the pictogram for “Health hazard” (GHS08) and the signal word “Danger” (ECHA, 2014b).

1.3.7.7.3 Legislation

DEHP is one of four phthalates listed in the REACH authorisation list (ECHA, 2013a). In immediate packaging of medical products, DEHP is banned in the EU (EC, 2011c), as well as in childcare articles and toys at concentrations of >0.01% by weight (EC, 2009c), and in cosmetic products (European Parliament, 2009). DEHP is prohibited in food contact materials designed for single-use and containing fatty foods, and a SML has been set out at 1.5 mg/kg food. However, as a technical support agent, DEHP is allowed to be present in the final product at a concentration of 0.1%. (EC, 2011e)

1.3.7.7.4 Production and usage

DEHP is a plasticiser mainly used in PVC materials. Its use (industrial and end-use) is divided into PVC, non-PVC polymers and non-polymers, as the three main product groups. 97% of DEHP is used in polymers, mainly PVC (ECB, 2008). Because of the addition of plasticisers, PVC becomes more flexible (EAG, 2007d). The variety of DEHP content in such flexible polymer products is around 30% in most cases (ECB, 2008). In the EU, ca. 341,000 tonnes of DEHP were produced in 2007, and of this, 187,000 tonnes were produced in Western Europe. Over the last decade the volume of DEHP manufactured has decreased. (COWI A/S, 2009) Examples of PVC containing DEHP as plasticizer for common use include flooring, roofing, toys, synthetic leather, wall coverings, shower curtains, child-care articles, shoes, sport and leisure articles, coatings, medical products (i.e. blood bags, dialysis equipment), cables, car under-coatings, profiles and roofs, etc. (EAG, 2007d; ECB, 2008). Information is scarce concerning the usage of DEHP in non-PVC polymer and non-polymer. Examples of non-polymer products which containing DEHP include adhesives, fillers, printing inks, ceramics, lacquers and paints. (ECB, 2008)

The main alternative substance for DEHP is DiNP. For some applications, non-phthalates alternatives are also used, especially for toys, food packaging materials or medical products. (COWI A/S, 2009; ECHA, 2009a) Currently, the use of DiNP as an alternative substance is the most inexpensive choice, although it is about 10% more expensive than DEHP. (COWI A/S, 2009)

1.3.7.7.5 Toxicokinetics

Routes of exposure

Humans can be exposed to DEHP through oral, dermal, and inhalation routes. Occupational exposure can occur during the production and industrial use of DEHP. Exposure to consumers can occur via end-use of DEHP-containing products, food contact materials and foods, as well as during treatment with medical equipment. Additionally, because of migration of DEHP into air and house dust, this route of exposure is also important, especially for children. (ECB, 2008)

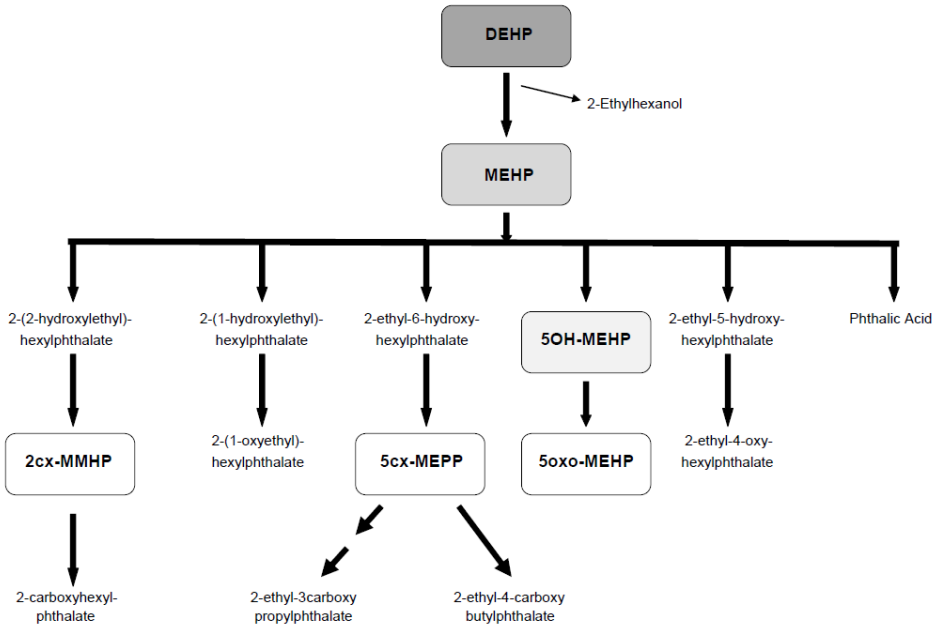
Metabolism and elimination

Orally ingested DEHP becomes primary absorbed and metabolised in the gastrointestinal tract (GIT) and hydrolysed to its primary metabolite MEHP as well as 2-etyhlhexanol (2-EH) by ester hydrolases. The main metabolism to MEHP occurs in the GIT, but high levels of hydrolytic activity of DEHP can also be found in the pancreatic juice, in intestinal contents or tissues, and in liver tissues. Furthermore, the metabolism of MEHP follows one of three pathways:

- Hydrolysis to phthalic acid and 2-ethylhexonal
- Conjugation to form glucuronide ester and excretion, or
- Hydroxylation on the ethylhexyl chain by cytochrome P450 enzymes.

The main pathway is the hydroxylation of MEHP at the ω- or ω-1-position on the ethylhexyl chain and which results in the generation of several metabolites. (OEHHA, 2006) Figure 10 shows the extensive DEHP metabolism.

Koch, Preuss and Angerer (2006) have demonstrated a DEHP dose excretion via urine after 24 h of 67.0%, as five major metabolites: 5OH-MEHP (with 23.3%), 5cx-MEPP (18.5%), 5oxo-MEHP (15.0%), MEHP (5.9%) and 2cx-MMHP (4.2%). The excretion rate in the metabolism was not dependent on the dose. On the 2nd day, 3.8% of the DEHP dose was excreted via urine, comprising 2cx-MMHP (1.6%), 5cx-MEPP (1.2%), 5OH-MEHP (0.6%) and 5oxo-MEHP (0.4%). To sum up, the majority of orally ingested DEHP becomes absorbed, metabolised and excreted via urine. In comparison, the simple monoester MEHP has a shorter half-time of elimination and an earlier maximum of urinary excretion than the oxidative DEHP metabolites 5OH-MEHP, 5oxo-MEHP, 5cx-MEHP and 2cx-MMHP. (Koch, Preuss and Angerer, 2006)



Abbreviations: DEHP, Di-(2-ethylhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; 2cx-MMHP, mono-[2-(carboxymethyl)hexyl] phthalate; 5cx-MEPP, mono-(2-ethyl-5-carboxypentyl) phthalate; 5OH-MEHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; 5oxo-MEHP, mono-(2-ethyl-5-oxohexyl) phthalate.

Figure 10. Metabolism of DEHP (modified according to Koch, Preuss and Angerer, 2006)

Biomarkers

Appropriate biomarkers for DEHP exposure assessment are the hydrolytic monoester MEHP, and the oxidative secondary metabolites 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP (Koch and Angerer, 2012).

1.3.7.7.6 Health Effects

Many animal studies have been performed investigating DEHP effects. Studies in humans are limited, but in contrast to other phthalates, DEHP effects are more frequently investigated.

DEHP has a low acute toxicity, and can lead to slight eye and skin irritations. It has been shown in animal studies to induce peroxisome proliferation in the liver. Clear evidence was found for hepatocarcinogenicity in rodents and increased incidence of Leydig cell tumors in male rats. However, there is evidence that humans are less sensitive to the hepatotoxic effects of peroxisome proliferators. Thus, DEHP is not classified as a carcinogenic substance. (ECB, 2008)

Animal studies have shown the testes, liver and kidneys to be critical organs for DEHP. DEHP affects fertility and reproduction, and produces developmental effects in offspring. In rodents, decreased testes weight, pathological findings (sloughed

epithelial cells/residual cells, and aspermia/oligospermia in male rats), and atrophy of seminiferous tubules in the testes were identified. There is also some evidence that the primary DEHP metabolite MEHP affects the testes and reproductive functions both *in vivo* and *in vitro*. DEHP and MEHP showed direct effects on Leydig cells and Sertoli cells. DEHP may decrease levels of zinc and testosterone in the testes. Indications exist that oral DEHP exposure may lead to hypo-estrogenic anovulatory and polycystic ovaries in female rats, alter the estrogenous cycle and cause changes in testosterone and estradiol. (ECB, 2008) DEHP inhibits testosterone production in testes of fetuses and leads to demasculinisation, reduced AGD and malformations in male rats (Gray Jr. et al., 2000).

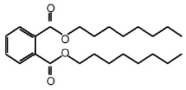
DEHP has anti-androgenic properties, and is an endocrine disrupting chemical. It shows interferences with endocrine function and influences sexual differentiation. (ECB, 2008)

Some epidemiological studies have shown significant associations between DEHP and the occurrence of asthma (Bornehag et al., 2004) and wheezing (Kolarik et al., 2008). Possible relationships between DEHP and thyroid hormones have been postulated (Meeker and Ferguson, 2011). In women with self-reported diabetes, associations were found with secondary DEHP metabolites (Svennson et al., 2011). Associations were also found for preterm birth (Latini et al., 2003), but more investigations are necessary. Relationships were found between DEHP and abdominal obesity (Stahlhut et al., 2007), BMI and WC (Hatch et al., 2008; Wolff et al., 2008). MEHP has also been shown to increase the incidence of obesity in a sex-dependent manner (Hao et al., 2012), and is able to decrease glyceroneogenesis and fatty acid re-esterification in human adipocytes (Ellero-Simatos et al., 2011).

1.3.7.8 Di-n-octyl phthalate (DnOP)

1.3.7.8.1 General information

Table 16. General information on DnOP (CERHR, 2003; Taylor and Bittner, 1997; U.S. EPA, 2006; Zhao et al., 2010)

EC Number	204-214-7
CAS Number	117-84-0
IUPAC Name	dioctyl benzene-1,2-dicarboxylate
Molecular formula	$C_{24}H_{38}O_4$
Molecular weight	390.54 g/mol
Synonyms and abbreviations	1,2-benzenedicarboxylic acid, dioctyl ester
Physico-chemical properties	Colourless, odourless oily liquid which is not able to evaporate easily; melting point at -25°C; boiling point at 390°C; water solubility of 0.05 µg/l (essentially insoluble).
Chemical structure	

1.3.7.8.2 Classification and labelling

According to CLP regulation, no harmonised classification and labelling currently exists for DnOP, but several self-classifications by the industry have been made. According to 23 notifiers, DnOP is classified as Aquatic Chronic category 4 (H413, “May cause long lasting harmful effects to aquatic life”). The strictest classification by two notifiers is Skin Sens. Category 1 (H317, “May cause an allergic skin reaction”), Respiratory Sens. Category 1 (H334, “May cause allergy or asthma symptoms or breathing difficulties if inhaled”) and Toxic to Reproduction category 2 (H361, “Suspected of damaging fertility or the unborn child”), as well as the labelling with the pictogram GHS08 (“Health hazard”) and the signal word “Danger” (state: 2014-06-06). (ECHA, 2014a)

1.3.7.8.3 Legislation

In the EU, DnOP is banned at concentrations above 0.01% by weight in toys and childcare articles that may be placed into the mouth (EC, 2009c).

1.3.7.8.4 Production and usage

DnOP is produced by phthalic anhydride and n-octanol in the presence of an acid catalyst. In C6-C10 phthalate mixtures it can be present up to 20% and is therefore a significant component. (Taylor and Bittner, 1997; CERHR, 2003) It is used as a

plasticiser in consumer products such as packaging film, medical tubing, blood storage bags, coatings, floorings, wire, cables and adhesives, cosmetics, as well as in pesticides, and can represent 5-60% of the total weight of a product. Other uses include its implementation as a dye carrier in PVC production, for cellulose ester and polystyrene resins, and as an intermediate for the production of adhesives, plastisols, and lacquer coatings. (Taylor and Bittner, 1997) DnOP may enter the environment through waste waters from industry, air emissions and solid waste from production and processing (Silva et al., 2005). For the EU, available information on its use is limited (ECHA, 2010a).

1.3.7.8.5 Toxicokinetics

Routes of exposure

Consumers are exposed to DnOP through oral and dermal routes, whereby the most likely source is food. Workers may be exposed via dermal contact and inhalation. (CERHR, 2003)

Metabolism and elimination

Following oral administration in rats, DnOP is metabolised to its primary metabolite MnOP, which is metabolised to the secondary oxidative metabolites 3cx-MPP, MCHpP (mono-7-carboxy-*n*-heptyl phthalate), 7-MOOP (mono-7-oxo-*n*-octyl phthalate), 7-MHOP (mono-7-hydroxy-*n*-octyl phthalate), MCMP (mono-carboxymethyl phthalate) and MCPeP (mono-5-carboxy-*n*-pentyl phthalate). It has been shown that urinary excretion concentrations of oxidative metabolites were much higher than the excretion of the monoester MnOP. Therefore, the assumption exists that the analysis of solely MnOP concentrations in urine may lead to underestimation. (Silva et al., 2005) It must be noted, however, that there may be differences between metabolism in rodents and in humans.

Biomarkers

The hydrolytic metabolite mono-n-ocytl phthalate (MnOP) is used as a biomarker for exposure assessment. Additionally, 3cx-MPP and 3cx-MiBP could be used (Koch and Angerer et al., 2012), but 3cx-MPP is also a secondary metabolite of DnBP and DiNP.

1.3.7.8.6 Health effects

DnOP is a structural isomer to DEHP, but it has different toxic effects and dose-response relationships. DnOP has low potential for reproductive toxicity in rodents.

Findings in animal studies suggest that DnOP does not lead to adverse effects in humans at environmental exposure levels. In *in vitro* assays, no estrogenic activity has been found. In rats, DnOP affects Leydig cells; however, indications that DnOP may cause endocrine disrupting effects are limited. (Silva et al., 2005; ECHA 2010a)

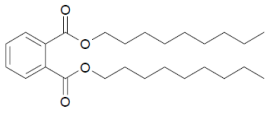
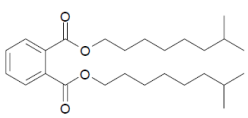
1.3.7.9 Di-isononyl phthalate (DiNP)

"DiNP" envelops three different DiNPs. They are manufactured in different ways: the first DiNP (CAS Number 68515-48-0) is produced by the so-called "Polygas" process, the second DiNP (CAS Number 28553-12-0) is produced n-butene based, and the third DiNP (same CAS number as the second DiNP) is produced n- and iso-butene based. Therefore, the DiNPs differ in their chemical structure and can have different physico-chemical properties and toxicity. Because of the following reasons, it is not possible to deal with these 3 DiNPs separately: the production of the third DiNP was stopped in 1995, the second and third DiNP have the same CAS Number, therefore it is not possible to differ between them in the results of several physico-chemical and toxicological tests, and "pure" DiNP is a complex mixture. (ECB, 2003a)

1.3.7.9.1 General information

In Table 17 general information on DiNP is summarised:

Table 17. General information on DiNP (ECB, 2000b; ECB, 2003a)

EC Number	271-090-9 and 249-079-5
CAS Number	68515-48-0 and 28553-12-0
IUPAC Name	1,2-Benzenedicarbocylic acid, di-C8-10-branched alkyl esters, C9-rich; Di-isononyl phthalate
Molecular formula	$C_{26}H_{42}O_4$
Molecular weight	420.6 g/mol (average)
Physico-chemical properties	Oily viscous liquid; flash point at 236°C; water solubility of 0.6 µg/l at 20°C.
Chemical structures	CAS: 68515-48-0  CAS No: 28553-12-0 

1.3.7.9.2 Classification and labelling

For DiNP, no harmonised classification currently exists. 796 notifiers did not classify DiNP by self-classification by the industry, whereat 23 notifiers classified this phthalate as Aquatic Acute category 1 (H400, “Very toxic to aquatic life”) and Aquatic Chronic category 1 (H410, “Very toxic to aquatic life with long lasting effects”) and labelled it with the pictogram GHS09 (“Environment”) and the signal word “Warning”, which is additionally the strictest classification and labelling amongst all others available (state: 2014-06-06). (ECHA, 2014d)

1.3.7.9.3 Legislation

In the EU, DiNP is banned at concentrations of >0.01% by weight in toys and childcare articles that may be placed into the mouth (EC, 2009c). DiNP is banned in food contact materials for single-use and materials containing fatty foods, as well as in infant and follow-on formulae, but it is allowed to be present in final products as a technical support agent at a concentration of 0.1% (EC, 2011e).

1.3.7.9.4 Production and usage

As explained above, commercially available DiNP is a mixture of diesters of *o*-phthalic acid which contains C8-C10 (C9 rich) alkyl side chains. DiNP-1 (CAS No 68515-48-0) and DiNP-2 (CAS No 28553-12-0) are produced in two different ways. DinP-1 is produced by the so-called “polygas” process, whereby propylene, *n*-butene and isobutene are oligomerised. Further, oxonation, hydrogenation and reaction with phthalic anhydride lead to DiNP-1. In the case of DiNP-2 production, *n*-butene undergoes dimerization, oxonation, hydrogenation and esterification with phthalic anhydride. (Saravanabhavan and Murray, 2012)

Because of strict regulations on DEHP in consumer products, DiNP (as well as DiDP) substitute DEHP in PVC applications, whereby about 95% of DiNP is used in PVC products. These substitutions occur as one consequence of classification and labelling according to CLP regulation, and lead to a move toward non-classified high molecular weight phthalates like DiNP. Additionally, DiNP is used in medical devices, wire and cables, coatings, automotive applications, building and construction, floorings, foot wear, sealings, paints, lacquers, wall coverings, toys, food contact materials, and clothing to name a few examples. (ECHA, 2010b) In Europe, approximately 500,000 tonnes of DiNP are produced per year (Koch and Angerer, 2007). Since 1994, the use of DiNP has increased constantly, and in Western Europe today DiNP, DiDP and

DPHP (di-propylheptyl phthalate) are represent about 65% of the overall use of plasticisers (ECHA, 2010b).

1.3.7.9.5 Toxicokinetics

Routes of exposure

Humans can be exposed to DiNP through consumer products, occupationally, or through the environment. Exposure routes can be oral (food contact materials, toys, consumer products), dermal (direct skin contact), and through inhalation (manufacture, processing, aerosol forming activities, etc.) (ECB, 2003a).

Metabolism and elimination

Following oral administration in rats, DiNP (CAS No. 68515-48-0) is rapidly metabolised in the GIT to its monoester MiNP, and is absorbed into the body. After application, DiNP is found in the liver and kidneys, but does not accumulate in organs or tissues. About 50% of the orally administered DiNP dose is excreted via urine, mainly as oxidised metabolites of the primary metabolite MiNP. The pharmacokinetic properties of DiNP are similar to those of high molecular weight phthalates. Findings in rodents are to some extent contrary to findings in humans and primates, which indicate a low absorption at low doses and more limited absorption at high doses. (McKee et al., 2002)

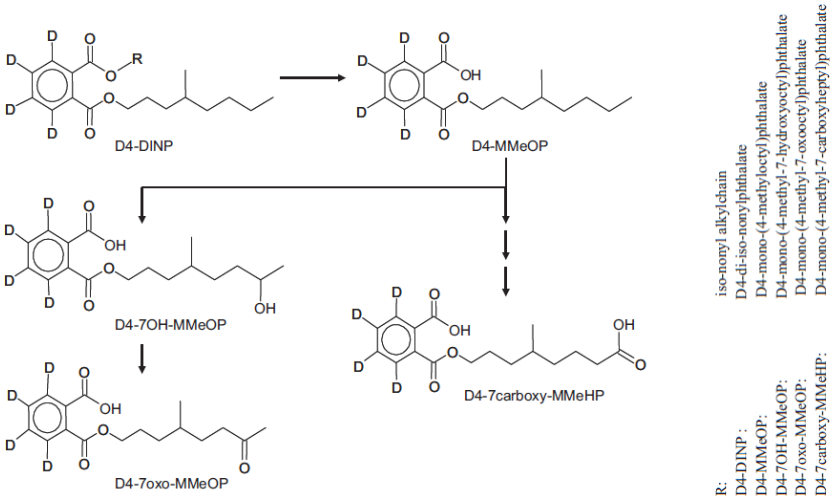


Figure 11. Suggested human DiNP metabolism illustrated for the 4-methyloctyl-side chain (four-times deuterium labelled DiNP is shown) (Koch and Angerer, 2007)

Koch and Angerer (2007) investigated the DiNP metabolism and elimination in one male volunteer, applying a single oral dose of DiNP of 1.27 mg/kg bw. They analysed the urinary excretion of MiNP (simple monoester), OH-MiNP, oxo-MiNP and cx-MiNP (oxidised monoesters). Within 48 h, 43.6% of the administrated DiNP dose was excreted via urine as 20.2% OH-MiNP, 10.7% cx-MiNP, 10.6% oxo-MiNP and 2.2% MiNP. The elimination followed a multi-phase pattern. This result shows that the oxidised metabolites are suitable biomarkers for human biomonitoring. (Koch and Angerer, 2007) Figure 11 shows the suggested DiNP metabolism in humans with four-time deuterium labelled DiNP, provided from Koch and Angerer (2007).

Biomarkers

Biomarkers for Biomonitoring studies in DiNP are the primary hydrolysed metabolite MiNP (mono-isononyl phthalate) and the secondary oxidised metabolites OH-MiNP (7OH-mono-methyloctyl phthalate), oxo-MiNP (7oxo-methyloctyl phthalate) and cx-MiNP (7carboxy-mono-methylheptyl phthalate) (Koch and Angerer, 2012).

1.3.7.9.6 Health effects

DiNP has low acute oral, dermal and inhalation toxicity, but is considered to be a very slight irritant for eyes and skin. Repeated-dose studies in rodents have demonstrated that DiNP acts as a peroxisome proliferator, similar to DEHP and DiDP. Additionally, changes in liver and kidney weights, and nephropathy have also been shown. Effects of DiNP exposure on the reproductive system such as increased testis weight, abnormal/immature sperm forms in epididymis, and effects on the uterus and ovaries were found in mice. (ECB, 2003a) DiNP has anti-androgenic activity, but it is 10- to 20-fold less potent than DEHP or BBzP (Gray Jr. et al., 2000). Although findings from several studies have identified effects of DiNP on the reproductive system and development, EU classification is not justified (ECB, 2003a).

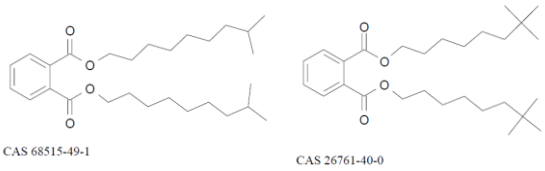
1.3.7.10 Di-isodecyl phthalate (DiDP)

1.3.7.10.1 General information

DiDP contains two di-isodecyl products with two different CAS numbers. Both are manufactured by an identical olefin oligomerisation process and by a similar oxo alcohol production and esterification process. Additionally, both are completely

interchangeable in their end uses. Generally, DiDP is a complex mixture that containing mainly C10-branched isomers. (ECB, 2003b)

Table 18. General information on DiDP (ECB, 2003b; IHCP, n.r.)

EC Number	2271-091-4 and 47-977-1
CAS Number	68515-49-1 and 26761-40-0
IUPAC Name	1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich and di-isodecyl phthalate
Molecular formula	$C_{28}H_{46}O_4$ (average)
Molecular weight	446.68 g/mol (average)
Physico-chemical properties	Oily viscous liquid; melting point between -50 and -45°C; boiling point at 257°C; water solubility of 0.2 µg/l.
Chemical structures	 CAS 68515-49-1 CAS 26761-40-0

1.3.7.10.2 Classification and labelling

According to CLP regulation, currently (2014-06-06) no harmonised classification exists for DiDP. Concerning the industry's self-classification, 100 notifiers additionally did not classify DiDP. 43 notifiers classified this phthalate as Aquatic Chronic category 2 with the hazard statement code H411 ("Toxic to aquatic life with long lasting effects") and labelled with the pictogram GHS09 ("Environment"). The strictest classification and labelling by 24 notifiers is Aquatic Acute category 1 (H400, "Very toxic to aquatic life") and Aquatic Chronic category 1 (H410, "Very toxic to aquatic life with long lasting effects"), and the pictogram GHS09 ("Environment") and the signal word "Warning" (state: 2014-06-06). (ECHA, 2014g)

1.3.7.10.3 Legislation

The use of DiDP in toys and childcare articles that may be placed into the mouth is prohibited at concentrations of >0.01% by weight within the EU (EC, 2009c). DIDP is prohibited in single-use food contact materials, materials containing fatty foods, and in infant and follow-on formulae. However, as a technical support agent, it is allowed to be present in final products at a concentration of up to 0.1%. (EC, 2011e)

1.3.7.10.4 Production and usage

DiDP is produced from propylene and butenes through a process of oligomerisation, further distillation, oxonation, hydrogenation, and finally esterification with phthalic anhydride.

DiDP is mainly used as a softener in PVC products with a typical content of 25 to 50%. PVC products containing DiDP are for example coated products, floorings, wall coverings, roofings, wires and cables, footwear, car undercoatings, sealants, paints and lacquers. Non-PVC products than contain DiDP are used in paints and varnished industry, as well as in textile industry (e.g. textile inks). (ECB, 2003b)

1.3.7.10.5 Toxicokinetics

Routes of exposure

Humans can be exposed to DiDP through direct skin contact during manufacture and formulation of products (workers) or by contact with DiDP-containing products (consumers), through inhalation, and through oral ingestion via e.g. food contact materials or toys (ECB, 2003b).

Absorption, metabolism and elimination

The absorption of orally administered DiDP is rapid. Similar to DiNP, commercial DiDP formulations consist of different structural isomers which result in the formation of several structurally similar metabolites during metabolism. Metabolism of DiDP (as well as of DiNP) is very similar to the metabolism of DEHP: in phase I, DiDP is hydrolysed to hydrolytic monoesters which are the primary metabolites. The monoester is then oxidised through ω- or ω-1-oxidation, forming secondary metabolites with hydroxyl-, oxo-, and carboxy-functional groups. The secondary metabolites can also undergo further metabolisation to tertiary metabolites. DiDP metabolites can also be further metabolised in phase II metabolism by conjugation with glucoronic acid and sulphonic acid. Formed conjugates are eliminated via urine. (Saravanabhavan and Murray, 2012)

Biomarkers

For Biomonitoring studies, the primary hydrolysed metabolite MiDP (mono-isodecyl phthalate) and the secondary oxidised metabolites OH-MiDP (6-hydroxy-mono-isodecyl phthalate), oxo-MiDP (6oxo-mono-isodecyl phthalate) and cx-MiDP (mono-carboxyl-isooctyl phthalate) are used as biomarkers because they are the most important metabolites (Koch and Angerer, 2012).

1.3.7.10.6 Health effects

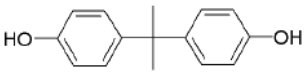
DiDP has a low acute toxicity following oral, dermal or inhalation exposure. In mice, DiDP can affect the serum levels of IgG1 and IgE following subcutaneous or intraperitoneal exposure. Thus, atopic responses in humans due to DiDP exposure cannot be ruled out. Studies in rats have demonstrated that DiDP act as peroxisome proliferators in the liver; however, humans may be less sensitive compared than rats. Additionally in rats, exposure to DiDP resulted in increased kidney weights. Identified effects on the reproductive system and on development include changes in sex ratio, decrease in absolute testes weight in male rats, and skeletal variations, respectively. The most sensitive effect due to DiDP, but also due to DiNP, observed in different repeated dose toxicity studies is spongiosis hepatis, whereby the induction-mechanisms are not clear, but are likely to be related to peroxisome proliferation. In mice, the induction of liver adenomas was observed following DiDP exposure. However, the incidence of adenomas in the livers of mice is related to peroxisome proliferation and should not be relevant for humans. For DiDP, no estrogenic activity was shown in either *in vitro* or *in vivo* tests. However, investigations in humans are currently rarely available. (ECB, 2003b; ECHA, 2012c)

1.4 BISPHENOL A

1.4.1 General Information

General information on BPA is provided in Table 19:

Table 19. General information on BPA (European Communities, 2008; ECHA, 2012b, 2013h)

EC Number	201-245-8
CAS Number	80-05-7
IUPAC Name	2,2-bis(4-hydroxyphenyl)propane
EC Name	4,4´-isopropylidenediphenol
Molecular formula	$C_{15}H_{16}O_2$
Molecular weight	228.3 g/mol
Trade names, abbreviations, synonyms	Bisphenol A, BPA, Diphenylol propane, DPP, Bisphenol A ER grade – Flake, PARABIS(R) Resin intermediate, Bisphenol A - Polycarbonate grade
Physico-chemical properties	Organic solid flake or powder with a density of 1.2 kg/m^3 at 25°C; water solubility of 300 mg/l; flash point at ca. 207°C; log K_{OW} of 3.4; purity 99.0-99.8% (impurities: water (<0.2%), *ortho*- and *para*-isomers of BPA (<0.2%), and phenol (<0.06%)).
Chemical structure	

Bisphenol A (BPA) is an industrially manufactured and utilised chemical substance. The production occurs worldwide at high annual quantities. In general, BPA is used as monomer in polycarbonate (PC) and epoxy resin production, PVC production and processing, and in thermal paper production. Thus, BPA is present in a multitude of consumer products. Because of its chemical structure, the migration from contact materials and products into food, beverages, water, air, house dust or soil can occur. Human exposure through various routes may lead to various adverse health effects. (Vandenberg et al., 2007; European Communities, 2008; IHCP, n.r.)

1.4.2 Production and usage

BPA is produced by alkaline or acidic catalysed condensation of phenol and acetone in high purity (99.0-99.8%). BPA is mainly used for the manufacturing of PC (about 71%) and epoxy resins (25%). Furthermore, it is used for the production of phenoplast resins, unsaturated polyester resins, can coatings, PVC, thermal paper, modified polyamides, polyol/polyurethane, tyre and break fluids. (European Communities, 2008)

Polycarbonates (PC) are thermoplastic polymers and are used for the production of many consumer products such as digital media (CDs, DVDs), casing of mobile phones and computers, containers, identity cards, toys, food contact materials and articles, medical devices (about 3% of total PC production), refillable PC reservoirs, tableware, chocolate moulds, kettles, kitchen utensils, water bottles, eyeglass lenses, consumer electronics and electrical equipment. Additionally, it is used in automotive industry and for pipes in public water distribution networks. (European Communities, 2008; CEF, 2013)

Epoxy resins, which represent the second largest use of BPA after PC, are thermosetting polymers. They are used in coatings in food contact materials (especially in canned foods and beverages), dental fillings, electronics, fibre-reinforced plastic materials, powder coatings, industrial protective coatings, floorings and in adhesives. (EAG, 2010; CEF, 2013; IHCP, n.r.)

Thermal paper is a smooth paper with an applied coating, which is made from a dye and a phenol developer such as BPA. Thermal paper containing BPA is used for cash receipts, bus or airline tickets, lottery tickets and papers for laboratory use. (CEF, 2013; EFSA, 2013b)

In *PVC production*, BPA is used as a stabiliser for the vinyl chloride monomer, for the polymerisation of PVC plastics and as antioxidant in plasticisers used in PVC materials (CEF, 2013).

Other uses of BPA are *BPA methacrylate containing resins* (e.g. used for dental sealants), *polyetherimides* that are synthesised by melt condensation of BPA di-anhydride (e.g. used in microwave cookware, medical applications, electronic components and aircraft interiors), *polysulfone resins* made by condensation of BPA disodium salt (used in electrical components, appliances, medical equipment, valves, pumps, and pipes), *polyarylates,* which are amorphous polymers made by co-polymerisation of BPA (used in automotives, electronics, aircraft, (food) packaging applications), and *flame retardants*. Additionally, BPA can be present in *recycled paper* if BPA containing paper products are included and if BPA is not completely removed during the recycling process, as well as in *cosmetics* on the EU market through migration from packaging materials or as impurities in cosmetic ingredients. (CEF, 2013)

1.4.3 Classification and Labelling

According to Annex VI of CLP regulation (Regulation (EC) No 1272/2008), BPA is classified as Repr. 2;H361f (Toxic to reproduction category 2; Suspected to damage fertility), Skin Sens. 1;H317 (Skin Sensitiser; May cause an allergic skin reaction), Eye Dam. 1;H318 (Eye Damage; Causes serious eye damage), and STOT SE 3;H355 (Specific target organ toxicity – single exposure category 3; May cause respiratory irritation). BPA is labelled with the signal word “Danger”, and the pictograms “Exclamation mark”, “Corrosion”, and “Health hazard”. (ECHA, 2013h)

1.4.4 Legislation in the EU

BPA, used as a monomer for the production of PC and epoxy resins, must be registered under REACH following reduced requirements, since monomers are defined as intermediates. For this reason, BPA is also exempt from REACH authorisation. Because PC and epoxy resins are polymers, they are not subject to the REACH registration process, except BPA releases from articles during normal or reasonable use. (CIRS, 2008-2012; PlasticsEurope, 2010, 2011, 2013)

Several directives and regulations apply to the legislation of BPA within the EU:

By the Commission Directive 2002/72/EC of 6 August 2002, BPA was authorised for the use as monomer and additive in plastic materials production (CEF, 2013; EC, 2002). In this Directive regulating plastic materials and articles for food contact, a specific migration limit (SML) was set at 3 mg BPA/kg of food (EC, 2002). In 2005, a ban on BPA in cosmetic products came into force by the Directive 2005/80/EC (EC, 2005). BPA was included into the list of prohibited substances in cosmetic products in 2009 by the Regulation (EC) No 1223/2009 (Annex II) for harmonising the rules within the EU (EC, 2009a). Also in 2009, a so-called Indicative Occupational Exposure Limit Value (IOELV) was set out at 10 mg/m^3 for BPA (EC, 2009b). In 2011, the Directive 2002/72/EC was amended by the Directive 2011/8/EU and a temporary ban on BPA use in the production of PC infant feeding bottles and their placement on the market. Also in 2011, the Directive 2002/72/EC was replaced by the Regulation (EU) No 10/2011, which fixed the ban of BPA in PC infant feeding bottles, and set out a SML of 0.6 mg BPA/kg of food, but removed the use of BPA as an additive or polymer production aid. (CEF, 2013; EC, 2011a, 2011b, 2011e)

Furthermore, BPA is listed as a substance suspected to be an endocrine disruptor in CoRAP and was required to be evaluated by the EU Member State Germany in 2012 (ECHA, 2011, 2012a).

In the EU, several countries have passed additional national legislations:

Denmark passed in 2010 an interim BPA ban in food contact materials for children aged 0-3 years based on an assessment of the Technical University of Denmark and the principle of precaution (Danish Ministry of Food, Agriculture and Fisheries, 2010; EC, 2011a).

France temporarily banned in 2010 the production, import, export and even the placement on the market of BPA in infant feeding bottles. This decision was based on opinions of the French Food Safety Agency (AFFSA) and the Institut National de la Santé et de la Recherche Médicale (INSERIM). (EC, 2011a) In 2011, the French National Assembly extended the ban from infant feeding bottles to all food contact materials by 2014. A ban on all packaging materials containing BPA was additionally planned, as well as the inclusion of warning labels on packaging materials containing BPA for children aged 0-3 years and pregnant women. (Audran, 2012; ITRI, 2011)

Sweden banned the use of BPA or BPA containing compounds in varnishes and coatings of food packaging materials intended for children aged 0-3 years in 2013 (CEF, 2013).

Belgium banned the marketing or placing on the market, as well as the production of containers for food commodities that containing BPA for children aged 0-3 years in 2013 (CEF, 2013).

1.4.5 Acceptable levels of exposure

Acceptable levels of exposure (AL) are set out by agencies and derived for various endpoints based on reliable studies. Definitions of several ALs are given in chapter 1.3.6.1.

EFSA TDI

In 2006, EFSA completed their risk assessment report of BPA and set out a TDI of 50 µg/kg bw/d. In 2008, 2009, 2010 and 2011, EFSA reviewed newly available scientific studies and information and concluded that there is no new evidence to revise the current TDI. (EFSA, 2013a) In 2012, the EFSA's Panel on Food Contact Materials, Enzymes, Flavouring and Processing Aids (CEF) decided to perform a complete re-evaluation of BPA risks through different exposure sources (dietary and non-dietary) and reviewed more than 450 studies. They identified likely adverse effects on the liver, kidneys and mammary glands. In 2014, the CEF published their new opinion relating to BPA and derived a temporary TDI of 5 µg/kg bw/d, reflecting the current uncertainties related to BPA effects. (EFSA, 2014a, 2014b)

U.S. EPA RfD

The oral RfD for BPA set out by the U.S. EPA is 50 µg/kg bw/d based on reduced mean bodyweight (LOAEL 50 mg/kg/d) and an uncertainty factor of 1000 (U.S. EPA, 2012b).

1.4.6 Toxicokinetics

1.4.6.1 Routes of exposure

Humans are exposed to BPA via oral ingestion (e.g. through food and dental products), inhalation (through air and house dust), and dermal contact (e.g. through thermal paper).

Food and food contact materials

BPA is present in a multitude of food contact materials due to its use as application of epoxy resins for inner can coatings, or as a monomer in PC production, and can

therefore migrate into food (Vandenberg et al., 2007). Several studies have investigated BPA migration under various conditions and reported BPA leaching from cans into foodstuff or beverages (Brotons et al., 1995; Goodson et al., 2004; Kang, Kito and Kondo, 2003; Takao et al., 2002). Additionally, food and beverages packaged in cans are well investigated regarding to their BPA content (cf. Appendix C.1) and have been identified as important sources of BPA exposure to humans. BPA can also migrate from plastic food contact materials such as stretch films and bottles made from PC into foodstuffs (Kuwabo et al., 2009; López-Cervantes and Paseiro-Losada, 2003). Another possibility of exposure to BPA via food contact materials is the utilisation of papers because of the use of BPA in paper production. Studies have shown that kitchen towels made from recycled papers can contain BPA in notable concentrations. Investigations of virgin papers showed low or no BPA content. Additionally, several other studies have indicated papers and cardboards designed for food contact as potential BPA sources. (Ozaki et al., 2004; Vandenberg et al., 2007)

Dental products

Resin-based monomers are used in dentistry as adhesives, preventative sealants and restorative materials. BPA diglycidyl methacrylate synthesised from BPA has been used in many dental materials since the 1960s, and it has been demonstrated that parts of the unpolymerised monomers are able to leach from dental materials immediately after application to teeth and be dissolved in salvia. Therefore, dental products can also lead to BPA exposure in humans. (Rathee, Malik and Singh, 2012; Sasaki, Okuda and Kato, 2005; Vandenberg et al., 2007).

Air and house dust

During the course of production and utilisation, BPA can leach into the environment and be present in air and house dust. Several studies have investigated BPA levels in house dust, which can be found in a high percentage of dust samples. (Geens et al., 2009; Rudel et al., 2003; Uhl et al., 2004; Vandenberg et al., 2007). In a study from Japan investigating BPA concentrations in outdoor air, mean BPA levels of 0.51 ng/m^3 were found with mild seasonal variations (increasing BPA concentrations from autumn to winter, decreasing levels from winter to spring) (Matsumoto, Adachi and Suzuki, 2005).

Thermal paper, paper currencies

BPA is an additive in thermal paper used as a colour developer (Geens et al., 2012) and found in receipts, car park, plane, train and bus tickets, queue tickets and lottery

slips for example (Mielke, Partosch and Gundert-Remy, 2011). Humans can be exposed to BPA through oral intake by contact of unwashed hands with mouth or food, or by dermal exposure after contact with this type of paper. Additionally, thermal paper represents a source of BPA contamination for recycled paper. (Geens et al., 2012) Although oral exposure to BPA seems to be the major route of BPA uptake in the body, exposure through dermal contact is also very important and may be relevant to overall internal exposure (Mielke, Partosch and Gundert-Remy, 2011). Additionally, humans may be exposed to BPA through paper currencies, in which BPA is present as a free monomer. Therefore, absorption of BPA through dermal contact may occur due to the handling of e.g. paper money. (Liao and Kannan, 2011) BPA's penetration through skin depends on specific conditions. However, studies have demonstrated that BPA can enter the skin to depths at which it can no longer be removed by washing one's hands, resulting in its remaining in the skin until the latter's renewal, or a deeper migration. (Biedermann, Tschudin and Grob, 2009)

Medical devices, healthcare applications

Small amounts of BPA can leach from polycarbonates and polysulfones used in medical devices and healthcare applications such as eye lenses, tube connections, inhaler housing, blood oxygenators, newborn incubators, nebulisers and humidifiers. Additionally, BPA can migrate into drug formulations packaged in containers made of PC or lined with epoxy. BPA can also leach from PVC used in the production of medical products. (Geens et al., 2012) As shown in a study of premature infants undergoing intensive medical intervention for therapy, for example, the exposure of the infants to BPA was one order of magnitude higher than that of the general population (Calafat et al., 2009).

1.4.6.2 Absorption and elimination

In humans, BPA is rapidly absorbed by the GIT into the body following oral administration and is conjugated with glucuronic acid to its main metabolite BPA-glucuronide (BPA-G) in the liver, whereas the glucuronidation rate is limited by its transport rate from the GIT into the blood and the liver. Hepatocytes and microsomes are catalysators for this glucuronidation. Other metabolites (e.g. BPA sulphate) are also formed after the glucuronisation pathway, but this occurs only after a BPA exposure at higher doses. Further, BPA is eliminated via urine within 24 hours. In rodents, BPA metabolism follows the enterohepatic circulation, which is different from its metabolism in humans. (Doerge and Fisher, 2010; Völkel et al., 2002)

In a study of BPA metabolism and toxicokinetics conducted by Völkel et al. (2002), 5 mg D_{16}-BPA (54-90 µg/kg bw) were orally administrated to eight volunteers. This dose was about 10-fold higher than estimated levels of humans exposure of 0.6 mg/d. The authors reported a half-time for D_{16}-BPA-G of 5.4 hours for the elimination via urine, and a terminal half-time of 5.3 hours for the clearance from blood. After 24 to 34 hours, D_{16}-BPA-G levels were below the detection limit (LOD). Thus, D_{16}-BPA-G had a urinary recovery rate of 100%. In blood, no D_{16}-BPA-G was detectable, which supported the rapid absorption of BPA by the GIT, its conjugation with glucuronic acid in the liver, and its rapid elimination as BPA-G via urine. Additionally, these results suggested that BPA does not pass the enterohepatic circulation in humans, contrary to rodents. (Chapin et al., 2008; Völkel et al., 2002)

1.4.6.3 Mechanisms of action

Studies on humans and non-human primates have shown the rapid and extensive absorption of BPA following oral exposure and the extensive metabolisation during absorption by the GIT, and thereafter by the liver to glucuronidate and sulphate metabolites which are biologically inactive. Thus, systemic exposure to free and therefore biologically active BPA is limited to ca. 1%. The distribution of BPA occurs widely. BPA metabolites are eliminated via urine in a rapid manner. In blood, BPA is reversibly bound to proteins (95%) or is present in an unbound fashion (5%). Unbound BPA traverses the capillaries and perfuse cells and tissues, where it is able to bind to receptors with various affinities. When BPA reaches concentrations sufficient to bind and activate signalling, its estrogenicity manifests. (Teeguarden et al., 2013) BPA is able to bind to estrogen receptors (ER) and also to androgen receptors (AR), can alter steroid synthesis and circulating steroid hormone levels, is able to disrupt PPAR, as well as thyroid and glucocorticoid signalling (Nagel and Bromfield, 2013). Additionally, BPA is able to suppress aromatase activity and can bind to estrogen-related receptor gamma (EERγ) (Teng et al., 2013).

Estrogenic activity

Estrogen is a steroid hormone and influences the growth, differentiation and functions of many tissues including reproductive systems in males and females, and is important for the central nervous and cardiovascular systems and bone maintenance. The binding of estrogen to ER with a high specificity and affinity is necessary for actions in the body. (Kuiper et al., 1998) By binding to its cognate ligands, ERα acts as a ligand-activated transcription factor and mediates its action in cells and tissues. In addition to

natural ERα-ligands (estrogen), other different compounds are able to bind ERα, such as BPA as an environmental chemical which is structurally similar to estrogenic ligands. In dependence of the chemical structures of the ligands, they can act as estrogen-agonists or estrogen-antagonists. Ligands bind to ligand-binding domains of the ERα protein, which leads to the conformation of the ligand-ERα complex. Further, this complex interacts with co-activators or co-regulators at the promoters of estrogen-responsive genes and modulates the transcriptional activity of the genes. Therefore, the outcome of ERα-dependent responses of cells or tissues might be determined. (Sengupta et al., 2013) As mentioned above, BPA is able to bind and activate ERα, but with a lower affinity for genomic ERα compared to estradiol (Nagel and Bromfield, 2013). The affinity to bind ERs is about 10,000-fold weaker than that of estrogen (Kuiper et al., 1998). However, the bioactivity of BPA is similar to estradiol for several responses, especially responses mediated by non-genomic signalling. (Nagel and Bromfield, 2013) The estrogenic activity is demonstrated for free (active) BPA, but not for the metabolite BPA-glucuronide which is inactive (FDA, 2008).

Effects on estrogen-related receptor gamma (EERγ)

EERγ is part of the nuclear receptor family in humans and the ERR superfamily that is closely related to ERα and ERβ. EERγ is highly expressed in a tissue-restricted manner, e.g. in the brain and the placenta. BPA is able to bind to EERγ strongly and with high specificity, which can lead to various physiological effects. Further, BPA accumulation in the placenta can be facilitated and thereby increasing the exposure to the fetus. (Okada et al., 2008; Teng et al., 2013)

Anti-androgen activity

Androgens are steroid hormones necessary for normal sexual development and reproduction in males which stimulate the masculinisation of the fetus and induce male imprinting of the developing brain. They bind to androgen receptors (AR), which are ligand-activated transcription factors. Compounds that act as anti-androgens can bind to the ARs and inhibit them. (Lee et al., 2003) BPA is an antagonist for AR, but molecular mechanisms are unclear. However, studies have shown that BPA is able to inhibit the efficient nuclear translocation of AR. (Teng et al., 2013)

Effects on peroxisome proliferator-activated receptor (PPAR)

PPARs are nuclear receptors and exist in three isoforms: PPARα, PPARβ/δ and PPARγ, whereby PPARα is expressed mainly in tissues in which fatty acids are catabolised, and PPARγ is restricted to other adipose tissues. Additionally, both are

found in vascular endothelium. PPARs are important for immune responses especially for inflammation and can be found in macrophages, dendritic cells, and T and B cells. BPA can act as an antagonist and may therefore lead to pro-inflammatory outcomes. (Rogers, Metz and Yong, 2013) PPARγ expressed in adult adipocytes regulates lipogenesis, and PPARγ activators lead to increased fat deposition. BPA can elevate PPARγ in abdominal adipocytes. (Vom Saal et al., 2012)

Effects on the thyroid receptor (TR)

Thyroid hormones are important for the normal development of behaviour and intellect, as well as for neurological development. The TR is, similar to the estrogen receptor, a nuclear hormone receptor. The function of T_3 in the body is mediated by several TR isoforms (TRα1, TRβ1-3, TRα and TRβ). BPA as antagonist for TR reduces the binding of T_3 to nuclear TRs and recruits co-repressors which result in transcriptional inhibition. (Moriyama et al., 2002)

Effects on the glucocorticoid receptor (GR)

The GR is a nuclear receptor for steroid hormones and regulates glucose homeostasis, bone turnover, cell differentiation, lung maturation and inflammation. The natural ligand that binds to GR is cortisol in most species. BPA is able to bind GR as an agonist and may produce effects that are similar to effects produced by glucocorticoids. Studies have reported that inappropriate glucocorticoid exposure can lead to adverse effects on development in critical periods and can alter programming of tissues in glucocorticoid-sensitive endocrine and immune systems. (Prasanth, Divya and Sadasivan, 2010)

1.4.7 Health Effects

BPA has a low acute toxicity by all exposure routes, but is considered to produce skin sensation responses (ECB, 2003d). It is classified according to CLP as a substance causing serious eye damage, skin sensitisation and respiratory irritation (ECHA, 2013h).

BPA is able to bind to estrogen and androgen receptors; however, the affinity of binding to estrogen receptors is about 10,000-fold weaker than the affinity of estrogen. BPA can alter steroid synthesis and circulating steroid hormone levels, is able to disrupt PPAR and the signalling of thyroids and glucocorticoids, supresses aromatase activity and binds to the estrogen-related receptor γ. (Kuiper et al., 1998; Nagel and Bromfield, 2013; Teng et al., 2013) Prenatal and neonatal BPA exposures have shown

associations with the early onset of sexual maturation, the induction of preneoplastic mammary glands, lesions of the reproductive tract, increased prostate sizes and decreased sperm production in offspring. Studies have also shown possible associations between BPA exposure and cardiovascular diseases, diabetes, liver diseases and neural differentiation. (Prasanth, Divya and Sadasivan, 2010) Some concerns about possible reproductive and developmental toxicity exist, but results are not clear (Chapin et al., 2008). BPA can stimulate cell responses and molecular endpoints even at low doses. However, further investigations on health effects of BPA are needed. (Vandenberg et al., 2007)

1.5 HUMAN BIOMONITORING

Human Biomonitoring (HBM) is a method for the examination of human exposure to chemicals, which is performed in order to avoid environmentally related diseases. Additionally, HBM is also an instrument for health and environment policy. HBM can be performed on the general population, various population groups or individuals, and it is an important tool for exposure and risk assessment. Concentrations of environmental pollutants can be detected in several body fluids (such as blood, cord blood, urine and breast milk), hairs and tissues. All routes of exposure (oral, dermal, inhalation) can be determined. (Angerer, Ewers and Wilhelm, 2007; EAG, 2013a; Sattelberger, n.r.) Generally, two different types of HBM exist:

- *dose-monitoring* (quantification of concentrations of substances or their metabolites in different body fluids and tissues) and
- *effect-monitoring* (identification of reactions of the organism to the exposure).

One disadvantage of dose-monitoring is that no conclusion can be made on a substance regarding to its effects in the organism. Contrarily, effect-monitoring allows the identification of the effect, but no information can be given on the specific substances causing this effect. (Sattelberger, n.r.)

For the interpretation and evaluation of HBM data, clear criteria are necessary. The Commission of Human Biomonitoring in Germany - established in 1992 at the German Environment Agency (EAG) - published such criteria for so-called reference and HBM-values, as well as those values itself. Whereby reference values are statistically derived values describing the exposure of a substance to a population or population

group, HBM-values are toxicologically derived values based on scientific data establishing the occurrence of adverse health effects. (EAG, 2007a, 2007b)

1.5.1 Requirements for Human Biomonitoring

For HBM, existing requirements are qualified biological matrices, qualified biomarkers that are capable of reflecting exposure or effects, qualified and reliable analytical methods, as well as reference and limit values to make interpretation of results possible (Angerer, Ewers and Wilhelm, 2007).

Biological matrices

Chemicals enter the body via various exposure routes. They reach the circulatory system, are distributed into various body compartments, tissues and organs, and/or get eliminated e.g. via urine and faeces. The correct biological matrix must be chosen for exposure assessment in relation to the toxicokinetics and specific purposes of the particular substance. Generally, non-persistent chemicals are detected in urine due to their rapid metabolism and elimination, whereby persistent chemicals are analysed in blood. Still, blood may also be important for the analysis of non-persistent chemicals with the aim of the investigation of their toxicokinetics. The ideal requirement of analysing chemicals in urine is the availability of 24h urine samples, but often collection is difficult in epidemiological studies (e.g. among newborns or young children). Therefore, spot urine samples can be used, but a correction by creatinine adjustment would be necessary. Additionally, the correct matrix is needed for the specific purpose required (e.g. cord blood for investigating prenatal exposure). (Koch and Angerer, 2012)

Biomarkers

For exposure assessment, the use of suitable biomarkers is necessary. First of all, metabolism and elimination of a substance must be known for interpretation of internal exposure of the substance and/or its metabolites to be possible. For example, short-chain parent phthalates (low molecular weight phthalates) are metabolised to their monoesters, which are eliminated via urine. Contrarily, long-chain phthalates (high molecular weight phthalates) are metabolised to the corresponding monoesters (primary metabolites) in a first step and further to their oxidised metabolites (secondary metabolites) in a second step. Those oxidised metabolites are the main metabolites eliminated via urine. Thus, the sole use of single monoesters is not suitable for exposure assessment. (Koch and Angerer, 2012) This supports the need for detailed

knowledge of the behaviour of substances in organisms and the importance of using correct biomarkers for assessing exposure.

Analytical methods

Because of the importance of exposure assessments, the reliability of analytical results has to be guaranteed. The analytical method consists of the pre-analytic phase, the analytic phase, quality assurance, and the evaluation and interpretation of analytical results. In the pre-analytic phase, influences and interferences must be considered (e.g. time and procedure of sample collection, possible changes of analyte concentrations by e.g. degradation or possible contaminations). Standard operation protocols (SOPs) are a good tool for minimising these effects. In the analytic phase, quality assessments by internal and external quality controls are important, which can guarantee a high level of reliability. (Angerer, Ewers and Wilhelm, 2007)

Reference and limit values

For the evaluation of determined HBM data, clear criteria are necessary. The German HBM-commission has recommended criteria for reference and HBM values (see below). (Angerer, Ewers and Wilhelm, 2007)

1.5.2 Reference Values

In Human Biomonitoring, reference values describe the basic exposure of a population or population group and are determined based on data from a suitable reference population. According to the IUPAC guideline (Poulsen, Holst and Christensen, 1997), reference values are defined within the 95% confidence interval of the 95th percentile of estimated concentrations of a substance or metabolite in a representative sample of the general population or a population group (Bader and Lichtnecker, 2003; EAG, 2011). These values are descriptive and are influenced by several factors such as age, sex and geographic region, chosen sample and sample size, or lifestyle (e.g. smoking behaviour, nutrition, pharmaceutical intake and environmental exposure). Therefore, reference values are subject to change. For their estimation it is important to use representative samples. (Bader and Lichtnecker, 2003) Additionally, it must be considered that reference values are statistically derived values (EAG, 2009).

1.5.3 HBM values

Human biomonitoring (HBM) values are derived values based on epidemiological and toxicological studies. Two levels exist:

- *HBM-I values:* HBM-I values are control values. According to current knowledge, no need for action exists, because adverse health effects are not expected.
- *HBM-II values:* HBM-II values are intervention values. Concentrations of a substance in a body fluid/tissue which exceed this value at the current state of evaluation by the HBM-commission may lead to adverse health effects. Acute need for action to reduce exposure exists, and care by experts of environmental medicine is necessary. (EAG, 2009, 2012)

Table 20. Definition of HBM-I and HBM-II values and possible need for action (according to EAG, 2009, 2012)

Damage to health	Need for action
possible	- Care by experts of environmental medicine - Acute need of action to reduce exposure
HBM-II	
Cannot be ruled out with sufficient certainty	- Control of exposure values - Identification of exposure routes - Reduction of exposure
HBM-I	
Currently not expected	- Currently no need for action

2 METHODS AND MATERIALS

2.1 STUDY DESIGN

Since 1991, the Department of Nutritional Sciences of the University of Vienna (IfEW) has regularly determined and documented the nutritional status of the Austrian population (Austrian Study on Nutritional Status, ASNS). Every four years, the results of the ASNS are published in the Austrian Nutrition Report. With this survey, a multitude of data from a representative sample of the Austrian population is collected. The last survey was conducted between 2010 and 2012 and was published in the Austrian Nutrition Report 2012. (Elmadfa et al., 2012) Along with this survey, the Environment Agency Austria, Vienna (EAA) collected additional data for so-called contaminant monitoring and used urine samples as well as other data collected by the IfEW to assess the exposure of the population to various pollutants, their exposure routes and their possible adverse health effects in humans. This PhD thesis aims to investigate this exposure and determine possible correlations between pollution levels in human urine samples and effects on human health, as well as set out reference values for further risk assessments.

Performed by the IfEW, the ASNS has received a positive vote from the ethics commission of the City of Vienna (EK_10_037_0310) as well as insurance for the participants and the study personnel (insurance policy No. 08-U875.328; 23.02.2010; Wiener Städtische Versicherung).

The recruitment of the participants occurred though a quota sampling of a cross-sectional study. For regional comparisons, Austria was divided into East Austria (Burgenland, Vienna, Lower Austria and Styria) and West Austria (Upper Austria, Salzburg, Tyrol and Vorarlberg), according to the “Nomenclature des unites territoriales statistiques” (NUTS). The fieldwork was performed between August 2010 and February 2012. For detailed study design see Elmadfa et al. (2012).

In total, the IfEW recruited and investigated 1002 male and female participants aged 6 to 80 years from Austria (Elmadfa et al., 2012). For this study, participants were chosen and included if a proper amount of urine samples was available. Exposure to phthalates and BPA were analysed in 595 participants, respectively. Table 21 shows the distribution of the investigated participants. It must be noted, however, that no participants were available from the federal state of Carinthia.

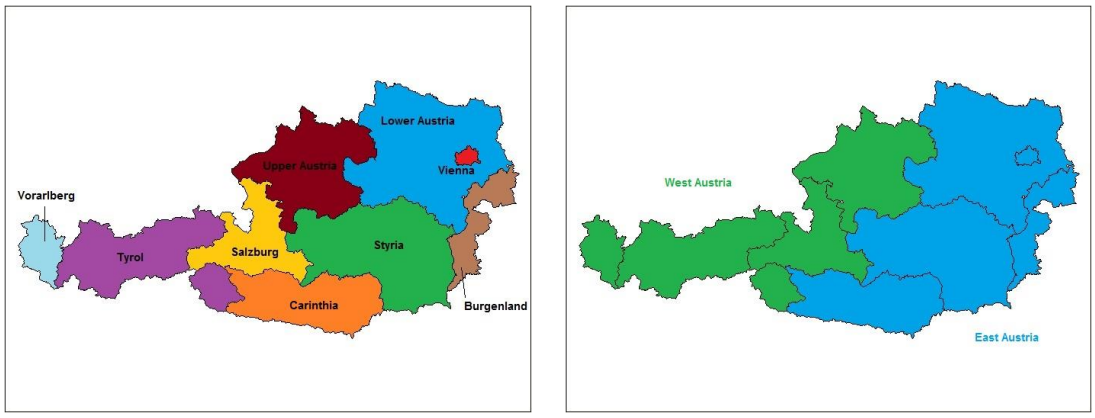


Figure 12. Austria divided into geographic regions according to NUTS[9]: East and South Austria (summarised as East Austria) (Vienna, Burgenland, Lower Austria, Styria and Carinthia) and West Austria (Upper Austria, Salzburg, Tyrol and Vorarlberg)

Table 21. Distribution of investigated samples

Sex	Age groups	n (recruitments of the IfEW)[1]	n (analysis of phthalate metabolites)[2]	n (analysis of BPA)[2]
All	***All***	***1002***	***595***	***595***
	6-9	61	34	56
	10-12	90	53	36
	13-15	37	22	24
female	18-24	40	30	30
	25-50	154	93	94
	51-64	57	39	39
	65-80	133	38	36
	6-9	69	48	61
	10-12	105	71	54
	13-15	25	23	23
male	18-24	18	15	15
	25-50	99	66	65
	51-64	51	29	33
	65-80	63	34	29

Abbreviations: BPA, Bisphenol A; n, sample size;
[1] Analytical investigations, anthropometric measurements, and questionnaires. Source: Elmadfa et al. (2012), p. 22
[2] Sample sizes depend on the availability of urine samples

In Appendix A, original questionnaires (in German) of the ASNS are added to this thesis.

[9] NUTS (Nomenclature des unités territoriales statistiques): for comparison between East and West Austria, the classification of NUTS 1 was used. (EC, 2011d; Elmadfa et al. 2012)

Table 22. Collected parameters and investigation methods by the IfEW used for this study (modified according to Elmadfa et al., 2012)

Method	Parameter
Anthropometric measurements	Bodyweight, Bodyheight, Body Mass Index (BMI) / Percentiles, Abdominal circumferences (AC), Hip circumference (HC), Waist circumference (WC), Waist-to-Hip Ratio (WHR)
Bioelectrical impedance analysis (BIA)	Body fat / body fat percentage, Body water, Lean Body Mass, Extracellular Mass (ECM), Body Cell Mass (BCM) / Body Cell Mass Ratio, Basal metabolic rate (BMR), Phase Angle, Extracellular water (ECW), Intracellular water (ICW)
Health indicators	Cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, leucocytes, lymphocytes, monocytes, granulocytes, erythrocytes, thrombocytes, mean corpuscular volume (MCV), haematocrit, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red blood cell distribution width (RDW), haemoglobin, mean platelet volume (MPV), glucose, glycated haemoglobin (HbA1c), total antioxidant reactivity, bilirubin, total protein, albumin, uric acid
Questionnaire Children I	Personal questions, family prosperity, nutrition and physical activity
Questionnaire Children II	Personal questions, Food Frequency Questionnaire (FFQ), meal frequency, subjective body sensation, family prosperity, tobacco consumption
Questionnaire Parents	Personal questions, Food Frequency Questionnaire (FFQ) (child), meal frequency (child), nutrient supplements (child), education and employment, education and employment of the partner, Contaminants Monitoring[1]
Questionnaire Adults and Elderly	Personal questions, education and employment, diseases, subjective health status, nutrient supplements, tobacco consumption, International Physical Activity Questionnaire (IPAQ), Food Frequency Questionnaire (FFQ), Contaminants Monitoring[1]
3-day food records Children	Energy and nutrient intake, intake in food groups
Two 24-hours-Recalls Adults and Elderly	Energy and nutrient intake, intake in food groups
Photometric measurement (Vitros) in urine	Creatinine

[1] The contaminants monitoring contained questions regarding place of work, place of residence, leisure time and additional questions about personal health.

The intake of food and beverages was surveyed in the groups of Children I and II by three consecutive daily food intake records and in the groups of Adults and Elderly People by two non-consecutive 24-h recalls. The first 24-h recall was surveyed with the assistance of experts and the second recall was surveyed after ca. 2 weeks by telephone. For the evaluation of portion sizes, a special photo book was used. (Elmadfa et al., 2012)

Laboratory parameters and health indicators were analysed by the IfEW. Creatinine levels were measured using the Jaffe-method. The analysis of haematograms was performed with a haematogram automat (Melet Schloesing MS4s, Osny, France). Several parameters (e.g. haematocrit) were calculated based on analysed leucocytes, eosinophil granulocytes, erythrocytes, haemoglobin and mean cell volumes (MCV). HDL, LDL, triglycerides, bilirubin, total protein, albumin and uric acid were measured photometrically in plasma by a Vitros 250 autoanalyser. (Elmadfa et al., 2012) Analysed and calculated parameters were provided by the IfEW by Excel data files and SPSS data files, respectively.

2.2 STUDY POPULATION

The recruitment of children occurred in several schools in various federal states. Adults and elderly people were recruited by the IfEW via companies, clubs, municipal offices and retirement homes. The participants received written information about the study and potential risks. Written consent of the participants was collected and archived. In the case of children not of full age, additional written information and the consent of parents or legal guardians was delivered. (Elmadfa et al., 2012)

An overview of surveyed participants is given in Table 21. The total study population is categorised into four groups: Children I (aged 6-8 years; 1st and 2nd education level), Children II (aged 7-15; 3rd to 8th education level), Adults (aged 18-65 years) and Elderly People (aged 64-81). Detailed information on the study population and the study population groups is given for phthalate analysis in Chapter 3.1.1 and for BPA analysis in Chapter 3.2.1. Overlaps in age exist among the study population groups of Children I and Children II, because recruitment of children was performed in relation to the specific levels of education. Among Adults and Elderly People, one overlap in age also exists. The reason for this is that one participant at the age of 64 years was surveyed within the group of Elderly People, which received a slightly different questionnaire. Therefore, the allocation to the group of Adults was not possible in this one case.

2.3 ANALYTICAL METHODS

Urine samples were collected by the IfEW between 2010 and 2012 and were transmitted to the Environment Agency Austria (EAA) in aluminium bottles and glass tubes provided by the IfEW. The samples were labelled with specific laboratory codes for identification. Until the measurement of phthalate metabolites and BPA could take place, the urine samples were stored in the EAA's laboratory at -20°C. Additionally, data collected by the IfEW (cf. Table 22) were provided to the EEA in the form of Excel and SPSS data files, respectively. Before analysis, available samples and data were elicited. For the analysis of phthalate metabolites, the available urine samples were separated into blocks of approximately 45 samples each, which were measured sequentially. The allocation of the samples to the different blocks occurred according to a prioritisation: samples with completely or nearly completely available data provided from questionnaires were measured first, except for samples from the study population groups Children I and Elderly People, since these were measured completely at the beginning of the procedure due to their small sample sizes. Each block was analysed in two batches. BPA analysis occurred in relation to sorted samples, with each batch including 50 samples.

The analysis of urinary phthalate metabolites occurred between June and December 2012 by HPLC-MS/MS, and that of BPA between July and September 2013 by on-line-SPE-HPLC-MS/MS. Samples stored in aluminium bottles were preferred for analysis, whereas samples from glass tubes were only used in the event of missing aluminium bottles. Urine samples were unfrozen before sample preparation and were frozen again immediately after the sample preparation at -20°C in the EEA´s laboratory. For phthalate metabolite analysis, samples were analysed undiluted and in a 1+4-dilution. For BPA analysis, each sample was measured singularly after scission by β-glucuronidase. If urinary total BPA levels in samples were >10 ng/ml, they were double-checked by an additional measurement without scission by glucuronidase, in order to exclude potential contaminations of the samples.

The evaluation of analysis results was performed with the software Analyst version 1.6.1 (AB SCIEX).

2.3.1 Phthalate metabolite analysis

Phthalate metabolites were analysed with an implemented accredited analytical method which has been proven by several inter-laboratory comparison tests.

Urine samples were mixed with a sodium acetate buffer and isotope ^{13}C- and D_4-labelled internal standard, respectively, and were enzymatically hydrolysed by β-glucuronidase during incubation for >12h at 37°C. Further, samples were centrifuged in order to eliminate potential depositions, and injected into the high-performance liquid chromatography (HPLC) system, at which point separation occurred. The detection was performed by 4000 QTRAP tandem-mass spectrometry through specific mass disintegration in electrospray (ESI) negative mode, and the quantification by multiple reaction monitoring (MRM) mode.

Calibration curves were obtained using standard solutions of different known phthalate metabolite concentrations, and two standards (low and high concentration, respectively) were analysed after every four urine samples within a sequence. For controls, samples spiked with a native (external) standard were analysed twice in each sequence. Labelled internal standards, calibration standards, and native standards were standard mixes containing each analysed phthalate metabolite.

2.3.1.1 Equipment, reagents and chemicals

Reagents and chemicals, as well as equipment used for phthalate metabolites analysis are listed in Table 23 and Table 24:

Table 23. Reagents and chemicals used for phthalate metabolite analysis

Reagents and chemicals	Manufacturer	CAS No.
Water Optigrade for HPLC (H_2O)	Promochem, LGC Standards GmbH (Wesel, Germany)	7732-18-5
Acetonitrile (ACN)	Promochem, LGC Standards GmbH (Wesel, Germany)	75-05-8
Sodium acetate trihydrate extra pure ($CH_3COONa * 3 H_2O$)	Merck (Darmstadt, Germany)	6131-90-4
β-Glucuronidase H-5 from *Helix pomatia*	Sigma-Aldrich, Co. (Missouri, USA)	9001-45-0
Acetic acid glacial 98-100% (HAc)	Merck (Darmstadt, Germany)	64-19-7
Tetrahydrofuran for chromatography (THF)	Merck (Darmstadt, Germany)	109-99-9

Table 24. Equipment used for phthalate metabolite analysis

Equipment		Manufacturer
Pipettes	Eppendorf Reference 2-20 µl, 50-200 µl, and 100-1000 µl	Eppendorf (Hamburg, Germany)
Centrifuge tubes	15 ml, 120x17 mm, PP	Sarstedt (Nümbrecht, Germany)
Vortex	Vibrofix VF 1 Electronic	IKA GmbH & Co. KG (Staufen im Breisgau, Germany)
pH meter	Sonorex	Bandelin GmbH (Berlin, Germany)
Autosampler vials and caps	1.5 ml, winding 8-425; 32x11.6 mm, brown glass; caps 0.1 ml microinsert/ 15 mm	Markus Bruckner Analysetechnik (Linz, Austria)
	Caps: Screw Caps N9	Caps: Macherey-Nagel GmbH & Co.KG (Düren, Germany)
HPLC	Agilent Technologies 1290 Infinity Series (pump, autosampler, thermostatted column compartment, degasser)	Agilent Technologies (Santa Clara, CA, USA)
MS detector	AB Applied Biosystems MDS SCIEX 4000 Q TRAP LC/MS/MS System	AB Sciex Technologies (Framingham, MA, USA)
Analytical column	Kinetex 2.6 µ Phenyl-Hexyl 100A, LC Column 100x4.6 mm	Phenomenex (California, USA)
Water bath	Type 1086	Gesellschaft für Labortechnik GmbH (Burgwedel, Germany)
Centrifuge	Type 3-18K	Sigma (Osterode am Harz, Germany)

2.3.1.2 Standards and solutions

Internal standard

For the preparation of the internal standard, ^{13}C- and D_4-labelled phthalate metabolites (stock solutions) were used (Table 25). The concentrations of the stock solutions amount to 0.1 mg/ml. 10 µl of each stock solution were mixed with 370 µl ACN to a final volume of 0.5 ml and a final concentration of 2.0 µg/ml.

Native (external) standard

For the preparation of the external standard, native phthalate metabolites were used as listed in Table 26. The concentration of each single stock solution amounted to 0.1 mg/ml, except for the MBzP stock solution, which had a concentration of 0.989 mg/ml. 20 µl of each stock solution and 2.0 µl of the MBzP stock solution were mixed with 718 µl THF/ACN (1+4) solution to a final volume of 1.0 ml and a final concentration of 2.0 µg/ml.

Table 25. Internal Standard stock solutions used for phthalate metabolite analysis

Stock solution	Manufacturer / Reference Number
Monomethyl phthalate-3,4,5,6-D4 / MMP-D_4	CDN Isotopes / D-7298
Mono-iso-butyl phthalate-3,4,5,6-D4 /MiBP-D_4	CDN Isotopes / D-7079
Mono-benzyl phthalate-3,4,5,6-D4 / MBzP-D_4	CDN Isotopes / D-7208
Monoethyl phthalate (Ring-1,2-$^{13}C_2$,Dicarboxyl-$^{13}C_2$, 99%) - MEP -C13	CIL / CLM-4586-1.2
Mono-n-butyl phthalate (Ring-1,2- Ring-1,2-$^{13}C_2$,Dicarboxyl-$^{13}C_2$, 99%) - MnBP -C13	CIL / CLM-4590-1.2
Mono-cyclohexyl phthalate (Ring-1,2-$^{13}C_2$,Dicarboxyl-$^{13}C_2$, 99%) –MCHP –C13	CIL / CLM-4592-1.2
Mono-n-octyl phthalate (Ring-1,2-$^{13}C_2$,Dicarboxyl-$^{13}C_2$, 99%) – MnOP –C13	CIL / CLM-4589-1.2
Mono-isononyl phthalate (Ring-1,2-$^{13}C_2$,Dicarboxyl-$^{13}C_2$, 99%) – MiNP –C13	CIL / CLM-4587-1.2
Mono(2-ethylhexyl)phthalate (Ring-1,2-$^{13}C_2$,Dicarboxyl-$^{13}C_2$, 99%) – MEHP –C13	CIL / CLM-4584-1.2
Mono(2-ethyl-5-hydroxyhexyl)phthalate-C13 ($^{13}C_4$, 99%) – 5-OH-MEHP –C13	CIL / CLM-6641-1.2
Mono(3-carboxypropyl)phthalate (Ring-1,2-$^{13}C_2$,Dicarboxyl-$^{13}C_2$, 99%) –3cx-MPP –C13	CIL / CLM-6847-1.2
Mono-(5-carboxy-2-ethylpentyl)phthalate ($^{13}C_4$, 99%) – 5cx-MEPP –C13	CIL / CLM-8148-1.2
Mono-(2-ethyl-5-oxohexyl)phthalate ($^{13}C_4$, 99%) – 5oxo-MEHP –C13	CIL / CLM-6640-1.2

Abbreviation: CIL, Cambridge Isotope Laboratories, Inc.

Table 26. External Standard stock solutions used for phthalate metabolite analysis

Stock solution	Manufacturer / Reference Number
Mono-butylbenzyl phthalate / MBzP	Chiron / 3808.15-K-MX
Mono-methyl phthalate / MMP	CIL / ULM-6697-1.2
Mono-ethyl phthalate / MEP	CIL / ULM-4585-1.2
Mono-n-butyl phthalate / MnBP	CIL / ULM-6148-1.2
Mono-isobutyl phthalate / MiBP	CIL / ULM-7919-1.2
Mono-n-pentyl phthalate / MnPeP	CIL / ULM-7393-1.2
Mono(2-ethylhexyl) phthalate / MEHP	CIL / ULM-4583-1.2
Mono-cyclohexyl phthalate / MCHP	CIL / ULM-7394-1.2
Mono-n-octyl phthalate / MnOP	CIL / ULM-4593-1.2
Mono-(2-ethyl-5-hydroxyhexyl)phthalate (DEHP Metabolite IX) / 5OH-MEHP	CIL / ULM-4662-1.2
Mono-(2-ethyl-5oxohexyl)phthalate / 5oxo-MEHP	CIL / ULM-4663-1.2
Mono-(5-carboxy-2-ethylpentyl)phthalate / 5cx-MEPP	CIL / ULM-8149-S
Mono-isononyl phthalate / MiNP	CIL / ULM-4651-1.2
Mono-isodecyl phthalate / MiDP	CIL / ULM-4652-1.2
Mono(3-carboxypropyl)phthalate / 3cx-MPP	CIL / ULM-6848-1.2

Abbreviations: CIL, Cambridge Isotope Laboratories, Inc.

Calibration standards

For the preparation of calibration standards (Table 27), different volumes of buffer:H_2O (1+4), external standard (in ACN/THF, concentration 2 µg/mL), and internal standard were mixed in glass vials. Prepared standard concentrations were 0.0 ng/ml, 0.3 ng/ml, 0.4 ng/ml, 0.6 ng/ml, 0.8 ng/ml, 1.0 ng/ml, 2.0 ng/ml, 4.0 ng/ml, 10 ng/ml, 20 ng/ml, 50 ng/ml, and 100 ng/ml. Three standards at different concentrations were measured after a series of 4 samples (two undiluted and two corresponding diluted).

Table 27. Preparation of calibration standards (Phthalates)

Stock solutions [µl]		***Calibration standard 20 ng/ml[1] [µl]***	**Buffer/H_2O (1+4) [µl]**	**Final c [ng/ml]**
Internal standard (c=2000 ng/ml)	*External standard (c=2000 ng/ml)*			
10	50		950	100
10	25		975	50
10	10		990	20
10	5		995	10
10	2		998	4.0
10		100	900	2.0
10		50	950	1.0
10		40	960	0.8
10		30	970	0.6
10		20	980	0.4
10		15	985	0.3
10		0	1000	0.0

[1] An additional calibration standard at a concentration of 20 ng/ml was used for the preparation of calibration standards of 0.3-2.0 ng/ml final concentration.

Sodium Acetate Buffer (0.1M, pH 5.5)

3.4 g sodium acetate (NaAc, molecular weight 136.08 g/mol) were dissolved in 150 ml H_2O, HAc was added until a pH of 5.5 was achieved (measurement with pH meter), and H_2O was added until a final volume of 250 ml as achieved.

β-glucuronidase

β-glucuronidase H-5 from *Helix pomatia* was used as an enzyme (17.000 units/ml). For preparation, 29.7 mg dry glucuronidase (572.400 units/g) were weighed out and dissolved in 1 ml of sodium acetate buffer (0.1 M, pH 5.5).

Eluents

For phthalate metabolites analysis, the following eluents were used:

- Eluent A: ACN/H_2O (9+1), 1% HAc
- Eluent B: H_2O/ACN (9+1), 1% HAc

For the preparation of eluent A, 900 ml acetonitrile (ACN), 100 ml water optigrade for HPLC (H_2O), and 10 ml acetic acid (HAc) were mixed in 1000 ml glass bottles, and 100 ml ACN, 900 ml H_2O, and 10 ml HAc for the preparation of eluent B.

2.3.1.3 Sample preparation

Depending on the available analysis time in the laboratory, one or two sequences (batches) of urine samples were refrozen per measurement day. For sample preparation (Table 29) 200 µl sodium acetate buffer, 10 µl internal standard, 10 µl β-glucuronidase and 800 µl urine sample were mixed in a centrifuge tube labelled with the corresponding laboratory code. In each sequence, two blanks were measured (1+4-diluted and undiluted, respectively), which were prepared in the same way as the samples, but H2O was used instead of urine. Additionally, controls were analysed in each sequence. Prepared samples and blanks were incubated in a water bath at 37°C for >12h, and further centrifuged for 30 minutes at 4700 rotations per minute at 10°C. Samples, blanks and controls were filled in insert glass vials undiluted and 1+4-diluted with final volumes of 350 µL and 250 µL, respectively, and analysed by HPLC-MS/MS. Analysed phthalate metabolites are shown in Table 28.

Table 28. Analysed phthalate metabolites

Parent compound	Analysed parameters
DEHP (Di-2-ethylhexyl phthalate)	MEHP (Mono-2-ethylhexyl phthalate)
	5OH-MEHP (Mono-(2-ethyl-5-hydroxyhexyl) phthalate)
	5cx-MEPP (Mono-5-carboxy-2-ethylpentyl phthalate)
	5oxo-MEHP (Mono-2-ethyl-5-oxohexyl phthalate)
DEP (Diethyl phthalate)	MEP (Monoethyl phthalate)
DiBP (Di-isobutyl phthalate)	MiBP (Mono-isobutyl phthalate)
DnBP (Di-n-butyl phthalate)	MnBP (Mono-n-butyl phthalate)
BBzP (Butyl benzyl phthalate)	MBzP (Mono-benzyl phthalate)
DCHP (Di-cyclohexyl phthalate)	MCHP (Mono-cyclohexyl phthalate)
DnOP (Di-n-ocytl phthalate)	MnOP (Mono-n-octyl phthalate)
DiNP (Di-isononyl phthalate)	MiNP (Mono-isononyl phthalate)
DiDP (Di-isodecyl phthalate)	MiDP (Mono-isodecyl phthalate)
DnPeP (Di-n-pentyl phthalate)	MnPeP (Mono-n-pentyl phthalate)
DnBP, DnOP, and DiNP[1]	3cx-MPP (3-carboxy-mono-propyl phthalate)

[1] 3cx-MPP is the metabolite of several phthalates. Conclusion of origin is not possible.

Table 29. Schedule of phthalate metabolite measurement

Sample preparation (in Eppendorf centrifuge tubes)		
	Pipetting scheme	
Urine samples		200 µl Sodium Acetate Buffer 10 µl Internal Standard 10 µl β-Glucuronidase 800 µl Urine Sample
Blank		200 µl Sodium Acetate Buffer 10 µl Internal Standard 10 µl β-Glucuronidase 800 µl HPLC-water
Control		200 µl Sodium Acetate Buffer 10 µl Internal Standard 10 µl External Standard 800 µl HPLC-water
	Further treatment	
	Vortex	
	Incubation (water bath, 37°C, 100 moves/min overnight)	
	Centrifugation (30 min, 4700 circulations/min,10°C)	
	Preparation in insert glass vials: 1+4 dilution and undiluted	
	Vortex	
Analysis (HPLC-MS/MS)		
Eluents		A: ACN/H_2O (9+1), 1% HAc B: H_2O/ACN (9+1), 1% HAc
Evaluation		
AB SCIEX Analyst Software Version 1.6.1		
Estimation		

2.3.1.4 Quality control

In each sequence containing approximately 23 samples, two controls were measured in the same way than the samples, 1+4-diluted and undiluted. The preparation procedure of controls is described above. Analysed phthalate metabolite concentrations of controls were recorded in control charts which are shown in Appendix D. Index values (statistical means) and the one-, two- and threefold standard deviation

(+/- SD) as tolerance ranges are marked in the control charts. For phthalate metabolites analysis, the relative standard deviations (RSDs) ranged between 10.8 and 19.8% and the mean relative recoveries between 94.6 and 115.8% in dependence on the specific substance (between-day imprecision and accuracy).

2.3.1.5 HPLC-MS/MS analysis

Instrumental conditions

MRM transitions as well as instrumental conditions of HPLC-MS/MS analysis of phthalates are shown in Table 30 and Table 31, respectively:

Table 30. MRM transitions and conditions for phthalate metabolite analysis

Substance	Precursor [Da]	Fragment [Da]	Dwell time [msec]	Declustering Potential (DP) [Volt]	Collision Energy (CE) [Volt]	Collision Cell Exit Potential (CXP) [Volt]
MEP	192.988	77.000	30	-40.000	-40.000	-13.000
MEP-^{13}C	196.935	79.000	30	-45.000	-24.000	-5.000
5cx-MEPP	307.043	159.000	30	-50.000	-18.000	-7.000
5cx-MEPP-^{13}C	311.044	158.900	30	-50.000	-18.000	-13.000
5oxo-MEHP	290.975	129.900	30	-60.000	-26.000	-7.000
5oxo-MEHP-^{13}C	295.007	123.900	30	-60.000	-26.000	-9.000
MCHP	247.001	96.900	30	-55.000	-22.000	-5.000
MCHP-^{13}C	251.001	79.000	30	-55.000	-22.000	-5.000
MEHP	276.966	133.800	30	-60.000	-22.000	-9.000
MEHP-^{13}C	281.040	136.800	30	-65.000	-22.000	-11.000
MnBP	220.922	76.900	30	-50.000	-26.000	-3.000
MnBP-^{13}C	224.948	79.000	30	-55.000	-24.000	-5.000
MnOP	276.989	126.900	30	-60.000	-24.000	-7.000
MnOP-^{13}C	281.052	126.800	30	-70.000	-24.000	-9.000
MnPeP	234.996	77.000	30	-45.000	-28.000	-5.000
5OH-MEHP	293.052	120.900	30	-50.000	-26.000	-9.000
5OH-MEHP-^{13}C	297.043	123.800	30	-60.000	-26.000	-7.000
3cx-MPP	250.922	102.900	30	-55.000	-12.000	-7.000
3cx-MPP-^{13}C	255.073	103.000	30	-55.000	-12.000	-5.000
MiNP	291.000	142.900	30	-60.000	-20.000	-5.000
MiNP-^{13}C	295.100	123.900	30	-60.000	-20.000	-5.000
MiDP	305.100	154.900	30	-55.000	-26.000	-5.000
MBzP	255.053	183.000	30	-55.000	-18.000	-11.000
MBzP-D_4	258.920	167.000	30	-55.000	-18.000	-11.000
MiBP	221.033	133.600	30	-55.000	-18.000	-9.000
MiBP-D_4	224.947	138.000	30	-55.000	-18.000	-9.000

Table 31. Instrumental conditions (HPLC-MS/MS) for phthalate metabolite analysis

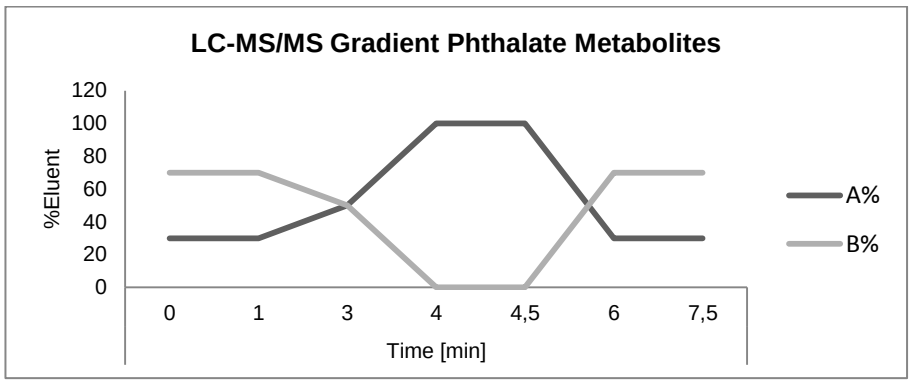
HPLC conditions	
Column	Kinetex 100x2.1 mm, 6 µ, PN 00DF-4495-AN, SN 606226-2
Injection Volume	10 µl
Column Oven Temperature	30°C
MS conditions	
Scan type	MRM
Polarity	Negative
Curtain Gas (CUR)	30
Collision Gas (CAD)	High
Ion Spray Voltage (IS)	-4000
Temperature (TEM)	300
Ion Source Gas 1 (GS1)	60
Ion Source Gas 2 (GS2)	60

Gradient

The gradient used for phthalate metabolites analysis is given and Table 32, as well as in Figure 13. The total time of one run was 7.5 min. The mobile phase consists of variable composition of eluents (A%, B%) during the run.

Table 32. HPLC-MS/MS gradient for phthalate metabolite analysis

Total Time [min]	**Flow rate [µl/min]**	**Eluent A [%]** (ACN/H_2O (9+1), 1% HAc)	**Eluent B [%]** (H_2O/ACN (9+1), 1% HAc)
0.00	400	30	70
1.00	400	30	70
3.00	400	50	50
4.00	400	100	0
4.50	400	100	0
6.00	400	30	70
7.50	400	30	70



Abbreviations: A%, percentage of eluent A; B%, percentage of eluent B

Figure 13. HPLC-MS/MS gradient for phthalate metabolite analysis

Analysis

Before the start of phthalate metabolite analysis, the HPLC-system was purged for 7 minutes with an eluent composition of 95% eluent A and 5% eluent B, and for a further 7 minutes with a composition of 5% eluent A and 95% eluent B at a flow of 5 ml/min for entering of pipes and capillaries, as well as to eliminate potential air bubbles. After purging, the method was loaded to achieve the starting conditions of the gradient (eluent A:eluent B = 30:70 %). For arriving constant pressure and vacuum, the system was equilibrated for 1 to 3 minutes, and values were compared with values from previous measurements. Usually, calibration standards at different concentrations were measured several times before a sequence of urine samples was started, and chromatograms were compared with chromatograms of corresponding calibration standards from previous measurements to ensure sufficient sensitivity. Afterwards, the analysis was started.

Each sequence contained approximately 23 samples (diluted and undiluted), 2 blanks, 2 controls, and the calibration standards. 3 calibration standards at different concentrations were measured after each series of 6 samples (3 undiluted and the corresponding diluted samples). An example of a sequence is shown in Figure 14.

2.3.1.6 Evaluation

The preparation of analysis, the analysis itself and the evaluation were all performed with the AB Sciex software Analyst Version 1.6.1. Chromatograms derived from measurements were (re)integrated, and metabolite concentrations were quantitated in Analyst. For each sequence for several phthalate metabolites, calibration curves were generated based on analysed internal standards at different concentrations (Figure 15) by quadratic regression whereat concentrations were weighted 1/x. Further calculations (e.g. calculation of recoveries) were performed in Microsoft Excel 2010. Values below the limit of detection (LOD) were indicated as n.d. (not detectable), and values between the LOD as the lowest limit and the LOQ (limit of quantitation) as the upper limit were indicated as <LOQ.

	Sample Name	Rack Code	Rack Position	Plate Code	Plate Position	Vial Position	Data File	Inj.Volume (µl)
1	Phth, 100 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	2	20120821_A	10,000
2	Phth, 10 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	5	20120821_A	10,000
3	Phth, 1 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	8	20120821_A	10,000
4	BW Box 6 (21.8.2012), 1+4	2 Well Plates	1	*54VialPlate*	1	13	20120821_A	10,000
5	BW Box 6 (21.8.2012)	2 Well Plates	1	*54VialPlate*	1	14	20120821_A	10,000
6	KS (21.8.2012)	2 Well Plates	1	*54VialPlate*	1	15	20120821_A	10,000
7	KS (21.8.2012)	2 Well Plates	1	*54VialPlate*	1	16	20120821_A	10,000
8	Phth, 20 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	4	20120821_A	10,000
9	Phth, 2 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	7	20120821_A	10,000
10	Phth, 0.6 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	10	20120821_A	10,000
11	1104 1969 (AS_1162) (21.8.2012), 1+4	2 Well Plates	1	*54VialPlate*	1	17	20120821_A	10,000
12	1104 1970 (AS_1163) (21.8.2012), 1+4	2 Well Plates	1	*54VialPlate*	1	19	20120821_A	10,000
13	1105 2746 (AS_1185) (21.8.2012), 1+4				1	21	20120821_A	10,000
14	1105 2746 (AS_1185) (21.8.2012)				1	22	20120821_A	10,000
15	1104 1970 (AS_1163) (21.8.2012)	2 Well Plates	1	*54VialPlate*	1	20	20120821_A	10,000
16	1104 1969 (AS_1162) (21.8.2012)	2 Well Plates	1	*54VialPlate*	1	18	20120821_A	10,000
17	Phth, 50 ng/ml in H2O/Puffer 1+1, 21.8.2012			*54VialPlate*	1	3	20120821_A	10,000
18	Phth, 4 ng/ml in H2O/Puffer 1+1, 21.8.2012			*54VialPlate*	1	6	20120821_A	10,000
19	Phth, 0.4 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	11	20120821_A	10,000
20	1105 2747 (AS_1186) (21.8.2012), 1+4	2 Well Plates	1	*54VialPlate*	1	23	20120821_A	10,000
21	1105 2748 (AS_1187) (21.8.2012), 1+4	2 Well Plates	1	*54VialPlate*	1	25	20120821_A	10,000
22	1105 2754 (AS_1193) (21.8.2012), 1+4	2 Well Plates	1	*54VialPlate*	1	27	20120821_A	10,000
23	1105 2754 (AS_1193) (21.8.2012)	2 Well Plates	1	*54VialPlate*	1	28	20120821_A	10,000
24	1105 2748 (AS_1187) (21.8.2012)	2 Well Plates	1	*54VialPlate*	1	26	20120821_A	10,000
25	1105 2747 (AS_1186) (21.8.2012)	2 Well Plates	1	*54VialPlate*	1	24	20120821_A	10,000
26	Phth, 100 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	2	20120821_A	10,000
27	Phth, 10 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	5	20120821_A	10,000
28	Phth, 0.8 ng/ml in H2O/Puffer 1+1, 21.8.2012	2 Well Plates	1	*54VialPlate*	1	9	20120821_A	10,000
29	1105 2756 (AS_1195) (21.8.2012), 1+4	2 Well Plates	1	*54VialPlate*	1	29	20120821_A	10,000

Blanks

Controls

Samples (undiluted and 1+4-diluted)

Calibration standards

Figure 14. Screenshot of a selected segment of a sequence as an example for phthalate metabolite analysis with HPLC-MS/MS (Software: AB Sciex Analyst Version 1.6.1)

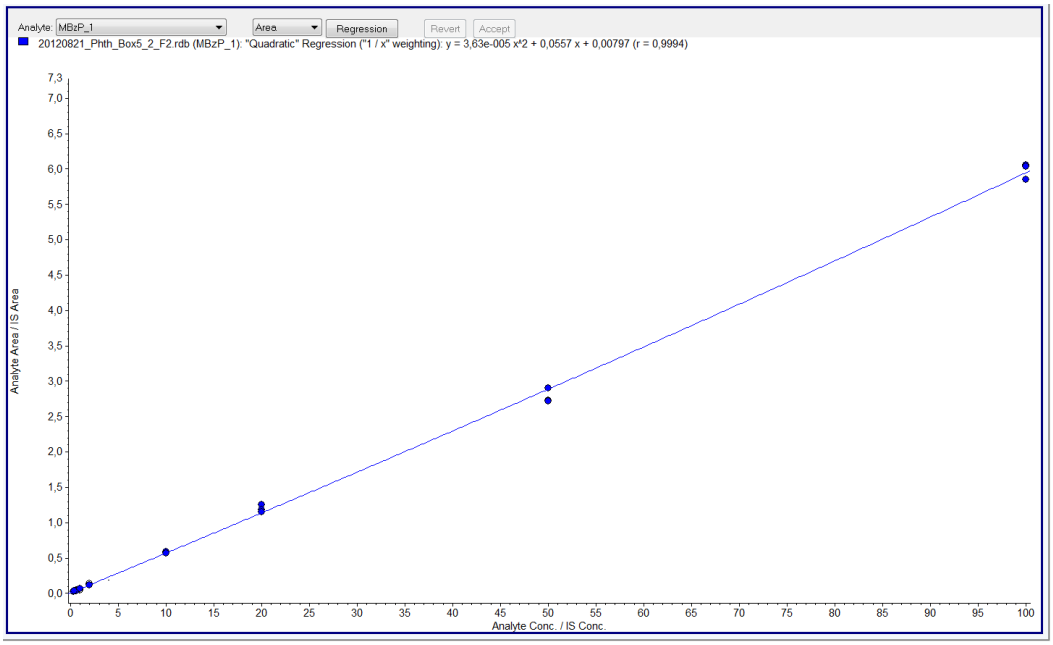
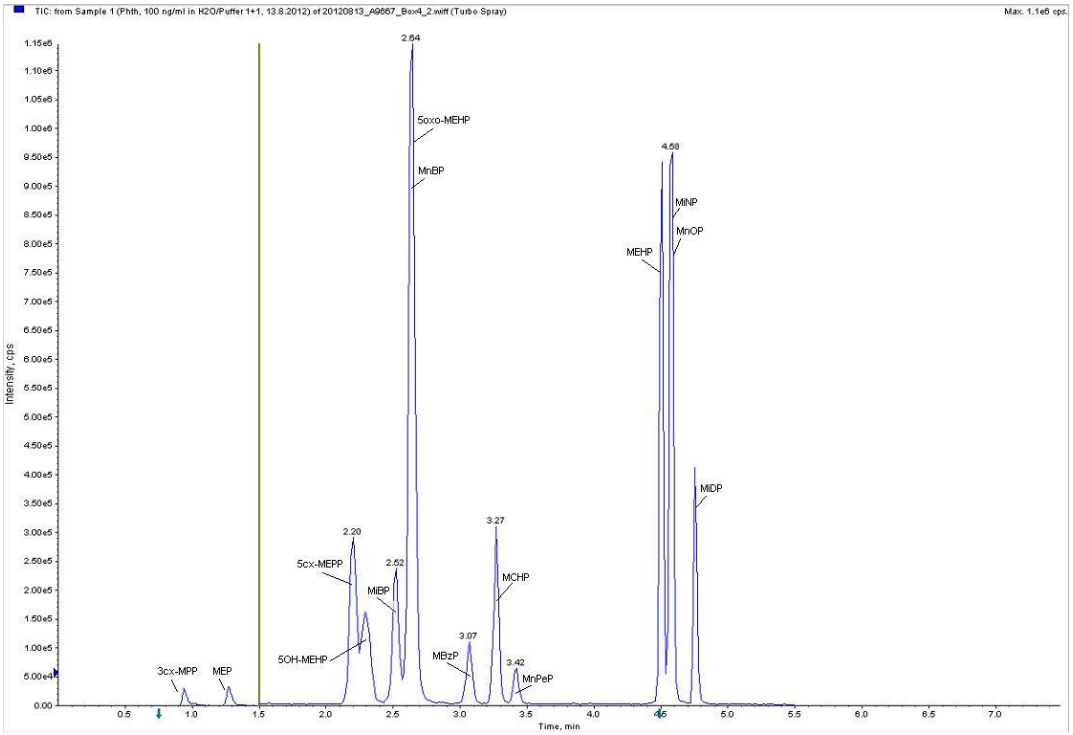


Figure 15. Example of a calibration curve of MBzP (AB Sciex Analyst Version 1.6.1)

Chromatogram of a 100 ng/ml calibration standard:



Notes: Not all of the investigated metabolites could be chromatographically separated, but were separated based on selective mass transitions.

Figure 16. Total Ion Current (TIC) chromatogram of a 100 ng/ml phthalate metabolite calibration standard

2.3.1.7 Limits of quantitation (LOQ) and limits of detection (LOD)

The limit of detection (LOD) is the lowest measureable signal, and the limit of quantitation (LOQ) is the lowest concentration of an analyte which can be measured quantitatively. Table 33 shows LOQs and LODs of investigated phthalate metabolites. Instrumental LOQs of phthalate metabolites were carried out by a basic validation by SQS 2010 Version 1.46 according to DIN 32645. LOD is given as LOQ/2.

Urine samples have variable matrix effects. Thus, isotopically labelled standards for almost all analytes are used to correct these effects.

2.3.1.8 Calculations

Calculations were performed in Microsoft Excel 2010 based on data derived from Analyst.

Diluted samples were multiplied by the dilution factor of 5. Values from diluted and undiluted samples were compared; if both values showed a variation of not more than

30%, the mean was used as a final concentration [ng/ml], if both values showed a variation of more than 30%, the value of the undiluted sample was chosen.

Possible blank values were subtracted from corresponding phthalate metabolite concentrations.

The recovery of each sample was calculated with the formula:

$$\text{Recovery } [\%] = \left(\frac{\text{Sample Peak Area}}{\text{Mean IS Peak Area}}\right) * 100 * \text{dilution factor}$$

with IS being the internal standard, and the dilution factor being 5 for diluted samples and 1 for undiluted samples.

Table 33. Limits of quantitation (LOQ) and of detection (LOD) of analysed phthalate metabolites

Substance	LOQ [µg/l]	LOD [µg/l]
MEP (Monoethyl phthalate)	4.92	2.46
MEHP (Mono-(2-ethylhexyl) phthalate)	1.38	0.69
5oxo-MEHP (Mono-2-ethyl-5-oxohexyl phthalate)	1.12	0.56
5OH-MEHP (Mono-)2-ethylhydroxyhexyl) phthalate)	1.58	0.79
5cx-MEPP (Mono-5-carboxy-2-ethylpentyl phthalate)	0.92	0.46
MBzP (Mono-butylbenzyl phthalate)	1.18	0.59
MnBP (Mono-n-butyl phthalate)	1.06	0.53
MiBP (Mono-isobutyl phthalate)	1.18	0.59
MnOP (Mono-n-octyl phthalate)	0.90	0.45
MCHP (Mono-cyclohexyl phthalate)	1.02	0.51
3cx-MPP (3-carboxy-2-ethylpentyl phthalate)	3.20	1.60
MiNP (Mono-isononyl phthalate)	0.94	0.47
MiDP (Mono-isodecyl phthalate)	0.94	0.47
MnPeP (Mono-n-pentyl phthalate)	1.10	0.55

Abbreviations: LOD, limit of detection; LOQ, limit of quantitation. *Notes:* LOD=LOQ/2

2.3.2 Bisphenol A

For the development of the analytical method for determining BPA in urine samples, detailed information was provided from the LGL, Munich, Germany during a research internship in March 2013. The method as well as the sample preparation was adopted from the LGL, with some changes and modifications resulting from the use of different analytical instruments. The provided method was published in Völkel, Kiranoglu and Fromme (2008).

Urine samples, ammonium acetate buffer, and D_{16}-BPA labelled internal standard were mixed in centrifuge tubes, followed by enzymatic hydrolysis by β-glucuronidase for approximately 12h at 37°C in a water bath. Samples were centrifuged in order to eliminate possible depositions, and were then injected into the on-line SPE-HPLC-MS/MS system for analysis. Similar to phthalate metabolite analysis, calibration curves were obtained by using standard solutions at different known BPA concentrations. Each sequence contained about 50 urine samples, with two standards (low and high concentration, respectively) measured after a series of four samples. Additionally, each sequence contained one blank, as well as two or three controls measured at the beginning and at the end of each sequence, or in between. For the preparation of controls, a urine sample was spiked with BPA, aliquoted and stored at -20°C until analysis.

Contrarily to phthalate metabolite analysis, samples were focused on a TRAP column for BPA analysis. Therefore, a two-pump system was required.

2.3.2.1 Equipment, reagents and chemicals

Table 34 and Table 35 show reagents and chemicals, as well as equipment which were used for the BPA analysis:

Table 34. Reagents and chemicals used for BPA analysis

Reagents and chemicals	Manufacturer	CAS Number
Water Optigrade for HPLC	Promochem, LGC Standards GmbH (Wesel, Germany)	7732-18-5
Water Optigrade for LC/MS	Promochem, LGC Standards GmbH (Wesel, Germany)	7732-18-5
Acetonitrile (ACN)	Promochem, LGC Standards GmbH (Wesel, Germany)	75-05-8
Ammonium acetate	Merck (Darmstadt, Germany)	631-61-8
β-Glucuronidase H-5 from *Helix pomatia*	Sigma-Aldrich, Co. (Missouri, USA)	9001-45-0
Methanol hypergrade for LC-MS (MeOH)	Merck (Darmstadt, Germany)	67-56-1
Ammonia (NH_3)	Merck (Darmstadt, Germany)	7664-41-7

Table 35. Equipment used for BPA analysis

Equipment		Manufacturer
Pipettes	Eppendorf Reference 2-20 µl, 50-200 µl, and 100-1000 µl	Eppendorf (Hamburg, Germany)
Centrifuge tubes	15 ml, 120x17 mm, PP	Sarstedt (Nümbrecht, Germany)
Vortex	Vibrofix VF 1 Electronic	IKA GmbH & Co. KG (Staufen im Breisgau, Germany)
pH meter	Sonorex	Bandelin GmbH (Berlin, Germany)
Autosampler vials, and caps	1.5 ml, winding 8-425; 32x11.6 mm, brown glass; caps 0.1 ml microinsert/ 15 mm	Markus Bruckner Analysetechnik (Linz, Austria)
	Caps: Screw Caps N9	Caps: Macherey-Nagel GmbH & Co.KG (Düren, Germany)
UPLC	Agilent Technologies 1290 Infinity Series (pump, autosampler, thermostatted column compartment, degasser)	Agilent Technologies (Santa Clara, CA, USA)
HPLC	Agilent Technologies 1200 Infinity Series (pump, autosampler, thermostatted column compartment, degasser)	Agilent Technologies (Santa Clara, CA, USA)
MS detector	AB Applied Biosystems MDS SCIEX 4000 Q TRAP LC/MS/MS System	AB Applied Biosystems (Framingham, MA, USA)
Analytical column	Luna 5µ C18(2) 100A, 100 x 2.00 mm 5 micron	Phenomenex (California, USA)
TRAP column	Oasis HLB 25 µm 2.1x20 mm	Waters Corporation (Massachusetts, USA)
Water bath	Type 1086	Gesellschaft für Labortechnik GmbH (Burgwedel, Germany)
Centrifuge	Type 3-18K	Sigma (Osterode am Harz, Germany)
pH meter	pH 196	WTW GmbH (Weilheim, Germany)

2.3.2.2 Standards and solutions

Internal standard

Used internal standard for BPA analysis was D_{16}-labelled with a concentration of 1 µg/ml dissolved in H_2O (Manufacturer: Cambridge Isotope Laboratories, Inc.; Reference Number: DLM-1839).

Native (external) standard

The used external standard had a concentration of 10 µg BPA/ml ACN (Manufacturer: Sigma-Aldrich; Reference Number: 23 965-8).

Calibration standards

For the preparation of BPA calibration standards (Table 36), different volumes of ACN/H_2O (1+3), external standard (10 µg/ml), and 15 µl D_{16}-BPA (1 µg/ml) were transferred into glass vials. Calibration standards were prepared in concentrations of 0.0 ng/ml, 0.1 ng/ml, 0.25 ng/ml, 0.5 ng/ml, 0.75 ng/ml, 1.0 ng/ml, 2.5 ng/ml, 5.0 ng/ml, 7.5 ng/ml, 10 ng/ml, 25 ng/ml, and 50 ng/ml, with a concentration of 0.5 ng/ml being the lowest possible for quantitation. Two standards, one with a lower and one with a higher concentration were measured in each sequence after each series of four samples.

Table 36. Preparation of calibration standards (BPA)

Stock solutions [µl]		***Calibration standard 100 ng/ml[1] [µl]***	***Calibration standard 10 ng/ml [µl][1]***	**ACN/H_2O (1+3) [µl]**	**Final c [ng/ml]** (final volume: 1500 µl)
Internal standard (c=1 µg/ml)	*External standard (c=10 µg/ml)*				
15	7.50			1492.5	50
15	3.75			1496.25	25
15		150		1350	10
15		112.5		1387.5	7.5
15		75		1425	5.0
15		37.5		1462.5	2.5
15		15		1485	1.0
15			112.5	1372.5	0.75
15			75	1410	0.50
15			37.5	1447.5	0.25
15			15	1470	0.10
15				1500	0.00

[1] Additional calibration standards at concentrations of 100 ng/ml and 10 ng/ml were used for the preparation of calibration standards of 0.1 -10 ng/ml final concentration.

Ammonium Acetate Buffer

15.42 g ammonium acetate (NH_4Ac, molecular weight 77.08 g/mol) were dissolved in 1000 ml H_2O (0.2M, pH 6.5).

β-glucuronidase

Similar to phthalate metabolite analysis, β-glucuronidase H-5 from *Helix pomatia* was used as an enzyme (17.000 units/ml). For preparation, 29.7 mg dry glucuronidase

(572.400 units/g) were weighed in and dissolved in 1 ml of sodium acetate buffer (0.1 M, pH 5.5).

Eluents

For BPA analyses, the following eluents were used:

1290 Binary Pump (analytical pump):

- Eluent A1: MeOH
- Eluent B1: H_2O + NH_3 (pH 8.5)

1200 Binary Pump (loading pump):

- Eluent A2: MeOH
- Eluent B2: H_2O

For the preparation of eluent B1, LC/MS-H_2O was mixed with NH_3 until a pH of 8.5 was achieved.

2.3.2.3 Sample preparation

For the preparation of urine samples for analysing total BPA, 400 µl urine sample, 80 µl ammonium acetate buffer (0.1 M, pH 6.5), 20 µl D_{16}-BPA as internal standard (concentration: 1 µg/ml), and 10 µl β-glucuronidase were mixed to a final volume of 510 µl, and were incubated for 12h at 37°C in a water bath. In previous investigations, the correct functioning of the glucuronidase at an incubation time of 12h or more has been proven. Following incubation, 500 µl ACN were added, and the mixture was then centrifuged for 15 minutes at 4700 rpm. 750 µl of the sample, as well as 750 µl H_2O, were transferred into glass vials to the final volume of 1500 µl. The sample preparation for the analysis of free BPA followed the same procedure, with the exceptions being the addition of glucuronidase and incubation. Free BPA was only analysed if analysed total BPA concentrations were >10 ng/ml, for the purpose of identifying possible contaminations. Table 37 shows the detailed schedule for the sample preparation of total BPA.

Table 37. Sample preparation of total BPA

Sample preparation (in Eppendorf centrifuge tubes) – Total BPA	
Pipetting scheme	
Urine samples	80 µl Ammonium Acetate Buffer 20 µl BPA-D_{16} (internal standard) 10 µl β-Glucuronidase 400 µl Urine Sample
Blank	80 µl Ammonium Acetate Buffer 20 µl BPA-D_{16} (internal standard) 10 µl β-Glucuronidase 400 µl HPLC-water
Control urine	80 µl Ammonium Acetate Buffer 20 µl BPA-D_{16} (internal standard) 10 µl β-Glucuronidase 400 µl Spiked Control Urine Sample
Control	80 µl Ammonium Acetate Buffer 20 µl BPA-D_{16} (internal standard) 10 µl external standard 400 µl HPLC-water
Further treatment	
Vortex Incubation (water bath, 37°C, 100 moves/min, >12 h) Addition of 500 µl ACN Centrifugation (15 min, 4700 circulations/min) Preparation in glass insert vials: 750 µl sample + 750 µl H_2O (final volume: 1500 µl) Vortex	

2.3.2.4 Quality control

Per sequence, two to three control urines were analysed at the beginning, the end, and in some cases in the middle of the sequence, as well as one control standard. For control preparation, 990 µl urine were spiked with 10 µl external BPA (10 µg/ml ACN), aliquoted and stored in glass vials until analysis. The sample preparation of control urines occurred in the same way as investigated urine samples. Analysed BPA concentrations of controls were recorded similarly to phthalate metabolites in control charts, where index values (statistical means) and tolerance ranges (one-, two-, and threefold standard deviations (+/- SD)) are marked. Control charts of BPA analysis are

shown in Appendix D. For between-day imprecision and accuracy, the relative standard deviation (RSD) for BPA was 14.4% and the mean relative recovery 98.3%.

2.3.2.5 On-line SPE-HPLC-MS/MS analysis

Instrumental conditions

Table 38 and Table 39 show the instrumental conditions and transitions of on-line SPE-HPLC-MS/MS analysis:

Table 38. Instrumental conditions (on-line SPE-HPLC-MS/MS) for BPA analysis

HPLC conditions	
Column	Luna 5µ C18
Injection Volume	100 µl
Column Oven Temperature	30°C
MS conditions	
Scan type	MRM
Polarity	Negative
Curtain Gas (CUR)	40
Collision Gas (CAD)	High
Ion Spray Voltage (IS)	-4000
Temperature (TEM)	500
Ion Source Gas 1 (GS1)	50
Ion Source Gas 2 (GS2)	20

Table 39. MRM transitions and conditions for BPA analysis

Substance	Precursor [Da]	Fragment [Da]	Dwell time [msec]	Declustering Potential (DP) [Volt]	Collision Energy (CE) [Volt]	Collision Cell Exit Potential (CXP) [Volt]
BPA	226.994	132.800	20	-85.000	-34.000	-9.000
BPA-D_{16}	240.994	141.800	20	-85.000	-34.000	-9.000

Gradients

Table 40 shows the gradient of BPA analysis, which is also graphically illustrated in Figure 17.

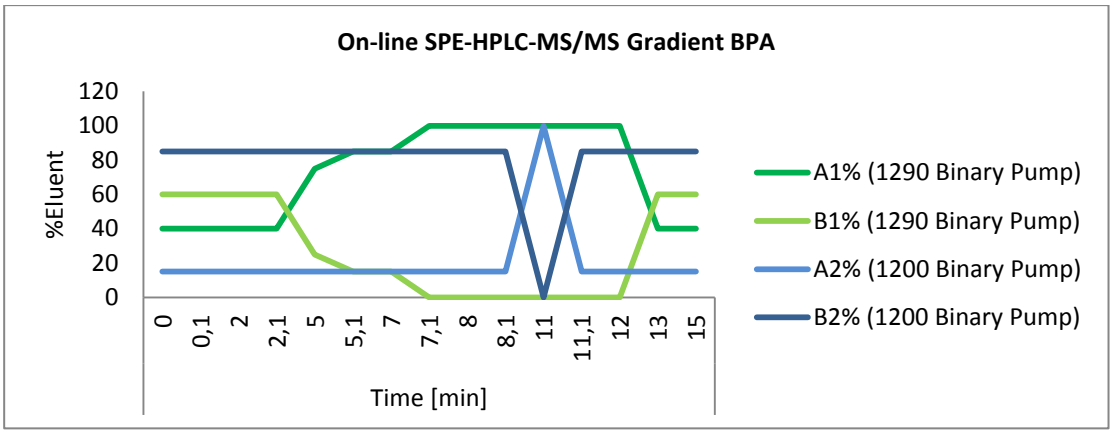


Figure 17. On-line SPE-HPLC-MS/MS gradient for BPA analysis

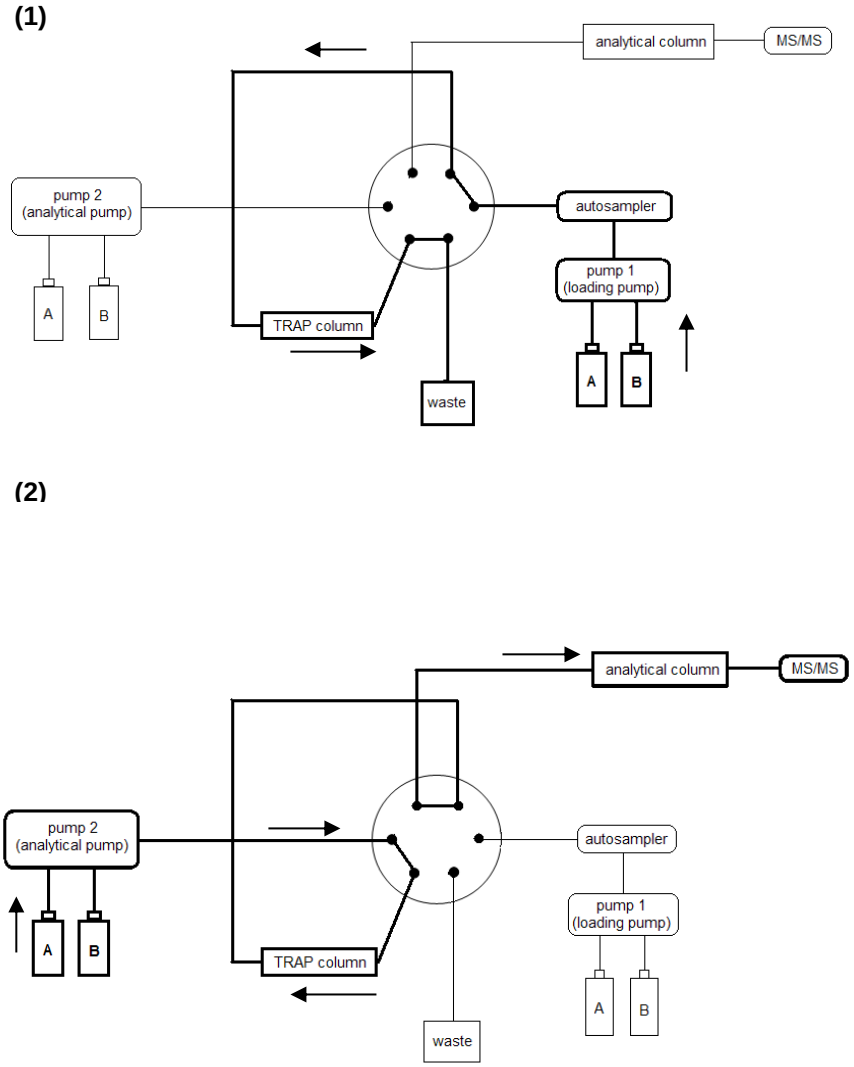
Table 40. On-line SPE-HPLC-MS/MS gradient for BPA analysis

Agilent 1290 Binary Pump			
Time [min]	***Flow [µl/min]***	***A1 [%]*** *(MeOH)*	***B1 [%]*** *(H_2O + NH_3)*
0.0	400	40	60
0.1	400	40	60
2.1	400	40	60
5.0	400	75	25
5.1	400	85	15
7.0	400	85	15
7.1	400	100	0
12.0	400	100	0
13.0	400	40	60
15.0	400	40	60
Agilent 1200 Binary Pump			
Time [min]	***Flow [µl/min]***	***A2 [%]*** *(MeOH)*	***B2 [%]*** *(H_2O)*
0.0	1000	15	85
2.0	1000	15	85
2.1	0	15	85
8.0	0	15	85
8.1	1000	15	85
11.0	1000	100	0
11.1	1000	15	85
15.0	1000	15	85

Column-switching on-line SPE-HPLC-MS/MS system

BPA was analysed with a column-switching on-line SPE-HPLC-MS/MS method which requires two pumps. Thus, the binary pump of a 1200 infinity HPLC and the binary pump of a 1290 infinity HPLC were combined. In a first step, the urine sample was

cleaned up and BPA was focused on the TRAP column via pump 1 (1200 HPLC pump), and further, after the switch of the columns, BPA was transferred to the analytical column via pump 2 (1290 HPLC pump), chromatographically separated and detected via MS/MS (Figure 18).



(1) Loading: clean-up and enrichment of BPA via pump 1 (Agilent 1200 Binary Pump); (2) Elution: analyte transfer onto analytical column via pump 2 (Agilent 1290 Binary Pump), chromatographic separation and detection via mass spectrometer

Figure 18. Column-switching HPLC system (modified according to Modick et al., 2013)

Analysis

Both used HPLC pumps (1200 infinity HPLC, and 1290 infinity HPLC) were each purged twice for 10 minutes, with an eluent composition 95% A and 5% B, and with an eluent composition of 5% A and 95% B at flow rates of 5 ml/min for running-in of pipes

and capillaries, and for elimination of air bubbles. After purging, the analytical method was loaded for achieving gradient start conditions. Before analysis began, the system was equilibrated in a manner similar to that previously described for phthalate metabolites analysis.

In a first step (cf. Figure 18: 1), the autosampler injected 100 µl of the sample into the system. Pump 1 (1200 HPLC pump) carried the mobile phase with a composition of 15% MeOH and 85% H_2O at a flow rate of 1000 µl/min for loading the sample on the TRAP column, which was completed after two minutes. Thereon, the 6-port valve switched to elution position (cf. Figure 18: 2), where BPA gets back flushed from the TRAP column to the analytical column by pump 2 (1290 UPLC pump) at a mobile phase composition of 40% MeOH and 60% H_2O+NH_3 at a flow rate of 400 µl/min. After between 5 and 7 minutes, the mobile phase changed to a composition of 85% MeOH and 15% H_2O+NH_3. After 7 minutes, the mobile phase increased to 100% MeOH for 6 minutes. Between 13 and 15 minutes, the content of MeOH in the mobile phase decreased to the starting conditions of 40%. The flow rate during the measurement was consistently 400 µl/min at pump 2. After 8 minutes, the system switched back to loading position, flushing the TRAP column with 100% MeOH at a flow rate of 1000 µl/min (pump 1). After one minute, the composition of the mobile phase changed to 15% MeOH and 85% H_2O, and was kept until the end of the measurement.

2.3.2.6 Evaluation

Similar to phthalate metabolite measurement, the preparation of analysis, the analysis itself and the evaluation were all performed with AB Sciex software Analyst (Version 1.6.1). Chromatograms derived from analysis were (re)integrated, and BPA concentrations were quantitated with “Quantitation Wizard” in Analyst. Calibration curves were generated based on analysed calibration standards (Figure 19). Further calculations such as the calculation of recoveries, were performed in Excel 2010. Values below LOD were indicated as n.d., and values between LOD as the lowest limit and LOQ as the upper limit were indicated as <LOQ.

2.3.2.7 Limits of quantitation (LOQ) and limits of detection (LOD)

The LOQ of BPA is 2.5 ng/ml, and the LOD is 1.25 ng/ml (LOQ/2). The instrumental LOQ for BPA was carried out by a basic validation by SQS 2010 Version 1.46 according to DIN 32645.

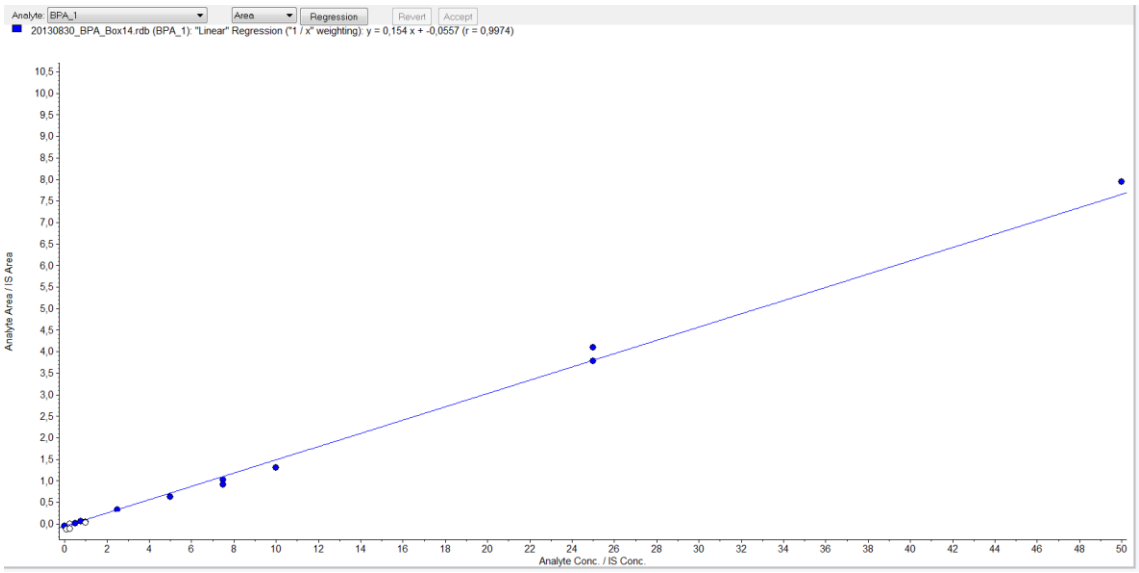


Figure 19. Example of a calibration curve of BPA (AB Sciex Analyst Version 1.6.1)

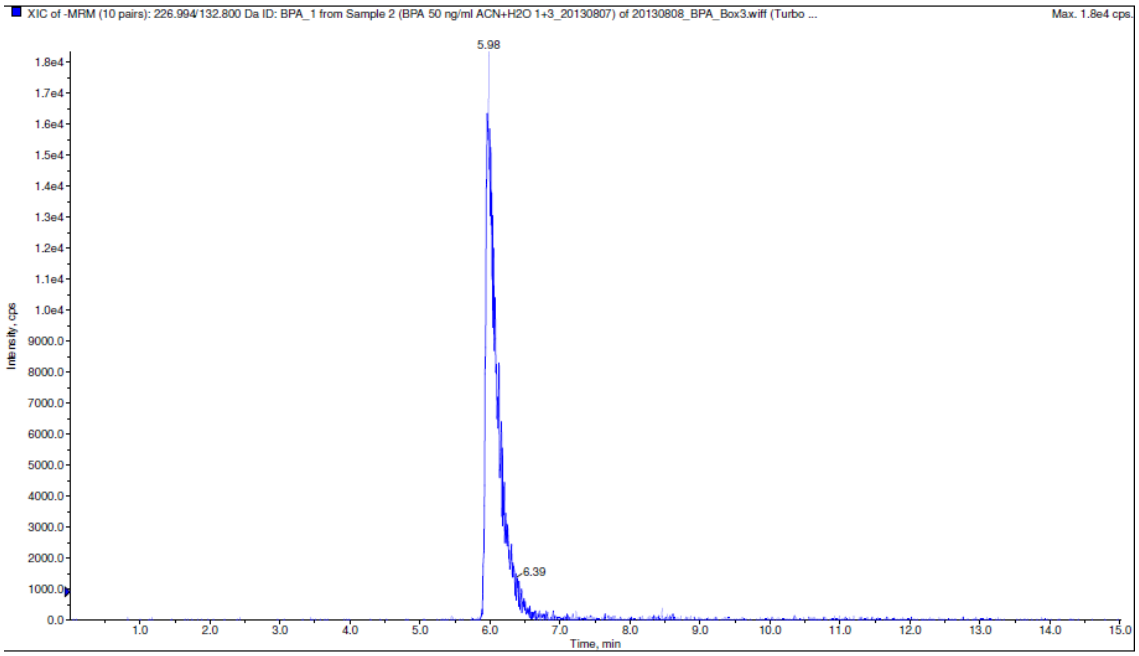


Figure 20. Extracted Ion Chromatogram (XIC) of a 50 ng/ml BPA calibration standard

2.3.2.8 Calculations

Based on data derived from Analyst, calculations were performed in Excel 2010.

Samples were multiplied by a dilution factor 5, because 300 µl urine sample was finally present in a volume of 1500 µl after sample preparation.

Possible blank values were subtracted from measured BPA concentrations from the corresponding sequence.

For the calculation of the individual recovery [%] of each sample, the mean peak area of the internal standards of the contiguous calibration standards was divided by the peak area of the sample and multiplied by 100:

$$\text{Recovery } [\%] = \left(\frac{\text{Sample Peak Area}}{\text{Mean IS Peak Area}}\right) * 100$$

2.4 STATISTICAL METHODS

Statistical analyses were performed with the software IBM® SPSS® Statistics Version 21 and partly with Microsoft Excel 2010. Urinary phthalate metabolite and total BPA concentrations below the limit of quantitation (LOQ) were set to LOQ/2 and concentrations below the limit of detection (LOD) were set to 0 for further data treatment. Descriptive statistics mainly involved ranges, medians, 95th percentiles and quantiles for metric data, as well as frequencies for ordinal and nominal data. Phthalate metabolite and BPA concentrations in urine were tested for normal distribution by Kolmogorov-Smirnov tests whereat the majority was not normal distributed. Thus, non-parametric tests were used. Correlations between different metric data were analysed using Spearman's rank correlation. Differences between groups (e.g. between study population groups, age groups or living area) were investigated depending on the type of data with Mann-Whitney U tests and Kruskal-Wallis tests both at 0.05 significance level. Calculations of creatinine-adjusted metabolites, daily intakes, cumulative risk assessment and scenario exposure estimations were performed in Excel 2010. For the investigation of possible associations between urinary phthalate metabolite concentrations and food intake, linear models were performed. Reference values, which are statistically derived values based on urinary substance concentrations from a reference population and are defined within the 95% confidence interval of the 95th percentile of the population, were estimated with Excel 2010.

Detailed calculation procedures and used statistical tests are mentioned in the related chapters.

2.5 CALCULATIONS

2.5.1 Creatinine adjustment

Analyte concentrations can be affected by urine concentrations or dilution, depending on the fluid balance. To compensate for this effect, the creatinine concentrations have been measured in the urine samples. Creatinine (crea), as the metabolite of creatine which is an energy store for muscles, depends on the individual renal function as well as the lean body mass. Creatinine concentrations vary by sex, age and ethnicity. Creatinine production increases from childhood to adulthood and decreases slowly after the age of 65. For the correction of variations, creatinine adjustment is performed. (Blount et al., 2000; CDC, n.r.; Cocker et al., 2011)

1 µmol/l creatinine is equivalent to 0.01 mg/dl creatinine (Universitätsklinikum Ulm, 2012). Creatinine concentrations of the participants were measured by the IfEW in mmol/l. For the estimations, creatinine concentrations were converted into mg/dl, and the measured urinary analyte concentrations in µg/l were converted into ng/dl. The following formula was used for the calculation:

$$c_{\text{crea-adjusted analyte}} / g_{\text{crea}}\ [\mu g/g] = \frac{c_{\text{analyte}}\ [ng/dl]}{c_{\text{creatinine}}[mg/dl]}$$

2.5.2 Daily Intake estimation

The estimation of Daily Intakes (DIs) of phthalates is performed based on the analysed urinary concentrations of the corresponding phthalate metabolites. In this study, DIs were calculated based on analysed phthalate metabolite and BPA levels in urine, and possible exceedances of acceptable exposure levels were identified. Detailed information on the calculation parameters used and calculation procedure of DI estimation are given in the related chapters.

2.5.3 Cumulative Risk Assessment estimation for phthalates

The group of phthalates includes a number of similar substances with varying characteristics. Usually, chemical risk assessment does not account for combined exposure effects, and risks can potentially be underestimated. Therefore, a cumulative risk assessment is needed. One method is dose-addition, which uses the so-called Hazard-Index (HI) approach for the estimation of the overall effect potential of several

chemicals, which allows the assumption of adverse effects to human health resulting from simultaneous exposures. (Kortenkamp and Faust, 2010; U.S. EPA, 1989) In the present study, a cumulative risk assessment was performed for phthalates. Detailed information on the calculation procedure can be found in Chapter 3.1.6.

2.5.4 Scenario Exposure Calculations

The ingestion of food and beverages is the main route of exposure to phthalates and BPA. Aims of the Scenario Exposure Calculations were to estimate the potential (theoretical) phthalate and BPA intake of the study population via various foodstuffs separately from their analysis in urine, and to investigate possible statistical correlations between daily intakes derived from scenario exposure calculations and daily intakes derived from analysed phthalate metabolite and BPA concentrations in urine. The theoretical estimation of the intake of substances via food was performed based on surveyed food frequency questionnaires, 24-h recalls and average concentrations of phthalates and BPA in various foodstuffs derived from a multitude of published studies. In Chapter 3.2.6, the detailed approach, estimation procedure, and possible limitations and results of the scenario exposure calculations are shown.

2.6 LITERATURE ANALYSIS

Literature research was undertaken between 2012 and 2014 through internet sources, mainly via “www.google.com” and “www.ncbi.nlm.nih.gov/pubmed”. Other important websites used were the related homepages of the European Commission and the ECHA. Additionally, literature research was also conducted in libraries of the University of Vienna.

Study results for the preparation of meta-analyses were provided from a multitude of scientific studies, which were searched by means of key words in Pubmed or Google. In the following, a short description is given of the searched study data for calculations or comparisons:

Urinary phthalate metabolite and BPA concentrations in other study populations

For the comparison of phthalate and BPA concentrations analysed in urine of the present study population and results of other study populations, research papers published in several journals were used. The data collected included information on the

study population (sample size, age and sex), time of sample collection, name of the study (if available), analyte concentrations (ranges and medians/means in µg/l urine), detection rates (in %), LOD or LOQ (in µg/l) and analytical method used, and were sorted by analyte and time of sample collection separately for children and adults.

Daily phthalate and BPA intake

Daily phthalate and BPA intakes derived from various international scientific studies were collected in order to compare them with the results of the present study. Information on the study population (sample size, age and sex), time of sample collection, name of the study, analyte concentrations (ranges, medians/means, and 95th percentiles in µg/kg bw/d) and type of calculation model performed (creatinine-based or volume-based daily intake) were collected. The data was sorted by analyte and time of sample collection for children and adults.

Phthalate and BPA concentrations in foodstuffs

Measured phthalate and BPA concentrations in various foodstuffs published by several studies were collected for the performance of scenario exposure calculations. The data was collected according to the surveyed food groups based on food frequency questionnaires (FFQ). Analyte concentrations in various food types (ranges and means/medians in µg/kg), sample size, type of packaging, analytical method, LOD or LOQ (in µg/kg), collection year and production site (country) were collected.

3 RESULTS

3.1 PHTHALATES

3.1.1 Description of the study population

Descriptions of the study population exist for both phthalate analysis and BPA analysis (see related chapter), because in some few cases, urine samples were only analysed for either phthalates or BPA, respectively. Table 41 to Table 44 show the descriptive data of the groups of Children I, Children II, Adults and Elderly People.

Table 41. Data Children I (Phthalate analysis) (n=31)

	All	**Males**	**Females**
SEX	31 (100%)	16 (52%)	15 (48%)
AGE [years] (range; mean±SD)	6-8; 7±0.5	6-8; 7±0.4	6-8; 7±0.6
FEDERAL STATE (n=30)[1,2]			
Vienna	4 (13%)	2 (13%)	2 (13%)
Burgenland	7 (23%)	3 (20%)	4 (27%)
Lower Austria	5 (17%)	3 (20%)	2 (13%)
Styria	2 (7%)	1 (7%)	1 (7%)
Salzburg	12 (40%)	6 (40%)	6 (40%)
REGION (n=30)[1,2]			
East Austria	18 (60%)	9 (60%)	9 (60%)
West Austria	12 (40%)	6 (40%)	6 (40%)
RESIDENTIAL AREA (n=29)[1,3]			
urban	7 (24%)	3 (21%)	4 (27%)
suburban	3 (10%)	1 (7%)	2 (13%)
rural	19 (66%)	10 (72%)	9 (60%)
ANTHROPOMETRIC CHARACTERISTICS			
Bodyheight [cm] (n=31) (range; mean±SD)	118-141; 128±6	120-141; 129±5	118-141; 128±7
Bodyweight [kg] (n=31) (range; mean±SD)	21-39; 28±4	23-33; 28±3	21-39; 28±5
WC [cm] (n=31) (range; mean±SD)	50-68; 59±4	55-67; 60±4	50-68; 58±5
HC [cm] (n=31) (range; mean±SD)	62-81; 70±5	62-80; 71±5	63-81; 69±5
AC [cm] (n=31) (range; mean±SD)	50-75; 62±6	54-70; 62±5	50-75; 63±6
WHR (n=31) (range; mean±SD)	0.77-0.96; 0.84±0.04	0.77-0.96; 0.85±0.05	0.78-0.91; 0.84±0.04
Percentiles (n=31)[4]:			
10th-90th P (normal weight)	27 (87%)	14 (87%)	13 (86%)
90th-97th P (overweight)	3 (10%)	2 (13%)	1 (7%)
>97th P (adipositas)	1 (3%)	0 (0%)	1 (7%)

Abbreviations: AC, abdominal circumference; BMI, body mass index; HC, hip circumference; n, sample size; P, percentile; SD, standard deviation; WC, waist circumference; WHR, waist-to-hip ratio.
[1] in some cases, sample sizes differ because of missing values in the participants' questionnaire. [2] n(female)=15; n(male)=15.
[3] n(female)=15; n(male)=14. [4] Percentiles according to Kormeyer-Hauschild et al. (2001)

Table 42. Data Children II (Phthalate analysis) (n=220)

	All	Males	Females
SEX	220 (100%)	126 (57%)	94 (43%)
AGE [years] (range; mean±SD)	7-15; 11±2	7-15; 11±2	8-14; 11±2
FEDERAL STATE (n=204)[1,3]			
Vienna	61 (30%)	33 (28%)	28 (32%)
Burgenland	56 (28%)	36 (31%)	20 (23%)
Lower Austria	27 (13%)	14 (12%)	13 (15%)
Styria	8 (4%)	3 (3%)	5 (6%)
Upper Austria	23 (11%)	13 (11%)	10 (11%)
Tyrol	29 (14%)	18 (15%)	11 (13%)
REGION (n=220)			
East Austria	168 (76%)	95 (75%)	73 (78%)
West Austria	52 (24%)	31 (25%)	21 (22%)
RESIDENTIAL AREA (n=201)[1,4]			
urban	50 (25%)	25 (22%)	25 (29%)
suburban	21 (10%)	13 (11%)	8 (9%)
rural	130 (65%)	76 (67%)	54 (62%)
ANTHROPOMETRIC CHARACTERISTICS			
Bodyheight [cm] (n=219)[1,2] (range; mean±SD)	116-187; 150±12	124-187; 150±13	116-172; 149±11
Bodyweight [kg] (n=219)[1,2] (range; mean±SD)	24-91; 45±14	24-91; 46±15	24-75; 43.3±12.1
WC [cm] (n=219)[1,2] (range; mean±SD)	49-90; 67±9	53-88; 68±9	49-90; 65±8
HC [cm] (n=219)[1,2] (range; mean±SD)	64-111; 83±10	64-111; 83±11	66-110; 82±10
AC [cm] (n=219)[1,2] (range; mean±SD)	53-106; 74±11	53-106; 74±11	54-100; 72±10
WHR (n=219)[1,2] (range; mean±SD)	0.6-1.0; 0.81-0.05	0.72-1.0; 0.82±0.05	0.6-0.93; 0.79±0.05
Percentiles (n=219)[1,2,5]:			
<3rd P (distinctive underweight)	4 (2%)	2 (2%)	2 (2%)
3rd-10th P (underweight)	6 (3%)	2 (2%)	4 (4.5%)
10th-90th P (normal weight)	149 (68%)	83 (66%)	66 (70%)
90th-97th P (overweight)	41 (18%)	23 (18%)	18 (19%)
>97th P (adipositas)	19 (9%)	15 (12%)	4 (4.5%)

Abbreviations: AC, abdominal circumference; BMI, body mass index; HC, hip circumference; n, sample size; SD, standard deviation; WC, waist circumference; WHR, waist-to-hip ratio.
[1] in some cases, sample sizes differ because of missing values in the participants' questionnaire.
[2] n(female)=94; n(male)=125
[3] n(female)=87; n(male)=117
[4] n(female)=97; n(male)=114
[5] Percentiles according to Kormeyer-Hauschild et al. (2001)

Among the study population groups Children I and Children II, overlaps in ages exist, because the groups consist of children of 1st to 2nd education level (Children I), and 3rd to 8th education level (Children II), respectively.

Table 43. Data Adults (Phthalate analysis) (n=272)

	All	Males	Females
SEX	272 (100%)	110 (40%)	162 (60%)
AGE [years] (range; mean±SD)	18-65; 39±14	18-64; 40±13	18-65; 38±14
FEDERAL STATE (n=268)[1,2]			
Vienna	27 (10%)	14 (13%)	13 (8%)
Burgenland	51 (19%)	27 (25%)	24 (15%)
Lower Austria	30 (11%)	15 (14%)	15 (9.5%)
Styria	27 (10%)	12 (11%)	15 (9.5%)
Upper Austria	13 (5%)	3 (3%)	10 (6%)
Salzburg	22 (8%)	10 (9%)	12 (8%)
Tyrol	96 (36%)	27 (25%)	69 (43%)
Vorarlberg	2 (1%)	0 (0%)	2 (1%)
REGION (n=271)[1,3]			
East Austria	138 (51%)	70 (64%)	68 (42%)
West Austria	133 (49%)	40 (36%)	93 (58%)
RESIDENTIAL AREA (n=270)[1,4]			
urban	105 (39%)	49 (45%)	56 (35%)
suburban	43 (16%)	20 (18%)	23 (14%)
rural	122 (45%)	41 (37%)	81 (51%)
ANTHROPOMETRIC CHARACTERISTICS			
Bodyheight [cm] (n=269)[1,5] (range; mean±SD)	145-194; 171±9	158-194; 178±7	145-182; 165±7
Bodyweight [kg] (n=269)[1,5] (range; mean±SD)	42-123; 72±15	55-123; 83±12	42-109; 65±11
BMI [kg/m^2] (n=269)[1,5] (range; mean±SD)	16.3-39.2; 25±4	19.2-39.2; 26±4	16.3-38.9; 24±4
WC [cm] (n=260)[1,6] (range; mean±SD)	61-120; 83±13	72-120; 91±11	61-113; 76±11
HC [cm] (n=269)[1,5] (range; mean±SD)	59-128; 100±9	89-121; 103±7	59-128; 98±10
AC [cm] (n=269)[1,5] (range; mean±SD)	66-129; 90±12	75-129; 95±11	66-127; 86±10
WHR (n=260)[1,6] (range; mean±SD)	0.62-1.2; 0.83±0.09	0.75-1.0; 0.89±0.07	0.62-1.2; 0.78±0.08

Abbreviations: AC, abdominal circumference; BMI, body mass index; HC, hip circumference; n, sample size; SD, standard deviation; WC, waist circumference; WHR, waist-to-hip ratio.

[1] in some cases, sample sizes differ because of missing values in the participants' questionnaire.

[2] n(female)=160; n(male)=108

[3] n(female)=161; n(male)=110

[4] n(female)=160; n(male)=110

[5] n(female)=160; n(male)=109

[6] n(female)=155; n(male)=105

Table 44. Data Elderly People (Phthalate analysis) (n=72)

	All	Males	Females
SEX	72 (100%)	34 (47%)	38 (53%)
AGE [years] (range; mean±SD)	64-81; 71±5	64-81; 72±5	65-79; 71±4
FEDERAL STATE (n=72)			
Vienna	15 (21%)	5 (15%)	10 (26%)
Burgenland	2 (3%)	2 (6%)	0 (0%)
Lower Austria	9 (12%)	3 (9%)	6 (16%)
Styria	7 (10%)	3 (9%)	4 (11%)
Upper Austria	6 (8%)	6 (18%)	0 (0%)
Salzburg	18 (25%)	8 (23%)	10 (26%)
Tyrol	15 (21%)	7 (20%)	8 (21%)
REGION (n=71)[1,2]			
East Austria	33 (46%)	13 (39%)	20 (53%)
West Austria	38 (54%)	20 (61%)	18 (47%)
RESIDENTIAL AREA (n=70)[1,3]			
urban	46 (66%)	19 (58%)	27 (73%)
suburban	11 (16%)	5 (15%)	6 (16%)
rural	13 (18%)	9 (27%)	4 (11%)
ANTHROPOMETRIC CHARACTERISTICS			
Bodyheight [cm] (n=71)[1,2] (range; mean±SD)	139-185; 166±7	162-185; 174±6	139-176; 159±8
Bodyweight [kg] (n=71)[1,2] (range; mean±SD)	54-112; 76±12	67-112; 81±11	54-103; 72±12
BMI [kg/m^2] (n=71)[1,2] (range; mean±SD)	22.3-44.6; 28±4	22-35; 27±3	22.3-44.6; 29±5
WC [cm] (n=71)[1,2] (range; mean±SD)	72-123; 95±11	83-123; 99±10	72-122; 92±12
HC [cm] (n=71)[1,2] (range; mean±SD)	90-162; 106±11	93-162; 104±12	90-137; 107±9
AC [cm] (n=71)[1,2] (range; mean±SD)	77-129; 101±10	88-129; 102±9	77-125; 100±11
WHR (n=71)[1,2] (range; mean±SD)	0.65-1.1; 0.90±0.09	0.65-1.11; 0.95±0.08	0.74-1.0; 0.85±0.06

Abbreviations: AC, abdominal circumference; BMI, body mass index; HC, hip circumference; n, sample size; SD, standard deviation; WC, waist circumference; WHR, waist-to-hip ratio.
[1] in some cases, sample sizes differ because of missing values in the participants' questionnaire.
[2] n(female)=38; n(male)=33
[3] n(female)=37; n(male)=33

3.1.2 Urinary phthalate metabolite concentrations

Fourteen phthalate metabolite concentrations (MEP, MEHP, 5oxo-MEHP, 5OH-MEHP, 5cx-MEPP, MBzP, MnBP, MiBP, MnOP, MCHP, 3cx-MPP, MiNP, MiDP and MnPeP) were analysed in urine via HPLC-MS/MS in 2012. Detection rates (DR) differed related to the different metabolites. Whereas metabolites such as 5oxo-MEHP, 5OH-MEHP, 5cx-MEPP, MBzP, MnBP, MiBP and 3cx-MPP were found in the majority of the samples, others such as MCHP, MiNP, DiDP, MnOP and MnPeP were detected only in a small number of samples. For the metabolites MiNP and MiDP, which are the primary metabolites of DiNP and DiDP, respectively, metabolism studies have shown that these metabolites are eliminated via urine only in small concentrations because of their further metabolism into secondary oxidised metabolites in organisms. Therefore, the analysed primary metabolites are not accurate biomarkers for the identification of exposure to the parent compounds. Nevertheless, they are still listed in the following tables and figures.

Analysed urinary phthalate metabolite concentrations were additionally creatinine-adjusted (cf. Chapter 2.5.1) for the recognition of differences in individual renal function and body mass, as well as in sex, age and ethnicity. The levels of urinary creatinine of each sample were provided by the IfEW who analysed creatinine concentrations photometrically.

The phthalate metabolite concentrations that were analysed followed no normal distribution. For comparisons between the different study population groups, medians and 95th percentiles (P95) were used. Comparing the medians of the different metabolites, metabolite levels generally decreased with increasing age (in children and adults). Participants from the group of Elderly People showed slightly higher median concentrations than those from the group of Adults. An exception was MEP, where an increase with increasing age was identified (cf. Figure 26). Similar distributions were shown for P95 values for MEP, as well as MEHP, MBzP and MiBP compared with median values. In the group of Elderly People, P95 values of 5oxo-MEHP were similar to the values of children, and 5cx-MEPP exhibited the highest P95 values among this study population group (cf. Figure 25).

In the following section, results of phthalate metabolite analysis of urine in children, adults and elderly people (in µg/l), as well as creatinine-adjusted concentrations (in g/g) are presented (Table 45 - Table 52). Furthermore, Figure 25 and Figure 26 contain distributions of measured metabolites (P95 values and medians, respectively) among all study population groups.

3.1.2.1 Children I

Table 45. Concentrations of creatinine-unadjusted urinary phthalate metabolites [µg/l] in the group of Children I (age 6-8) (n=31)

Phthalate metabolites	Range [µg/l]	Mean±SD [µg/l]	Median [µg/l]	P95 [µg/l]	DR [%]	LOD [µg/l]
MEP	n.d.-447	49.8±91.1	15.7	308	96.8	2.46
MEHP	n.d.-11.2	1.8±2.7	<LOQ	10.1	58.1	0.69
5oxo-MEHP	<LOQ-26.2	10.0±5.8	8.7	21.4	100	0.56
5OH-MEHP	<LOQ-40.4	13.8±8.9	10.8	34.3	100	0.79
5cx-MEPP	2.3-57.4	23.5±14.2	22.6	52.5	100	0.46
MBzP	n.d.-53.3	9.6±12.4	5.3	45.3	96.8	0.59
MnBP	2.0-69.6	28.1±14.9	26.5	65.0	100	0.53
MiBP	5.6-177	61.2±38.9	53.6	156	100	0.59
MnOP	n.d.-<LOQ	<LOQ	n.d.	<LOQ	12.9	0.45
MCHP	n.d.-2.3	<LOQ	n.d.	<LOQ	3.2	0.51
3cx-MPP	<LOQ-14.2	4.6±3.2	22.6	11.8	100	1.6
MiNP	n.d.-12.7	<LOQ	n.d.	5.1	3.2	0.47
MiDP	n.d.-<LOQ	<LOQ	n.d.	<LOQ	3.2	0.47
MnPeP	n.d.-<LOQ	<LOQ	n.d.	<LOQ	6.5	0.55

Abbreviations: DR, detection rate; LOD, limit of detection; LOQ, limit of quantitation; n, sample size; n.d., not detected; P95, 95th percentile; SD, standard deviation. *Notes:* LOD=LOQ/2.

Table 46. Concentrations of creatinine-adjusted urinary phthalate metabolites [µg/g] in the group of Children I (age 6-8) (n=30)

Phthalate metabolites	Range [µg/g]	Mean±SD [µg/g]	Median [µg/g]	P95 [µg/g]
MEP	n.d.-336	55.6±86.0	20.0	331
MEHP	n.d.-17.4	2.9±4.4	1.3	14.5
5oxo-MEHP	1.8-62.3	17.1±14.9	12.9	60.0
5OH-MEHP	2.5-99.4	23.8±22.1	17.5	85.6
5cx-MEPP	7.1-135	39.1±31.9	30.7	133
MBzP	n.d.-66.5	16.3±19.5	7.0	64.1
MnBP	6.1-516	63.2±98.1	33.0	371
MiBP	17.5-494	122±127	70.2	461
MnOP	n.d.-2.3	7.6±0.52	n.d.	1.8
MCHP	n.d.-1.2	<LOQ	n.d.	<LOQ
3cx-MPP	<LOQ-40.5	7.6±7.5	5.2	30.7
MiNP	n.d.-12.3	<LOQ	n.d.	5.6
MiDP	n.d.-<LOQ	n.d.	n.d.	n.d.
MnPeP	n.d.-2.3	<LOQ	n.d.	1.3

Abbreviations: DR, detection rate; LOD, limit of detection; LOQ, limit of quantitation; n, sample size; n.d., not detected; P95, 9th percentile; SD, standard deviation. *Notes:* LOD=LOQ/2.

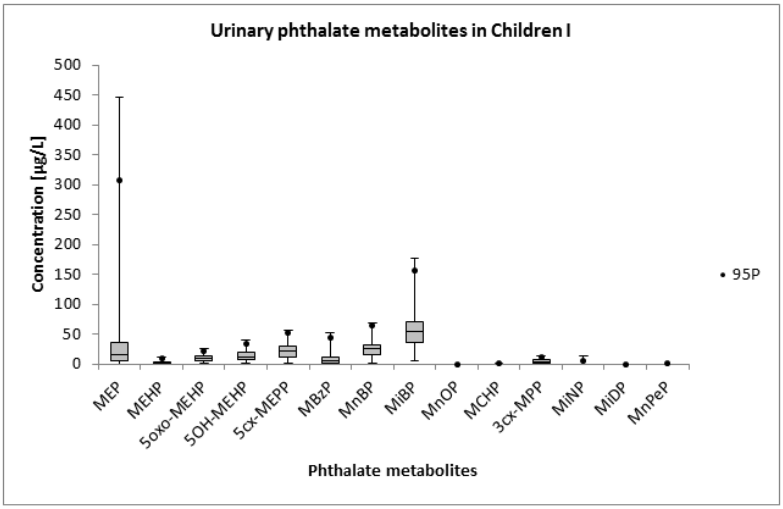


Figure 21. Distributions of creatinine-unadjusted urinary phthalate metabolites [µg/l] in the group of Children I (age 6-8) (n=31)

3.1.2.2 Children II

Table 47. Concentrations of creatinine-unadjusted urinary phthalate metabolites [µg/l] in the group of Children II (age 7-15) (n=220)

Phthalate metabolites	Range [µg/l]	Mean±SD [µg/l]	Median [µg/l]	P95 [µg/l]	DR [%]	LOD [µg/l]
MEP	n.d.-463	35.1±57.4	19.5	108	98.6	2.46
MEHP	n.d.-20.1	2.1±3.0	<LOQ	8.0	65.5	0.69
5oxo-MEHP	n.d.-57.3	6.0±7.3	3.0	19.8	99.1	0.56
5OH-MEHP	n.d.-80.0	8.1±10.0	4.0	27.4	99.1	0.79
5cx-MEPP	2.6-102	20.7±17.0	15.5	56.5	100	0.46
MBzP	n.d.-57.1	5.5±8.1	2.6	20.6	94.1	0.59
MnBP	n.d.-87.7	16.9±14.0	12.0	47.2	99.5	0.53
MiBP	n.d.-207	47.2±39.7	35.0	131	99.5	0.59
MnOP	n.d.-3.4	<LOQ	n.d.	<LOQ	6.4	0.45
MCHP	n.d.-5.5	<LOQ	n.d.	1.3	15.5	0.51
3cx-MPP	n.d.-62.5	4.0±7.6	<LOQ	17.2	70.5	1.6
MiNP	n.d.-5.4	<LOQ	n.d.	1.7	17.7	0.47
MiDP	n.d.-1.0	<LOQ	n.d.	<LOQ	23.6	0.47
MnPeP	n.d.-4.5	<LOQ	n.d.	<LOQ	5.5	0.55

Abbreviations: DR, detection rate; LOD, limit of detection; LOQ, limit of quantitation; n, sample size; n.d., not detected; P95, 95th percentile; SD, standard deviation. *Notes:* LOD=LOQ/2.

Table 48. Concentrations of creatinine-adjusted urinary phthalate metabolites [µg/g] in the group of Children II (age 7-15) (n=215)

Phthalate metabolites	Range [µg/g]	Mean±SD [µg/g]	Median [µg/g]	P95 [µg/g]
MEP	n.d.-1645	40.0±117	20.7	114
MEHP	n.d.-23.2	2.1±3.2	0.94	8.5
5oxo-MEHP	n.d.-93.9	6.8±10.2	3.3	24.8
5OH-MEHP	n.d.-131	63.8±115	31.1	213
5cx-MEPP	2.7-179	23.2±25.0	15.0	67.3
MBzP	n.d.-52.9	6.0±8.4	2.5	25.7
MnBP	n.d.-699	23.4±53.0	12.0	73.1
MiBP	n.d.-1086	63.8±115	31.1	213
MnOP	n.d.-3.6	<LOQ	n.d.	<LOQ
MCHP	n.d.-6.9	<LOQ	n.d.	1.2
3cx-MPP	n.d.-206	5.5±19.1	<LOQ	16.9
MiNP	n.d.-5.7	<LOQ	n.d.	1.7
MiDP	n.d.-2.2	<LOQ	n.d.	<LOQ
MnPeP	n.d.-3.4	<LOQ	n.d.	<LOQ

Abbreviations: DR, detection rate; LOD, limit of detection; LOQ, limit of quantitation; n, sample size; n.d., not detected; P95, 95th percentile; SD, standard deviation. *Notes:* LOD=LOQ/2.

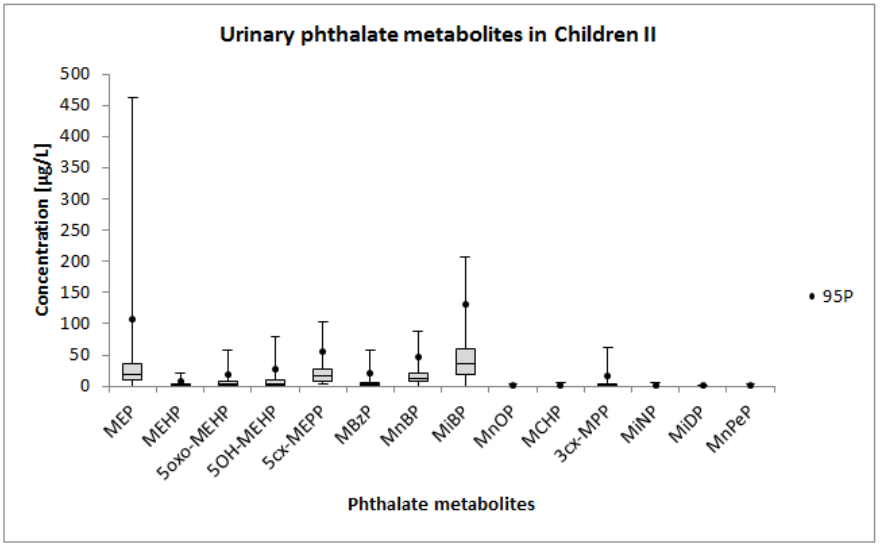


Figure 22. Distributions of creatinine-unadjusted urinary phthalate metabolites [µg/l] in the group of Children II (age 7-15) (n=220)

3.1.2.3 Adults

Table 49. Concentrations of creatinine-unadjusted urinary phthalate metabolites [µg/l] in the group of Adults (age 18-65) (n=272)

Phthalate metabolites	Range [µg/l]	Mean±SD [µg/l]	Median [µg/l]	P95 [µg/l]	DR [%]	LOD [µg/l]
MEP	n.d.-1088	87.4±150	31.9	400	98.2	2.46
MEHP	n.d.-17.2	<LOQ	n.d.	3.6	36.4	0.69
5oxo-MEHP	n.d.-29.3	2.1±3.0	1.2	7.9	93.0	0.56
5OH-MEHP	n.d.-46.6	3.1±4.6	1.8	10.7	93.8	0.79
5cx-MEPP	n.d.-219	11.4±16.8	7.8	29.0	99.3	0.46
MBzP	n.d.-40.2	2.6±3.9	1.4	9.8	86.4	0.59
MnBP	n.d.-73.7	12.0±12.3	7.9	40.7	99.3	0.53
MiBP	n.d.-248	33.2±31.8	24.3	109	96.0	0.59
MnOP	n.d.-2.0	<LOQ	n.d.	<LOQ	7.7	0.45
MCHP	n.d.-3.5	<LOQ	n.d.	1.4	35.7	0.51
3cx-MPP	n.d.-188	4.0±13.3	<LOQ	19.0	58.1	1.6
MiNP	n.d.-5.4	<LOQ	n.d.	1.4	12.1	0.47
MiDP	n.d.-0.91	<LOQ	n.d.	<LOQ	11.4	0.47
MnPeP	n.d.-2.9	<LOQ	n.d.	n.d.	4.4	0.55

Abbreviations: DR, detection rate; LOD, limit of detection; LOQ, limit of quantitation; n, sample size; n.d., not detected; P95, 95th percentile; SD, standard deviation. *Notes:* LOD=LOQ/2.

Table 50. Concentrations of creatinine-adjusted urinary phthalate metabolites [µg/g] in the group of Adults (age 18-65) (n=269)

Phthalate metabolites	Range [µg/g]	Mean±SD [µg/g]	Median [µg/g]	P95 [µg/g]
MEP	n.d.-1276	80.9±147	28.6	335
MEHP	n.d.-6.1	<LOQ±1.2	n.d.	3.4
5oxo-MEHP	n.d.-18.0	1.8±2.3	<LOQ	6.3
5OH-MEHP	n.d.-28.6	2.7±3.6	1.6	9.6
5cx-MEPP	n.d.-131	9.3±11.6	6.0	24.3
MBzP	n.d.-33.5	2.1±3.1	1.3	7.1
MnBP	n.d.-78.4	10.7±11.4	6.5	35.3
MiBP	n.d.-497	32.4±43.3	21.2	104
MnOP	n.d.-1.3	<LOQ	n.d.	<LOQ
MCHP	n.d.-5.2	<LOQ	n.d.	1.3
3cx-MPP	n.d.-122	3.9±12.3	<LOQ	17.6
MiNP	n.d.-44.5	<LOQ	n.d.	1.2
MiDP	n.d.-3.1	<LOQ	n.d.	<LOQ
MnPeP	n.d.-2.2	<LOQ	n.d.	n.d.

Abbreviations: DR, detection rate; LOD, limit of detection; LOQ, limit of quantitation; n, sample size; n.d., not detected; P95, 95th percentile; SD, standard deviation. *Notes:* LOD=LOQ/2.

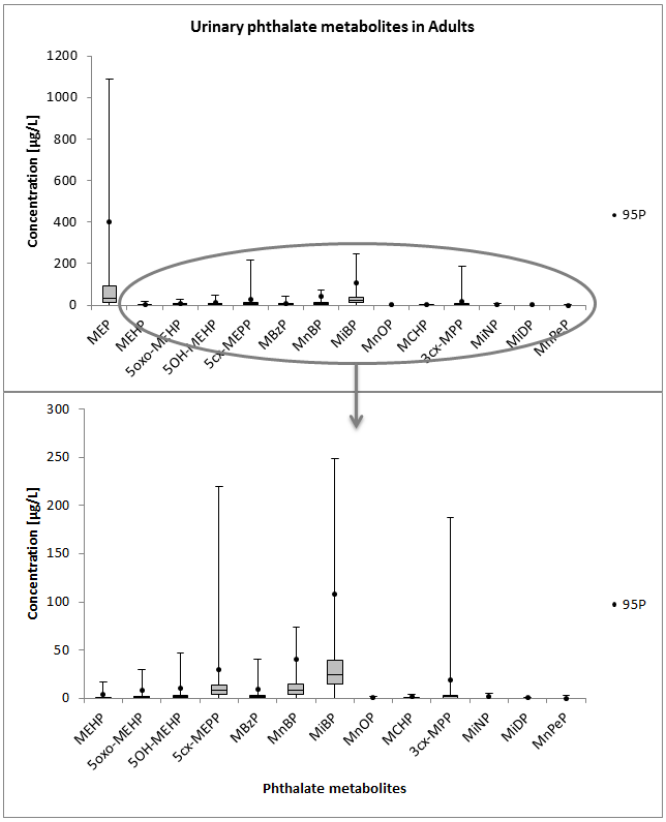


Figure 23. Distributions of creatinine-unadjusted urinary phthalate metabolites [µg/l] in the group of Adults (age 18-65) (n=272)

3.1.2.4 Elderly People

Table 51. Concentrations of creatinine-unadjusted urinary phthalate metabolites [µg/l] in the group of Elderly People (age 64-81) (n=72)

Phthalate metabolites	Range [µg/l]	Mean±SD [µg/l]	Median [µg/l]	P95 [µg/l]	DR [%]	LOD [µg/l]
MEP	n.d.-1188	170±381	38.0	1188	98.6	2.46
MEHP	n.d.-11.8	<LOQ	n.d.	6.6	36.1	0.69
5oxo-MEHP	n.d.-55.4	4.2±8.9	1.6	20.1	93.1	0.56
5OH-MEHP	n.d.-76.2	6.9±12.0	3.3	31.1	98.6	0.79
5cx-MEPP	1.0-134	18.6±25.8	10.0	80.5	100	0.46
MBzP	n.d.-16.6	2.9±4.0	1.3	12.7	81.9	0.59
MnBP	n.d.-84.5	16.7±17.5	10.4	57.0	97.2	0.53
MiBP	2.5-152	36.3±30.7	25.7	111	100	0.59
MnOP	n.d.-<LOQ	<LOQ	n.d.	<LOQ	6.9	0.45
MCHP	n.d.-1.0	<LOQ	n.d.	<LOQ	6.9	0.51
3cx-MPP	n.d.-38.4	4.0±5.9	<LOQ	16.2	86.1	1.6
MiNP	n.d.-2.4	<LOQ	n.d.	0.95	15.3	0.47
MiDP	n.d.-1.1	<LOQ	n.d.	<LOQ	22.2	0.47
MnPeP	n.d.-2.0	<LOQ	n.d.	n.d.	2.8	0.55

Abbreviations: DR, detection rate; LOD, limit of detection; LOQ, limit of quantitation; n, sample size; n.d., not detected; P95, 95th percentile; SD, standard deviation. *Notes:* LOD=LOQ/2.

Table 52. Concentrations of creatinine-adjusted urinary phthalate metabolites [µg/g] in the group of Elderly People (age 64-81) (n=69)

Phthalate metabolites	Range [µg/g]	Mean±SD [µg/g]	Median [µg/g]	P95 [µg/g]
MEP	n.d.-3394	214±551	31.7	1012
MEHP	n.d.-11.1	<LOQ	n.d.	6.6
5oxo-MEHP	n.d.-52.3	3.9±7.9	1.6	17.4
5OH-MEHP	n.d.-71.9	6.6±10.9	2.9	31.0
5cx-MEPP	1.8-150	18.7±26.1	9.2	71.3
MBzP	n.d.-14.3	2.5±3.2	1.4	12.4
MnBP	n.d.-98.4	17.0±18.3	11.7	53.9
MiBP	4.6-241	41.1±44.8	27.3	152
MnOP	n.d.-1.0	<LOQ	n.d.	<LOQ
MCHP	n.d.- <LOQ	<LOQ	n.d.	<LOQ
3cx-MPP	n.d.-36.2	4.3±6.2	<LOQ	21.3
MiNP	n.d.-5.5	<LOQ	n.d.	1.0
MiDP	n.d.-4.4	<LOQ	n.d.	1.3
MnPeP	n.d.-2.0	<LOQ	n.d.	n.d.

Abbreviations: DR, detection rate; LOD, limit of detection; LOQ, limit of quantitation; n, sample size; n.d., not detected; P95, 95th percentile; SD, standard deviation. *Notes:* LOD=LOQ/2.

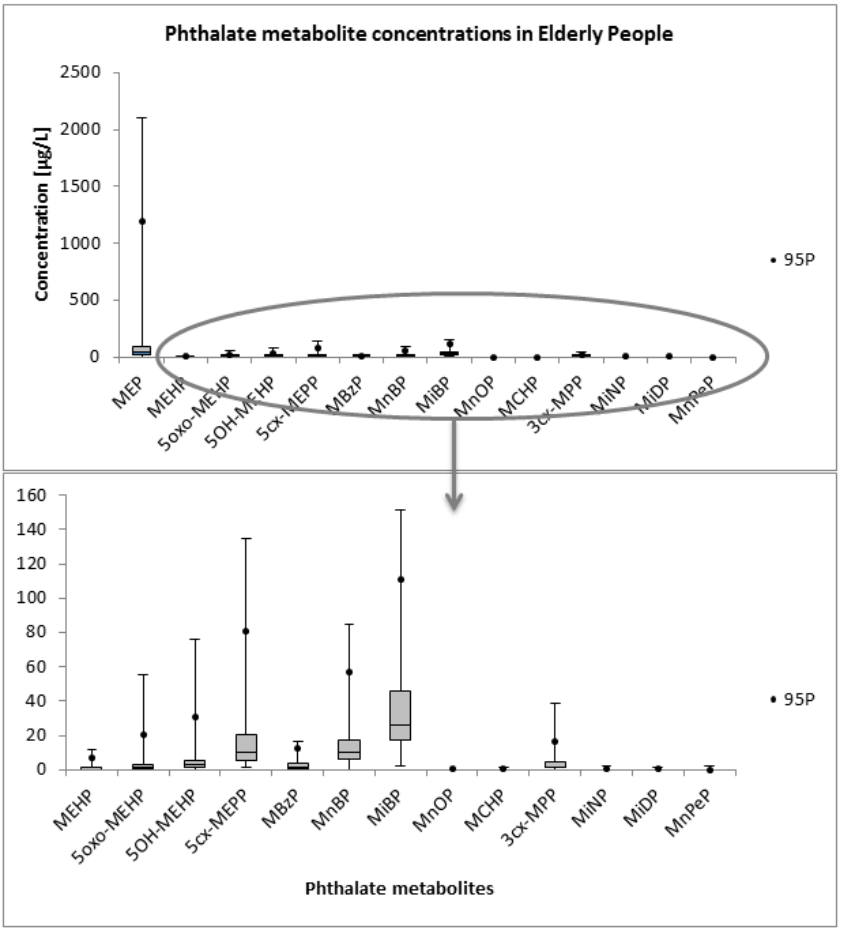


Figure 24. Distributions of creatinine-unadjusted urinary phthalate metabolites [µg/l] in the group of Elderly People (age 64-81) (n=72)

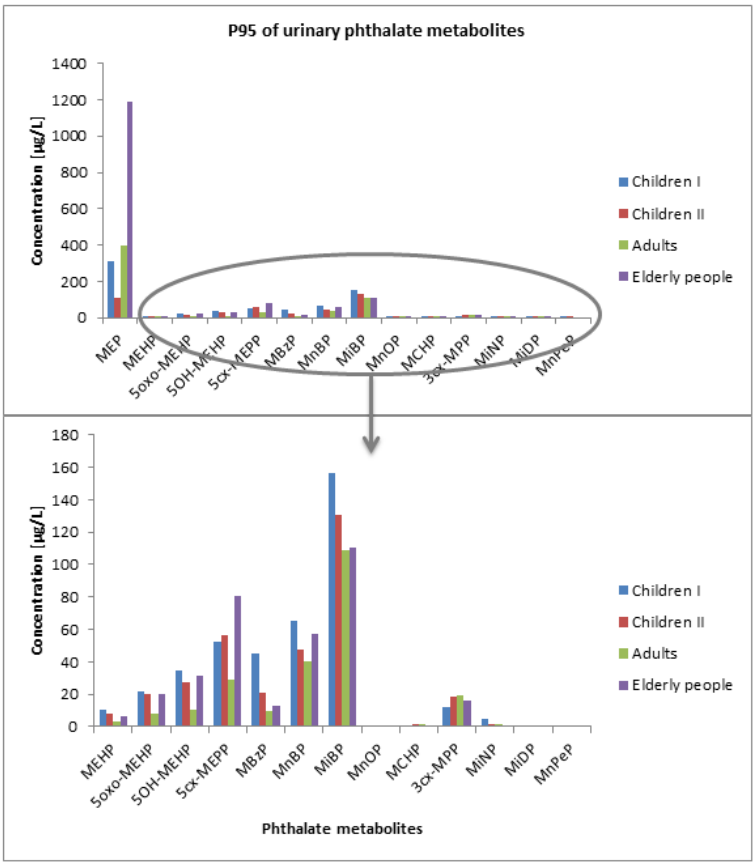


Figure 25. 95th percentiles of creatinine-unadjusted urinary phthalate metabolite concentrations [µg/l] in the groups of Children I (n=31), Children II (n=220), Adults (n=272) and Elderly People (n=72)

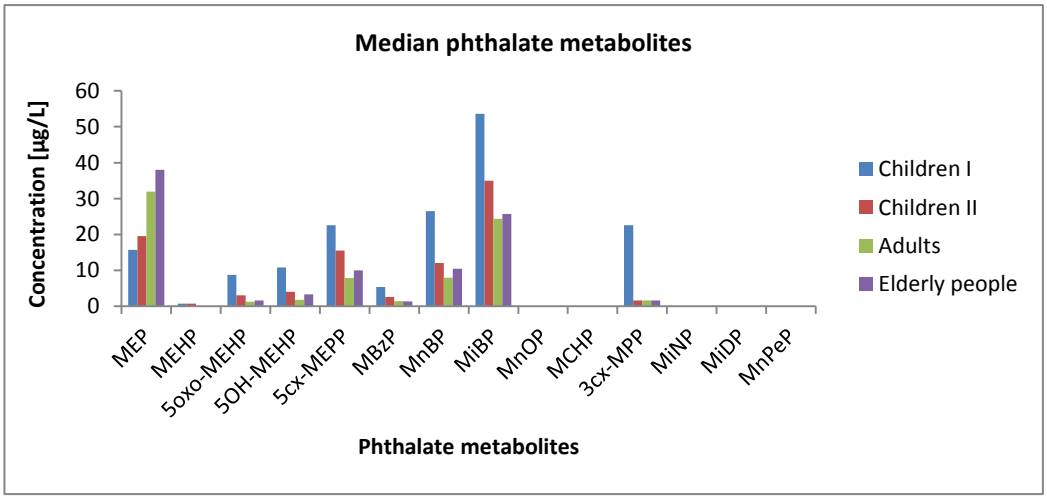


Figure 26. Median urinary creatinine-unadjusted phthalate metabolite concentrations [µg/l] in the groups of Children I (n=31), Children II (n=220), Adults (n=272) and Elderly People (n=72)

Among the total study population, statistically significant positive correlations (Spearman correlation) between several analysed phthalate metabolites existed (Table

53), with most of the correlations being significant at a significance level of 0.01. Thus, participants were not solely exposed to single phthalates, but showed a generally high phthalate exposure to nearly all investigated phthalates.

Table 53. Correlations (Spearman, two-sided) between creatinine-unadjusted phthalate metabolites in all samples (n=595)

Spearman's correlation coefficients														
	MEP	MEHP	5oxo-MEHP	OH-MEHP	5cx-MEPP	MBzP	MnBP	MiBP	MnOP	MCHP	3cx-MPP	MnPeP	MiNP	MiDP
MEP		-0.015	0.030	0.067	0.129**	0.034	0.120**	0.130**	0.023	0.102*	0.073	-0.010	0.026	0.053
MEHP	-0.015		0.589**	0.566**	0.527**	0.442**	0.471**	0.464**	0.063	0.129**	0.176**	0.139**	-0.045	-0.079
5oxo-MEHP	0.030	0.589**		0.939**	0.830**	0.637**	0.626**	0.477**	0.061	0.108**	0.331**	0.122**	-0.072	0.022
5OH-MEHP	0.067	0.566**	0.939**		0.814**	0.626**	0.627**	0.461**	0.055	0.109**	0.344**	0.123**	-0.062	0.000
5cx-MEPP	0.129**	0.527**	0.830**	0.814**		0.569**	0.548**	0.420**	0.047	0.107**	0.384**	0.115**	-0.054	0.070
MBzP	0.034	0.442**	0.637**	0.626**	0.569**		0.628**	0.444**	-0.001	0.144**	0.269**	0.152**	-0.92*	-0.069
MnBP	0.120**	0.471**	0.626**	0.627**	0.548**	0.628**		0.715**	0.035	0.129**	0.374**	0.051	-0.047	-0.045
MiBP	0.130**	0.464**	0.477**	0.461**	0.420**	0.444**	0.715**		0.046	0.149**	0.240**	0.099*	-0.037	-0.007
MnOP	0.023	0.063	0.061	0.055	0.047	-0.001	0.035	0.046		0.046	0.068	0.027	-0.020	-0.054
MCHP	0.102*	0.129**	0.108**	0.109**	0.107**	0.144**	0.129**	0.149**	0.046		0.028	0.063	-0.084*	-0.167**
3cx-MPP	0.073	0.176**	0.331**	0.344**	0.384**	0.269**	0.374**	0.240**	0.068	0.028		-0.043	-0.017	0.129**
MnPeP	-0.010	0.139**	0.122**	0.123**	0.115**	0.152**	0.051	0.099*	0.027	0.063	-0.043		-0.038	-0.056
MiNP	0.026	-0.045	-0.072	-0.062	-0.054	-0.092*	-0.047	-0.037	-0.020	-0.084*	-0.017	-0.038		0.001
MiDP	0.053	-0.079	0.022	0.000	0.070	-0.069	-0.045	-0.007	-0.054	-0.167**	0.129**	-0.056	0.001	

* Correlation is significant at 0.05 level (2-tailed)
** Correlation is significant at 0.01 level (2-tailed)

3.1.3 Comparison with other study results

3.1.3.1 International studies

Phthalate exposure in different populations from several countries worldwide has been investigated in a multitude of scientific studies conducted in recent decades. In Appendix B.1, data on urinary phthalate metabolite concentrations provided from different studies are illustrated (tables are not exhaustive).

Figure 27 shows the median urinary DEHP metabolite concentrations in adults from different studies. 2cx-MMHP was analysed in some cases, but not in the present study. Therefore, it is included in the figure for completeness without further discussion. Since 2002, the urinary levels of several DEHP metabolites have decreased in several countries. Measured DEHP metabolite concentrations in the present study were lower than those identified in previous studies. Median 5cx-MEPP levels in Austria (Adults: 7.8 µg/l, Elderly People: 10.0 µg/l) were similar to those found in Denmark in 2011 (8.2 µg/l). Also, among children, a decline of DEHP metabolite concentrations (except for 5cx-MEPP in Egypt, which is approximately twice as high) has been identified in recent years (Figure 28). In the present study, 5cx-MEPP showed the highest urinary levels among the DEHP metabolites analysed, which corresponds with findings from other

studies. Compared with other results, the findings of the present study in Austrian children from the group of Children II (15.5 µg/l) were rather comparable to findings from Denmark in 2011 (15.0 µg/l).

Median urinary MEP levels in different adult study populations are given in Figure 29. Findings in Austrian adults and elderly people (32 and 38 µg/l, respectively) were similar to those from Sweden in 2001 (35 µg/l), France in 2007 (44 µg/l) and Denmark in 2011 (29 µg/l). The highest MEP concentrations were generally found in the USA (1988-1994: 305 µg/l, 1996-1997: 211 µg/l, 1998-2002: 380 µg/l, 2000-2003: 145 µg/l and 2003-2004: 208 µg/l). Similar distributions were shown for children (Figure 31): Austrian children exhibited MEP excretion levels (Children I: 15.7 µg/l, Children II: 19.5 µg/l) comparable to those of Danish children (2008-2009: 16.6 µg/l, 2011: 20.0 µg/l). The highest levels were reported in studies conducted in the USA, and were equal to those of adults.

Median urinary MnBP concentrations in Austrian adults and elderly people were lower than those reported in other studies (Figure 31). The highest median value was found in Germany in 1988-2003 (112 µg/l). In the Children I group (with a median MnBP level of 26.5 µg/l), findings were similar to results from Canada in 2007-2009 (33.1 µg/l) and Denmark in 2011 (32.0 µg/l) (Figure 32). However, MnBP concentrations in Austrian children were lower than levels from other countries.

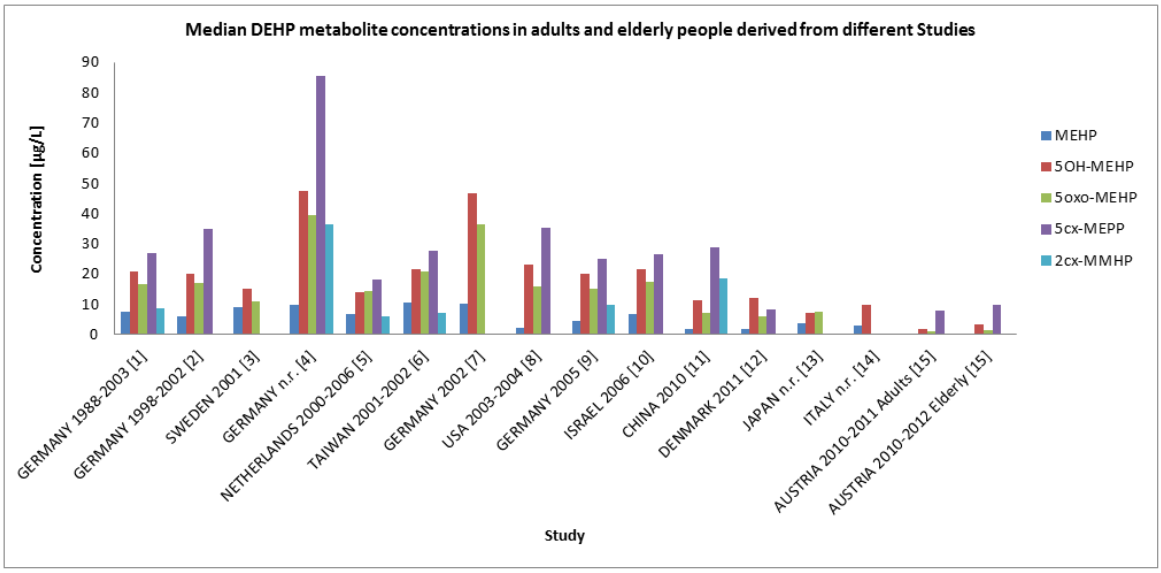
Median urinary MiBP concentrations in adult populations were lower in the USA. The highest median level was found in China in 2010 (61 µg/l). In the present study, the groups of Adults and Elderly People exhibited higher MiBP concentrations (about 25 µg/l for both groups) than adults from the USA in 1998-2004 (6.2 µg/l), Sweden in 2001 (16.0 µg/l), Taiwan in 2001-2002 (10.3 µg/l) and Israel in 2006 (15.6 µg/l), but lower concentrations than adult populations from Germany in 1988-2003 (34.5 µg/l), the Netherlands in 2002-2006 (42.0 µg/l), Germany in 2005 (36.1 µg/l), France in 2007 (53.7 µg/l), China in 2010 (61.0 µg/l) and Denmark in 2011 (36 µg/l). These results lead to the assumption that Austrian adults and elderly people were generally less exposed to MiBP than adults from other European countries (Figure 33). Several studies investigating MiBP concentrations in the urine of children have been conducted in Denmark. Median urinary MiBP levels decreased between 2006 and 2011 (Figure 34) and the results of Austrian children from the Children I group in 2010-2011 were equal to those published for Denmark in 2011 (54 µg/l).

Median urinary MBzP levels in Austrian adults (1.4 µg/l) and elderly people (1.3 µg/l) were similar to those found in Germany in 2002 (1.2 µg/l) (Figure 35). Compared to

other countries, levels were lower. The highest levels were found in the USA (1988-1994: 21.2 µg/l, 1998-2002: 31.5 µg/l, 1999-2006: 22 µg/l, 2003-2004: 7.5 µg/l, 2004-2009: 17.4 µg/l) and in the Netherlands in 2002-2006 (21.0 µg/l). In Austrian children, median MBzP concentrations in urine were lower (Children I: 5.3 µg/l, Children II: 2.6 µg/l) compared to other study results, except for Egypt in 2009, where even lower levels were reported (rural: 0.4 µg/l, urban: 2.2 µg/l). In the group of Children I, levels were almost similar to findings from Denmark in 2011 (7.0 g/l) (Figure 36).

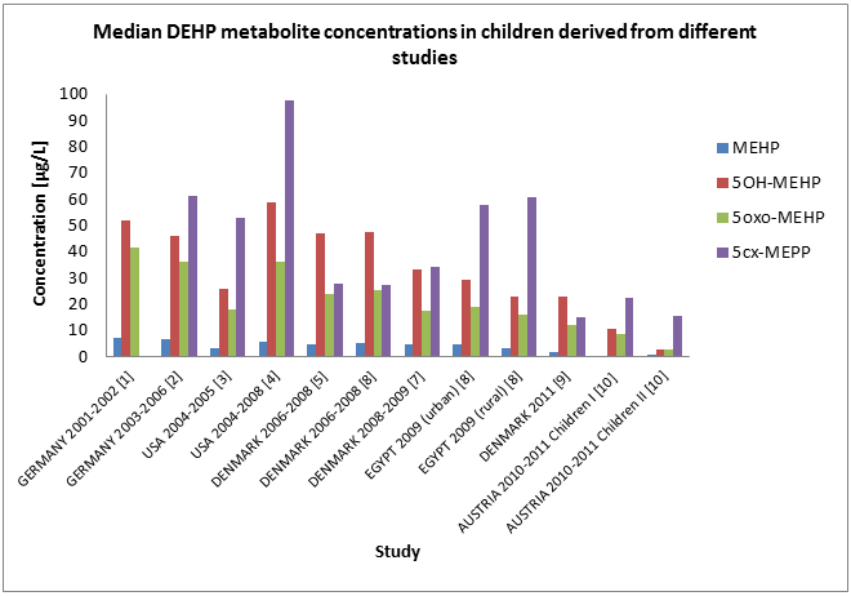
Median MnOP levels in the Austrian population were also similar to other findings. Overall, detection rates were low, as were analysed concentrations.

Generally, findings (median concentrations) from population groups investigated in the present study best fit with findings from Denmark in the same timeframe of sample collection for most of the phthalate metabolites analysed. Summing up, median urinary excretion levels of 5cx-MEPP and MEP in adults, and of 5cx-MEPP, MEP, MnBP, MiBP and MBzP in children were quiet similar to Danish results.



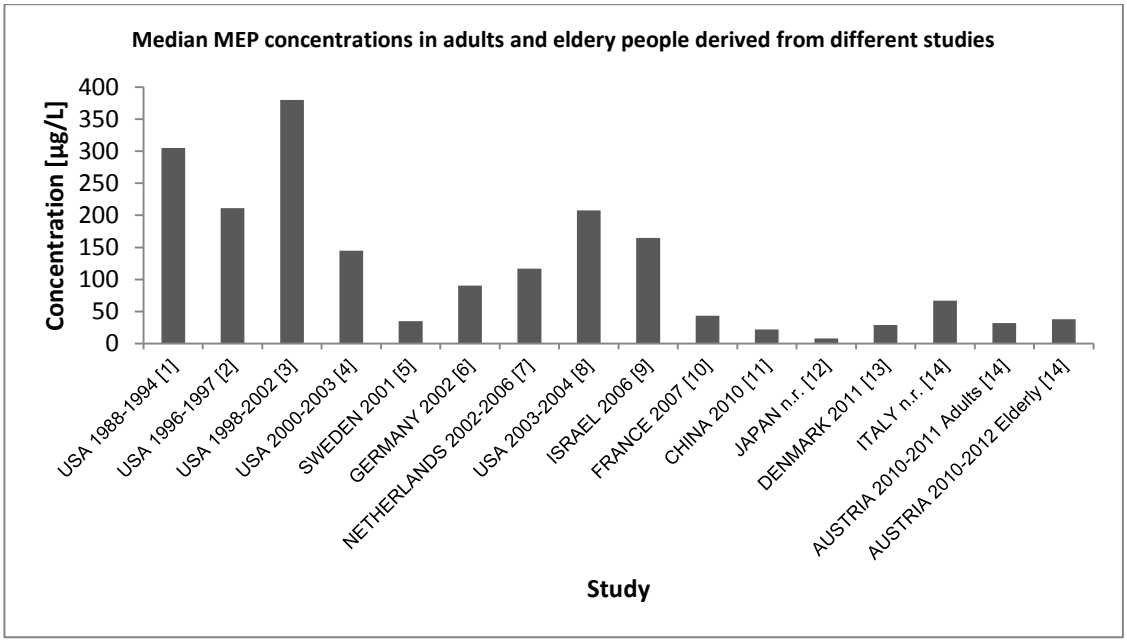
Abbreviations: n.r., not reported. *Notes:* corresponding data are given in Table 134 of Appendix B.1.
References: [1] Wittassek et al. (2007b); [2] Wolff et al. (2008); [3] Högberg et al. (2009); [4] Preuss, Koch and Angerer (2005); [5] Ye et al. (2008); [6] Lin et al. (2011) (pregnant women); [7] Koch et al. (2003); [8] Colacino, Harris and Schlecter (2010); [9] Fromme et al. (2007); [10] Berman et al. (2009); [11] Guo, Wu and Kannan (2011); [12] Frederiksen et al. (2013); [13] Suzuki et al. (2012) (pregnant women); [14] Tranfo et al. (2013); [15] this study.

Figure 27. Median creatinine-unadjusted urinary DEHP metabolites concentrations (MEHP, 5OH-MEHP, 5oxo-MEHP, 5cx-MEPP, and 2cx-MMHP) [µg/l] in different study populations of adults and elderly people from several countries between 1988 and 2012 compared with the results of this study



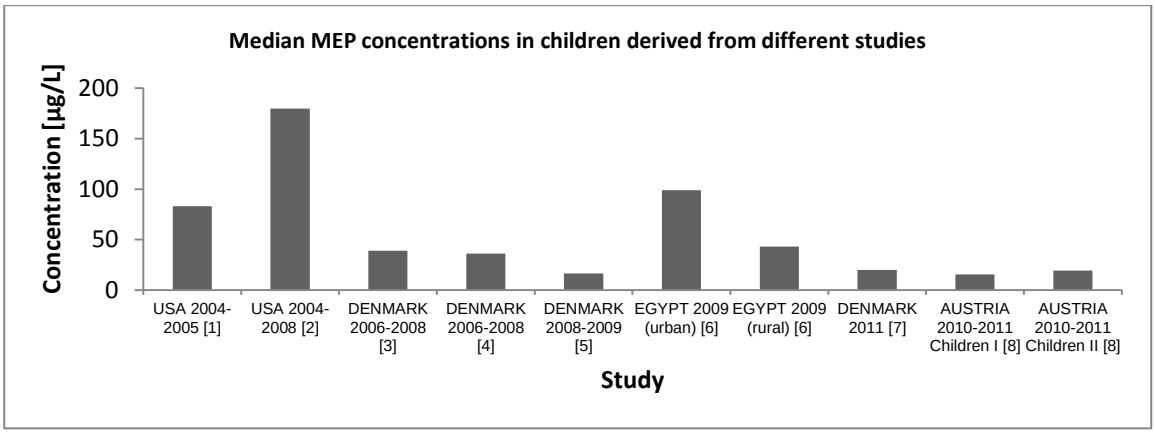
Notes: corresponding data are given in Table 135 of Appendix B.1. *References:* [1] Becker et al. (2004); [2] Becker et al. (2009); [3] Wolff et al. (2007) (females); [4] Teitelbaum et al. (2012); [5] Frederiksen et al. (2012) (females); [6] Mieritz et al. (2012) (males); [7] Langer et al. (2014); [8] Colacino et al. (2011) (premenstrual females); [9] Frederiksen et al. (2013); [10] this study.

Figure 28. Median creatinine-unadjusted urinary DEHP metabolites concentrations (MEHP, 5OH-MEHP, 5oxo-MEHP, and 5cx-MEPP) [µg/l] in different study populations of children from several countries between 2001 and 2011 compared with the results of this study



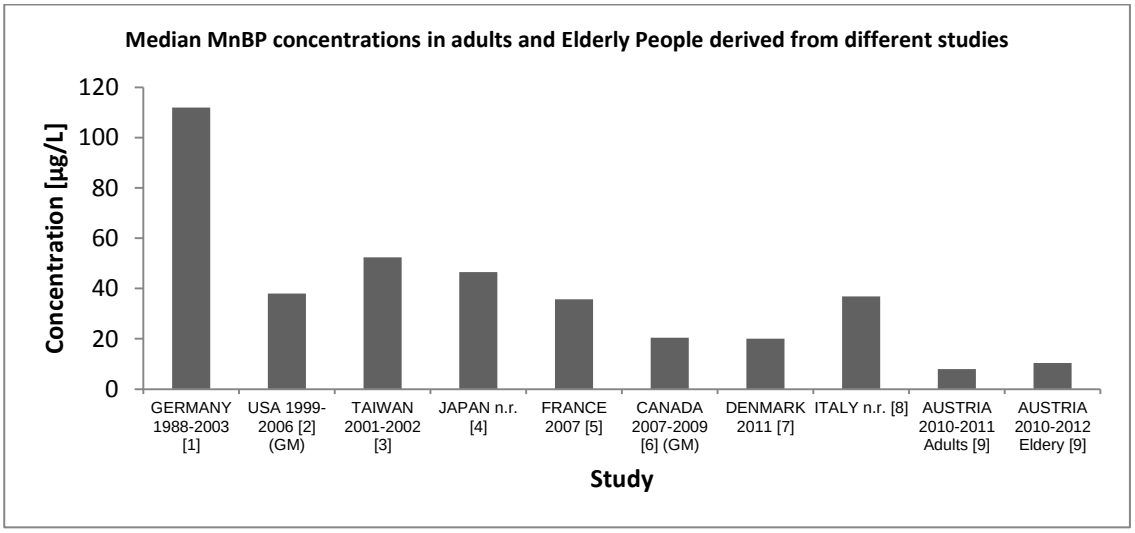
Abbreviations: n.r., not reported. *Notes:* corresponding data are given in Table 132 of Appendix B.1.
References: [1] Blount et al. (2000); [2] Hoppin et al. (2002); [3] Wolff et al. (2008) (pregnant women); [4] Duty et al. (2005); [5] Högberg et al. (2009) (females); [6] Koch et al. (2003); [7] Ye et al. (2008) (pregnant women); [8] Colacino et al. (2010); [9] Berman et al. (2009) (pregnant women); [10] Zeman et al. (2013) (pregnant women); [11] Guo, Wu and Kannan (2011); [12] Suzuki et al. (2012) (pregnant women); [13] Frederiksen et al. (2013) (females); [14] Tranfo et al. (2013); [15] this study.

Figure 29. Median creatinine-unadjusted urinary MEP levels [µg/l] in different study populations of adults and elderly people from several countries between 1988 and 2012 compared with the results of this study



Notes: corresponding data are given in Table 133 of Appendix B.1. *References:* [1] Wolff et al. (2007) (females); [2] Teitelbaum et al. (2012); [3] Frederiksen et al. (2012) (females); [4] Mieritz et al. (2012) (males); [5] Langer et al. (2014); [6] Colacino et al. (2011) (premenstrual females); [7] Frederiksen et al. (2013); [8] this study.

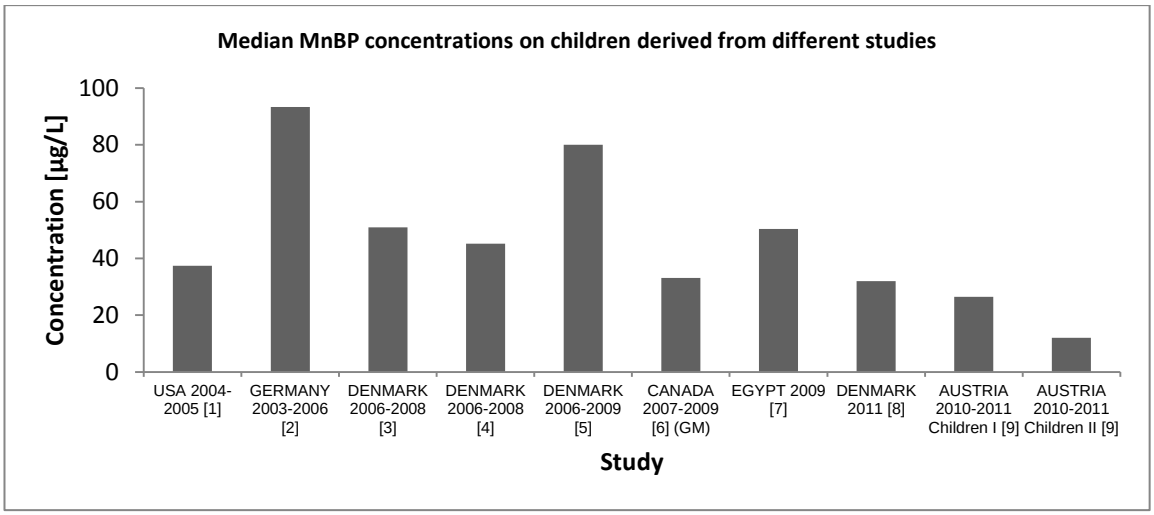
Figure 30. Median creatinine-unadjusted urinary MEP levels [µg/l] in different study populations of children from several countries between 2004 and 2011 compared with the results of this study



Abbreviations: GM, geometric mean; n.r., not reported. *Notes:* corresponding data are given in Table 136 of Appendix B.1.

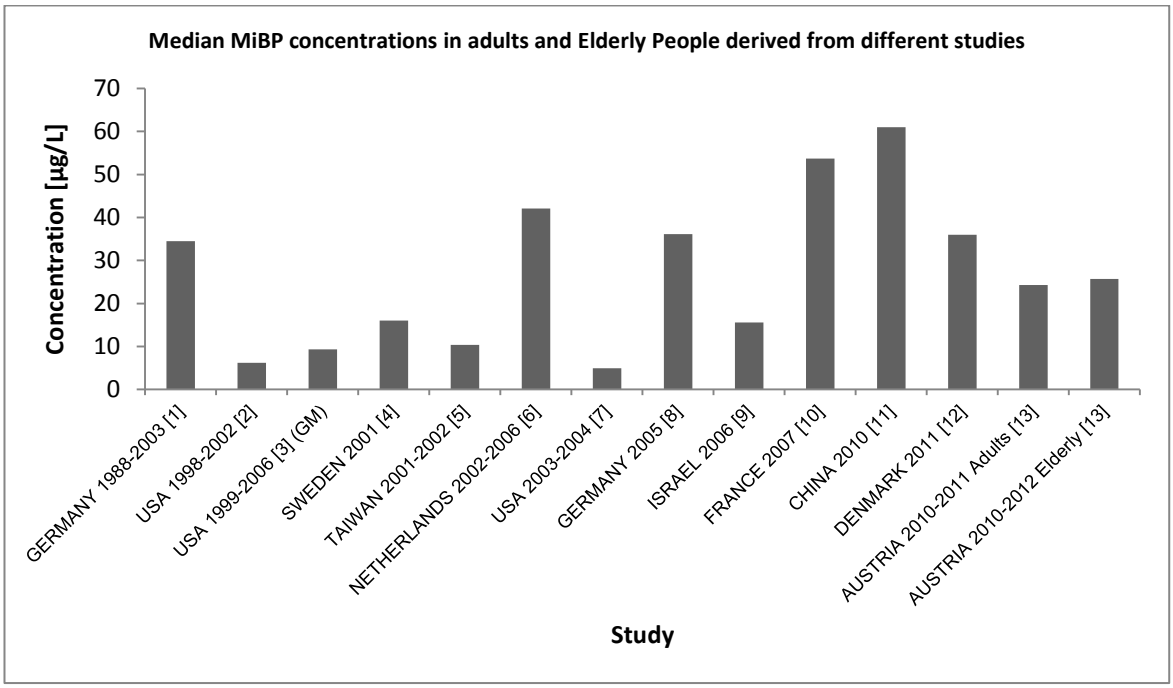
References: [1] Wittassek et al. (2007b); [2] Whyatt et al. (2012) (pregnant women; geometric mean); [3] Lin et al. (2011) (pregnant women); [4] Suzuki et al. (2012) (pregnant women); [5] Zeman et al. (2013) (pregnant women); [6] Saravanabhavan et al. (2013) (geometric mean); [7] Frederiksen et al. (2013) (females); [8] Tranfo et al. (2013); [9] this study.

Figure 31. Median (or geometric mean of) creatinine-unadjusted urinary MnBP levels [µg/l] in different study of adults and elderly people from several countries between 1988 and 2012 compared with the results of this study



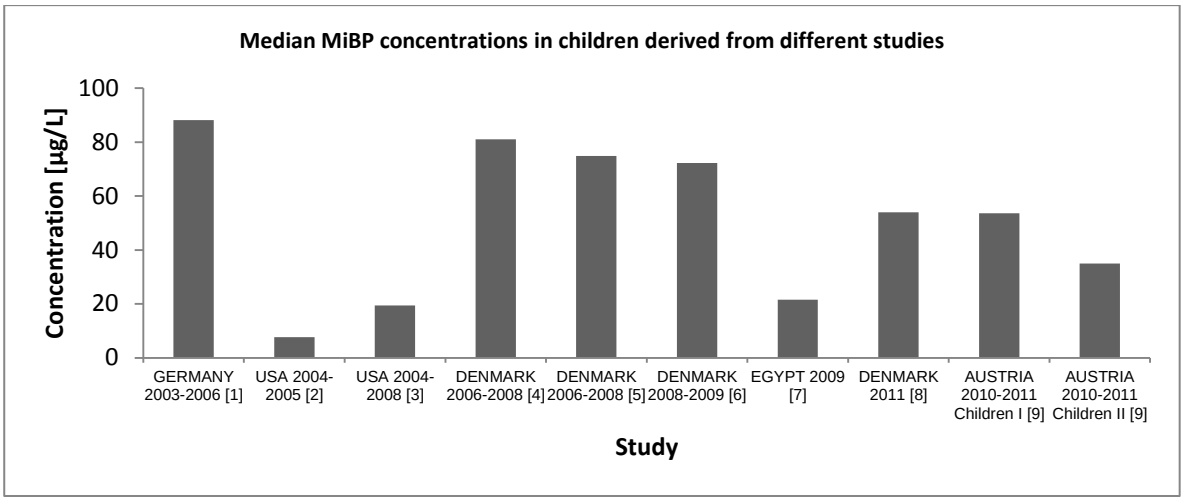
Abbreviations: GM, geometric mean. *Notes:* corresponding data are given in Table 136 of Appendix B.1.
References: [1] Wolff et al. (2007) (females); [2] Becker et al. (2009); [3] Frederiksen et al. (2012) (females); [4] Mieritz et al. (2012) (males); [5] Langer et al. (2014); [6] Saravanabhavan et al. (2013); (geometric mean); [7] Colacino et al. (2011) (premenstrual females); [8] Frederiksen et al. (2013); [9] this study

Figure 32. Median (or geometric mean of) creatinine-unadjusted urinary MnBP levels [µg/l] in different study populations of children from several countries between 2003 and 2011 compared with the results of this study



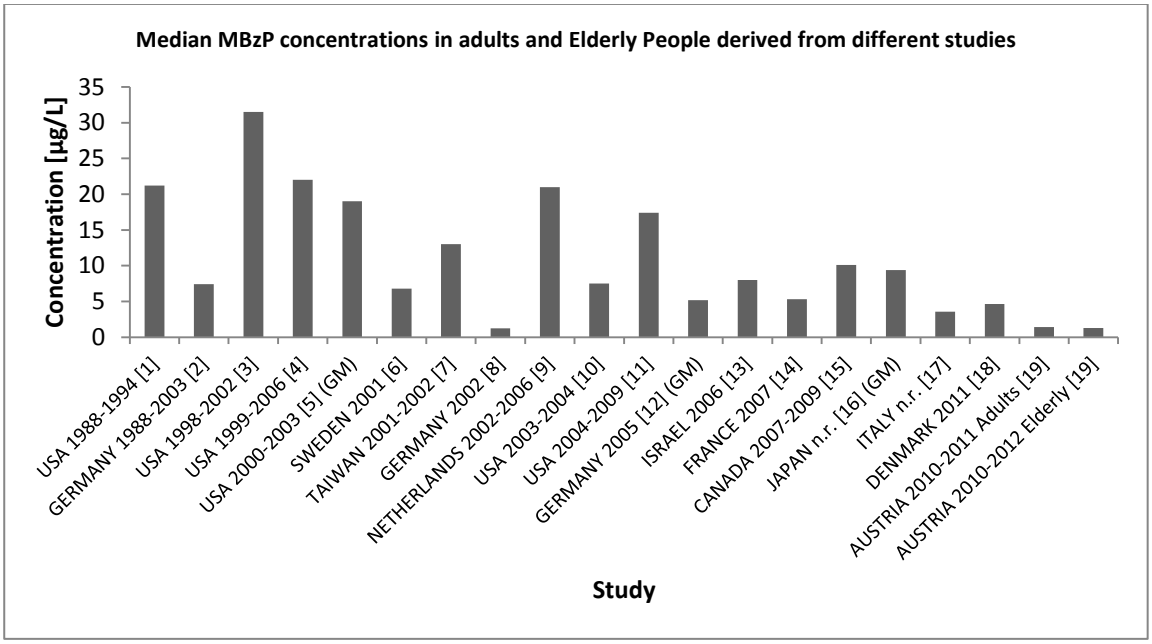
Abbreviations: GM, geometric mean. *Notes:* corresponding data are given in Table 137 of Appendix B.1.
References: [1] Wittassek et al. (2007); [2] Wolff et al. (2008) (pregnant women); [3] Whyatt et al. (2012) (pregnant women; geometric mean); [4] Högberg et al. (2009) (females); [5] Lin et al. (2011) (pregnant women); [6] Ye et al. (2008) (pregnant women); [7] Colacino, Harris and Schlecter (2010); [8] Fromme et al. (2007); [9] Berman et al. (2009) (pregnant women); [10] Zeman et al. (2007) (pregnant women); [11] Guo, Wu and Kannan (2011); [12] Frederiksen et al. (2013) (females); [13] this study

Figure 33. Median (or geometric mean of) creatinine-unadjusted urinary MiBP levels [µg/l] in different study populations of adults and elderly people from several countries between 1988 and 2012 compared with the results of this study



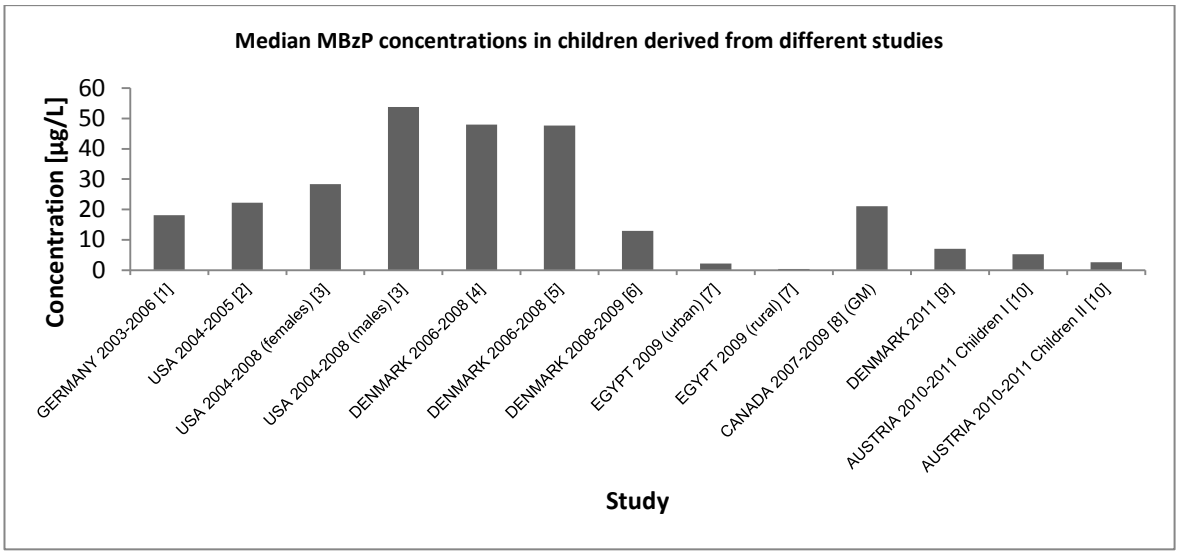
Notes: corresponding data are given in Table 138 of Appendix B.1.
References: [1] Becker et al. (2009); [2] Wolff et al. (2007) (females); [3] Teitelbaum et al. (2012); [4] Frederiksen et al. (2012) (females); [5] Mieritz et al. (2012) (males); [6] Langer et al. (2014); [7] Colacino et al. (2011); [8] Frederiksen et al. (2013); [9] this study

Figure 34. Median creatinine-unadjusted urinary MiBP levels [µg/l] in different study populations of children from several countries between 2003 and 2011 compared with the results of this study



Abbreviations: GM, geometric mean; n.r., not reported. *Notes:* corresponding data are given in Table 140 of Appendix B.1.
References: [1] Blount et al. (2000); [2] Wittassek et al. (2007b); [3] Wolff et al. (2008) (pregnant women); [4] Whyatt et al. (2012) (pregnant women); [5] Duty et al. (2005) (males; geometric mean); [6] Högberg et al. (2009) (females); [7] Lin et al. (2011) (pregnant women); [8] Koch et al. (2003); [9] Ye et al. (2008) (pregnant women); [10] Colacino, Harris and Schlecter (2010); [11] Braun et al. (2012) (females); [12] Fromme et al. (2007) (females; geometric mean); [13] Berman et al. (2009) (pregnant women); [14] Zeman et al. (2013) (pregnant women); [15] Saravanabhavan et al. (2013); [16] Suzuki et al. (2012) (pregnant women; geometric mean); [17] Tranfo et al. (2013); [18] Frederiksen et al. (2013) (females); [19] this study

Figure 35. Median (or geometric means of) creatinine-unadjusted urinary MBzP levels [µg/l] in different study populations of adults and elderly people from several countries between 1988 and 2011 compared with the results of this study



Abbreviations: GM, geometric mean. *Notes:* corresponding data are given in Table 140 of Appendix B.1.
References: [1] Becker et al. (2009); [2] Wolff et al. (2007) (females); [3] Teitelbaum et al. (2012); [4] Frederiksen et al. (2012) (females); [5] Mieritz et al. (2012) (males); [6] Langer et al. (2014); [7] Colacino et al. (2011); [8] Saravanabhavan et al. (2013) (geometric mean); [9] Frederiksen et al. (2013); [10] this study

Figure 36. Median (or geometric mean of) creatinine-unadjusted urinary MBzP levels [µg/l] in different study populations of children from several countries between 2003 and 2011 compared with the results of this study

3.1.3.2 National studies

In 2009, the EAA conducted a Human Biomonitoring study to investigate the phthalate exposure of male and female children (aged 6-11 years) and female adults (mean age of 38 years). The study was published in Hohenblum and Hutter (2011), and its results have been compared with those from the present study, with similar population groups being chosen for the comparison. Investigated urinary phthalate metabolite concentrations (creatinine-adjusted and creatinine-unadjusted) are shown in Table 54 for female adults and in Table 55 for male and female children.

Among female adults, results for several phthalates were very similar: median urinary phthalate metabolite levels of MEP, MBzP, 5OH-MEHP, 5oxo-MEHP, MnOP, MiNP and MiDP were comparable (Figure 36). MCHP was not detected in any sample in 2009, whereas in 2010-2011 about 38% of the participants showed positive results. The exposure to MiBP and MnBP was higher in the present study compared to results from 2009. Contrarily, however, exposure to 5cx-MEPP was higher in females from the previous study.

Table 54. Urinary creatinine-unadjusted phthalate metabolite concentrations [µg/l] and corresponding creatinine-adjusted phthalate metabolite concentrations [µg/g creatinine] among Austrian females (mean age 38 years) from both the present study and from Hohenblum and Hutter (2011)

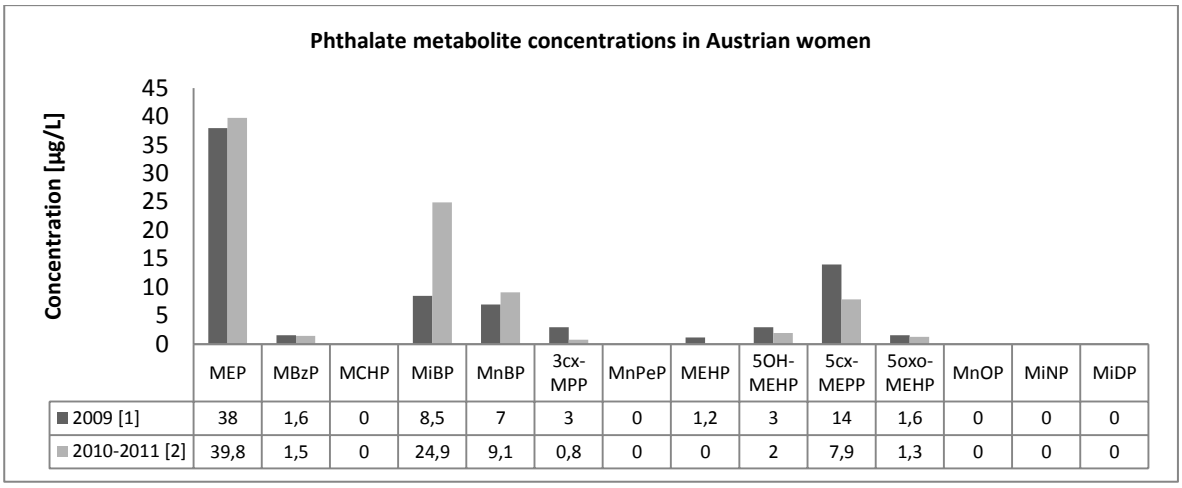
Phthalate metabolite creatinine-unadjusted [µg/l] ***Phthalate metabolite creatinine-adjusted [µg/g]***	**Austrian females (age 37.6±5.2) from 2009 (Hohenblum and Hutter, 2011)**			**Austrian females from this study (age 38.2±14.0) from 2010-2011**		
	n	*Range (median; P95)*	*DR [%]*	*n*	*Range (median; P95)*	*DR [%]*
MEP [µg/l]	48	4.8-480 (38.0; 280)	100	162	n.d.-930 (39.8; 268)	99
MEP [µg/g]		*3.9-437 (35.0; 165)*		*160*	*n.d.-823 (31.5; 313)*	*99*
MBzP [µg/l]	48	n.d.-5.7 (1.6; 4.2)	77	162	n.d.-40.2 (1.5; 11.5)	89
MBzP [µg/g]		*n.d.-6.2 (1.3; 3.6)*		*160*	*n.d.-33.5 (1.6; 8.1)*	*89*
MCHP [µg/l]	48	n.d.	0	162	n.d.-3.5 (n.d.; 1.6)	38
MCHP [µg/g]		*n.d.*		*160*	*n.d.-5.2 (n.d.; 1.3)*	*39*
MiBP [µg/l]	48	n.d.-27.0 (8.5; 22.0)	90	162	n.d.-248 (24.9; 120)	95
MiBP [µg/g]		*n.d.-20.0 (8.0; 15.0)*		*160*	*n.d.-497 (26.0; 124)*	*95*
MnBP [µg/l]	48	1.5-30.0 (7.0; 21.0)	100	162	<LOD-73.7 (9.1; 49.9)	100
MnBP [µg/g]		*1.1-30.0 (5.6; 18.0)*		*160*	*<LOD-78.4 (8.3; 41.3)*	*100*
3cx-MPP [µg/l]	48	<LOD-26.0 (3.0; 13.0)	96	161	n.d.-42.6(<LOD; 18.1)	58
3cx-MPP [µg/g]		*<LOD-15.0 (2.9; 11.0)*		*159*	*n.d.-111 (<LOD; 18.7)*	*59*
MnPeP [µg/l]	48	n.d.	0	162	n.d.-1.5 (n.d.; n.d.)	3
MnPeP [µg/g]		*n.d.*		*160*	*n.d.-0.57 (n.d.; n.d.)*	*4*
MEHP [µg/l]	50	n.d.-30.0 (1.2; 5.4)	64	162	n.d.-17.2 (n.d.; 4.9)	41
MEHP [µg/g]		*n.d.-39.0 (0.8; 5.3)*		*160*	*n.d.-6.1 (n.d.; 3.9)*	*41*
5OH-MEHP [µg/l]	50	<LOD-140 (3.0; 18.0)	98	162	n.d.-46.6 (2.0; 13.3)	94
5OH-MEHP [µg/g]		*<LOD-183 (2.3; 10.0)*		*160*	*n.d.-28.6 (2.0; 13.5)*	*94*
5cx-MEPP [µg/l]	50	4.0-810 (14.0; 147)	100	162	n.d.-122 (7.9; 31.2)	99
5cx-MEPP [µg/g]		*3.1-1057 (12.0; 95.0)*		*160*	*n.d.-74.8 (7.2; 23.4)*	*99*
5oxo-MEHP [µg/l]	48	<LOD-67.0 (1.6; 12.0)	94	162	n.d.-29.3 (1.3; 10.0)	94
5oxo-MEHP [µg/g]		*<LOD-87.0 (1.5; 6.1)*		*160*	*n.d.-18.0 (1.5; 7.5)*	*95*
MnOP [µg/l]	48	n.d.-<LOD	0	162	n.d.-2.0 (n.d.; <LOD)	8
MnOP [µg/g]		*n.d.-<LOD*		*160*	*n.d.-1.3 (n.d.; 0.49)*	*9*
MiNP [µg/l]	48	n.d.	0	162	n.d.-5.4 (n.d.; 1.2)	7
MiNP [µg/g]		*n.d.*		*160*	*n.d.-44.5 (n.d.; 0.95)*	*9*
MiDP [µg/l]	48	n.d.	0	162	n.d.-0.64 (n.d.; <LOD)	9
MiDP [µg/g]		*n.d.*		*160*	*n.d.-3.1 (n.d.; <LOD)*	*10*

Abbreviations: DR, detection rate; LOD, limit of detection; n, sample size; n.d., not detected; P95, 95th percentile.

Table 55. Urinary creatinine-unadjusted phthalate metabolite concentrations [µg/l] and corresponding creatinine-adjusted phthalate metabolite concentrations [µg/g creatinine] among Austrian male and female children (aged 6-11 years) from both this study and from Hohenblum and Hutter (2011)

Phthalate metabolite creatinine-unadjusted [µg/l] ***Phthalate metabolite creatinine-adjusted [µg/g]***	**Austrian male and female children (age 6-11) from 2009 (Hohenblum and Hutter, 2011)**			**Austrian male and female children (age 6-11) from 2010-2011**		
	n	*Range (median; P95)*	*DR [%]*	*n*	*Range (median; P95)*	*DR [%]*
MEP [µg/l] ***MEP [µg/g]***	44 *44*	4.1-190 (29.0; 140) *3.6-340 (25.0; 212)*	100 *100*	165 *161*	n.d.-447 (16.9; 110.2) *n.d.-1645 (20.7; 123)*	98 *98*
MBzP [µg/l] ***MBzP [µg/g]***	44 *44*	n.d.-29.0 (2.6; 8.6) *n.d.-23.0 (2.0; 9.3)*	93 *93*	165 *161*	n.d.-55.8 (2.7; 30.3) *n.d.-66.5 (3.5; 39.5)*	95 *95*
MCHP [µg/l] ***MCHP [µg/g]***	44 *44*	n.d.-<LOD *n.d.-<LOD*	0 *0*	165 *161*	n.d.-5.5 (n.d.; 0.69) *n.d.-6.9 (n.d.; 1.2)*	11 *12*
MiBP [µg/l] ***MiBP [µg/g]***	44 *44*	n.d.-120 (12.0; 33.0) *n.d.-87.0 (10.0; 36.0)*	95 *95*	165 *161*	n.d.-177 (35.2; 128.4) *n.d.-1086 (39.5: 337)*	99 *99*
MnBP [µg/l] ***MnBP [µg/g]***	44 *44*	1.5-32.0 (9.1; 22.0) *1.1-42.0 (7.9; 25.0)*	100 *100*	165 *161*	<LOD-69.6 (12.8; 46.3) *<LOD-699 (15.2; 115)*	100 *100*
3cx-MPP [µg/l] ***3cx-MPP [µg/g]***	44 *44*	1.6-230 (7.0; 20.0) *1.8-251 (5.9; 20.0)*	100 *100*	165 *161*	n.d.-62.5 (1.89; 14.1) *n.d.-206 (2.7; 22.6)*	78 *78*
MnPeP [µg/l] ***MnPeP [µg/g]***	44 *44*	n.d. *n.d.*	0 *0*	165 *161*	n.d.-4.5 (n.d.; <LOD) *n.d.-3.3 (n.d.; <LOD)*	5 *7*
MEHP [µg/l] ***MEHP [µg/g]***	49 *44*	n.d.-9.6 (1.1; 4.6) *n.d.-11.1 (0.9; 7.9)*	65 *65*	165 *161*	n.d.-20.1 (0.76; 7.3) *n.d.-17.4 (0.88; 10.8)*	61 *61*
5OH-MEHP [µg/l] ***5OH-MEHP [µg/g]***	50 *44*	1.1-25.0 (4.6; 8.9) *0.7-27.0 (4.4; 10.0)*	100 *100*	165 *161*	n.d.-47.9 (5.2; 28.6) *n.d.-99.4 (6.8; 43.7)*	99 *99*
5cx-MEPP [µg/l] ***5cx-MEPP [µg/g]***	50 *44*	9.0-120 (33.0; 105) *6.9-120 (28.0; 83.0)*	100 *100*	165 *161*	2.3-102 (15.8; 57.1) *2.9-179 (20.3; 85.3)*	100 *100*
5oxo-MEHP [µg/l] ***5oxo-MEHP [µg/g]***	44 *44*	0.8-11.0 (2.9; 6.6) *0.2-12.0 (2.9; 6.2)*	100 *100*	165 *161*	<LOD-43.8 (3.7; 20.3) *<LOD-68.9 (5.5; 33.6)*	100 *100*
MnOP [µg/l] ***MnOP [µg/g]***	44 *44*	n.d. *n.d.*	0 *0*	165 *161*	n.d.-3.4 (n.d.; <LOD) *n.d.-3.6 (n.d.; 0.78)*	9 *12*
MiNP [µg/l] ***MiNP [µg/g]***	44 *44*	n.d. *n.d.*	0 *0*	165 *161*	n.d.-12.7 (n.d.; 1.5) *n.d.-12.3 (n.d.; 1.4)*	12 *15*
MiDP [µg/l] ***MiDP [µg/g]***	44 *44*	n.d. *n.d.*	0 *0*	165 *161*	n.d.-1.0 (n.d.; 0.68) *n.d.-2.2 (n.d.; 0.82)*	20 *21*

Abbreviations: DR, detection rate; LOD, limit of detection; n, sample size; n.d., not detected; P95, 95th percentile.

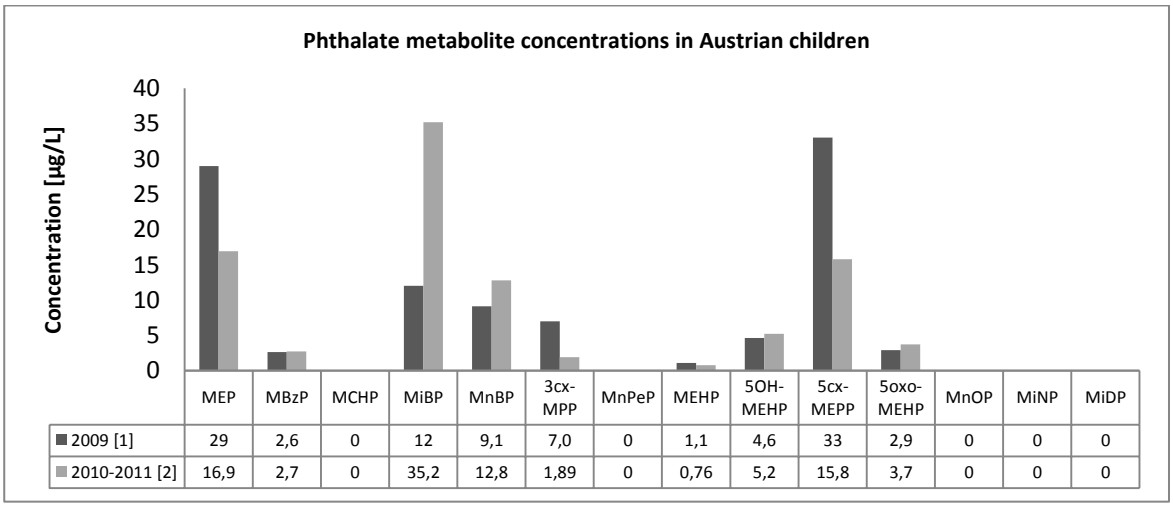


	MEP	MBzP	MCHP	MiBP	MnBP	3cx-MPP	MnPeP	MEHP	5OH-MEHP	5cx-MEPP	5oxo-MEHP	MnOP	MiNP	MiDP
2009 [1]	38	1,6	0	8,5	7	3	0	1,2	3	14	1,6	0	0	0
2010-2011 [2]	39,8	1,5	0	24,9	9,1	0,8	0	0	2	7,9	1,3	0	0	0

[1] Hohenblum and Hutter (2011); [2] this study

Figure 37. Median creatinine-unadjusted urinary phthalate metabolite levels [µg/l] in Austrian women (mean age 38 years) from 2009 (n=48-50) compared with results from the present study (n=161-162)

In Austrian male and female children aged 6 to 11 years (Figure 38), similar results were identified for the phthalate metabolite MBzP. In the study from 2009, exposure to MEP, 3cx-MPP and 5cx-MEPP was found to be higher than the levels detected in the present study, and lower exposure in the case of MiBP and MnBP. However, it must be considered that the sample size of the present study was more than three times larger than that of the study conducted in 2009.



	MEP	MBzP	MCHP	MiBP	MnBP	3cx-MPP	MnPeP	MEHP	5OH-MEHP	5cx-MEPP	5oxo-MEHP	MnOP	MiNP	MiDP
2009 [1]	29	2,6	0	12	9,1	7,0	0	1,1	4,6	33	2,9	0	0	0
2010-2011 [2]	16,9	2,7	0	35,2	12,8	1,89	0	0,76	5,2	15,8	3,7	0	0	0

[1] Hohenblum and Hutter (2011); [2] this study

Figure 38. Median creatinine-unadjusted urinary phthalate metabolite levels [µg/l] in Austrian male and female children (aged 6-11 years) from 2009 (n=44-50) compared with the results of this study (n=165)

3.1.4 Reference values for the Austrian population

Reference values define the exposure to chemicals of a population group and are estimated based on data from a suitable reference population (EAG, 2011).

Table 56. Data used as a basis for the derivation of reference values for urinary creatinine-unadjusted phthalate metabolites [µg/l] of the general population of Austria

Phthalate / Phthalate Metabolite(s) *(LOD)* [µg/l]						
Population group	***n***	***Median***	***P95***	***Range***	***DR [%]***	***CI-PP95***
DEP / MEP *(2.46)*						
6-15 years	230	19.2	112	n.d.-463	98.7	83.7-163
18-81 years	311	34.2	436	n.d.-2105	98.4	353-636
DEHP / Σ 5OH-MEHP *(0.79)* + 5oxo-MEHP *(0.56)*						
6-15 years	230	8.3	47.6	n.d.-137	99.6	45.3-55.6
18-81 years	311	3.2	21.9	n.d.-132	97.7	16.7-28.7
DEHP / Σ MEHP *(0.69)* + 5OH-MEHP *(0.79)* + 5cx-MEPP *(0.46)* + 5oxo-MEHP *(0.46)*						
6-15 years	230	26.0	100	3.5-240	100	94.0-126
18-81 years	311	12.1	50.5	n.d.-278	99.4	44.6-68.3
DEHP / 5OH-MEHP *(0.79)*						
6-15 years	230	4.8	27.6	n.d.-80.0	99.1	26.3-34.9
18-81 years	311	2.0	13.1	n.d.-76.2	95.2	10.4-16.7
DEHP / 5oxo-MEHP *(0.56)*						
6-15 years	230	3.6	19.8	n.d.-57.3	99.1	18.1-24.9
18-81 years	311	1.3	8.0	n.d.-55.4	94.2	7.0-12.3
DEHP / 5cx-MEPP *(0.46)*						
6-15 years	230	17.0	56.6	2.3-102	100	45.6-72.7
18-81 years	311	8.3	32.5	n.d.-219	99.4	28.6-41.8
DnBP / MnBP *(0.53)*						
6-15 years	230	13.3	45.4	n.d.-87.7	99.6	40.9-60.6
18-81 years	311	8.4	41.9	n.d.-84.5	98.7	33.1-52.1
DiBP / MiBP *(0.59)*						
6-15 years	230	35.8	132	n.d.-207	99.6	126-161
18-81 years	311	24.4	108	n.d.-248	96.8	87.3-118
BBzP / MBzP *(0.59)*						
6-15 years	230	2.7	24.8	n.d.-57.1	95.2	17.8-33.6
18-81 years	311	1.3	9.3	n.d.-40.2	85.5	7.2-11.8
DCHP / MCHP *(0.51)*						
6-15 years	230	0.0	1.2	n.d.-5.5	13.5	0.64-1.6
18-81 years	311	0.0	1.2	n.d.-3.5	29.3	0.95-1.8

Abbreviations: CI-PP95, confidence interval of 95th population percentile; DR, detection rate; LOD, limit of detection; n, sample size; n.d., not detected; P95, 95th percentile. *Notes:* LOD=LOQ/2.

Following the recommendations of the WHO and further of the HBM commission (EAG, 2005), only urine samples with creatinine concentrations between 0.3 and 3 g/l were used for the derivation of reference values. Thus, for phthalates, reference values were

calculated based on the urine samples of 230 children (aged 6-15) including 128 males and 102 females, and of 311 adults (aged 18-81) including 133 males and 178 females. On the basis of analysed urinary phthalate metabolite concentrations, the data used for the derivation of the reference values are shown in Table 56.

Reference values for the Austrian population based on urinary phthalate metabolites derived from the present study are listed in Table 57. Generally, reference values for children are approximately twice as high as values for adults in the case of almost all phthalate metabolites, except for MnBP, MiBP and MCHP, the values for which are more similar, and for MEP, for which adults exhibit values about four times higher than the reference values of children.

Table 57. Reference values for the urinary metabolites of several phthalates in children and adults in Austria

Phthalate	Urinary phthalate metabolite(s)	Children 6-15 years of age 2010-2011	Adults 18-81 years of age 2010-2011
DEP	***MEP***	110 µg/l	440 µg/l
DnBP	***MnBP***	45 µg/l	40 µg/l
DiBP	***MiBP***	130 µg/l	110 µg/l
BBzP	***MBzP***	25 µg/l	10 µg/l
DEHP	***Σ MEHP +5OH-MEHP + 5cx-MEPP + 5oxo-MEHP***	100 µg/l	50 µg/l
	Σ 5OH-MEHP + 5oxo-MEHP	50 µg/l	20 µg/l
	5OH-MEHP	30 µg/l	15 µg/l
	5oxo-MEHP	20 µg/l	10 µg/l
	5cx-MEPP	60 µg/l	35 µg/l
DCHP	***MCHP***	1.5 µg/l	1.5 µg/l

3.1.4.1 Comparison with reference values derived from Germany

The HBM commission of the EAG has published reference values for several urinary metabolites based on HBM studies of the German population. Compared with reference values derived from the present study (Table 58), the German reference values are higher. Nevertheless, it must considered that periods of sampling for the German and Austrian populations differ, as do the age groups investigated, with especially younger adults being used for the derivation of the reference values.

For the investigated DEHP metabolites except for 5cx-MEPP, reference values for Austrian children were similar to those of the adult German population.

Table 58. Reference values for several urinary phthalate metabolites of children and adults from Germany and Austria

Phthalate	Urinary phthalate metabolite(s)	Children (4-14 years)[1] [µg/l]	Adults (20-29 years)[2] [µg/l]	Children (6-15 years)[3] [µg/l]	Adults (18-81 years)[3] [µg/l]
DEHP	***Σ 5OH-MEHP + 5oxo-MEHP***	280	50	50	20
	5OH-MEHP	160	30	30	15
	5oxo-MEHP	120	20	20	10
	5cx-MEPP	200	30	60	35
DnBP	***MnBP***	300	70	45	40
DiBP	***MiBP***	300	140	130	110
BBzP	***MBzP***	75	15	25	10
DiNP	***Σ OH-MiNP + oxo-MiNP + cx-MiNP***	140	60	-	-
	OH-MiNP	50	20	-	-
	oxo-MiNP	30	15	-	-
	cx-MiNP	60	25	-	-

[1] from Germany, 2003-2006 (EAG, 2011)
[2] from Münster, Germany, 2006 and 2008 (EAG, 2011)
[3] from this study, Austria, 2010-2011

3.1.4.2 Comparison with HBM-values

The HBM-commission of the EAG has derived HBM-values for DEHP based on the urinary metabolites 5oxo-MEHP and 5OH-MEHP. 40% of orally administered DEHP is excreted via these two metabolites. The HBM-value refers to the complete urinary excretion per day [µg/d]. The HBM-I-value for DEHP is set out at 500 µg/l for children aged 6-13 years, 300 µg/l for females in childbearing years and 750 µg/l for males >14 years and the remaining population. No HBM-II-values have been derived. (EAG, 2007c) Additionally, no HBM-values currently exist for other phthalates.

The reference values for the Austrian population for DEHP based on the sum of the metabolites 5OH-MEHP and 5oxo-MEHP are 50 µg/l for children and 20 µg/l for adults. Thus, the derived reference values for the Austrian population are far below the HBM-I-values (6 times lower in children and about 38 times lower in adults). Regarding the statement of the HBM commission for reference values below the HBM-I-values, no action is currently necessary, since adverse health effects are not expected.

3.1.5 Daily Phthalate Intake

Through known phthalate metabolite concentrations excreted via urine, calculations of Daily Intakes (DI) of parent compounds are possible. Calculated DIs can be compared with existing acceptable levels of exposure (AL) such as the Tolerable Daily Intake (TDI) or the Reference Dose (RfD). These levels are estimated concentrations of a chemical that can be ingested daily over a lifetime without resulting in significant human health risks (cf. EFSA, 2011 and U.S. EPA, 2012a). DIs exceeding the acceptable levels may lead to potential health risks.

Based on analysed urinary phthalate metabolite concentrations in the present study population, DIs were estimated for several phthalates according to two models (urinary creatinine-based model and urinary volume-based model). Results were compared with ALs and possible associations with different parameters, for example sex, age or geographical distribution were also investigated.

3.1.5.1 Calculation

For the DI calculation, the knowledge of some parameters is essential. Depending on the calculation model used (creatinine-based or volume-based), knowledge of creatinine concentration or urine volumes excreted via urine is necessary. For the estimation of DIs, 24h urine samples would be ideal, but in many epidemiologic studies - especially when children are involved - only spontaneous urine samples or first morning urine samples are available. Therefore, the single urine samples must be extrapolated in order to reflect the metabolite excretion of an entire day. Additionally, physical properties within the investigated population must also be considered. Thus, reference values for the daily urinary creatinine excretion depending on bodyweight and age, and reference values for urinary volume excretion depending on age, bodyweight and/or sex are used for DI calculations. Another important parameter is the molar fraction (F_{UE}), which is the ratio between phthalate metabolite concentration excreted via urine and the ingested parent phthalate concentration. (Koch et al., 2007)

Based on analysed urinary phthalate metabolite concentrations, the DIs of the respective parent phthalates were estimated according to Koch et al. (2007). The calculation occurred in relation to two different models, whereby one model was based on the creatinine-adjusted metabolite concentrations and reference values for creatinine excretion, and the other model was based on volume-based metabolite

concentrations and reference values for weight-related urine volume per day. (Koch et al., 2007)

- *Creatinine-based model (Koch et al., 2007):*

Formula:

$$\mathbf{DI}\ [\mu\mathbf{g/kg\ bw/d}] = \frac{\mathrm{UE_{sum}}[\mu\mathrm{mol/g_{crea}}] * \mathrm{CE_{smoothed}}[\mathrm{g/d}]}{\mathrm{F_{UE}} * \mathrm{bw}\ [\mathrm{kg}]} * \text{Phthalate MW}\ [\mathrm{g/mol}]$$

UE_{sum}	Sum of urinary excretion: molar urinary excretion of the sum of phthalate metabolites per creatinine
$CE_{smoothed}$	Smoothed creatinine excretion: Reference values for the urinary creatinine excretion based on bodyheight and sex (children) and bodyweight (adults, elderly people)
F_{UE}	Molar fraction: Molar ratio between excreted phthalate metabolite amount in urine and the amount of the take up of the parent phthalate
Phthalate MW	Molecular weight of the parent phthalate
bw	bodyweight

- *Volume-based model (Koch et al., 2007):*

Formula:

$$\mathbf{DI}\ [\mu\mathbf{g/kg\ bw/d}] = \left(\frac{\mathrm{UE_{sum}}\ [\mu\mathrm{mol/l}] * \mathrm{UV_{norm}}\ [\mathrm{l/kg\ bw/d}]}{\mathrm{F_{UE}}}\right) * \text{Phthalate MW}\ [\mathrm{g/mol}]$$

UE_{sum}	Sum of urinary excretion: molar urinary excretion of the sum of phthalate metabolites per litre urine
UV_{norm}	Urinary volume: average urinary volume per bodyweight [kg] excreted per day
F_{UE}	Molar fraction: Molar ratio between excreted phthalate metabolite amount in urine and the amount of the take up of the parent phthalate
Phthalate MW	Molecular weight of the parent phthalate

Sum of urinary excretion (UE_{sum}):

Urinary phthalate metabolite concentrations were measured in µg/l. Therefore, the concentrations had to be converted into µmol/l by using the molecular weights of the different phthalate metabolites.

Smoothed creatinine excretion ($CE_{smoothed}$):

For the calculation of daily phthalate intakes in children, data of 24h urinary creatinine excretion reference values for healthy Caucasian children based on sex and

bodyheight were provided from Remer, Neubert and Maser-Gluth (2002). For adults and elderly people, 18 mg/kg bw/d for females and 23 mg/kg bw/d for males were used as creatinine excretion values according to Koch, Drexler and Angerer (2003).

Reference values for daily urinary volume (UV_{norm}):

Reference values of the daily excreted urinary volumes are shown in Table 59. The mean urine volumes excreted per day differ according to age (Koch et al., 2007).

Table 59. Mean daily excreted urinary volumes [ml/ kg bw/d] in relation to age

Age	Age Group	Male	Female	Reference
5-7 years	Children I	25 ml/kg bw/d		Geigy (1983)
7-11 years	Children II	25 ml/kg bw/d		Geigy (1983)
11-14 years	Children II	19 ml/kg bw/d		Geigy (1983)
>16 years	Adults, Elderly	1.7 l/d	1.6 l/d	Hays et al. (2011)

Molar fraction values (F_{UE}):

The molar fraction (F_{UE}) is defined as the molar ratio between the urinary excreted phthalate metabolite concentration and the parent phthalate concentration that was ingested. For the determination of the F_{UE}, studies have been performed to investigate the urinary concentration of a metabolite after oral administration of a known dose of labelled phthalate standards in volunteers after 24 or 48 hours. For example, in Anderson et al. (2001), 72.5% of an orally administrated dose of BBzP was excreted as MBzP in urine. Therefore, the estimated F_{UE} for BBzP is 0.725. (Koch et al., 2007)

Various studies have investigated the F_{UE}s of several phthalates. In 1985, Schmid and Schlatter investigated the kinetics of DEHP metabolites in two volunteers after a single oral dose of 30 mg by analysing metabolites in urine (Schmid and Schlatter, 1985). Anderson et al. (2001) determined the F_{UE}s for the phthalates DnBP and BBzP after an oral dose of labelled phthalate standards administrated to eight volunteers. They reported a F_{UE} for DnBP of 0.69 and a F_{UE} for BBzP of 0.725. (Anderson et al., 2001) Based on investigations of one volunteer, Koch et al. published F_{UE}s of DEHP and DINP (Koch et al., 2005; Koch, Müller and Angerer, 2007). In a study of 17 volunteers, the kinetics of DnBP and DiBP was investigated. Published F_{UE} for DnBP was 0.69. The F_{UE} of DiBP is assumed to be similar to DnBP. (Seckin, Fromme and Völkel, 2009) In a study by Anderson et al. (2011) of 20 volunteers (10 males and 10 females), kinetics and F_{UE}s were estimated for DEHP and DiNP and their primary and secondary

metabolites in urine up to 48h post-dose. These calculated F_{UE}s are lower compared to previous published values, which leads to higher daily intakes after calculation. (Anderson et al., 2011)

In the present study, daily phthalate intakes were calculated with the F_{UE}s listed in Table 60. Calculation of daily DEHP intakes was performed twice: with F_{UE}s derived from Koch et al. (2005), as well as with F_{UE}s derived from Anderson et al. (2011). This was done separately in order to make comparison of the results with newer and former F_{UE}s possible, as well as to enable comparison with results from other studies making use of different values.

Table 60. Molar fraction values (F_{UE}) of different phthalates (time 0-24h) for the estimation of daily phthalate intakes

Phthalate	Phthalate metabolite	Molecular fraction value (F_{UE})	Reference
DEP	MEP	0.69	Koch and Angerer (2012)
DnBP	MnBP	0.84	Koch et al. (2012a)
DiBP	MiBP	0.70	Koch et al. (2012a)
BBzP	MBzP	0.73	Anderson et al. (2001)
DEHP	*sum*	*0.669*	Koch et al. (2005)
	MEHP	0.059 / 0.062	Koch et al. (2005) / Anderson et al. (2011)
	5OH-MEHP	0.233 / 0.149	
	5oxo-MEHP	0.150 / 0.109	
	5cx-MEPP	0.185 / 0.132	
	2cx-MMHP	0.042	Koch and Angerer (2012)
DnOP	MnOP	0.043	Koch et al. (2003)
DiNP	*sum*	*0.396*	Koch and Angerer (2012)
	cx-MiNP	0.091 / 0.099	Koch and Angerer (2012) / Anderson et al. (2011)
	OH-MiNP	0.184 / 0.114	
	Oxo-MiNP	0.100 / 0.063	
	MiNP	0.021 / 0.03	
DiDP	*sum*	*0.34*	Koch and Angerer (2012)

Molecular weights:

Table 61 shows data on molecular weight of the parent compounds, and in Table 62, the molecular weights of the phthalate metabolites where summarised.

Table 61. Molecular weights of parent phthalates

Phthalate	Molecular weight (MW) [g/mol]	Reference
DEP	222.2	U.S. EPA (2013)
DnBP	278.3	Danish EPA (2011)
DiBP	278.3	Danish EPA (2011)
DnPeP	306.4	ECHA (2013i)
BBzP	312.4	Danish EPA (2011)
DCHP	330	ECB (2000a)
DEHP	390.6	U.S. EPA (2007a)
DnOP	390.5	CERHR (2003)
DiNP	approx. 420.6	ECB (2003a)
DiDP	approx. 446.7	ECB (2003b)

Table 62. Molecular weights of phthalate metabolites

Phthalate metabolite	Molecular weight [g/mol]	Reference
MEP	194	Wolff et al. (2010)
MiBP	222	Zeman et al. (2013)
MnBP	222	Zeman et al. (2013)
MnPeP	236	Calculation according to chemical structure shown in Figure 8
MCHP	248	www.chemicalregister.com
MBzP	258	Zeman et al. (2013)
MnOP	278	NCBI (2014)
MEHP	278	Wolff et al. (2010)
5oxo-MEHP	292	EAG (2007c)
5OH-MEHP	294	EAG (2007c)
5cx-MEPP	308	Zeman et al. (2013)

3.1.5.2 Acceptable levels of exposure

Acceptable levels of exposure for various phthalates are listed in Chapter 1.3.6.2.

3.1.5.3 Results

Calculated volume-based and creatinine-based DIs were compared with several acceptable levels of exposure (the EFSA TDIs, the U.S. EPA RfDs and the RfD AAs, respectively) to identify possible exceedances. Additionally, correlations and differences between creatinine- and volume-based values, as well as between study

population groups were investigated. Statistical analysis was conducted for the purpose of identifying potential associations between DIs and several parameters including sex, age, various anthropometric data and regional differences.

3.1.5.3.1 Comparison with Acceptable Levels

Table 63 and Table 64 illustrate the DIs (ranges, medians and P95 values) for several phthalates in children, adults and elderly people calculated with the creatinine-based model and the urinary volume-based model, respectively. In Figure 39 to Figure 53, the DIs of the phthalates are graphically illustrated, whereby creatinine-based and volume-based results are compared. If existent, exceedances of the respective acceptable exposure levels are labelled in the related graphics.

Table 63. Daily Phthalate Intakes (ranges, medians, 95th percentiles) [µg/kg bw/d] estimated according to the creatinine-based model in Austrian children, adults and elderly people

	Children I	**Children II**	**Adults**	**Elderly People**
[µg/kg bw/d]	range (median; P95)	range (median; P95)	range (median; P95)	range (median; P95)
Sample size (n)	*30*	*214*	*267*	*69*
DEP	0.0-10.1 (0.53; 9.9)	0.0-8.9 (0.61; 3.1)	0.0-48.7 (0.9; 11.2)	0.0-130 (1.2; 37.5)
DnBP	0.15-14.7 (0.84; 10.2)	0.0-18.6 (0.34; 1.8)	0.0-2.0 (0.24; 1.1)	0.0-2.6 (0.35; 1.9)
BBzP	0.0-2.1 (0.21; 1.9)	0.0-1.3 (0.08; 0.77)	0.0-1.0 (0.04; 0.23)	0.0-0.46 (0.05; 0.40)
DiBP	0.52-16.7 (2.3; 14.2)	0.0-34.3 (1.1; 7.0)	0.0-16.0 (0.78; 3.4)	0.15-8.7 (0.96; 4.9)
DEHP[1,2]	0.39-11.2 (2.4; 11.1)	0.09-15.2 (0.94; 5.2)	0.0-7.5 (0.39; 1.6)	0.10-9.8 (0.62; 6.1)
DEHP[1,3]	0.54-15.6 (3.3; 15.4)	0.13-21.1 (1.3; 7.2)	0.0-10.4 (0.53; 2.2)	0.14-13.6 (0.86; 8.5)

[1] based on urinary concentrations of MEHP, 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP.
[2] based on the F_{UE}s published in Koch et al. (2005).
[3] based on the F_{UE}s published in Anderson et al. (2011).

Table 64. Daily Phthalate Intakes (ranges, medians, 95th percentiles) [µg/kg bw/d] estimated according to the volume-based model in Austrian children, adults and elderly people

	Children I	**Children II**	**Adults**	**Elderly People**
[µg/kg bw/d]	range (median; P95)	range (median; P95)	range (median; P95)	range (median; P95)
Sample size (n)	*31*	*219*	*269*	*71*
DEP	0.0-18.5 (0.65; 12.8)	0.0-14.6 (0.70; 3.5)	0.0-41.6 (1.3; 14.2)	0.0-80.3 (1.4; 40.1)
DnBP	0.07-2.6 (0.99; 2.4)	0.0-2.5 (0.40; 1.6)	0.0-2.4 (0.28; 1.4)	0.0-2.9 (0.35; 1.9)
BBzP	0.0-2.2 (0.22; 1.9)	0.0-1.8 (0.09; 0.78)	0.0-1.2 (0.05; 0.38)	0.0-0.61 (0.05; 0.46)
DiBP	0.25-7.9 (2.4; 6.9)	0.0-7.1 (1.3; 4.7)	0.0-11.6 (0.99; 4.6)	0.08-5.3 (1.0; 4.4)
DEHP[1,2]	0.19-6.6 (2.3; 5.7)	0.14-11.2 (1.1; 5.0)	0.0-10.8 (0.54; 2.3)	0.04-12.2 (0.66; 6.3)
DEHP[1,3]	0.26-9.1 (3.3; 7.7)	0.19-15.5 (1.5; 6.9)	0.0-14.9 (0.75; 3.2)	0.06-16.9 (0.91; 8.7)

[1] based on urinary concentrations of MEHP, 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP.
[2] based on the F_{UE}s published in Koch et al. (2005).
[3] based on the F_{UE}s published in Anderson et al. (2011).

DEP

DIs of DEP were several times higher in participants of the groups of Adults and Elderly People compared to both Children groups for both creatinine-based and volume-based DIs. Thus, a dramatic increase of DIs existed with increasing age.

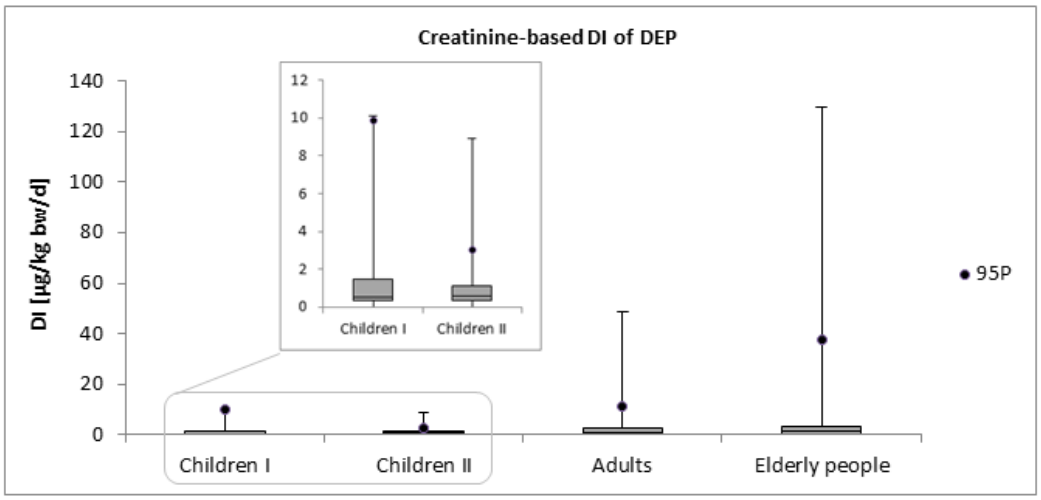


Figure 39. Distributions of creatinine-based daily DEP intake [µg/kg bw/d] in the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

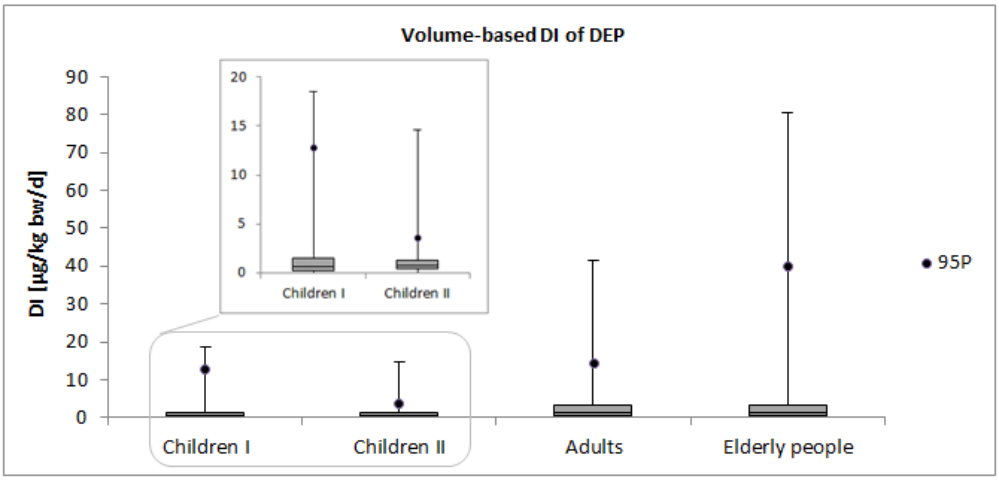


Figure 40. Distributions of volume-based daily DEP intake [µg/kg bw/d] in the groups of Children I (n=31), Children II (n=219), Adults (n=269) and Elderly People (n=71)

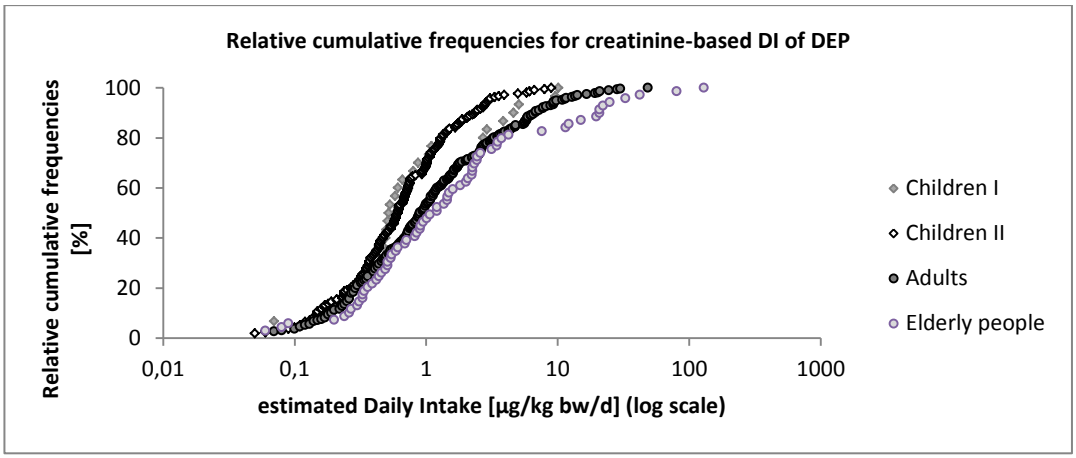


Figure 41. Relative cumulative frequencies [%] for creatinine-based daily DEP intakes [µg/kg bw/d] among the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

DnBP

Daily DnBP intakes decreased with increasing age among children and adults based on volume-based DIs. However, elderly people showed increased DIs (median, P95) compared to the other study population groups.

Wide differences between creatinine-based and volume-based values existed, especially among children. Highest DnBP levels were found in children for creatinine-based DIs. An exceedance of the EFSA TDI of 10 µg/kg bw/d was found at the 95th percentile (creatinine-based) in the group of Children I (10.2 µg/kg bw/d). One child within the group of Children I (3.3%) as well as one child from the group of Children II (0.47%) exceeded the TDI for creatinine-based results (14.7 and 18.6 µg/kg bw/d, respectively). Adults and elderly people showed DI values below all ALs.

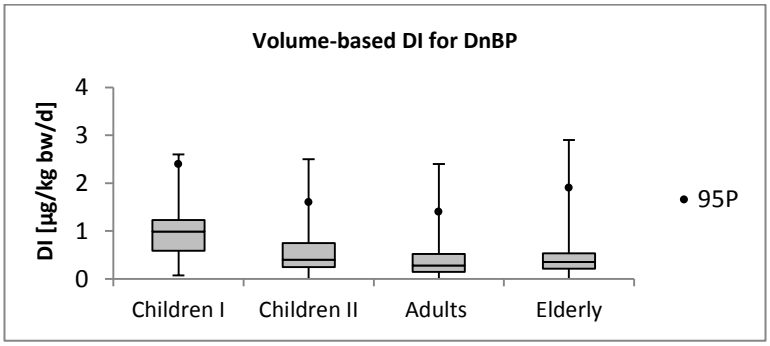


Figure 42. Distributions of volume-based daily DnBP intake [µg/kg bw/d] in the groups of Children I (n=31), Children II (n=219), Adults (n=269) and Elderly People (n=71)

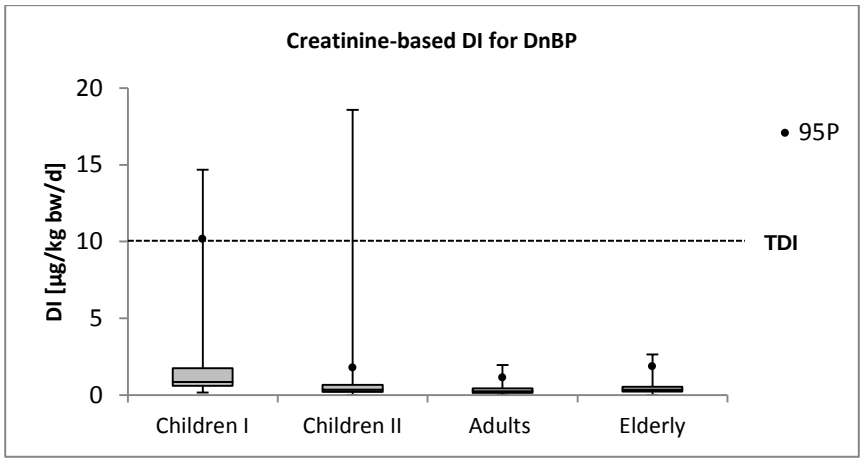


Figure 43. Distributions of creatinine-based daily DnBP intake [µg/kg bw/d] in the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

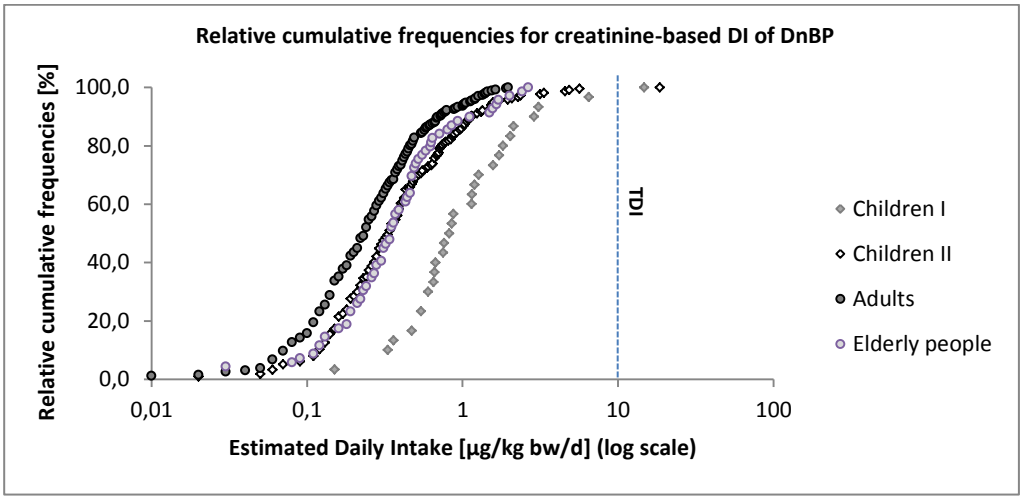


Figure 44. Relative cumulative frequencies [%] for creatinine-based daily DnBP intakes [µg/kg bw/d] among the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

DiBP

Creatinine-based daily DiBP intakes were higher than volume-based daily intakes, whereby the greatest differences were found in children. Among all groups, except among the group of Elderly People, exceedances of the TDI of 10 µg/kg bw/d existed for creatinine-based results. Four samples (13.3%) of the Children I group exceeded the TDI with daily intake values ranging between 11.3 and 16.7 µg/kg bw/d. Additionally, in this group, the 95th percentile (14.2 µg/kg bw/d; based on the creatinine-based model) exceeded the TDI. Exceedances of the TDI were found in the Children II group (four samples (1.9%), creatinine-based model, range: 16.6-34.3 µg/kg bw/d), in the Adults group (one sample (0.37%), creatinine-based model, 16.0 µg/kg bw/d, and

one sample (0.37%), volume-based model, 11.6 µg/kg bw/d). All samples among the group of Elderly People showed DI levels below all acceptable levels. Among all groups, median daily DiBP intakes were below these levels.

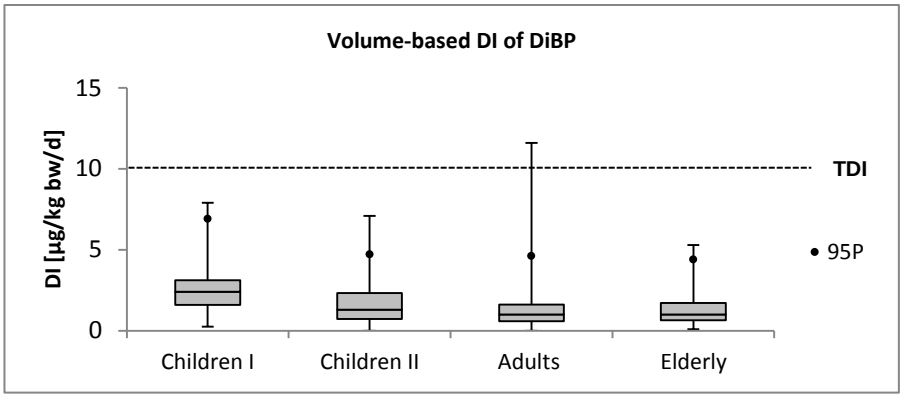


Figure 45. Distributions of volume-based daily DiBP intake [µg/kg bw/d] in the groups of Children I (n=31), Children II (n=219), Adults (n=269) and Elderly People (n=71)

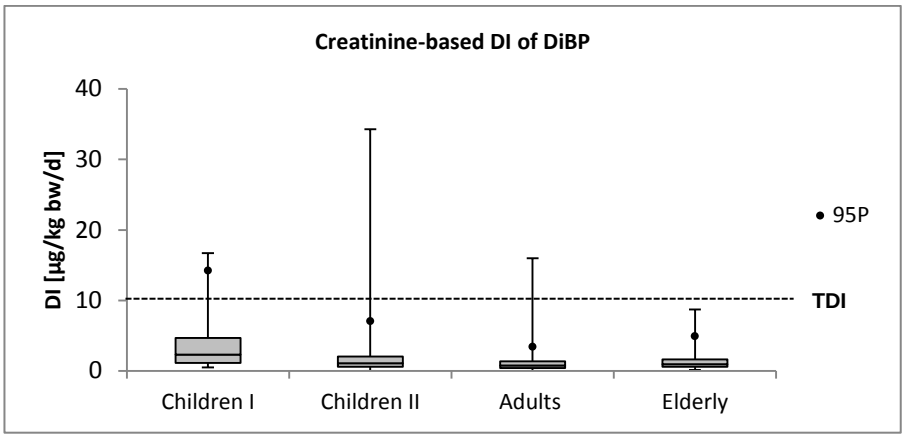


Figure 46. Distributions of creatinine-based daily DiBP intake [µg/kg bw/d] in the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

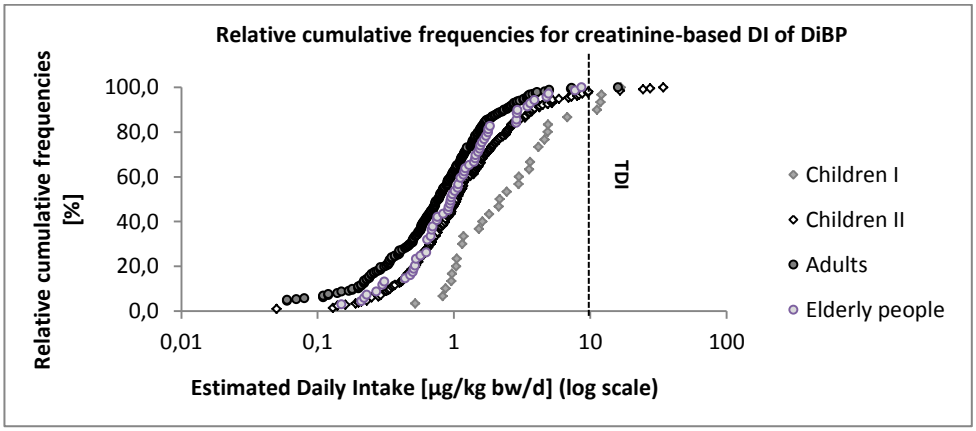


Figure 47. Relative cumulative frequencies [%] for creatinine-based daily DiBP intakes [µg/kg bw/d] among the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

BBzP

Daily BBzP intakes decreases with decreasing age. The highest levels were found among the Children I group. Slightly higher DI values were found in the group of Elderly People (P95 values and median) compared to the group of Adults. Thus, although there was a decrease in daily intake with increasing age, there was a slight increase at later ages for both DIs calculated according to the volume-based and the creatinine-based model. However, all daily intakes among all groups are below the AL.

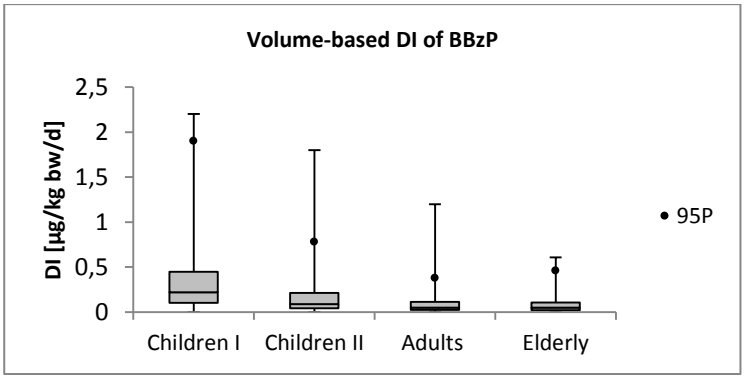


Figure 48. Distributions of volume-based daily BBzP intake [µg/kg bw/d] in the groups of Children I (n=31), Children II (n=219), Adults (n=269) and Elderly People (n=71)

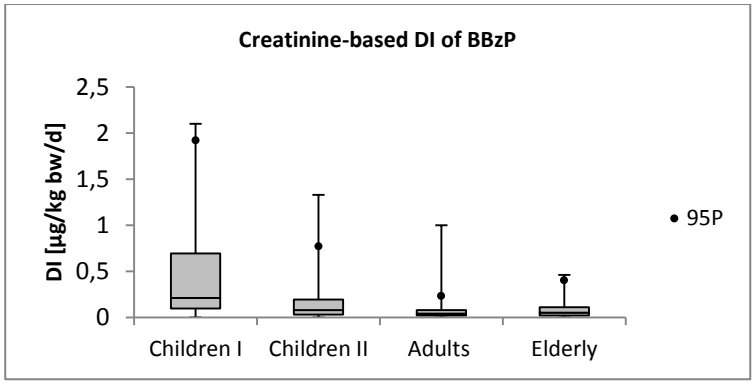


Figure 49. Distributions of creatinine-based daily BBzP intake [µg/kg bw/d] in the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

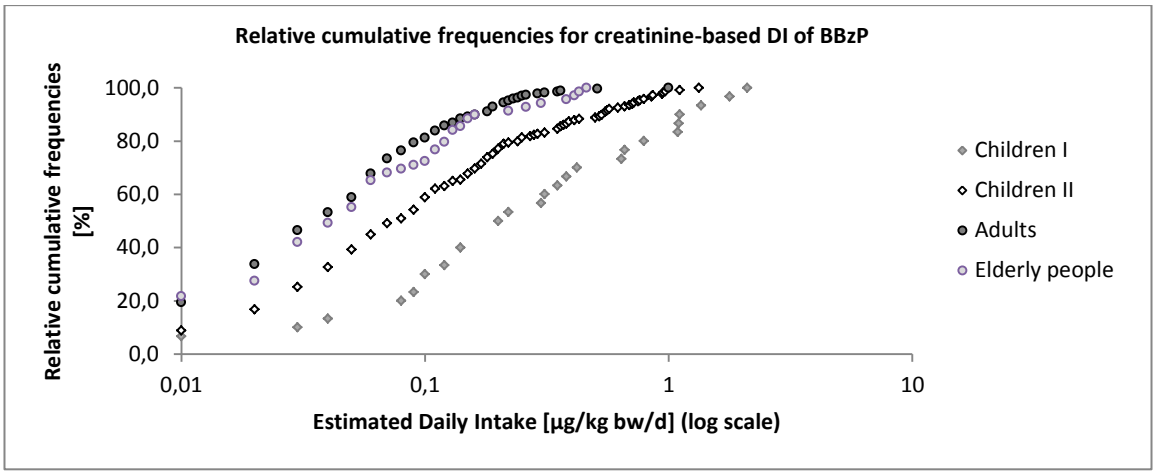
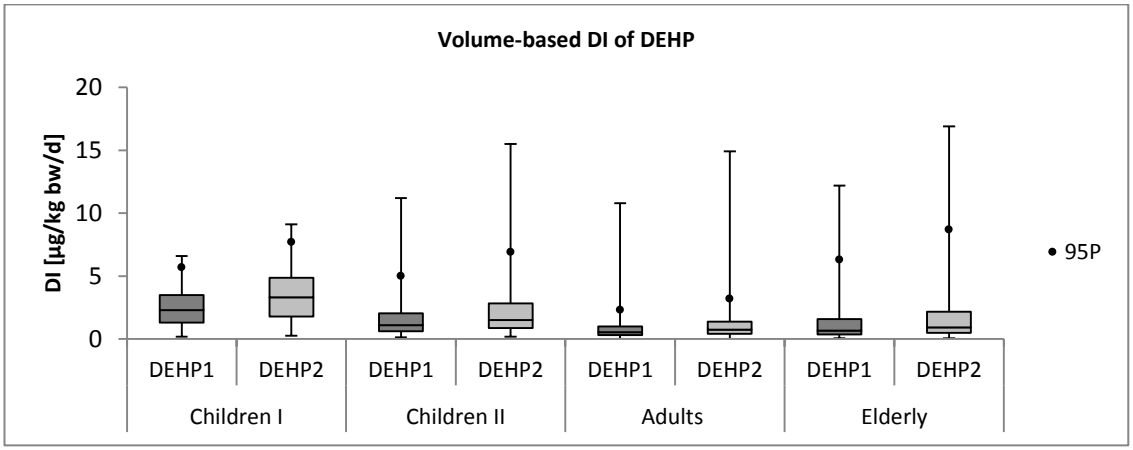


Figure 50. Relative cumulative frequencies [%] for creatinine-based daily BBzP intakes [µg/kg bw/d] among the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

DEHP

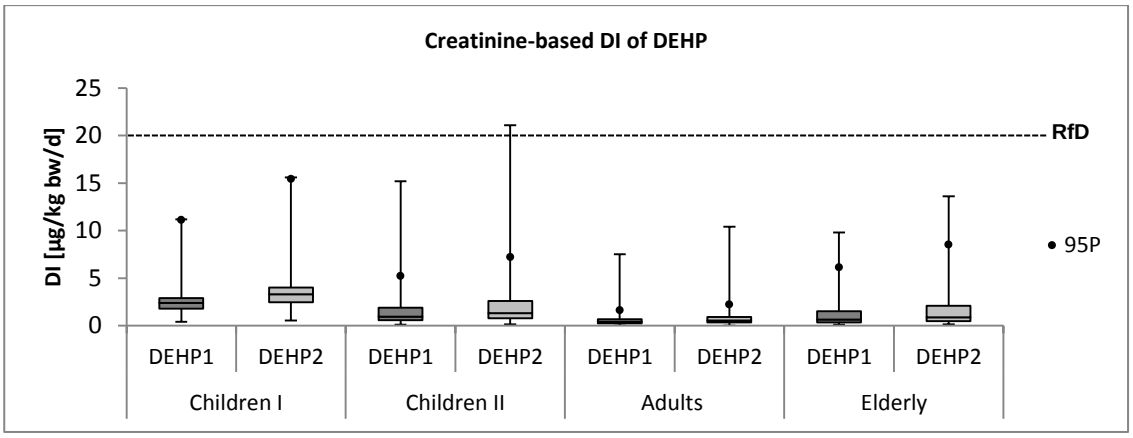
For DEHP, the calculation of the daily intake occurred twice: with F_{UE}s published by Koch et al. (2005) and with F_{UE}s published by Anderson et al. (2011). Reasons the for different calculations are that different studies use either F_{UE}s from Koch et al. or from Anderson et al. and thus, comparison with individual studies is possible. Additionally, F_{UE} values have an important influence on daily intakes. Differences between calculated DIs related to the F_{UE} values used can be discussed.



DEHP1: daily intakes of DEHP based on F_{UE} values derived from Koch et al. (2005)

DEHP2: daily intakes of DEHP based on F_{UE} values derived from Anderson et al. (2011)

Figure 51. Distributions of volume-based daily DEHP intake [µg/kg bw/d] based on molar fraction values (F_{UE}) derived from Koch et al. (2005) and Anderson et al. (2011), respectively in the groups of Children I (n=31), Children II (n=219), Adults (n=269) and Elderly People (n=71)

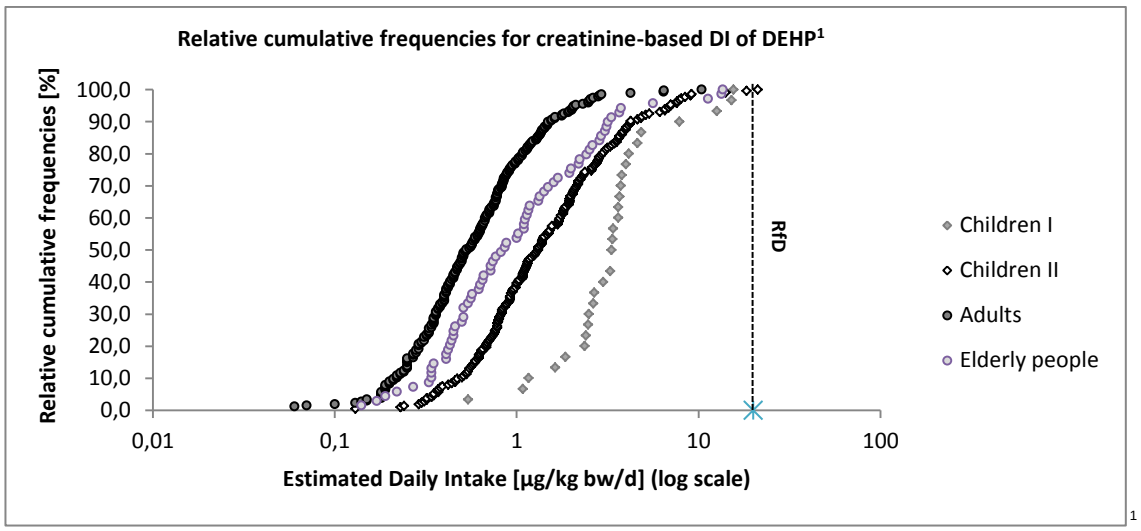


DEHP1: daily intakes of DEHP based on F_{UE} values derived from Koch et al. (2005).

DEHP2: daily intakes of DEHP based on F_{UE} values derived from Anderson et al. (2011).

Figure 52. Distributions of creatinine-based daily DEHP intake [µg/kg bw/d] based on molar fraction values (F_{UE}) derived from Koch et al. (2005) and Anderson et al. (2011), respectively in the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

Median daily DEHP intakes were higher in children when compared with other groups according to the calculation with F_{UE}s published in Koch et al., whereby there was a decline observed related to age between children and adults. All values were below the ALs. According to the calculation with F_{UE}s published in Anderson et al., the daily DEHP intake values were higher because of lower F_{UE} values. Among the Children II group, one sample (based on the creatinine-based model; 0.47%; 21.1 µg/kg bw/d) exceeded the RfD of 20 µg/kg bw/d.



Based on F_{UE} values derived from Anderson et al. (2011)

Figure 53. Relative cumulative frequencies [%] for creatinine-based daily DEHP intakes [µg/kg bw/d] based on F_{UE} from Anderson et al. (2011) among the groups of Children I (n=30), Children II (n=214), Adults (n=267) and Elderly People (n=69)

3.1.5.3.2 Correlations/differences between creatinine- and volume-based daily phthalate intakes

Between all corresponding creatinine-based and volume-based DIs, significant correlations existed (Table 65):

Table 65. Correlations (Spearman) between urinary creatinine-based and urinary volume-based daily intakes [µg/kg bw/d] among total study population (n=580)

Correlations between	Spearman correlation coefficient r
DI DEP crea / DI DEP vol	0.834**
DI DnBP crea / DI DnBP vol	0.850**
DI BBzP crea / DI BBzP vol	0.848**
DI DiBP crea / DI DiBP vol	0.739**
DI DEHP crea / DI DEHP vol	0.748**

** Correlation is significant at 0.01 level.

Because of the use of different calculation models for creatinine-based and urinary volume-based DIs, slight differences were observed. Generally, creatinine-based DI values (especially medians) were lower compared to volume-based DI values. For 95th percentiles, in some cases the creatinine-based values were higher compared to volume-based values, especially for the study population group of Children I.

3.1.5.3.3 Differences between study population groups

Comparing medians of creatinine-based and volume-based DIs, respectively, differences between the population groups were identified. The medians of daily DEP intakes (creatinine-based and volume-based) increased from the group of Children I to the group of Elderly People. Among creatinine-based and volume-based daily intakes of DnBP, BBzP, DiBP and DEHP, decreases were found from the Children I group to the Adults group. For these DIs, there were slightly higher medians in elderly people compared to adults. Related boxplots are illustrated above.

3.1.5.3.4 Associations with several selected parameters

Children I

Correlations between several daily phthalate intakes

Correlations between estimated daily intakes of several phthalates are shown in Table 66. DIs were not normally distributed, except DIs for volume-based DnBP and DEHP.

Table 66. Correlations (Spearman's correlation) between estimated daily phthalate intakes (creatinine-based and volume-based, respectively) in the group of Children I (n=30)

	DI DnBP crea	DI BBzP crea	DI DiBP crea	DI DEHP crea[1]	DI DEP vol	DI DnBP vol	DI BBzP vol	DI DiBP vol	DI DEHP vol[1]
DI DEP crea	**0.445***	**0.371***	**0.427***	**0.375***	**0.751****	0.352	0.216	0.321	0.178
DI DnBP crea		**0.647****	**0.918****	**0.642****	-0.021	**0.401***	0.246	**0.472****	-0.171
DI BBzP crea			**0.701****	**0.473****	0.142	**0.491****	**0.824****	**0.606****	0.206
DI DiBP crea				**0.484****	0.012	**0.410***	0.327	**0.629****	-0.180
DI DEHP crea					0.030	0.214	0.250	0.107	0.282
DI DEP vol						**0.467****	0.282	**0.371***	**0.463****
DI DnBP vol							**0.629****	**0.820****	**0.564****
DI BBzP vol								**0.652****	**0.614****
DI DiBP vol									**0.364***

[1] Correlation coefficients do not differ related to the used F_{UE} values derived from Koch et al. (2005), and from Anderson et al. (2011), respectively.
* Correlation is significant at 0.05 level.
** Correlation is significant at 0.01 level.

Sex

Statistically significant differences were found for volume-based daily DEP intakes (p=0.045) and for daily DnBP intakes (p=0.045) across sex (Mann-Whitney U test). Although the maximum daily DEP intake was observed in boys (18.5 µg/kg bw/d), girls were significantly higher exposed to DEP. Additionally, daily DnBP intakes were also significantly higher in girls.

Age

No statistically significant correlations were found between both age and creatinine-based daily intakes, or for volume-based DEP, BBzP and DiBP intakes (Spearman correlation). A significant correlation was observed between age and the DI for volume-based DEHP (Spearman correlation; r=0.358; p=0.05) in the group of Children I (n=31). DEHP exposure increased with increasing age. However, it must be considered that the sample size is small and the sample size distribution is not optimal.

Anthropometric data

The creatinine-based daily BBzP intakes correlated statistically significantly with waist-to-hip ratios (WHR) (r=0.38; p=0.05), and the volume-based daily DEP intakes with waist circumferences (WC) (r=-0.425; p=0.05) (Spearman correlation). Additionally, in males, creatinine-based BBzP intake correlated significantly with hip circumferences (HC) (r=-0.556; p=0.05), and volume-based DiBP (r=-0.534; p=0.05) and DnBP intake (r=-0.613; p=0.05) with WC. Among females, a significant correlation was found between WHR and volume-based BBzP intake (r=0.561; p=0.05).

Geographical distribution

Between East and West Austria, statistically significant differences were observed in relation to all creatinine-based daily intakes investigated: DEP (p=0.008), DnBP (p=0.001), BBzP (p=0.016), DiBP (p=0.000) and DEHP (p=0.014) (Mann-Whitney U test; n=29). For all named phthalates, children from East Austria were significantly higher exposed than children from West Austria.

Children II

Correlations between daily phthalate intakes

Correlations between the different DIs are shown in Table 67:

Table 67. Correlations (Spearman's correlation) between estimated daily phthalate intakes (creatinine-based and volume-based, respectively) in the group of Children II (n=214-219)

	DI DnBP crea	DI BBzP crea	DI DiBP crea	DI DEHP crea[1]	DI DEP vol	DI DnBP vol	DI BBzP vol	DI DiBP vol	DI DEHP vol[1]
DI DEP crea	0.118	0.018	0.130	**0.225****	**0.778****	-0.080	-0.098	-0.027	0.029
DI DnBP crea		**0.520****	**0.764****	**0.624****	**-0.184****	**0.730****	**0.286****	**0.487****	**0.225****
DI BBzP crea			**0.371****	**0.617****	**-0.142***	**0.419****	**0.862****	**0.247****	**0.424****
DI DiBP crea				**0.456****	-0.104	**0.540****	**0.177****	**0.786****	0.116
DI DEHP crea					-0.036	**0.418****	**0.433****	**0.252****	**0.700****
DI DEP vol						0.036	0.023	0.107	**0.223****
DI DnBP vol							**0.489****	**0.702****	**0.520****
DI BBzP vol								**0.326****	**0.591****
DI DiBP vol									**0.353****

[1] Correlation coefficients do not differ related to the used F_{UE} values derived from Koch et al. (2005), and from Anderson et al. (2011), respectively.
* Correlation is significant at 0.05 level.
** Correlation is significant at 0.01 level.

Sex

No differences were found between sex and creatinine-based and volume-based daily intakes, respectively (Mann-Whitney U test; n=220).

Age

A statistically significant correlation was observed between age and creatinine-based daily DEHP intake (r=-0.165; p=0.05; n=214) (Spearman correlation). Kruskal-Wallis tests were performed, demonstrating significant differences for DIs for creatinine-based DnBP (p= 0.010), BBzP (0.002), and DEHP (0.005) across different age groups[10].

[10] Age groups in the group of Children II: 7-9 years (n=82), 10-12 years (n=89) and 13-14 years (n=41).

Anthropometric data

Significant correlations were observed between measured bodyheight and daily intakes of creatinine-based BBzP (r=-0.156; p=0.05) and DEHP (r=-0.201; p=0.01), as well as between bodyweight and daily intakes for creatinine-based DnBP (r=-0.143; p=0.05) and DEHP (r=-0.190; p=0.01) (Spearman correlation; n=214).

A significant correlation was found between creatinine-based daily DEHP intake and hip circumference (HC) (r=-0.139; p=0.05) in the Children II group (Spearman correlation). In females (n=94), significant correlations were found between WC and volume-based daily intake of DnBP (r=0.209; p=0.05), BBzP (r=0.225; p=0.05) and DEHP (r=0.262; p=0.05), between abdominal circumference (AC) and volume-based DI of DEHP (r=0.221; p=0.05), as well as between HC and volume-based daily DnBP intake (r=0.223; p=0.05). In males (n=125), significant correlations existed between AC and volume-based and creatinine-based daily DEHP intake (r=-0.190; p=0.05 and r=-0.200; p=0.05, respectively), WC and creatinine-based daily DEHP intake (r=-0.241; p=0.01), as well as between HC and creatinine-based DEHP intake (r=-0.234; p=0.01).

Geographical distribution

No differences existed between East and West Austria.

Adults

Correlations between daily phthalate intakes

Table 68 shows correlations between estimated creatinine- and volume-based DI among adults (n=267):

Table 68. Correlations (Spearman's correlation) between estimated daily phthalate intakes (creatinine-based and volume-based, respectively) in the group of Adults (n=267)

	DI DnBP crea	DI BBzP crea	DI DiBP crea	DI DEHP crea[1]	DI DEP vol	DI DnBP vol	DI BBzP vol	DI DiBP vol	DI DEHP vol[1]
DI DEP crea	0.059	0.080	**0.225****	**0.204****	**0.858****	0.067	-0.049	0.093	-0.015
DI DnBP crea		**0.422****	**0.299****	**0.364****	**0.230****	**0.952****	**0.605****	**0.612****	**0.596****
DI BBzP crea			**0.300****	**0.473****	0.003	**0.412****	**0.803****	**0.212****	**0.307****
DI DiBP crea				**0.390****	-0.007	**0.292****	0.061	**0.682****	0.016
DI DEHP crea					0.060	**0.339****	**0.299****	**0.201****	**0.645****
DI DEP vol						**0.263****	**0.150***	**0.226****	**0.245****
DI DnBP vol							**0.624****	**0.648****	**0.615****
DI BBzP vol								**0.381****	**0.577****
DI DiBP vol									**0.408****

[1] Daily DEHP intakes calculated based on F_{UE} values derived from Koch et al. (2005), and from Anderson et al. (2011), respectively had identical correlation coefficients.

* Correlation is significant at 0.05 level.

** Correlation is significant at 0.01 level.

Sex

Sex-related differences were found for all estimated volume-based daily intakes, but not for creatinine-based (Mann-Whitney U Test). Significance levels were 0.016 for daily intakes of volume-based DEP, 0.000 for DnBP, 0.001 for BBzP, 0.000 for DiBP and 0.017 for DEHP. Table 69 shows median and maximum values for male and female adults of volume-based daily intakes. Females were more highly exposed compared to males. For DEP, females showed a higher median level; however, in males the P95 value was higher compared to female adults.

Table 69. Volume-based daily intake values (median, maximum) [µg/kg bw/d] of female (n=160) and male (n=109) adults

[µg/kg bw/d]	**Females (n=160) (median; maximum)**	**Males (n=109) (median; maximum)**
DI DEP vol	1.6; 41.6	0.99; 40.6
DI DnBP vol	0.32; 2.4	0.21; 1.1
DI BBzP vol	0.06; 1.2	0.04; 0.39
DI DiBP vol	1.1; 11.6	0.80; 4.2
DI DEHP vol[1]	0.59; 10.8	0.50; 9.5
DI DEHP vol[2]	0.82; 14.9	0.69; 13.2

[1] F_{UE} values derived from Koch et al. (2005)
[2] F_{UE} values derived from Anderson et al. (2011)

Age

Significant correlations were found between age and creatinine-based daily intakes of DEP (r=0.144; p=0.05), and volume-based daily intakes of DnBP (r=-0.163; p=0.01), BBzP (r=-0.194; p=0.01) and DEHP (r=-0.152; p=0.05) (Spearman correlation). Additionally, statistically significant differences were observed between different age groups (18-24 years, 25-50 years, and 51-64 years) and volume-based daily intakes of DnBP (p= 0.020), BBzP (p=0.010) and DEHP (p=0.040).

Anthropometric data

Regarding to anthropometric data, significant correlations were found between bodyheight and daily intakes of volume-based DEP (r=-0.171; p=0.01), DnBP (r=-0.197; p=0.01), DiBP (r=-0.148; p=0.05) and creatinine-based DEP (r=-0.122; p=0.05), as well as for bodyweight and daily intake of volume-based DEP (r=-0.144; p=0.05), DnBP (r=-0.286; p=0.01), BBzP (r=-0.178; p=0.01), DiBP (r=-0.190; p=0.01) and DEHP (r=-0.163; p=0.01). For BMI, statistically significant correlations existed between daily intakes of volume-based DnBP (r=-0.230; p=0.01), BBzP (r=-0.148; p=0.05), DiBP (r=-

0.135; p=0.05) and DEHP (r=-0.179; p=0.01) (Spearman correlation). Additionally, statistically significant differences were observed between different BMI categories[11] and DIs of volume-based DnBP (p=0.014), and of DEHP (p=0.220).

Geographical distribution

Statistically significant differences were found between the distribution in East and West Austria of volume-based daily DnBP (p= 0.070) and DiBP intakes (p=0.090) after Mann-Whitney U tests were performed. No differences were found between residential areas (urban, suburban and rural).

Elderly People

Correlations between daily phthalate intakes

Table 70 shows the correlations (Spearman correlation) between calculated creatinine- and volume-based daily phthalate intakes among the elderly:

Table 70. Correlations (Spearman's correlation) between estimated daily phthalate intakes (creatinine-based and volume-based, respectively) in the group of Elderly People (n=69)

	DI DnBP crea	DI BBzP crea	DI DiBP crea	DI DEHP crea[1]	DI DEP vol	DI DnBP vol	DI BBzP vol	DI DiBP vol	DI DEHP vol[1]
DI DEP crea	**0.487****	0.159	**0.433****	**0.357****	**0.883****	0.118	-0.047	0.115	-0.004
DI DnBP crea		**0.574****	**0.791****	**0.536****	**0.316****	**0.648****	**0.355****	**0.499****	0.212
DI BBzP crea			**0.397****	**0.417****	0.151	**0.615****	**0.866****	**0.452****	**0.432****
DI DiBP crea				**0.650****	**0.278***	**0.440****	0.200	**0.704****	**0.297***
DI DEHP crea					**0.243***	**0.278***	**0.258***	**0.428****	**0.740****
DI DEP vol						**0.309****	0.152	**0.276***	0.173
DI DnBP vol							**0.733****	**0.733****	**0.516****
DI BBzP vol								**0.541****	**0.592****
DI DiBP vol									**0.564****

[1] Daily DEHP intakes calculated based on F_{UE} values derived from Koch et al. (2005), and from Anderson et al. (2011), respectively had identical correlation coefficients.
* Correlation is significant at 0.05 level.
** Correlation is significant at 0.01 level.

Sex

Among elderly people, no sex differences related to daily intakes were observed.

Age

Significant correlations were found between age and creatinine-based daily intakes of DEP (r=0.330; p=0.01), DnBP (r=0.315; p=0.01), DiBP (r=0.259; p=0.05, and DEHP (r=0.289; p=0.05). For creatinine-based daily intakes, no correlations existed. After

[11] BMI categories for adults: BMI<18.5 (underweight), BMI 18.5-24.9 (normal weight), BMI 25-29.9 (overweight, preadipositas), BMI>30 (adipositas grade I-III) [kg/m^2]

Mann-Whitney U tests were performed, significant differences were found between different age groups[12] and creatinine-based daily DEP (p= 0.019) and DnBP intake (p=0.029).

Anthropometric data

Between bodyheight as well as bodyweight and creatinine-based and volume-based DIs no correlations were found. Additionally, there were no correlations for BMI. However, performing Kruskal-Wallis tests, a statistical significant difference existed for volume-based daily DEHP intake across BMI categories[13] (p=0.029).

Geographical distribution

There were no statistically significant differences between East and West Austria related to the investigated daily intakes, and no differences between urban, suburban and rural residential areas in the group of Elderly People.

3.1.5.3.5 Comparison with other study results

Table 71 shows the daily intakes calculated from analysed urinary phthalate metabolite concentrations from selected studies between 1999 and 2010. For comparison with the results of the present study, different calculation models (creatinine-based and volume-based) were used. It should be noted, however that only a few studies on daily phthalate intake were available.

In German children (n=239) aged 2-14 years from GerES IV pilot study (sample collection in 2001-2002), median creatinine-based DIs of DnBP, BBzP and DEHP of 4.1, 0.42 and 4.3 µg/kg bw/d respectively, were reported. Median volume-based DIs for the named phthalates were 7.6, 4.5 and 7.8 µg/kg bw/d, respectively. (Koch et al., 2007; Wittassek et al., 2007) In Danish children aged 6-11 years from urban areas (sample collection in 2011), reported median DIs [µg/kg bw/d] were 0.53 for DEP, 0.7 for DnBP, 2.4 for DiBP, 0.17 for BBzP and 2.7 for DEHP (Frederiksen et al., 2013). The highest median values were found for DEHP, followed by DnBP for all studies evaluated (Figure 54). In general, median DI levels were lower in the present study compared to results from Germany and Denmark, except for DEP, which showed similar results in the Danish population.

[12] 64-70 years (n=33) and 71-81 years (n=36)

[13] BMI categories for elderly people: BMI<23.9 (underweight), BMI 24-29.9 (normal weight), BMI>30 (overweight, adipositas) [kg/m^2]

Table 71. Several estimated daily phthalate intakes (ranges, medians, 95th percentiles) [µg/kg bw/d] from selected studies

Study	DEP Range (median; P95)	DnBP Range (median; P95)	DiBP Range (median; P95)	BBzP Range (median; P95)	DEHP Range (median; P95)
Germany					
Wittassek et al. (2007a), Koch et al. (2007): *239 male and female children from GerES IV pilot study (age 2-14), crea-based*[1] *2001-2002*		0.66-76.4 (4.1; 14.9)		0.06-13.9 (0.42; 2.6)	0.6-140 (4.3; 15.2)
Wittassek et al. (2007a), Koch et al. (2007): *239 male and female children from GerES IV pilot study (age 2-14), vol-based*[1] *2001-2002*		0.91-110 (7.6; 30.5)		0.05-31.3 (0.77; 4.5)	0.4-409 (7.8; 25.2)
Koch, Drexler and Angerer (2003): *25 male adults from South Germany (age 18-40), crea-based*[2] *2002*	(2.4; 20.0)	(6.0; 19.9)		(1.1; 4.1)	(16.9; 65.0)
Koch, Drexler and Angerer (2003): *34 female adults from South Germany (age 18-40), crea-based*[2] *2002*	(4.4; 33.6)	(8.1; 24.1)		(1.4; 5.0)	(12.5; 27.4)
Wittassek et al. (2007b): *59 male and female German students (retrospective), vol-based*[3] *2003*		0.49-71.8 (1.9; 5.3)	0.46-5.2 (1.4; 3.9)	0.05-1.7 (0.22; 0.91)	0.28-7.1 (2.4; 5.7)
Koch et al. (2011): *108 male and female primary school starters (age 5-6), crea-based*[4] *2007*		11.2 (max) (1.9; 6.4)	59.4 (max) (2.1; 11.0)	10.4 (max) (0.3; 2.6)	44.5 (max) (4.5; 18.0)
Fromme et al. (2013): *25 male and female children from INES 2 study (age 1.25-1.75), vol-based*[5] *2009-2010*	0.15 (max) (0.06; 0.14)	0.69 (max) (0.43; 0.68)	1.2 (max) (0.53; 1.1)		4.0 (max) (2.6; 4.0)
Denmark					
Frederiksen et al. (2011): *129 male and female Danish children from Copenhagen Puberty Study (age 6-16) and adolescents from a high school (age 17-21), vol-based*[6] *2006-2008*	18.2 (max) (1.1; 8.0)			10.0 (max) (0.62; 3.78)	52.9 (max) (4.0; 10.7)
Bekö et al. (2013): *431 Danish children (age 3-6), vol-based*[7] *2008-2009*	0.02-33.0 (0.62; 3.9)	0.25-163 (3.3; 10.0)		0.02-22.3 (0.49; 2.8)	0.38-533 (4.4; 16.9)
Frederiksen et al. (2013): *Danish children (age 6-11) from urban (74) and rural (67) area, crea-based*[8] *2011*	8.5 (max) (0.53; 3.0) 6.4 (max) (0.53; 2.7)	2.5 (max) (0.70; 2.2) 7.4 (max) (0.86; 2.0)	9.1 (max) (2.4; 7.6) 31.7 (max) (2.8; 7.4)	5.5 (max) (0.17; 1.1) 2.6 (max) (0.23; 1.1)	85.6 (max) (2.7; 8.1) 21.8 (max) (2.4; 12.5)
Frederiksen et al. (2013): *Danish women (age 31-52) from urban (75) and rural (69) area, crea-based*[8] *2011*	12.5 (max) (0.72; 3.6) 16.3 (max) (1.0; 10.5)	1.9 (max) (0.49; 1.0) 1.8 (max) (0.54; 1.3)	6.3 (max) (1.7; 3.0) 6.0 (max) (1.6; 5.2)	0.80 (max) (0.09; 0.43) 0.9 (max) 0.13; 0.47)	90.1 (max) (1.6; 5.1) 30.7 (max) (1.5; 4.4)

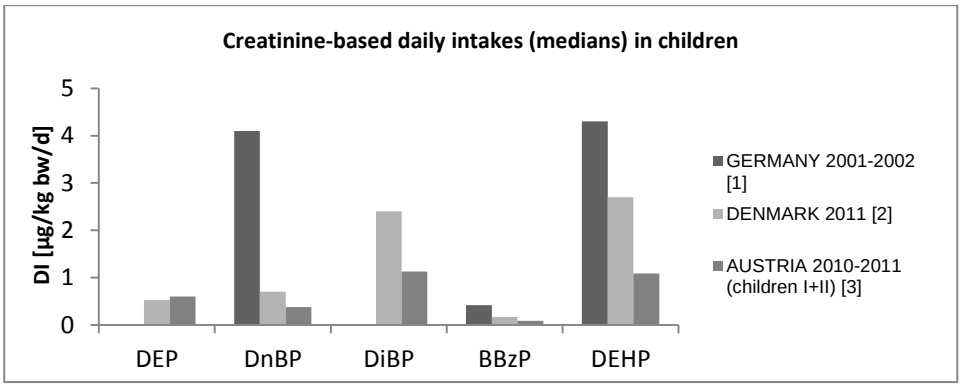
continued

France					
Zeman et al. (2013): *139-279 French pregnant women from ELFE pilot study, crea-based*[9] *2007*	(1.0; 20.2)	(1.5; 6.6)	(2.2; 11.1)	(0.4; 2.4)	(5.8; 65.1)
USA					
Marsee et al. (2006): *214 pregnant women from the Study for Future Families, crea-based*[10] *1999-2002*	1263 (max) 6.6; 112)	5.9 (max) 0.84; 2.33)	2.9 (0.12; 0.41)	15.5 (max) (0.5; 2.5)	41.1 (max) (1.3; 9.3)

Abbreviations: crea, creatinine; ELFE, Étude Longitudinale Francaise depuis l'Enfance; GerES IV, German Environmental Survey IV; F_{UE}, molar fraction; INES 2, Integrated Exposure Assessment Survey 2; P95, 95th percentile; vol, volume.
[1] F_{UE} adopted from Koch et al. (2005).
[2] F_{UE} adopted from Schmid and Schlatter (1985) for DEHP, and from Anderson et al. (2001) for DnBP and BBzP.
[3] F_{UE} adopted from Anderson et al. (2001) for DnBP, DiBP and BBzP, and from Koch et al. (2005) for DEHP.
[4] F_{UE} adopted from Koch et al. (2005) for DEHP; Koch and Calafat (2009) and Wittassek et al. (2011) for other phthalates.
[5] F_{UE} adopted from Anderson et al. (2001) for DEP and BBzP, Seckin, Fromme and Völkel (2009) for DnBP, and from Koch et al. (2005), Kessler et al. (2012), Anderson et al. (2011) related to specific DEHP-metabolite.
[6] F_{UE} adopted from Anderson et al. (2011), and Koch et al. (2005, 2007) for BBzP and DEHP, and from Koch and Calafat (2009) for DEP.
[7] F_{UE} adopted from Koch et al. (2012a) for DiBP.
[8] F_{UE} adopted from Anderson et al. (2001, 2011) for DEHP, BBzP and DBP, and from Koch and Calafat (2009) for DEP.
[9] F_{UE} adopted from Koch et al. (2005) for DEHP, Anderson et al. (2001) for DnBP, Fromme et al. (2007) for DEP and DiBP, and Koch et al. (2003) for BBzP.
[10] F_{UE} adopted from Anderson et al. (2001) for DBP and BBzP, Koch et al. (2003) for DEP, and Koch et al. (2005) for DEHP.

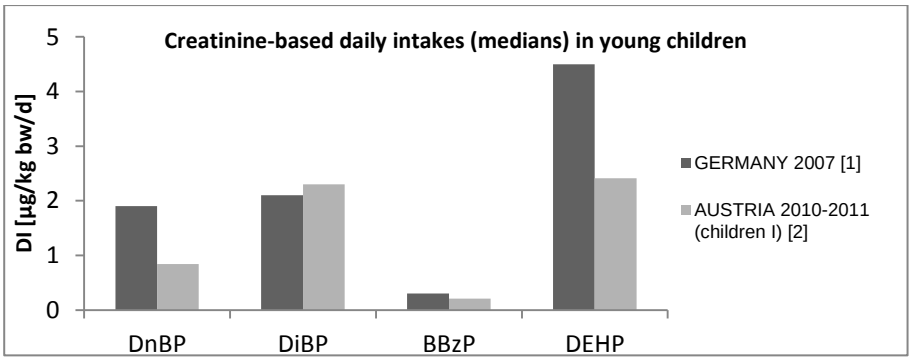
In 108 German primary school starters (5-6 years), median DIs of DnBP, DiBP, BBzP and DEHP based on the creatinine-based calculation model were 1.9, 2.1, 0.3 and 4.5 µg/kg bw/d, respectively (Koch et al., 2011). Compared to results from the present study in the group of Children I (6-8 years; n=30), median levels were lower for DnBP, BBzP and DEHP, but not for DiBP, which showed a slightly higher median DI (2.3 µg/kg bw/d). Median daily DEHP intake was about two times higher in the German study population compared to the Austrian study population, where a median value of 2.4 µg/kg bw/d was observed (Figure 55). However, samples differ somewhat in age (German children 5-6 years, Austrian children 6-8 years), as well as in sample size.

Frederiksen et al. (2013) published in their study of Danish females (31-52 years) from urban (n=75) and rural (n=69) areas median creatinine-based DIs for DEP of 0.72 and 1.0 µg/kg bw/d (urban and rural, respectively), for DnBP 0.49 and 0.54 µg/kg bw/d, for DiBP 1.7 and 1.6 µg/kg bw/d, for BBzP 0.09 and 0.13 µg/kg bw/d, and for DEHP 1.6 and 1.5 µg/kg bw/d (Table 71; Figure 56). In Austrian females (18-65 years) from (sub)urban (n=78) and rural (n=80) areas, creatinine-based median DI for DEP of 0.89 and 1.1 µg/kg bw/d ((sub)urban and rural, respectively), for DnBP of 0.27 and 0.22 µg/kg bw/d, for DiBP of 0.79 and 0.88 µg/kg bw/d, for BBzP of 0.05 and 0.04 µg/kg bw/d, and for DEHP of 0.54 and 0.66 µg/kg bw/d were obtained. For both studies, time of sampling is similar.



[1] Koch et al. (2007); Wittassek et al. (2007); [2] Frederiksen et al. (2013); [3] this study

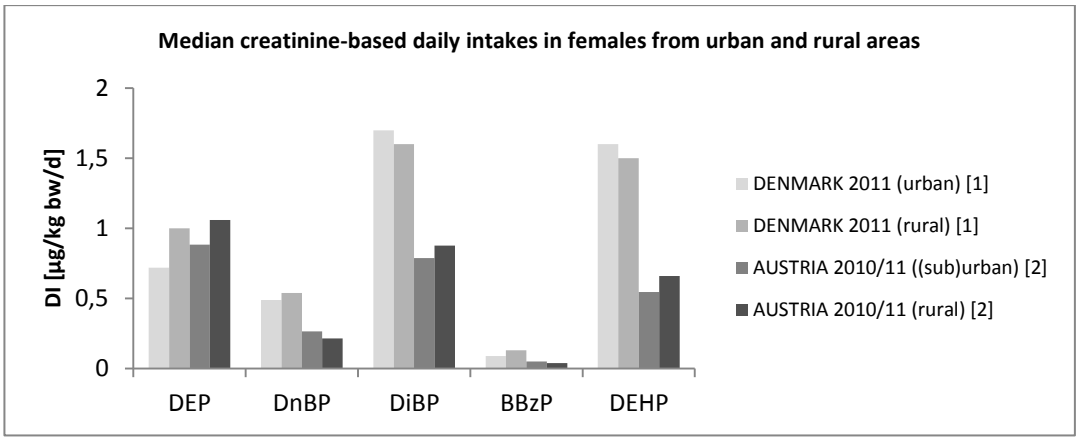
Figure 54. Median creatinine-based daily phthalate intakes (DEP, DnBP, DiBP, BBzP, and DEHP) [µg/kg bw/d] in German children (2-14 years, n=239), Danish children from urban areas (6-11 years, n=74), and Austrian children (6-15 years, n=244)



[1] Koch et al. (2011); [2] this study

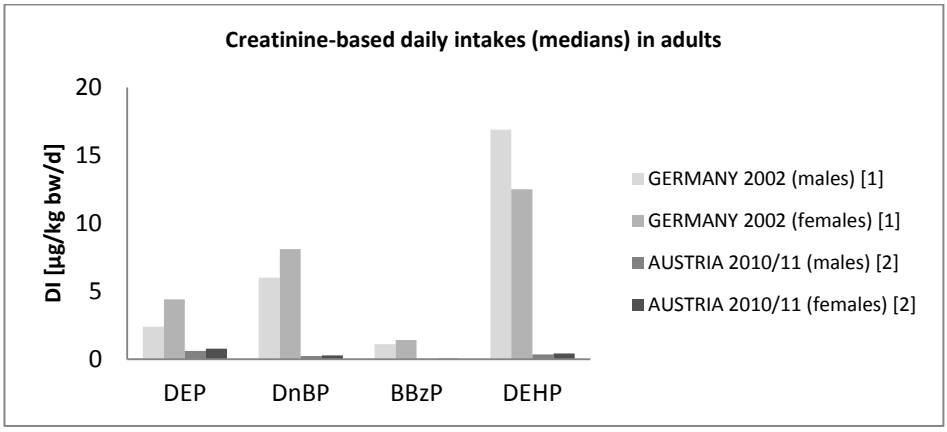
Figure 55. Median creatinine-based daily phthalate intakes (DnBP, DiBP, BBzP, and DEHP) [µg/kg bw/d] in German children (5-6 years, n=108) and Austrian Children I (6-8 years, n=30)

In the Austrian study population of adult females, median daily intakes (creatinine-based model) of participants from (sub)urban areas were slightly lower in relation to DEP, DiBP and DEHP, but slightly higher in relation to DnBP and BBzP. In the Danish population group, females from urban areas had lower median daily DEP, DnBP and BBzP intakes, and higher median daily DiBP and DEHP intakes, which differ slightly compared to Austrian females of the present study. Generally, investigated median DIs were higher in Danish females than in Austrian females, especially for DiBP and DEHP, which were both about two times higher. This was obtained for all investigated daily phthalate intakes, except for DEP, where medians from Austrian females were higher compared to Danish females (Figure 57).



[1] Frederiksen et al. (2013); [2] this study

Figure 56. Median creatinine-based daily phthalate intakes (DEP, DnBP, DiBP, BBzP, and DEHP) [µg/kg bw/d] in Danish females (31-52 years) from urban (n=75) and rural (n=69) areas, and in Austrian females (18-65 years) from (sub)urban (n=78) and rural (n=80) areas



[1] Koch, Drexler and Angerer (2003); [2] this study

Figure 57. Median creatinine-based daily phthalate intakes (DEP, DnBP, BBzP, and DEHP) [µg/kg bw/d] in German males (n=25) and females (n=34) (18-40 years), and in Austrian males (n=53) and females (n=90) (18-40 years)

In a study of male (n=25) and female (n=34) German participants (18-40 years), obtained median creatinine-based daily intakes were relatively high (cf. Table 71) (Koch, Drexler and Angerer, 2003). To compare results from the named study with results from the present study, participants were drawn from the same age group. In Austrian males (n=53) and females (n=90), median creatinine-based daily DEP intakes were 0.6 and 0.79 µg/kg bw/d (for males and females, respectively), daily DnBP intakes were 0.24 and 0.29 µg/kg bw/d, daily BBzP intakes were 0.03 and 0.05 µg/kg bw/d and daily DEHP intakes were 0.36 and 0.41 µg/kg bw/d. As shown in Figure 57, median daily intakes of all investigated phthalates were considerably higher in German samples compared to medians obtained from Austrian samples. The largest difference was identified for median daily DEHP intake in males, which was about 47 times

higher. Nevertheless, it must be recognised that samples from the German population were taken in 2002, which may be one reason for these large differences.

3.1.5.4 Discussion

Daily intakes (DI) of the phthalates DEP, DnBP, BBzP, DiBP and DEHP[14] were estimated based on phthalate metabolite concentrations analysed with creatinine-based and urinary volume-based calculation models according to Koch et al. (2007). Necessary for DI calculation is the knowledge of the so-called molar fraction (F_{UE}) of phthalates, which has been provided from several studies investigating the phthalate metabolite concentration in urine after an oral administration of a known dose of labelled phthalates. In the case of DEHP, the DIs were calculated based on F_{UE} values for DEHP metabolites published in Koch et al. (2005) and F_{UE} values published in Anderson et al. (2011), separately, to enable a comparison with results from other studies where different F_{UE} values for DEHP metabolites were used, and the investigation of varying outputs.

Between creatinine-based and volume-based DIs, slight differences existed. Comparing median values, creatinine-based DI values were generally lower compared to volume-based values. Nevertheless, corresponding creatinine- and volume-based DIs correlated at a 0.01 significance level. Differences were also observed between the study population groups. Medians of daily DEP, DiBP and DEHP intakes (creatinine-based and volume-based) decreased from the group of Children I to the group of Adults. In elderly people, slightly higher medians existed compared to younger adults. In the case of median creatinine-based and volume-based daily DEP intakes, there was an increase from the Children I group to the Elderly People group.

For risk assessment it is important to investigate possible daily intake exceedances of acceptable exposure levels (AL). Therefore, calculated DIs for phthalates were compared with the Tolerable Daily Intake (TDI), the Reference Dose (RfD) and the Reference Dose for Anti-Androgenicity (RfD AA). ALs are shown in Table 8. Daily intakes of DEP, BBzP and DEHP calculated with F_{UE} published by Koch et al. (2005) were below all investigated ALs. Some exceedances of ALs (mainly exceedances of the TDI) were observed, especially in children. Two children (from the groups Children I

[14] Daily DiNP and DiDP intakes were not calculated, because only primary metabolites were analysed. Missing levels of secondary metabolites make a correct estimation of daily intakes not possible. Both, DCHP and DnOP were estimated neither, because of unknown F_{UE} for DCHP, and because of urine levels of MCHP below limit of detection in a majority of samples.

and II) had higher daily DnBP intakes than the TDI for both creatinine-based and volume-based values. For creatinine-based daily DnBP intake, the P95 values exceeded the TDI in the group of Children I, but it must be noted that the sample size was small. For daily DiBP intakes, exceedances are similar to DnBP, whereby slightly more exceedances existed. Detailed results are shown in Chapter 3.1.5.3.1 above. Compared with daily DEHP intake values using F_{UE} values published by Koch et al. (2005), one daily DEHP intake estimated with F_{UE} provided by Anderson et al. (2011) among the group of Children II exceeded the corresponding RfD. These differences show the importance of exact knowledge regarding the toxicokinetics of various substances in humans.

In Table 72, the findings of statistical analysis of creatinine-based and volume-based DIs for several phthalates among the different study population groups are summarised.

Table 72. Summary of statistical analysis outcome for volume- and creatinine-based daily intakes of DEP, DnBP, BBzP, DiBP and DEHP, in the study population groups Children I, Children II, Adults and Elderly People for sex, age, bodyheight, bodyweight, Waist-to-Hip ratio, Body Mass Index and distribution between East Austria and West Austria

		DEP vol	DnBP vol	BBzP vol	DiBP vol	DEHP vol	DEP crea	DnBP crea	BBzP crea	DiBP crea	DEHP crea
Sex	*C I*	f ↑	f ↑								
	A	f ↑	f ↑	f ↑	f ↑	f ↑					
Age	*C I*					+					
	C II										-
	A		--			-	+				
	E						++	++		+	+
BH	*C I*								-		--
	A	--	--		-		-				
BW	*C II*							-			--
	A	-	--	--	--	--					
WHR	*C I*			+(f)					+		
BMI	*A*		--	--	-	--					
	E					overw. ↑					
Distr	*C I*						East ↑	East ↑	East ↑	East ↑	East ↑
	A		West ↑		West ↑						

- / +, negative / positive correlation at 0.05 significance level.

-- / ++, negative / positive correlation at 0.01 significance level.

Abbreviations: A, Adults; BH, bodyheight; BMI, Body Mass Index; BW bodyweight; crea, creatinine-based; C I, Children I; C II, Children II; Distr, distribution East and West Austria; E, Elderly People; f, females; overw., overweight; vol, volume-based; WHR, waist-to-hip ratio.

Several volume-based daily phthalate intakes differed between both sexes in the groups of Children I (n=31) and the group of Adults (n=269), whereby females showed higher intakes compared to males. Among adults, statistically significant higher DIs in females existed for all investigated phthalates, and among children, these findings applied to DEP and DnBP.

Different significant correlations between age and DIs were found in all study population groups. In the Children I group, daily intakes of volume-based DEHP increased with increasing age, whereas in the group of Adults, it was reversed. Additionally, daily intakes of volume-based DnBP decreased with increasing age in adults with high significance, and daily intakes of creatinine-based DEP increased. Increasing DIs of creatinine-based DEP, DnBP, DiBP and DEHP were shown in elderly people. In the Children II group, a decrease of creatinine-based daily DEHP intake with increasing age was found.

Between bodyheight and several DIs, significant correlations exist. In the Children I group, creatinine-based daily BBzP and DEHP intakes decreased with increasing bodyheight, and in adults, this was shown for volume-based daily DEP, DnBP and DiBP intakes, as well as for creatinine-based daily DEP intakes. Volume-based DIs of DEP, DnBP, BBzP, DiBP and DEHP decreased with increasing bodyweight among adults. A decrease was also shown for creatinine-based daily DnBP and DEHP intakes in the Children II group. Significant negative correlations between DIs and BMI were only found in adults, whereby volume-based DIs of DnBP, BBzP, DiBP and DEHP were higher in samples with low BMI compared to samples with high BMI, which had lower DI levels. In elderly people, significant differences were found for volume-based DEHP intake: higher levels were found in relation to higher BMI.

Among Children I group, there was a statistically significant east-west decline related to all investigated creatinine-based daily phthalate intakes. In adults, for volume-based DnBP and DiBP intake, a west-east decline existed. It must be noted that among the Children I group the sample size of 31 is very small.

Compared to results from other studies investigating daily intakes of several phthalates in various population groups, the daily phthalate intakes from the present study were for the most part lower. Reasons for these observations might include not only possible differences in lifestyle, behaviour and nutrition, but also different times of sampling. Especially great differences existed in daily phthalate intakes compared to results from a German male and female adult population (Koch, Drexler and Angerer, 2003), where urine samples were collected in 2002 (Figure 57). Such findings suggest that, because

of new legislations in the EU regarding to the use of phthalates in consumer products, exposure might have been reduced.

3.1.6 Cumulative Risk Assessment

In general, risk assessment of chemicals does not take into account effects of combined exposures, and as a result underestimations of risks are possible and a cumulative risk assessment is needed (Kortenkamp and Faust, 2010). Multiple phthalates have been identified as anti-androgens that reduce testosterone in a dose-additive fashion in rats. Thus, a cumulative risk assessment for combined phthalate exposure is important. (Kortenkamp and Faust, 2010; Søeborg, Frederiksen and Andersson, 2012) One method is the dose-addition concept by using the Hazard Index (HI) approach for the estimation of the overall potential for non-carcinogenic effects of several substances. This approach allows the assumption of adverse human health effects as result of simultaneous exposures. (Kortenkamp and Faust, 2010; U.S. EPA, 1989) It is defined as the sum of Hazard Quotients (HQ) divided by an acceptable level of exposure (AL) such as the TDI or the RfD AA of a substance using the following formula published in Kortenkamp and Faust (2010):

$$\mathrm{HI} = \sum_{i=1}^{n} \frac{EL_i}{AL_i}$$

HI	Hazard Index
EL_i	Exposure Level (or Daily Intake) of a substance
AL_i	Acceptable Level (e.g. TDI, RfD AA)
n	Number of substances in the mixture

For the ALs it is not necessary that all of them are based on the same toxicological endpoint, but in this analysis, only endpoints with relevance to anti-androgenicity were considered. Phthalates that are able to disrupt male sexual differentiation in rat models investigating reproductive toxicity are DnBP, DiBP, BBzP, DiNP and DEHP. HI values >1 indicate the exceedance of the considered AL for the total dose of all components of the mixture and the existence of cause for concern. (Kortenkamp and Faust, 2010)

Similar to the HI is the concept of relative cumulative Tolerable Daily Intake (TDI_{cum}). Therefore, the calculated DI is divided by the TDI for each substance, and the ratio is multiplied by 100% by use of the formula published in Koch et al. (2011):

$$\mathrm{TDI_{cum}} = \sum_{i=1}^{n} \frac{DI_i}{TDI_i} * 100$$

TDI_{cum}	Relative Cumulative Tolerable Intake [%]
DI_i	Daily Intake [µg/kg bw/d]
TDI_i	Tolerable Daily Intake [µg/kg bw/d]
n	Number of phthalates

At a TDI_{cum} of more than 100% it is indicated that the total TDI is exceeded and a potential cause for concern exists (Koch et al., 2011).

3.1.6.1 Calculation

For cumulative risk assessment calculations, individual HI values were estimated for children, adults and elderly people for DEHP, DnBP, DiBP and BBzP based on the RfD AA values, as well as for DEHP, DnBP and DiBP based on the corresponding TDI values using the formula published in Kortenkamp and Faust (2010) (see above). The TDIs of the named phthalate can be used because they are based on the same endpoints (anti-androgenicity) (Koch et al., 2011). TDI and RfD AA values of investigated phthalates are shown in Table 8. The calculation and results of daily intakes are described in Chapter 3.1.5. For cumulative risk assessment estimations, creatinine-based DI values were used.

3.1.6.2 Results

Table 73 illustrates the ranges, medians and P95 values of HIs based on available TDI and RfD AA values for the present study population, respectively, as well as the amount [%] of individual samples exceeding the respective total AL, which indicates a potential cause for concern.

Depending on the ALs used (TDI or RfD AA), samples predominantly exhibited HI values lower than the cumulated acceptable level of exposure. In some cases, exceedances existed, especially among children.

Table 73. Hazard Indices (HI) for Austrian children, adults and elderly people

	Children I (n=30)	**Children II (n=214)**	**Adults (n=266)**	**Elderly (n=69)**
	range (median; P95)	range (median; P95)	range (median; P95)	range (median; P95)
HI (TDI)	0.08-3.4 (0.37; 2.7)	0.02-5.4 (0.18; 0.94)	0.001-1.7 (0.12; 0.42)	0.02-1.1 (0.15; 0.77)
n>1 [%]	13.3	4.2	0.4	2.9
HI (RfD AA)	0.02-0.74 (0.13; 0.69)	0.01-0.72 (0.05; 0.28)	0.0-0.35 (0.27; 0.09)	0.01-0.48 (0.04; 0.31)
n>1 [%]	0	0	0	0

Abbreviations: HI, Hazard Index; n, sample size; P95, 95th percentile; RfD AA, Reference Dose for Anti-Androgenicity.
Notes: Daily intake calculations for DEHP based on F_{UE} values published in Anderson et al. (2011). HI calculation based on DnBP, DiBP, BBzP and DEHP for estimations based on RfD AA values and on DnBP, DiBP and DEHP for estimations based on TDI values because of same endpoint (anti-androgenicity).

HI values based on TDIs showed more exceedances of the HI of 1 than values based on RfD AA levels, because generally the TDIs for several phthalates are lower than the corresponding RfD AAs (Table 8). Based on the TDI as acceptable level, exceedances were identified among all study population groups, whereby the highest amount occurred among children. In the group of children at the age of 6-8 years (Children I group, n=30), four samples (13.3%) showed HI values above 1 and therefore the cumulated acceptable exposure level, with the highest HI of 3.4. Among children aged between 8 and 14 years (Children II group, n=214), nine samples (4.2%) have HI values above the cumulative acceptable exposure level. Among the group of Adults (n=266) and among the group of Elderly People (n=69), only one sample (0.4%) respective two samples (2.9%) showed HI above the cumulative acceptable exposure level. Based on the RfD AA, no exceedances were shown (c.f. Table 73).

These results demonstrate that a considerable number of samples had levels above the HI value of 1 (especially based on TDI values). Most exceedances were shown among children who remain one of the most vulnerable groups of the general population.

3.1.6.3 Comparison with other study results

In a study among Danish children and adolescents (n=129) investigating urinary phthalate metabolite exposure and the HI, the authors reported that 19 children (15%) exceeded the cumulative acceptable exposure level based on the TDI, and one child (0.8%) exceeded the acceptable level based on the RfD AA. (Søeborg, Frederiksen and Andersson, 2012) In a sample of 108 German children aged between 5 and 6 years, the calculated relative TDI_{cum} based on DnBP, DEHP and DiBP was exceeded by 26 children (24%). In 33 Danish young men (18-22 years) sampled in 2008, three 24-h urine samples were collected from each participant. The authors reported in two men exceedances of HI based on the TDI, and in one man an exceedance of the HI based on the RfD AA. (Kranich et al., 2014) Differences in the number of exceedances were related to specific acceptable exposure levels derived by different institutions. For example, the current TDI for DnBP is ten times lower compared to the RfD or the RfD AA for the same phthalate.

Compared with these study results, investigations of the present study showed slightly fewer HI exceedances in relation to the TDI among children when compared to results from Germany. However, the sample size in the present study was far lower. The number of exceeded HIs compared with Danish children was similar but slightly fewer.

In comparison with results from Kranich et al. (2014) in Danish men, among adults from the present study one exceedance of HI based on TDI out of 266 existed.

3.1.6.4 Discussion

The group of phthalates includes several different substances. Because of possible underestimations of risks, it is important to implement a risk assessment for cumulative effects. One possibility is the concept of the Hazard Index (HI) for the estimation of effects of several substances. An HI exceeding the value of 1 (100%) indicates potential cause for concern. Within the present study population, exceedances of HIs were found especially among children. Compared with the results of other studies, the findings of the present study were similar to those from Denmark concerning the TDI. In comparison to Germany, slightly fewer exceedances were observed. It should be noted, however, that currently only a few studies investigating cumulative risks exist due to the relatively recent attention these have received from the scientific community. Further and more detailed investigations are necessary, in particular with regard to the cumulative effects of the various substances to which we are exposed.

3.1.7 Associations with selected parameters

3.1.7.1 Age

The total study population (n=595) was categorised into several age groups: 6-10 years (n=118; 20%), 11-15 years (n=133; 22%), 18-24 years (n=45; 8%), 25-50 years (n=159; 27%), 51-64 years (n=68; 11%) and ≥65 years (n=72; 12%). Figure 58 illustrates the distribution. The analysed urinary phthalate metabolites showed statistically significant correlations with age, with these correlations being all significant at 0.01 level. MEP was the only metabolite that showed a positive correlation and thus an increase with increasing age, whereas the other phthalate metabolites showed reversed findings. Significant correlations of several phthalate metabolites are shown in Table 74. The median phthalate metabolite concentrations of each investigated age group are listed in Table 75 and Table 76.

In general, median and P95 values of the majority of DEHP metabolites (Figure 59) decreased with increasing age, except for the oldest age group (>65 years), which showed higher levels again.

The distribution of MEP, which is the only phthalate metabolite that showed an increased exposure with increasing age, is illustrated in Figure 60. Similar to findings from DEHP metabolites, a decrease with increasing age was also identified for MBzP (Figure 61). For MnBP and MiBP exposure (Figure 62 and Figure 63) significant differences between the investigated age groups were found, but no trend concerning age could be clearly identified.

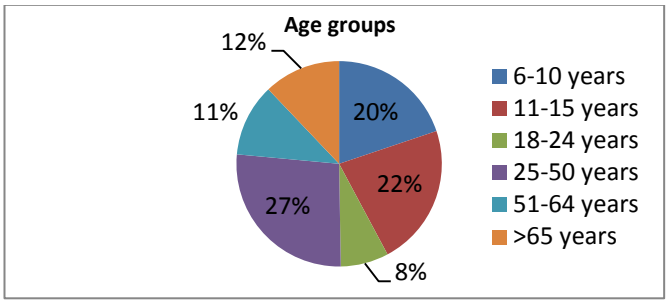


Figure 58. Distribution of age groups (Phthalate metabolites) (n=595)

Table 74. Significant correlations (Spearman correlation) between urinary phthalate metabolite concentrations [µg/l], and creatinine-adjusted phthalate metabolite concentrations [µg/g] and age in total study population (n=595)

Urinary phthalate metabolites [µg/l]								
Phthalate		*DEHP*			*DEP*	*BBzP*	*DnBP*	*DiBP*
Metabolite	***MEHP***	***5oxo-MEHP***	***5OH-MEHP***	***5cx-MEPP***	***MEP***	***MBzP***	***MnBP***	***MiBP***
Age [years]	-0.253	-0.408	-0.307	-0.311	0.254	-0.284	-0.222	-0.194
Urinary phthalate metabolites creatinine-adjusted [µg/g]								
Phthalate		*DEHP*			*DEP*	*BBzP*	*DnBP*	*DiBP*
Metabolite	***MEHP***	***5oxo-MEHP***	***5OH-MEHP***	***5cx-MEPP***	***MEP***	***MBzP***	***MnBP***	***MiBP***
Age [years]	-0.276	-0.429	-0.342	-0.397	0.181	-0.327	-0.241	-0.220

All correlations are significant at 0.01 level.

Table 75. Median phthalate metabolite levels [µg/l] for different age groups in the total population (n=595)

	Median phthalate metabolite levels [µg/l]					
	6-10 years (n=118)	***11-15 years (n=133)***	***18-24 years (n=45)***	***25-50 years (n=159)***	***51-64 years (n=68)***	***≥65 years (n=72)***
MEHP	0.88	1.2	0.69	n.d.	n.d.	n.d.
5oxo-MEHP	4.2	3.3	1.7	1.1	1.4	1.6
5OH-MEHP	5.7	4.4	2.5	1.5	2.0	3.3
5cx-MEPP	17.0	14.8	11.1	7.6	8.3	10.0
MEP	16.7	21.8	31.0	31.5	39.5	38.0
MBzP	2.6	2.9	2.1	1.3	1.2	1.3
MnBP	48.8	13.5	10.6	7.4	7.4	10.6
MiBP	37.4	36.1	26.6	22.9	23.3	26.5
MCHP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3cx-MPP	1.9	1.6	1.6	1.6	1.6	1.6
MnOP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
MnPeP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
MiNP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
MiDP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

Notes: for statistical analysis, phthalate metabolites <LOD, LOD/2 was used.

Table 76. Median creatinine-adjusted phthalate metabolite levels [µg/g] for different age groups in the total population (n=583)

	Median creatinine-adjusted phthalate metabolite levels [µg/g]					
	6-10 years (n=115)	***11-15 years (n=130)***	***18-24 years (n=44)***	***25-50 years (n=158)***	***51-64 years (n=67)***	***≥65 years (n=69)***
MEHP	1.1	0.85	0.29	n.d.	n.d.	n.d.
5oxo-MEHP	5.9	3.0	1.3	0.94	1.1	1.6
5OH-MEHP	7.0	4.3	1.5	1.7	1.7	2.9
5cx-MEPP	20.3	14.6	5.3	6.1	6.5	9.2
MEP	20.1	21.5	25.8	26.1	34.9	31.7
MBzP	3.4	2.5	1.4	1.4	1.1	1.4
MnBP	15.2	11.6	6.7	6.6	6.5	11.7
MiBP	39.5	29.1	21.5	20.1	24.5	27.3
MCHP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3cx-MPP	3.2	1.4	0.88	1.0	1.1	2.8
MnOP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
MnPeP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
MiNP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
MiDP	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

Notes: for statistical analysis, phthalate metabolites <LOD, LOD/2 was used.

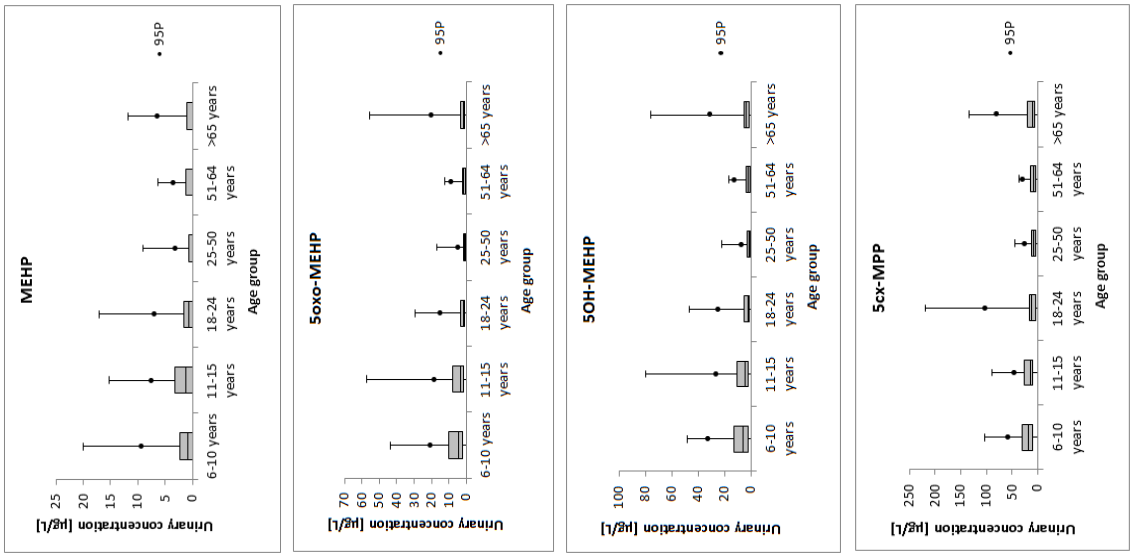


Figure 59. Distributions of urinary DEHP metabolite concentrations (MEHP, 5oxo-MEHP, 5OH-MEHP and 5cx-MEPP) [µg/l] among different age groups of the total study population (n=595)

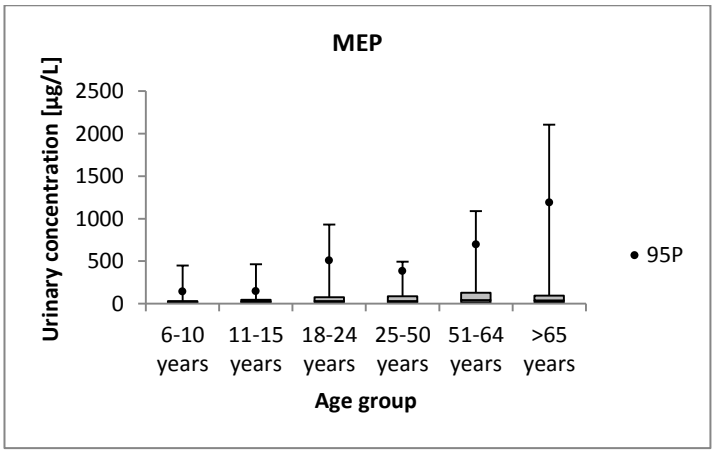


Figure 60. Distribution of urinary MEP concentrations [µg/l] among different age groups of the total study population (n=595)

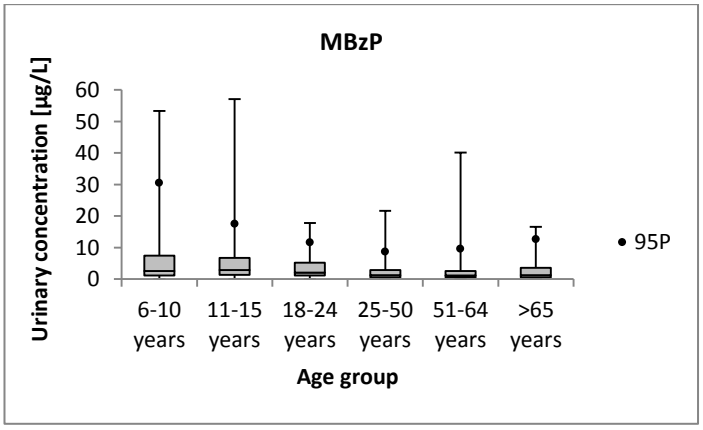


Figure 61. Distribution of urinary MBzP concentrations [µg/l] among different age groups of the total study population (n=595)

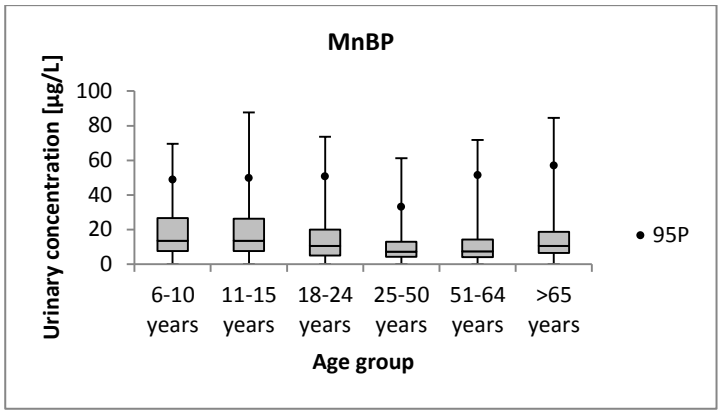


Figure 62. Distribution of urinary MnBP concentrations [µg/l] among different age groups of the total study population (n=595)

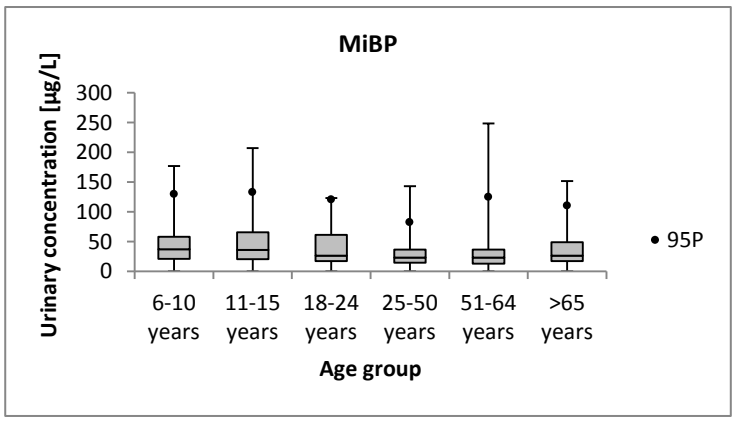


Figure 63. Distribution of urinary MiBP concentrations [µg/l] among different age groups of the total study population (n=595)

3.1.7.2 Sex

The total study population consisted of 309 females and 286 males. In order to identify potential associations between urinary phthalate metabolite concentrations and sex, Mann-Whitney U-tests were performed for each study population group. Among the group of Children II and the group of Elderly People, no statistically significant sex-related differences were identified. Among the Children I group, females (n=15) exhibited significantly higher MEP exposure (for both creatinine-adjusted and creatinine-unadjusted concentrations; p=0.045 each) and MnBP exposure (only for creatinine-unadjusted concentrations; p=0.045) than males (n=16). Nevertheless, the small sample size must be considered. Among the group of Adults, several statistically significant sex-related differences were identified for creatinine-adjusted MEP (p=0.021), 5oxo-MEHP (p=0.000), MBzP (p=0.010), MnBP (p=0.000), 5OH-MEHP (p=0.000), MiBP (p=0.000), 5cx-MEPP (p=0.021) and MiNP (p=0.007), as well as for creatinine-unadjusted 5oxo-MEHP (p=0.080), MBzP (p=0.021), MnBP (p=0.000), 5OH-

MEHP (p=0.019), MiBP (p=0.045) and MiNP (p=0.006). Concerning all these metabolites, females (n=162) were more highly exposed than males (n=110).

3.1.7.3 Regional differences

The study population was divided into two geographic regions (cf. Figure 12): East Austria including the federal states of Vienna, Lower Austria, Burgenland and Styria, and West Austria including the federal states of Vorarlberg, Tyrol, Salzburg and Upper Austria, with 60% of the total study population (n=357) being from the east and 40% (n=235) from the west of Austria. Creatinine-adjusted and creatinine-unadjusted phthalate metabolite concentrations were tested for regional differences with Mann-Whitney U-test for non-parametric hypotheses tests at a significance level of 0.05. Statistically significant differences were identified for the creatinine-unadjusted as well as the creatinine-adjusted phthalate metabolites 5oxo-MEHP (p=0.003 and 0.002, respectively), MBzP (p=0.029 and 0.011, respectively), MEHP (p=0.000 in both cases), 5OH-MEHP (p=0.011 and 0.003, respectively), 5cx-MEPP (0.003 in both cases) and MiNP (0.045 and 0.37, respectively). Participants from East Austria exhibited higher levels of exposure, and thus an east-west decline was identified. For all DEHP metabolites (MEHP, 5oxo-MEHP, 5OH-MEHP and 5cx-MEHP), significantly higher levels were found in East Austria, which suggests that DEHP exposure also follows an east-west decline.

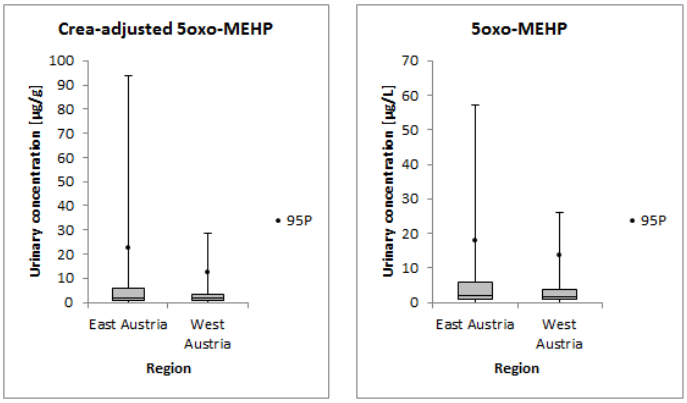


Figure 64. Distribution of creatinine-adjusted 5oxo-MEHP [µg/g] and 5oxo-MEHP [µg/l] among participants from East Austria (n=354 and 357, respectively), and from West Austria (n=228 and 235, respectively)

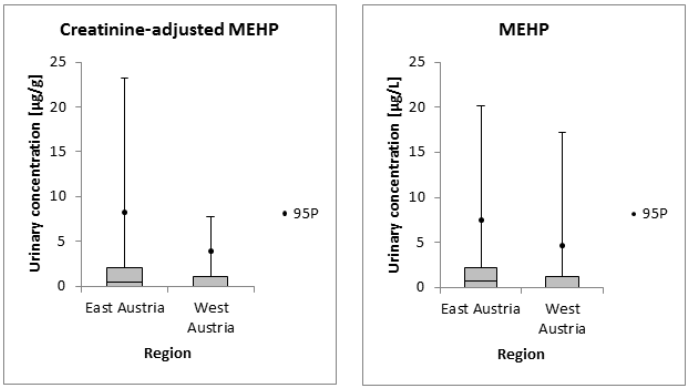


Figure 65. Distribution of creatinine-adjusted MEHP [µg/g] and MEHP [µg/l] among participants from East Austria (n=354 and 357, respectively), and from West Austria (n=228 and 235, respectively)

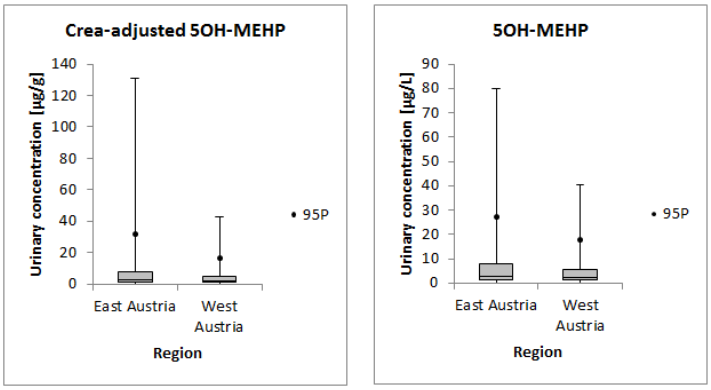


Figure 66. Distribution of creatinine-adjusted 5OH-MEHP [µg/g] and 5OH-MEHP [µg/l] among participants from East Austria (n=354 and 357, respectively), and from West Austria (n=228 and 235, respectively)

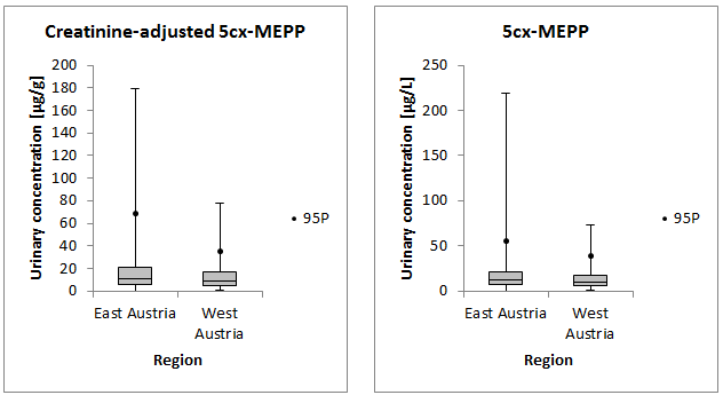


Figure 67. Distribution of creatinine-adjusted 5cx-MEPP [µg/g] and 5cx-MEPP [µg/l] among participants from East Austria (n=354 and 357, respectively), and from West Austria (n=228 and 235, respectively)

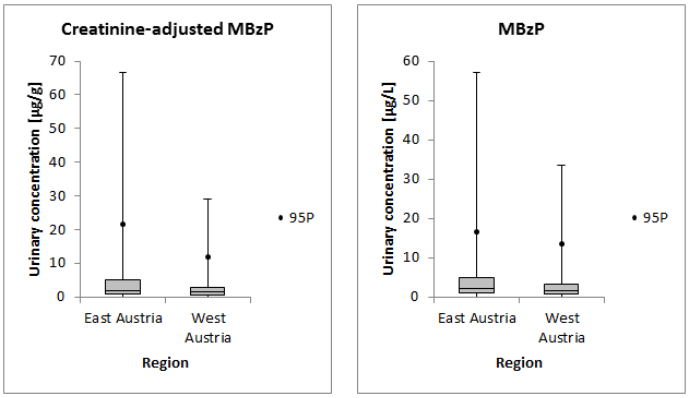


Figure 68. Distribution of creatinine-adjusted MBzP [µg/g] and MBzP [µg/l] among participants from East Austria (n=354 and 357, respectively), and from West Austria (n=228 and 235, respectively)

3.1.7.4 Residential area

Urban, suburban and rural areas were surveyed in the questionnaires. Because of the suboptimal distribution of participants and the similarity of the groups “urban” and “suburban”, they have been combined to form the single category “(sub)urban” in the following.

55% (n=229) of the participants from the total study population reported living in rural areas and 45% (n=284) in (sub)urban areas (Figure 69). The distribution was similarly divided as concerns the east and the west of Austria, with 57% (n=180) of the participants living in rural areas and 47% (n=136) in (sub)urban areas in East Austria, and 53% (n=92) living in rural areas and 43% (n=104) living in (sub)urban areas in West Austria.

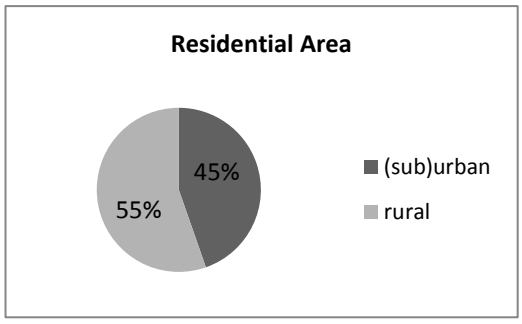


Figure 69. Distribution of participants of the total study population living in (sub)urban areas (n=229) and rural areas (n=284)

A Mann-Whitney U test at a 0.05 significance level identified significant differences between the residential area and creatinine-unadjusted and creatinine-adjusted MEP

(p=0.000 and 0.042, respectively), creatinine-adjusted 5oxo-MEHP (p=0.006), creatinine-adjusted 5OH-MEHP (p=0.021) and creatinine-unadjusted 5cx-MEPP (p=0.036).

In general, participants from (sub)urban areas showed significantly higher exposure levels to certain phthalate metabolites compared to participants from rural areas (Figure 70 - Figure 72). Although one participant from a rural area exhibited a higher maximum 5cx-MEPP level compared to the maximum level of a participant from a (sub)urban area, the overall exposure was higher in (sub)urban areas (Figure 72).

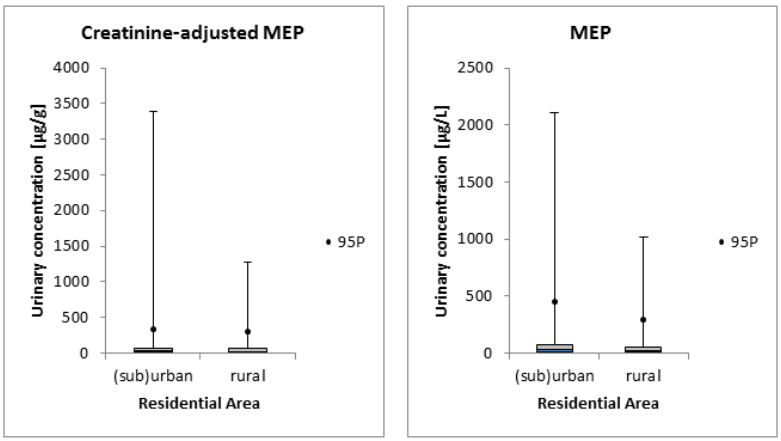


Figure 70. Distribution of creatinine-adjusted MEP [µg/g] and MEP [µg/l] among participants from (sub)urban areas (n=223 and 229, respectively) and from rural areas (n=280 and 284, respectively)

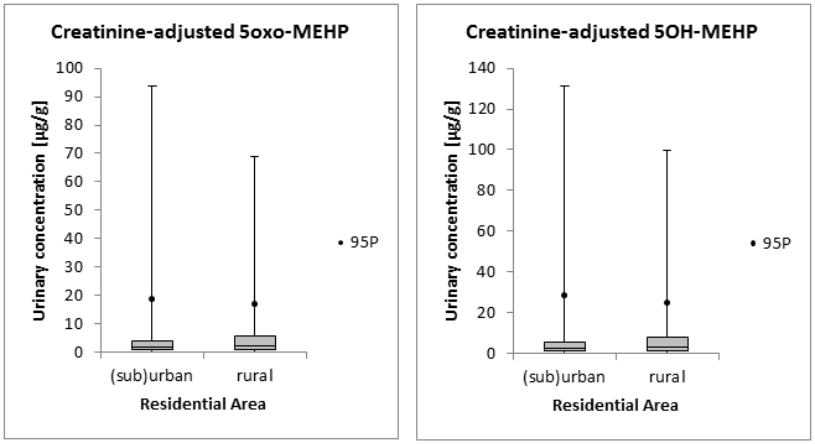


Figure 71. Distributions of two creatinine-adjusted DEHP metabolites (5oxo-MEHP and 5OH-MEHP [µg/g]) among participants from (sub)urban areas (n=223) and from rural areas (n=280)

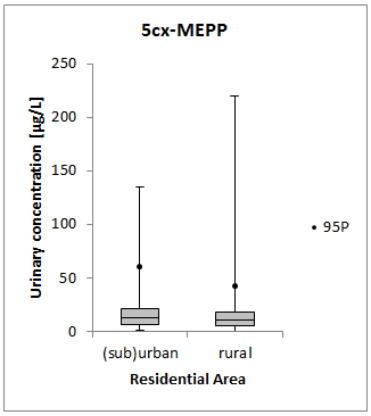


Figure 72. Distribution of 5cx-MEPP [µg/l] among participants from (sub)urban areas (n=229) and from rural areas (n=284)

3.1.7.5 Anthropometric characteristics

Anthropometric characteristics (BMI, WC, AC, HC and WHR) of each study population group are listed in Chapter 3.1.1.

Statistically significant differences between different BMI categories only existed in the group of Elderly People. Kruskal-Wallis tests at 0.05 significance level identified significant differences in the case of 5OH-MEHP (p=0.009), 5cx-MEPP (p=0.003) and 3cx-MPP (p=0.032). For these phthalate metabolites, increasing levels were found with increasing BMI (Figure 73 to Figure 75).

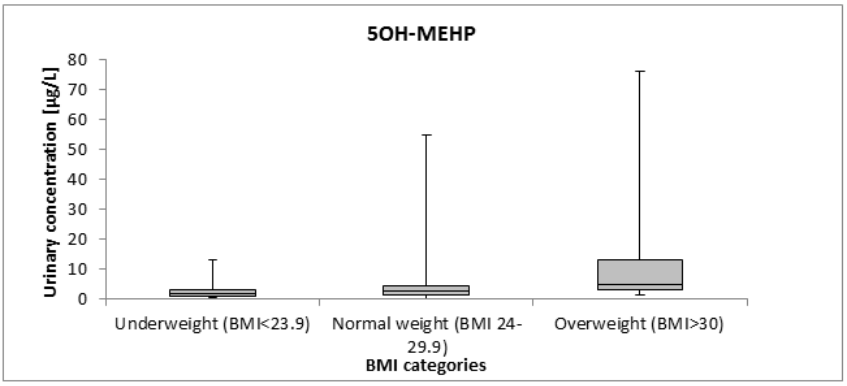


Figure 73. Distribution of urinary 5OH-MEHP concentrations [µg/l] in the group of Elderly People with underweight (n=11), normal weight (n=41) and overweight (n=19)

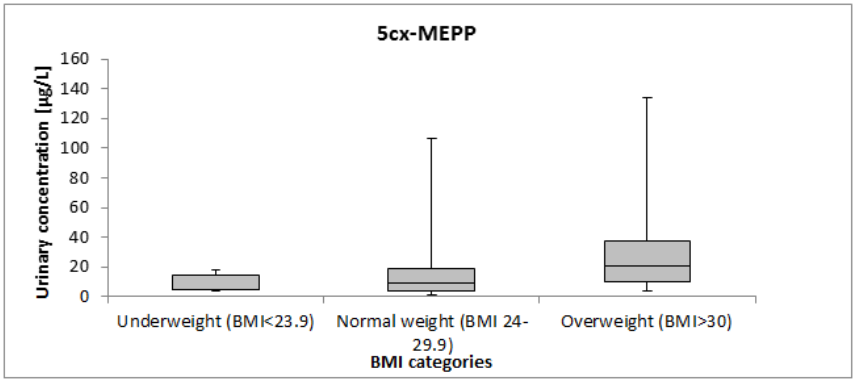


Figure 74. Distribution of urinary 5cx-MEPP concentrations [µg/l] in the group of Elderly People with underweight (n=11), normal weight (n=41) and overweight (n=19)

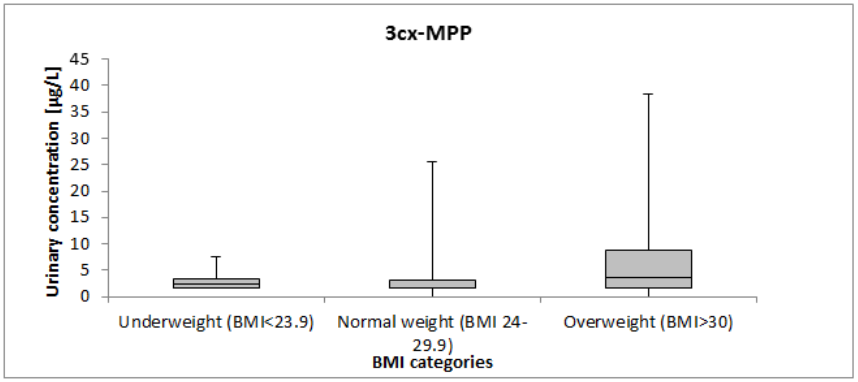


Figure 75. Distribution of urinary 3cx-MPP concentrations [µg/l] in the group of Elderly People with underweight (n=11), normal weight (n=41) and overweight (n=19)

For the investigation of possible correlations between several anthropometric data and urinary phthalate metabolite concentrations, two-sided Spearman correlations were performed. Among the group of Children I, a significant negative correlation was observed between MEP and WC (r=-0.425) and a significant positive correlation between creatinine-adjusted MBzP and WHR (r=0.397). Both correlations were significant at a significance level of 0.05. Among the Children II group, significant correlations were shown at a level of 0.01 for MCHP and WC (r=0.194), AC (r=0.230) and HC (r=0.220), as well as for creatinine-adjusted MCHP and AC (r=0.211) and HC (r=0.201). Additionally, in the same group, positive correlations were found at a 0.05 significance level between AC and MnBP (r=0.137). Among the group of Adults, significant negative correlations existed between MnBP and both WC (r=-0.138 at 0.05 significance level) as well as WHR (r=-0.171 at 0.01 significance level), between creatinine-adjusted MnBP and WC (-0.178 at 0.01 a significance level) and WHR (r=-0.200 at a 0.01 significance level), and between creatinine-adjusted 5oxo-MEHP and WHR (r=-0.135 at a 0.05 significance level). Among the group of Elderly People, positive correlations were identified between MEHP and WC (r=0.277), creatinine-

adjusted MEHP and WC (r=0.292), 5cx-MEPP and WC (r=0.273), AC (r=0.284) and HC (r=0.276), and between creatinine-adjusted 5cx-MEPP and HC (r=0.239). Additionally, positive correlations were found between 5OH-MEHP and WC (r=0.262), AC (r=0.249) and HC (r=0.261). These correlations were significant at a 0.05 significance level.

3.1.7.6 Diseases / disorders

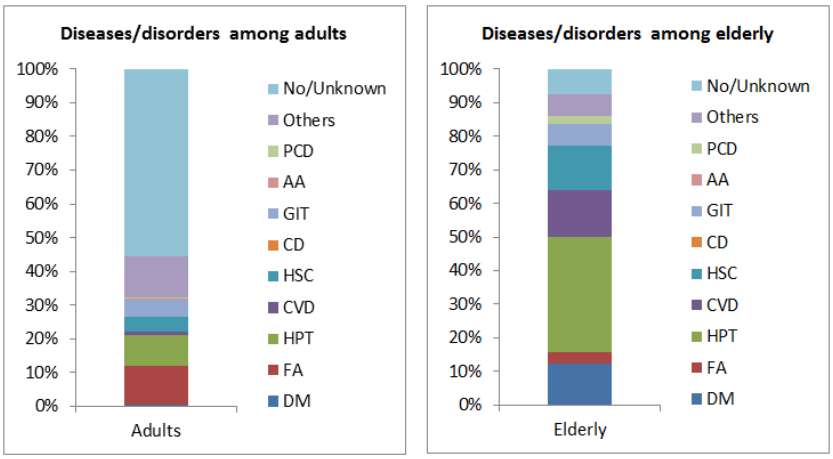
The occurrence of several diseases and/or disorders was surveyed among the study groups of Adults and Elderly People. The frequencies and distributions of reported diseases and disorders are illustrated in Table 77 and Figure 76. It is important to note that participants were allowed to report more than one disease/disorder. Conspicuously, most adults (60%) reported not currently suffering from nor being aware of having any diseases/disorders, whereas only a few elderly people (13%) reported the same.

Among the group of Adults, most reported disorders were food allergies/intolerances (n=30; 12%) and hypertension (n=24; 10%). Among the group of Elderly People, most reported diseases/disorders were hypertension (n=42; 62%), cardiovascular diseases (n=17; 25%), high serum cholesterol/hyperlipoproteinamiae (n=16; 24%) and diabetes mellitus (n=15; 22%). These diseases and/or disorders were investigated in relation to phthalate exposure.

Table 77. Occurrence of different diseases / disorders among the groups of Adults (n=242) and Elderly People (n=68)

Disease / disorder	Frequency in adults (n=242)	Frequency in elderly people (n=68)
Diabetes mellitus	1 (<1%)	15 (22%)
Food allergies, food intolerances	30 (12%)	4 (6%)
Hypertension	24 (10%)	42 (62%)
Cardiovascular diseases	3 (1%)	17 (25%)
High serum cholesterol, hyperlipoproteinamiae	11 (5%)	16 (24%)
Coeliac disease	0 (0%)	0 (0%)
Disorders of the gastrointestinal tract	13 (5%)	8 (12%)
Absence of appetite	1 (<1%)	0 (0%)
Problems with chewing and deglutition	1 (<1%)	3 (4%)
Other diseases / disorders	32 (13%)*	8 (12%)**
No disease / disorder known	145 (60%)	9 (13%)

* *Other reported diseases/disorders among the group of Adults (n):* hypothyreoidea (5), neurodermitis (4), sleeping disturbances (3), migraine (3), rhinitis (2), pollen allergy (2), Morbus Wilson (1), anemiae (1), penicillin allergy (1), iron deficiency (1), burnout (1), multiple sclerosis (1), chronic sinusiotis (1), blood coagulation disturbance factor 8 (1), hemiparesis (1), hepatitis B (1), glaucoma (1), periodontitis (1), apnoea (1), reflux (1)
** *Other reported diseases/disorders among the group of Elderly People (n):* increased prostate (2), chronic obstructive lung disease (1), Morbus Crohn (1), reflux (1), herniated disc (1), dyspnoea (laboured breathing) (1), stenosis (1)
Note: Participants were able to report more than one disease or disorder. Thus, the total number of all diseases/disorders is higher than total n of participants.



Abbreviations: AA, absence of appetite; CD, coeliac disease; CVD, cardiovascular diseases, FA, food allergies / intolerances; GIT, disorders of the gastrointestinal tract; HSC, high serum cholesterol/hyperlipoproteinaemia; HPT, hypertension; PCD, problems with chewing or deglutition.

Figure 76. Distributions of the occurrence of different diseases / disorders among the groups of Adults (n=242) and Elderly People (n=68)

Adults

Food allergies/intolerances

Among the group of Adults, 30 participants (12%) reported suffering from food allergies or food intolerances. Significant differences were identified for MiDP (p=0.038) and creatinine-adjusted MiDP (p=0.031) after Mann-Whitney U tests were performed. However, only a few samples showed positive MiDP levels. Additionally, MiDP is not an appropriate biomarker for DiDP exposure, because it is eliminated only in small amounts in urine. Thus, no clear and reasonable conclusion can be drawn.

Hypertension

24 participants from the group of Adults (10%) reported suffering from hypertension. Significant differences were found for 3cx-MPP (p=0.019) and creatinine-adjusted 3cx-MPP (p=0.027). Participants with self-reported hypertension showed significantly lower exposure to 3cx-MEPP than without hypertension (Figure 77). These results are contrary to findings from the group of Elderly People (see below). Additionally, sample size distribution may not have been ideal.

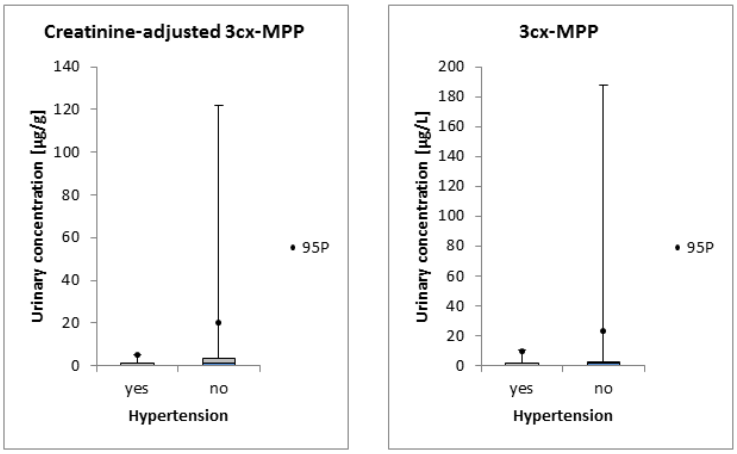


Figure 77. Distributions of creatinine-adjusted 3cx-MPP [µg/g] and creatinine-unadjusted 3cx-MPP [µg/l] among participants from the group of Adults with self-reported hypertension (n=23 and 215, respectively) and without (n=24 and 217, respectively)

Elderly People

Hypertension

Among the group of Elderly People, 42 participants (62%) reported suffering from hypertension in their questionnaires. Mann-Whitney U-tests revealed statistically significant differences between the occurrence of hypertension and creatinine-unadjusted 5oxo-MEHP (p=0.009), 5OH-MEHP (p=0.008), 3cx-MPP (p=0.015) and 5cx-MEPP (p=0.001), as well as between creatinine-adjusted 5OH-MEHP (p=0.037) and 5cx-MEPP (p=0.005). For all named phthalate metabolites, participants suffering from hypertension showed significantly higher exposure than those without hypertension (Figure 78 to Figure 81).

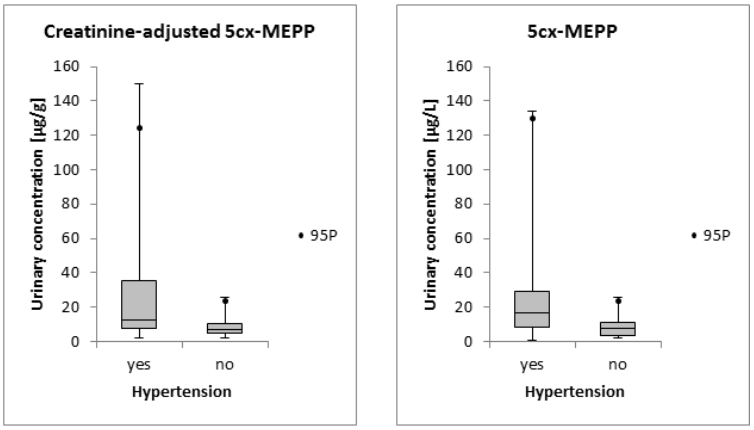


Figure 78. Distributions of creatinine-adjusted 5cx-MEPP [µg/g] and creatinine-unadjusted 5cx-MEPP [µg/l] among participants from the group of Elderly People with self-reported hypertension (n=40 and 42, respectively) and without (n=25 and 26, respectively)

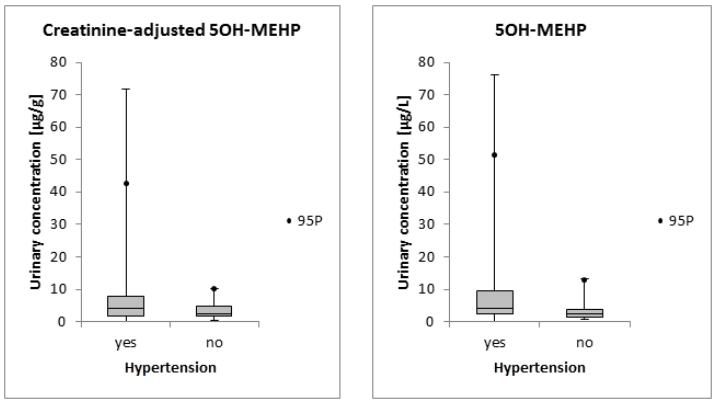


Figure 79. Distributions of creatinine-adjusted 5OH-MEHP [µg/g] and creatinine-unadjusted 5OH-MEHP [µg/l] among participants from the group of Elderly People with self-reported hypertension (n=40 and 42, respectively) and without (n=25 and 26, respectively)

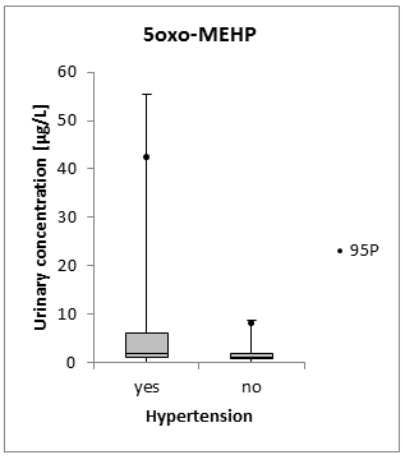


Figure 80. Distribution of 5oxo-MEHP [µg/l] among participants from the group of Elderly People with self-reported hypertension (n=42) and without (n=26)

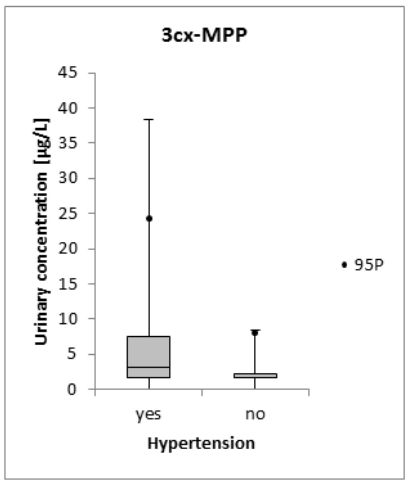


Figure 81. Distribution of 3cx-MPP [µg/l] among participants from the group of Elderly People with self-reported hypertension (n=42) and without (n=26)

High serum cholesterol, hyperlipoproteinamiae

24% (n=16) participants from the study group of Elderly People reported suffering from high serum cholesterol/hyperlipoproteinamiae. Mann-Whitney U tests identified statistically significant differences were identified for creatinine-adjusted and creatinine-unadjusted MnPeP (p=0.013 and 0.010, respectively). However, only two samples showed positive results for MnPeP, both of whom had high serum cholesterol. Thus, no clear or realistic relationship can be concluded.

Cardiovascular diseases

No significant differences were identified for participants from the group of Elderly People, regardless of the existence of self-reported cardiovascular diseases.

Diabetes mellitus

No significant differences were identified for the group of Elderly People, regardless of the existence of self-reported diabetes mellitus.

3.1.7.7 Allergies

Table 78. Distributions of participants with and without self-reported allergies from the groups of Children I, Children II, Adults and Elderly People

	Reported allergies	No reported allergies
Children I (n=26)	3 (12%)	23 (88%)
Children II (n=174)	41 (24%)	133 (76%)
Adults (n=222)	51 (23%)	171 (77%)
Elderly People (n=51)	12 (24%)	39 (76%)

Mann-Whitney U tests revealed several statistically significant differences between participants with and without self-reported allergies. Among the group of Adults, significant differences existed for creatinine-adjusted and creatinine-unadjusted MCHP (p=0.009 and 0.004, respectively), and among the group of Elderly People for creatinine-adjusted 5oxo-MEHP (p=0.023), MnBP (p=0.016) and MiBP (p=0.023). For all significant differences, participants who reported suffering from allergies showed lower urinary phthalate metabolite levels.

3.1.7.8 Intake of pharmaceuticals

Among the Adult group, 88 participants (34%) reported a daily consumption of one or more pharmaceuticals. Among the group of Elderly People, the rate of persons consuming pharmaceuticals was high (n=65; 92%).

Adults

Mann-Whitney U tests identified significant differences between the presence and lack of daily consumption of pharmaceuticals for creatinine-adjusted and creatinine-unadjusted MEHP (p=0.022 and 0.023, respectively), with participants who consumed pharmaceuticals daily exhibiting higher MEHP exposure levels, although the maximum urinary MEHP concentration was detected in an adult who did not consume any pharmaceuticals.

Elderly People

Table 79 illustrates the reported daily intake and types of pharmaceuticals consumed by participants from the group of Elderly People.

Among participants from the group of Elderly People who reported using pharmaceuticals daily, the number of pharmaceuticals consumed per day ranged between 1 and 13 pharmaceuticals (3.3±2.6, mean±SD). A Spearman correlation identified statistically significant correlations between the amount of pharmaceuticals consumed per day and creatinine-adjusted MBzP (r=0.320, p=0.05), MEHP (r=0.279, p=0.05), 5OH-MEHP (r=0.293, p=0.05), 5cx-MEPP (0.330, p=0.01), MiBP (r=0.274, p=0.05) and 3cx-MPP (r=0.471, r=0.01), and creatinine-unadjusted MiBP (r=0.248, p=0.05) and 3cx-MPP (r=0.0394, p=0.01). All statistically significant correlations were positive, which supports the possibility that the intake of pharmaceuticals may contribute to overall phthalate exposure. Additionally, it is notable that significant results were found for nearly all creatinine-adjusted DEHP metabolites, except for 5oxo-MEHP.

Between categories of daily pharmaceutical consumption, Mann-Whitney U tests revealed statistically significant differences for creatinine-unadjusted as well as creatinine-adjusted MEHP (p=0.032 and 0.027, respectively; Figure 82), and 3cx-MEPP (p=0.000; Figure 83).

Table 79. Overview of pharmaceutical intake among participants from the group of Elderly People

Frequency of pharmaceutical intake		
Daily intake of pharmaceuticals	yes	no
	65	6
Medication group		
Group		***n***
Cardiovascular System (drugs affecting the renin-angiotensin-system, drugs affecting lipid metabolism, vasoprotectors, peripheral antagonists, beta-adenoreceptor antagonists, vasodilators, heart therapy, anti-hypertonia)		81
Alimentary system and metabolism (vasoprotectors, drugs against acid reflux disease, anti-diabetic drugs excl. insulin, laxatives, drugs for functional gastrointestinal disorders)		22
Blood and haematopoietic organs (anti-thrombotic drugs, anti-anaemic drugs)		21
Nervous system (psychoanaleptica, other drugs for the nervous system, anti-Parkinson drugs, anti-epileptic drugs)		18
Hormones (thyroid hormones)		13
Muscle and skeletal system (anti-phlogistic and anti-rheumatic drugs)		4
Respiratory tract (drugs for obstructive respiratory diseases)		3
Sensory organs (Glaucoma drugs and mioticas)		2
Urogenital system and sex hormones (urologic drugs)		2
Antineoplastic and immunomodulating substances (Endocrine therapy)		1
Application type		
Type		***n***
Film tablets		80
Tablets		67
Capsules		15
Others		6

Notes: In several cases, participants reported the intake of more than one single pharmaceutical.

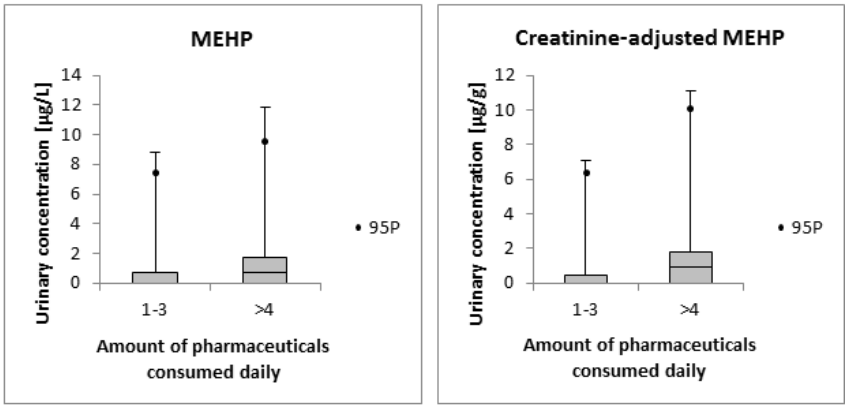


Figure 82. Distributions of creatinine-unadjusted MEHP [µg/l] and creatinine-adjusted MEHP [µg/g] from the group of Elderly People who reported either a consumption of 1-3 pharmaceuticals per day (n=38 and 37, respectively) or a consumption of more than 4 pharmaceuticals per day (n=26 and 24, respectively)

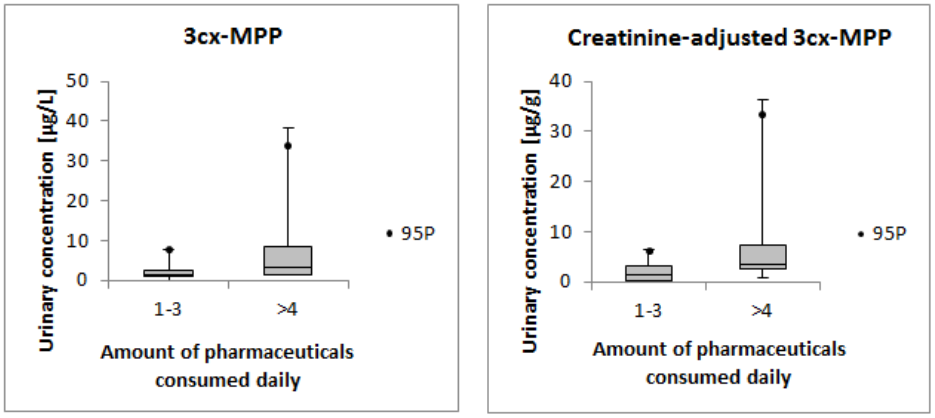


Figure 83. Distributions of creatinine-unadjusted 3cx-MPP [µg/l] and creatinine-adjusted 3cx-MPP [µg/g] from the group of Elderly People who reported either a consumption of 1-3 pharmaceuticals per day (n=38 and 37, respectively) or a consumption of more than 4 pharmaceuticals per day (n=26 and 24, respectively)

Concerning the daily intake of different application types, statistically significant differences were observed for the daily consumptions of both film tablets and capsules. Participants from the group of Elderly People who consumed capsules daily showed a significantly higher exposure to creatinine-adjusted MBzP (p=0.035), although the sample size distribution was imbalanced (Figure 84). Participants who consumed film tablets daily showed statistically significant exposures to creatinine-adjusted and creatinine-unadjusted 3cx-MPP (p=0.009 and 0.022, respectively) and creatinine-adjusted 5cx-MEPP (p=0.030) compared to participants who did not consume film tables each day.

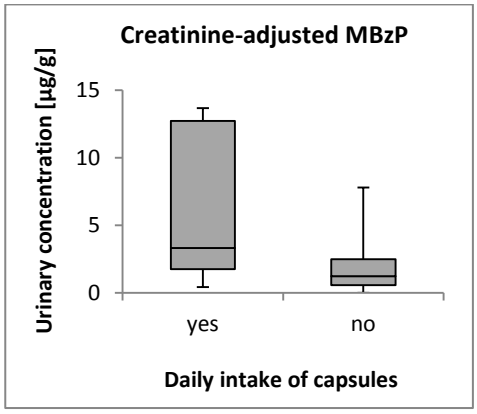


Figure 84. Distribution of creatinine-adjusted MBzP [µg/g] among participants from the group of Elderly People who either did (n=7) or did not consume capsules daily (n=47)

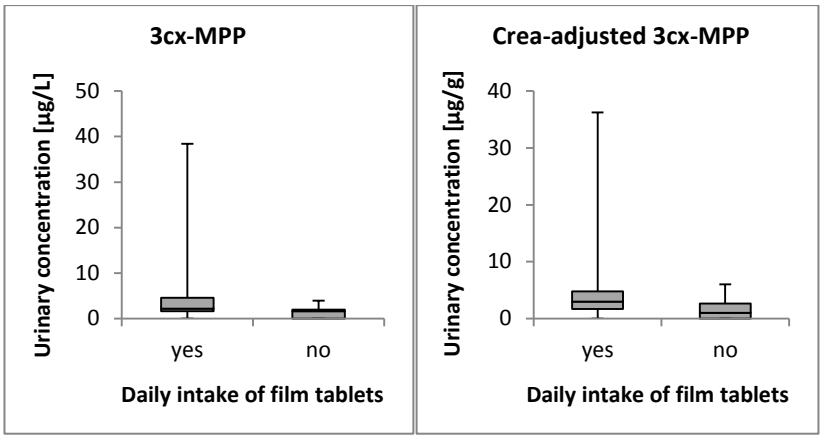


Figure 85. Distributions of creatinine-unadjusted 3cx-MPP [µg/l] and creatinine-adjusted 3cx-MPP [µg/g] among participants from the group of Elderly People who either did (n=42 and 40, respectively) or did not consume film tablets daily (n=14)

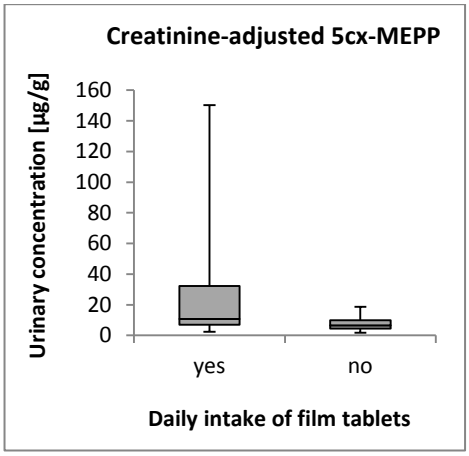


Figure 86. Distribution of creatinine-adjusted 5cx-MEPP [µg/g] among participants from the group of Elderly People who either did (n=40) or did not consume film tablets daily (n=14)

3.1.7.9 Smoking behaviour

Among participants from the group of Adults, 64 participants (24%) reported being smokers and 202 participants (76%) reported being non-smokers. Concerning smoking behaviour, significant differences were observed between the two groups for MnBP (p=0.030), and 5cx-MEPP (creatinine-adjusted and creatinine-unadjusted levels; p=0.047 and 0.037, respectively). Distributions are illustrated in Figure 87 and Figure 88. Conspicuously, non-smokers were significantly higher exposed to MnBP and 5cx-MEPP than smokers.

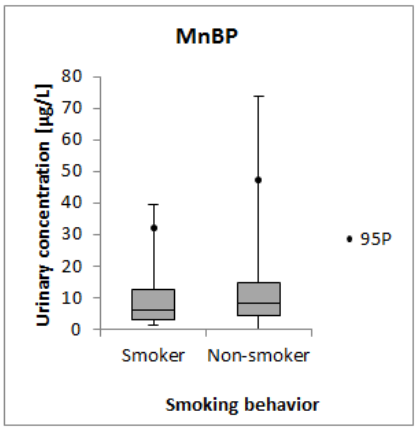


Figure 87. Distribution of MnBP concentrations [µg/l] in smokers (n=64) and non-smokers (n=202) from the group of Adults

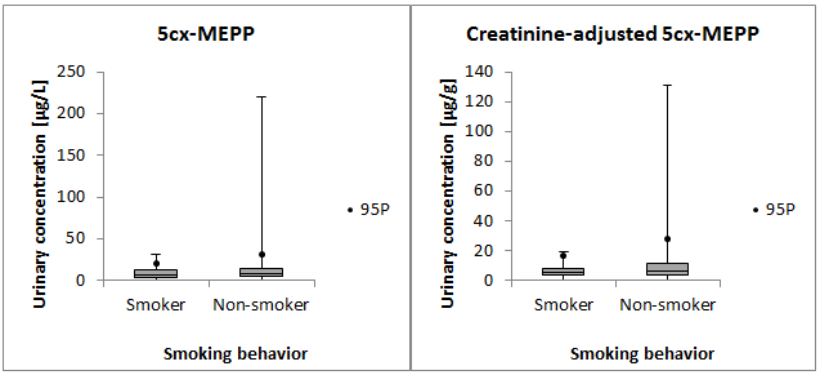


Figure 88. Distributions of 5cx-MEPP concentrations [µg/l] and creatinine-adjusted 5cx-MEPP concentrations [µg/g] in smokers (n=64) and non-smokers (n=202 and 199, respectively) from the group of Adults

Among the group of Elderly People, 5 participants (8%) reported being smoker, whereas 59 participants (92%) were non-smokers. On the one hand, no significant differences could be identified between smokers and non-smokers regarding phthalate metabolite exposure, but on the other hand, sample size distribution was not optimal.

3.1.7.10 Nutrition

Data on the frequency of food intake were surveyed by a Food Frequency Questionnaire (FFQ). The frequencies of food intakes were summarised into three different groups: no or infrequent intake, normal intake (1-3 times per week) and frequent intake (four times or more per week). In total, 33 food groups were surveyed. In Table 80, frequencies of food group intakes are shown for the total study population.

Table 80. Frequencies of intake of different food types among the total study population (n=563-575) in relation to the observed urinary phthalate metabolite concentrations

Food group	Total n	Intake		
		Never / infrequent	***Normal*** *(1-3 times/week)*	***Frequent*** *(4 times/week to >4 times/d)*
Rice, pasta	563	150 (27%)	346 (61%)	67 (12%)
Bread, brown	552	92 (17%)	142 (26%)	318 (57%)
Bread, white	550	158 (29%)	257 (47%)	135 (24%)
Bread, wholemeal	541	117 (33%)	204 (38%)	160 (29%)
Potatoes	567	145 (25%)	356 (63%)	66 (12%)
Vegetables	570	78 (14%)	222 (39%)	270 (47%)
Fruits, fresh	570	42 (7%)	142 (25%)	386 (68%)
Fruit pulp	549	408 (74%)	101 (19%)	40 (7%)
Milk, milk drinks	568	118 (21%)	145 (25%)	305 (54%)
Meat (beef, pork)	572	180 (32%)	321 (56%)	71 (12%)
Poultry	570	232 (41%)	311 (54%)	27 (5%)
Sausages, cold meat	560	129 (23%)	246 (44%)	185 (33%)
Fish	567	295 (52%)	255 (45%)	17 (3%)
Eggs	569	231 (40%)	282 (50%)	56 (10%)
Legumes	572	417 (73%)	141 (25%)	14 (2%)
Almonds, peanuts, nuts	575	361 (63%)	150 (26%)	64 (11%)
Butter, oils	556	104 (19%)	146 (26%)	306 (55%)
Pastries, cakes	568	160 (28%)	324 (57%)	84 (15%)
Chocolate, sweets	570	130 (23%)	235 (41%)	205 (36%)
Fruit or vegetable juices	563	198 (35%)	174 (31%)	191 (34%)
Soft drinks	560	329 (59%)	134 (24%)	97 (17%)
Carbonated beverages	569	234 (41%)	150 (26%)	185 (33%)
Tea	560	211 (38%)	156 (28%)	193 (34%)
Coffee	568	257 (45%)	41 (7%)	270 (48%)
Tab water, mineral water	566	32 (6%)	46 (8%)	488 (86%)
Alcoholic beverages	562	355 (63%)	146 (26%)	61 (11%)
Alcoholic beverages: Children I	*25*	*24 (96%)*	*0 (0%)*	*1 (4%)*
Alcoholic beverages: Children II	*208*	*201 (97%)*	*5 (2%)*	*2 (1%)*
Alcoholic beverages: Adults	*263*	*103 (39%)*	*122 (47%)*	*38 (14%)*
Alcoholic beverages: Elderly People	*66*	*27 (41%)*	*19 (29%)*	*20 (30%)*
Canned food	564	439 (78%)	111 (20%)	14 (2%)
Fast Food, Take Away	558	464 (83%)	79 (14%)	15 (3%)
French fries	568	465 (82%)	87 (15%)	16 (3%)
Microwave popcorn	561	503 (90%)	47 (8%)	11 (2%)
Beverages in TetraPak	555	362 (65%)	135 (24%)	58 (11%)
Beverages in PET	561	323 (57%)	133 (24%)	105 (19%)
Beverages in plastic containers	564	468 (83%)	49 (9%)	47 (8%)

The consumption frequencies of 33 different food types were summarised in three categories in order to enable appropriate statistical analysis. Potential statistically significant relationships were investigated for DEHP metabolites (MEHP, 5oxo-MEHP,

5OH-MEHP and 5cx-MEPP) and low molecular weight phthalate metabolites including MEP, MnBP, MiBP, MnPeP, MCHP and MBzP. Urinary phthalate metabolites were transformed into logarithmic values excluding zero values. A linear model with two covariates (age and BMI) and two fixed-effect factors (sex and food type) was used for the explanation of the variation.

DEHP metabolites

The variable “age” was statistically significant in most of the models. The food types rice/pasta, bread (brown), almonds/nuts/peanuts, butter/oils, tab water/mineral water, French fries and microwave popcorn were statistically significant at the 0.05 significance level. For all these models, the coefficient of determination (R^2) varied from 0.1 to 0.12.

The exposure to DEHP metabolites was lower in participants who consumed rice/pasta more frequently. Regarding the consumption of nuts, participants with infrequent intakes (<1 times/month) as well as participants with more frequent intakes (>3 times/month) showed greater exposure to DEHP metabolites. Thus, clear conclusions could not be made. Statistically significant contributions to the exposure to DEHP metabolites were observed for French fries and microwave popcorn, where a higher exposure was found in participants with more frequent consumptions.

Low molecular weight phthalate metabolites

For logarithmic low molecular weight phthalate metabolites, no statistically significant relationships with the frequency of intake of any food type could be identified. Additionally, in contrast to the logarithmic DEHP metabolites, age did not contribute significantly to the exposure to logarithmic low molecular weight phthalate metabolites.

3.1.7.11 Occupation

3.1.7.11.1 Current employment (among the group of Adults)

Table 81 shows the distributions of participants from the group of Adults who reported being either employed or unemployed during the survey period.

Among female adults, significant differences were identified by a Mann-Whitney U test at a 0.05 significance level between employed and unemployed participants and creatinine-unadjusted 5oxo-MEHP (p=0.034), MEHP (p=0.038), 5cx-MEPP (p=0.003), MBzP (p=0.017) and creatinine-adjusted MEP (p=0.039). For the DEHP metabolites

and MBzP, unemployed females exhibited higher exposure than to employed females (Figure 89 and Figure 90). For creatinine-adjusted MEP, findings were reversed; however, P95 and median values were similar for both groups (Figure 91). Among male adults, no significant differences were observed.

Table 81. Distribution of participants from the group of Adults who were either employed or unemployed during the survey period (n=266)

	employed	unemployed
Total (n=266)	188 (71%)	78 (29%)
Females (n=159)	107 (67%)	52 (33%)
Males (n=107)	81 (76%)	26 (24%)

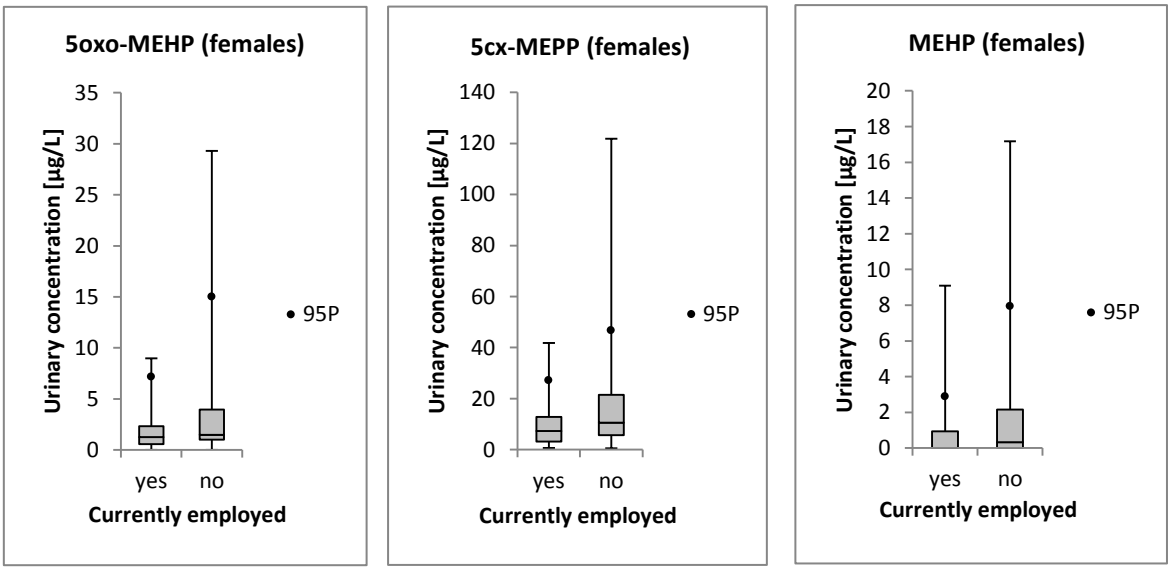


Figure 89. Distributions of urinary DEHP metabolites (5oxo-MEHP, 5cx-MEPP and MEHP) [µg/l] among employed females (n=107) and unemployed females (n=52) from the group of Adults

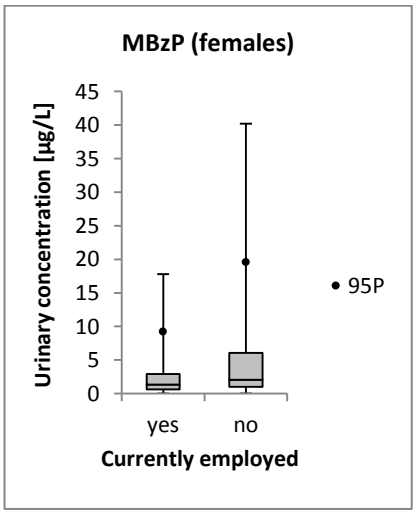


Figure 90. Distribution of urinary MBzP [µg/l] among employed females (n=107) and unemployed females (n=52) from the group of Adults

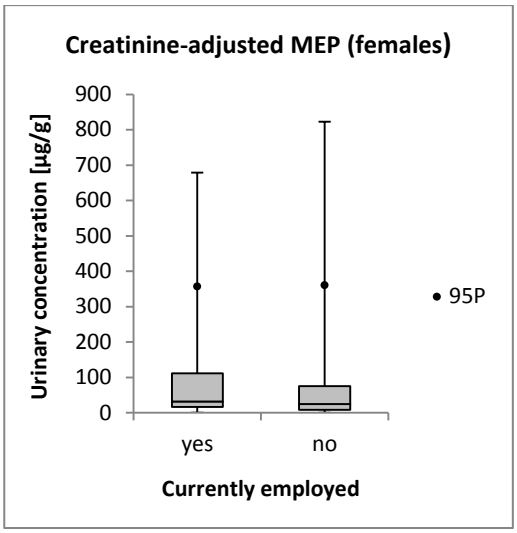


Figure 91. Distribution of creatinine-adjusted MEP [µg/l] among employed females (n=106) and unemployed females (n=51) from the group of Adults

Table 82 shows the distribution of employment positions among the Adults group, as well as among male and female adults who were gainfully employed during the survey period. Because of the small sample sizes among workers/unskilled workers, farmers and other employment positions in males, these groups were not included in the statistical analysis. Among females, skilled workers/craftsmen and farmers were excluded for the same reason.

Table 82. Distribution of employment positions among participants from the group of Adults (n=182) with paid employment during the survey period

	Total (n=182)	Males (n=80)	Females (n=102)
Company or public employee	102 (56%)	36 (45%)	66 (65%)
Company or public employee in leading position	25 (14%)	15 (19%)	10 (10%)
Worker / unskilled worker	19 (10%)	3 (4%)	16 (15%)
Skilled worker / craftsman	18 (10%)	17 (21%)	1 (1%)
Self-employed	11 (6%)	6 (8%)	5 (5%)
Farmer	1 (<1%)	1 (1%)	0 (0%)
Other employment	6 (3%)	2 (2%)	4 (4%)

Among females, no significant differences were identified, but among males, however, significant differences were identified by Kruskal-Wallis tests at a 0.05 significance level for MnBP (p=0.013) and 5cx-MEPP (p=0.002) between the different employment positions (Figure 92 and Figure 93).

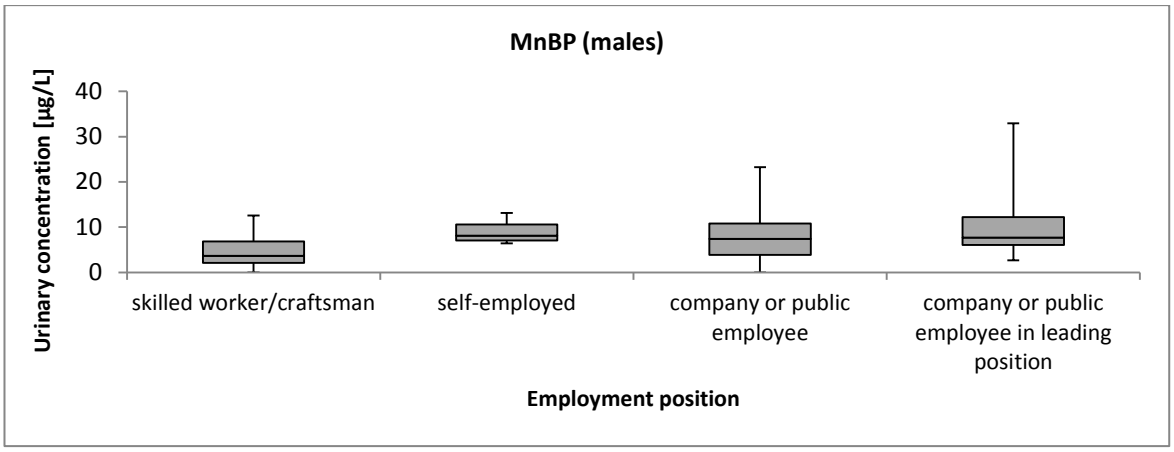


Figure 92. Distribution of urinary MnBP concentrations [µg/l] for the employment positions skilled worker/craftsman (n=17), self-employed (n=6), company or public employee (n=36) and company or public employee in leading position (n=15) among males from the group of Adults

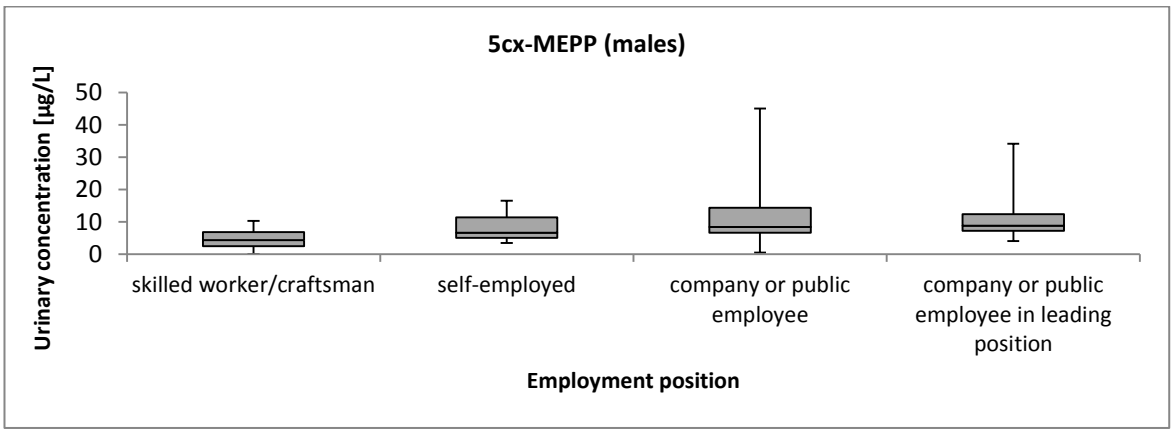


Figure 93. Distribution of urinary 5cx-MEPP concentrations [µg/l] for the employment positions skilled worker/craftsman (n=17), self-employed (n=6), company or public employee (n=36) and company or public employee in leading position (n=15) among males from the group of Adults

3.1.7.11.2 Working sectors

Adults

Participants from the Adult group were asked to report the sector in which they were working at time of completing the survey. Results are given in Table 83. The majority of adults worked at sectors other than those available for selection. The other sectors reported were the education sector (n=30), students (n=23), the IT sector (n=14), bureau work (n=11), the construction sector (n=6), the social sector and the recreational sector (n=6 in each case), working at home, retirees, the transport sector and the tourism sector (n=4 in each case), the cleaning sector and the service sector (n=3 in each case), as well as the property sector, the research sector and the sales

sector (n=2 in each case). Some other reported sectors could not be classified or were still missing.

Table 83. Distribution of participants (n=238) from the group of Adults working in different sectors

Working sector	Frequency (Percent) (n=238)
Food sector	36 (15%)
Medicine sector	16 (7%)
Construction materials sector	7 (3%)
Chemistry sector	7 (3%)
Wood sector	5 (2%)
Veterinary medicine sector	5 (2%)
Textile sector	3 (1%)
Animal breeding sector	2 (<1%)
Drugstore sector	2 (<1%)
Synthetics/plastics sector	2 (<1%)
Pharma sector	1 (<1%)
Furniture sector	0 (0%)
Cosmetic sector	0 (0%)
Other sector	153 (64%)

For statistical analysis, sectors in which 0-3 participants were working were excluded (the textile, plastics/synthetics, pharma, drugstore, furniture, cosmetics, animal breeding, cleaning, service, property, research and sales sectors). Kruskal-Wallis tests identified significant differences between working sectors for 5oxo-MEHP (p=0.029), 5cx-MEPP (p=0.002) and MiBP (p=0.017), as well as for creatinine-adjusted MnBP (p=0.045). The highest exposure to 5oxo-MEHP was observed in students and participants from the tourism sector, the highest exposure to 5cx-MEPP in students, the highest exposure to MiBP in participants from the tourism sector, students and the chemistry sector, and the highest exposure to creatinine-adjusted MnBP in participants from the social sector and from the veterinary medicine sector.

3.1.7.11.3 Workplace

Differences and associations between several parameters related to the workplace were solely investigated in participants from the group of Adults, because it is the main working-age population group.

Construction work

53 adults (24%) out of 220 participants reported there having been construction work at completed at their workplace within the last 5 years. Significant differences were

identified by a Mann-Whitney U test for creatinine-adjusted MEP (p=0.033), as well as creatinine-adjusted and creatinine-unadjusted MiNP (p=0.023 and 0.022, respectively). Adults who reported there having been construction work exhibited significantly higher exposure to creatinine-adjusted MEP (median, P95 and quantiles) (Figure 94). MiNP levels were higher in adults who reported there having been no construction work. However, MiNP is not accurate as a biomarker for investigating DiNP exposure, and additionally, only a few positive urinary MiNP levels were detected.

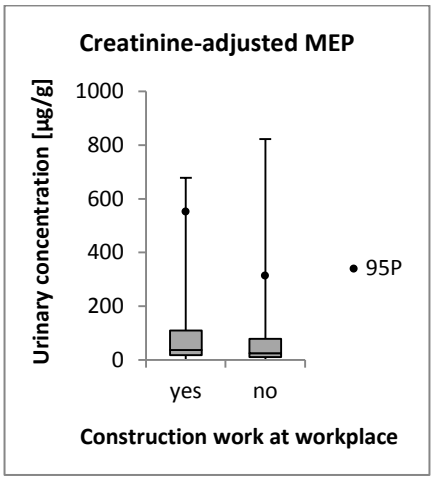


Figure 94. Distribution of creatinine-adjusted MEP concentrations [µg/g] in participants from the group of Adults who had construction work at their workplace within the last 5 years (n=53) and participants who had no construction work at their workplace (n=167)

Flooring

Figure 95 shows the distribution of different types of flooring materials at workplace. No statistically significant associations were identified between urinary phthalate metabolite concentrations and the type of flooring at the workplace.

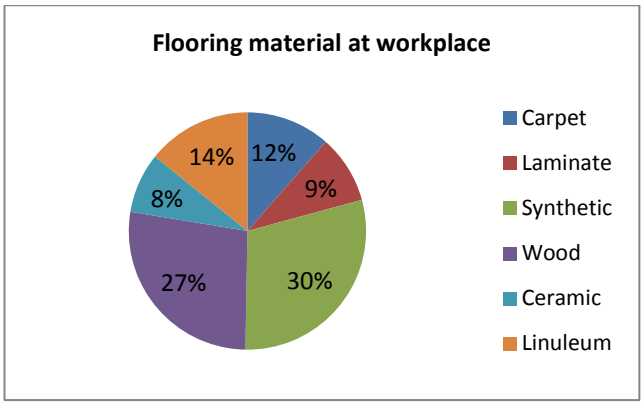


Figure 95. Distribution of flooring material types at the workplace among participants from the group of Adults (n=183)

Contact with cleaning products

A Mann-Whitney U test at a significance level of 0.05 identified statistically significant differences for creatinine-adjusted and creatinine-unadjusted MEHP (p=0.022 and 0.024, respectively). Participants who had regularly contact with cleaning products exhibited higher MEHP exposure than those without contact with cleaning products (Figure 96). However, sample size distribution is not optimal.

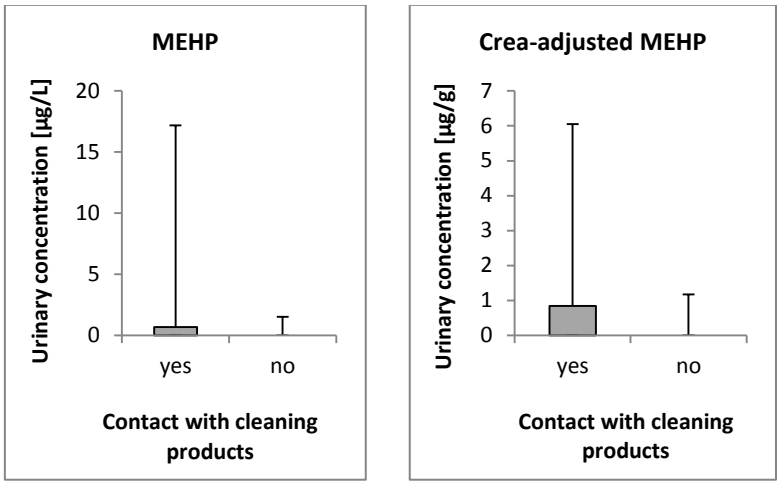


Figure 96. Distribution of MEHP [µg/l] and creatinine-adjusted MEHP [µg/g] among participants from the group of Adults who had contact with cleaning products (n=135 and 134, respectively) and those who had not (n=15)

For MCHP, a significant difference was observed (p=0.028; Figure 97), with adults who reported having no contact with cleaning products exhibiting slightly higher exposure to MCHP. As noted above, however, the sample size distribution was not optimal.

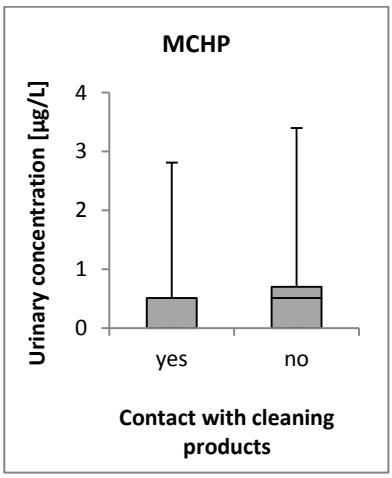


Figure 97. Distribution of MCHP [µg/l] among participants from the group of Adults who had contact with cleaning products (n=135) and those who did not (n=15)

For MiNP (creatinine-adjusted and creatinine-unadjusted) and for MnPeP (only the creatinine-adjusted) statistically significant differences were also identified (p=0.012, 0.009 and 0.045, respectively). However, although the results were statistically significant, a clear conclusion cannot be drawn, because only a few participants showed positive but low levels, and MiNP is not an accurate biomarker for DiDP exposure.

Contact with chemicals

Regarding contact with chemicals, a statistically significant difference was found for 5cx-MEPP (p=0.045; Figure 98), with adults who reported no contact with chemicals exhibiting higher exposure to 5cx-MEPP.

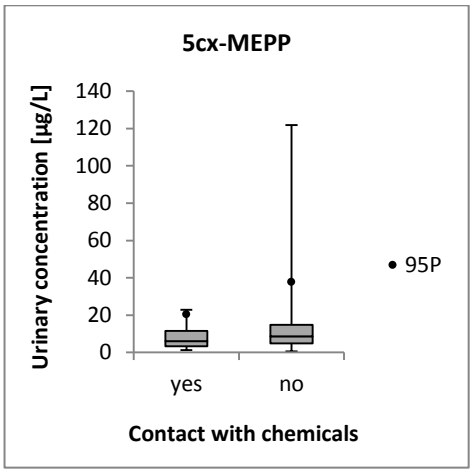


Figure 98. Distribution of 5cx-MEPP [µg/l] among participants from the group of Adults who had contact with chemicals (n=32) and who had not (n=117)

3.1.7.12 Place of residence

3.1.7.12.1 Current place of residence

Table 84 shows the distributions of children, adults and elderly people living in houses or apartments, and the date of the place of residence's construction, respectively. Significant differences between current place of residence and phthalate metabolite exposure were only observed in children.

Table 84. Distribution of current place of residence of participants from the different study population groups

	Current place of residence		Time of construction	
	House	*Apartment*	*before 1945*	*after 1945*
Children I	17	13	4	19
Children II	138	63	26	135
Adults	134	127	49	182
Elderly People	32	32	6	47

Children I

Among the Children I group, statistically significant differences existed between current place of residence (house or apartment) and creatinine-adjusted MEP (p=0.002), 5oxo-MEHP (p=0.028), 5OH-MEHP (p=0.032) and 5cx-MEPP (p=0.036), as well as creatinine-unadjusted and creatinine-adjusted MEHP (p=0.043 and 0.015, respectively). Children from this study population group were significantly more highly exposed to the named phthalate metabolites when lived in an apartment. Considerably, all creatinine-adjusted metabolites of DEHP showed higher exposures which leads to the conclusion that children living in apartments were more exposed to DEHP compared to children living in houses.

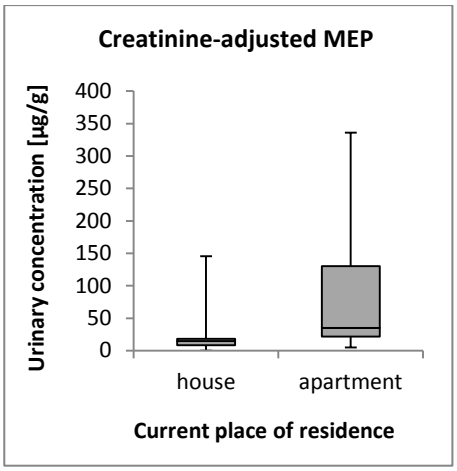


Figure 99. Distribution of creatinine-adjusted MEP [µg/g] among participants from the group of Children I living in houses (n=16) and apartments (n=13)

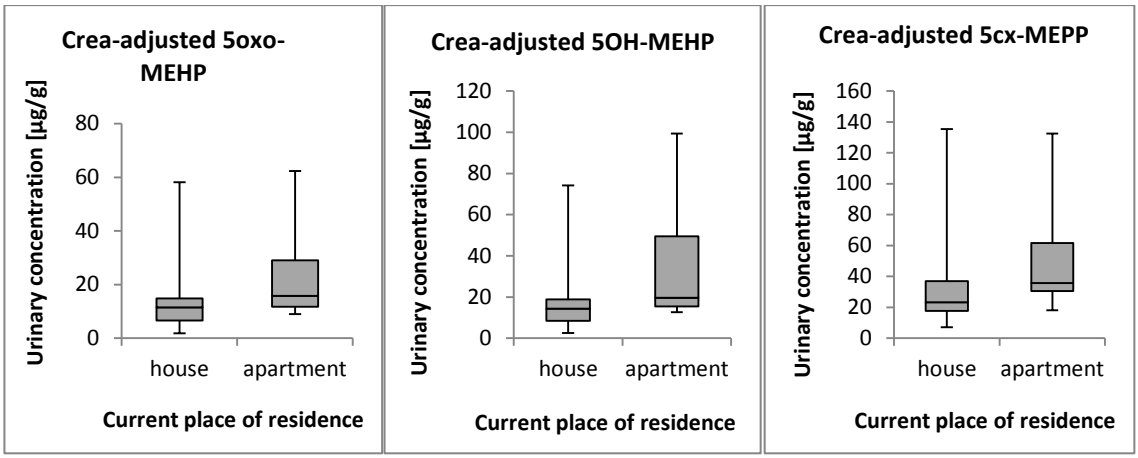


Figure 100. Distribution of creatinine-adjusted 5oxo-MEHP, 5OH-MEHP and 5cx-MEPP [µg/g] among participants from the group of Children I living in houses (n=16) and apartments (n=13)

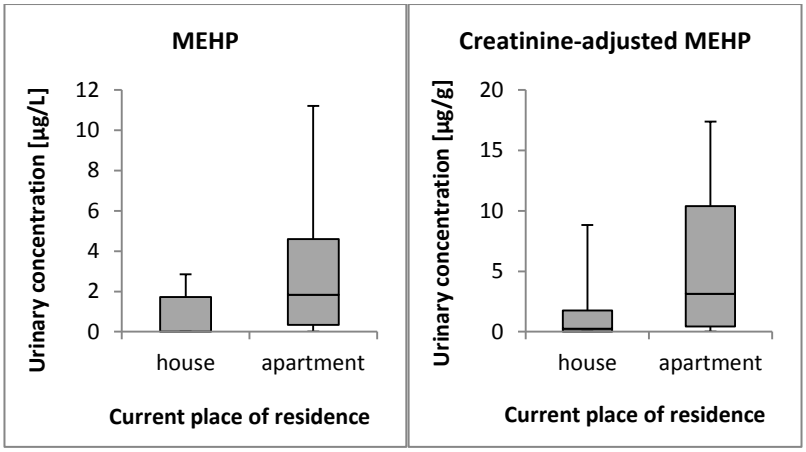


Figure 101. Distribution of creatinine-unadjusted MEHP [µg/l] and creatinine-adjusted MEHP [µg/g] among participants of the group of Children I living in houses (n=17 and 16, respectively) and apartments (n=13)

Children II

Among the Children II group, a Mann-Whitney U test identified significant differences for MEP (p=0.007) and creatinine-adjusted MEP (p=0.019), as well as for MCHP (p=0.004) and creatinine-adjusted MCHP (p=0.002). For MCHP, P95 values were higher among children living in apartments.

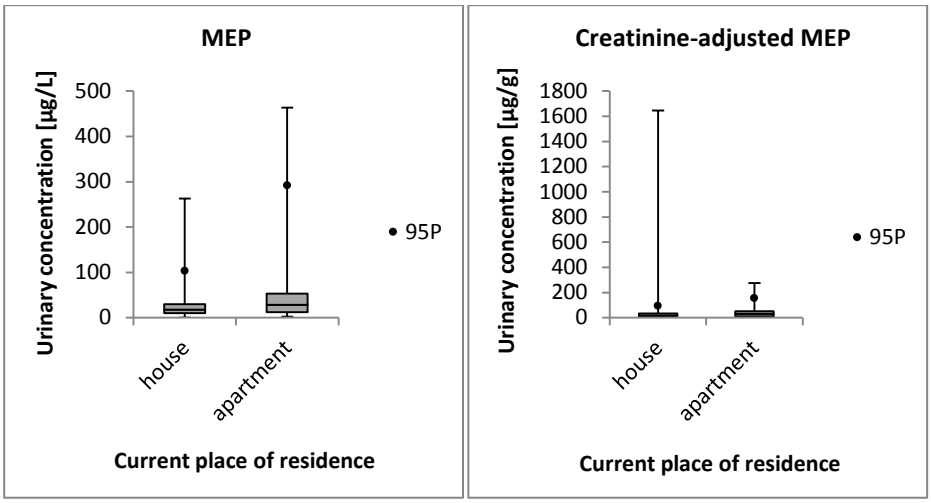


Figure 102. Distribution of MEP [µg/l] and creatinine-adjusted MEP [µg/g] among participants from the group of Children II living in houses (n=138 and 136, respectively) and apartments (n=63 and 62, respectively)

Adults

Among participants from the group of Adults, statistically significant differences were observed between creatinine-unadjusted 3cx-MPP and creatinine-adjusted 3cx-MPP (p=0.001 and 0.006, respectively) and the date of their homes' construction (Mann-Whitney U tests). Participants who lived in homes constructed before 1945 showed higher exposure to 3cx-MPP than the others (Figure 103):

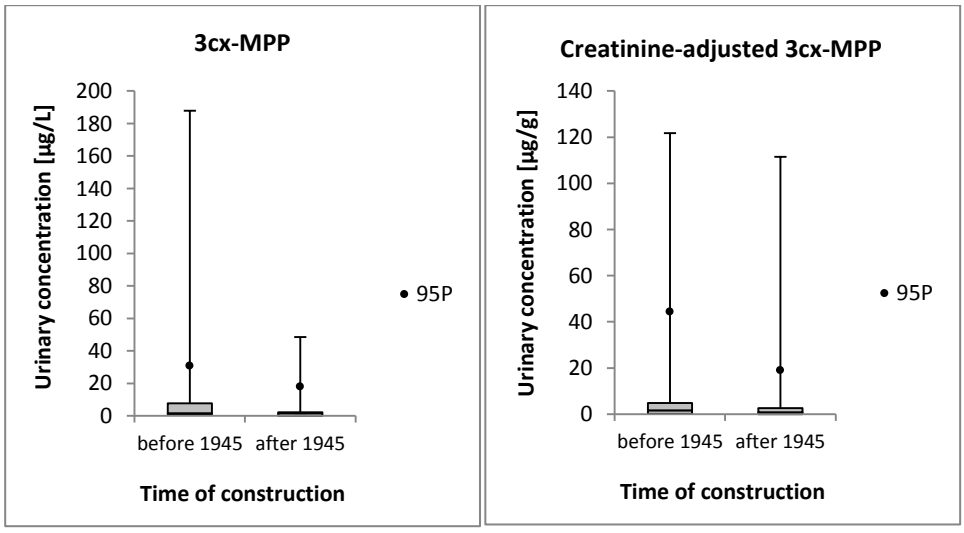


Figure 103. Distributions of urinary 3cx-MPP (µg/l] and creatinine-adjusted 3cx-MPP [µg/g] among participants from the group of Adults living in homes constructed before 1945 (n=49 and 48, respectively) and after 1945 (n=181 and 179, respectively)

3.1.7.12.2 Flooring

Among the total study population (n=547), 315 participants (57.6%) reported no changes in flooring at their place of residence, 107 (19.6%) reported having changed their flooring and 125 (22.8%) having changed their flooring within the last 5 years.

Table 85. Types of flooring material in the place of residence of participants from the total study population (n=391)

Type of flooring material	Frequency (Percent) (n=391)
Linoleum	4 (1%)
Carpet	13 (3%)
Synthetic/plastic	14 (4%)
Ceramic	20 (5%)
Laminate	106 (27%)
Wood	234 (60%)

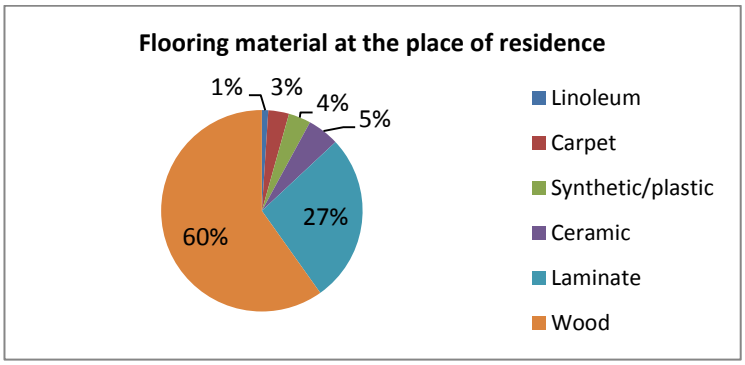


Figure 104. Distribution of types of flooring material in the place of residence of participants from the total study population (n=391)

Statistically significant differences were identified between the change of the flooring at the place of residence and the DEHP metabolites 5oxo-MEHP (p=0.006), 5OH-MEHP (p=0.007) and 5cx-MEPP (p=0.026), as well as MBzP (p=0.030) in the group of Children I, creatinine-adjusted and creatinine-unadjusted MnOP (p=0.046 and 0.047, respectively), and MiNP (p=0.012 and 0.015, respectively) in the group of Adults, and creatinine-adjusted MEP (p=0.047), creatinine-adjusted and creatinine-unadjusted MEHP (p=0.007 and 0.005, respectively), MiNP (p=0.010 and 0.027, respectively) and creatinine- creatinine-unadjusted 5cx-MEPP (p=0.034) in the group of Elderly People. No differences were found among participants from the group of Children II.

In the Children I group, exposure to the named phthalate metabolites was significantly higher in children who reported a change of flooring at their place of residence (Figure 105). In adults, significantly higher exposure to MnOP was identified in conjunction with

changed flooring, and contrarily to MiNP in conjunction with unchanged flooring. However, it should be noted that the number of positive detections in urine was very small for both metabolites. In elderly people, exposure to creatinine-adjusted MEP (Figure 106) and MEHP, and creatinine-unadjusted 5oxo-MEHP and 5cx-MEPP (Figure 107) was higher among participants who reported no changes of flooring having occurred at their homes. Concerning MiNP exposure, findings were vice versa, but similar to results from adults, with only a small number of positive MiNP levels existing.

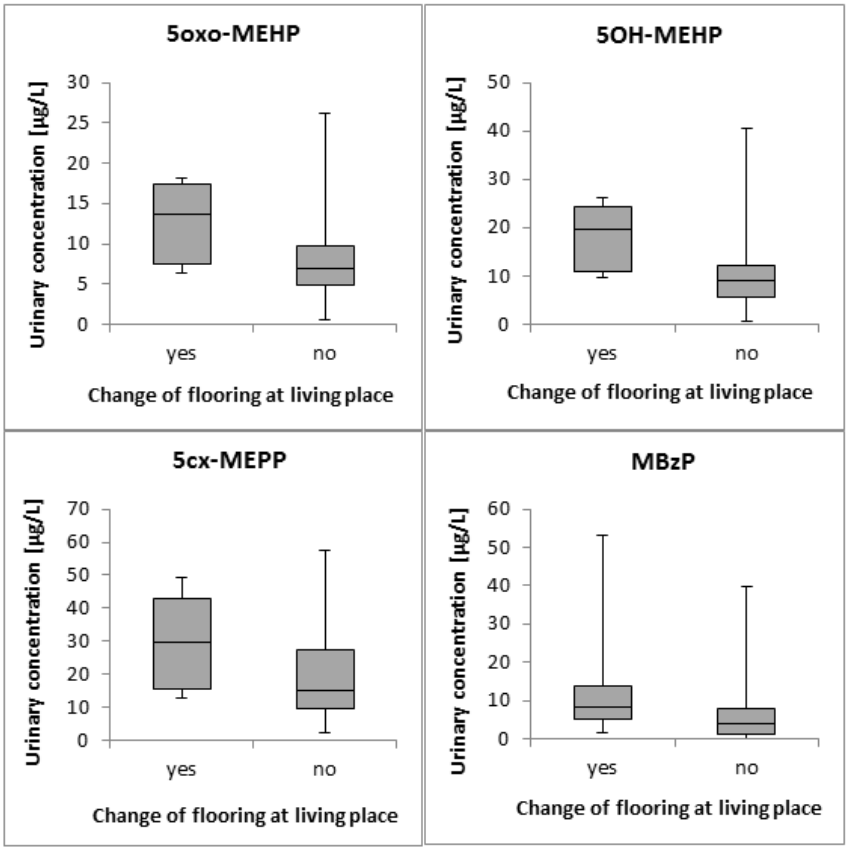


Figure 105. Distributions of urinary 5oxo-MEHP, 5OH-MEHP, 5cx-MEPP and MBzP concentrations [µg/l] among the participants from the group of Children I with changed flooring (n=11) and unchanged flooring at their homes (n=19)

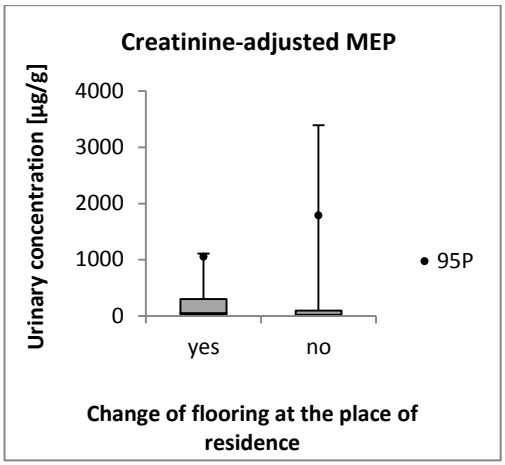


Figure 106. Distribution of creatinine-adjusted MEP [µg/g] among participants from the group of Elderly People with changed flooring (n=23) and unchanged flooring at their homes (n=33)

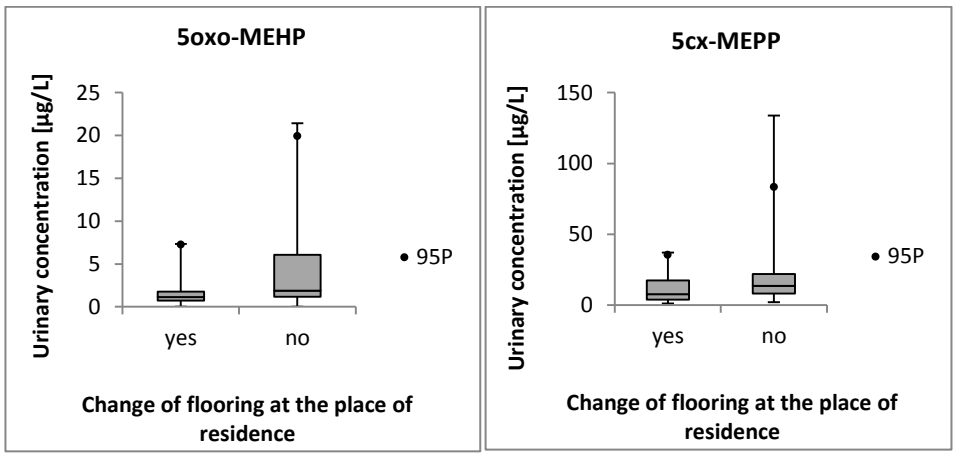


Figure 107. Distribution of urinary 5oxo-MEHP and 5cx-MEPP concentrations [µg/l] among participants from the group of Elderly People with changed flooring (n=24) and unchanged flooring at their homes (n=34)

3.1.7.12.3 Upholstery furniture

Among the total study population, 508 participants reported to own upholstery furniture at their homes. The distribution of the age of the furniture is shown in Figure 108.

Kruskal-Wallis tests revealed statistically significant differences for MEP (p=0.049), creatinine-adjusted MEHP (p=0.049), creatinine-adjusted 3cx-MPP (p=0.038), creatinine-adjusted and creatinine-unadjusted MCHP (p=0.039 and 0.028, respectively) and MiDP (p=0.035 and 0.031, respectively). Generally, MiDP exposure was very low. Additionally, MiDP is not an accurate biomarker for DiDP exposure, and thus results should be considered carefully.

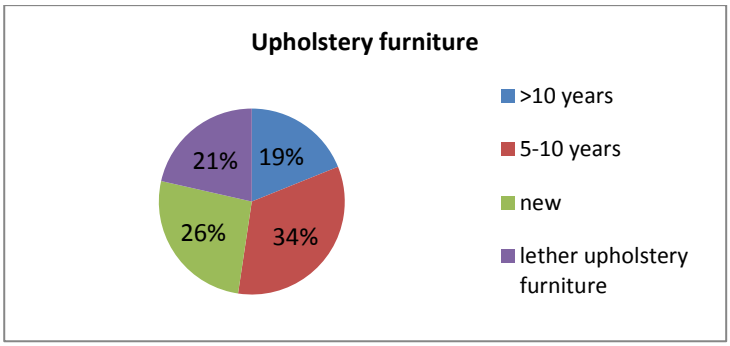


Figure 108. Distribution of the age of upholstery furniture at the place of residence of the total study population (n=508)

The newer the upholstery furniture was the higher was also the exposure of the owner to MEP. However, participants who owned leather furniture exhibited exposure similar to that of participants who owned new upholstery furniture (Figure 109). Similar results were also found for creatinine-adjusted MEHP, but it must be noted that there were only small differences (Figure 110).

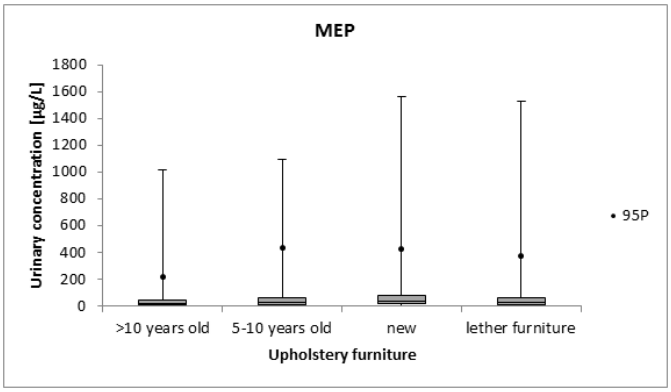


Figure 109. Distribution of urinary MEP concentrations [µg/l] among participants who owned upholstered furniture older than 10 years (n=96), 5-10 years old (n=170), new upholstered furniture (n=133) or leather furniture (n=109)

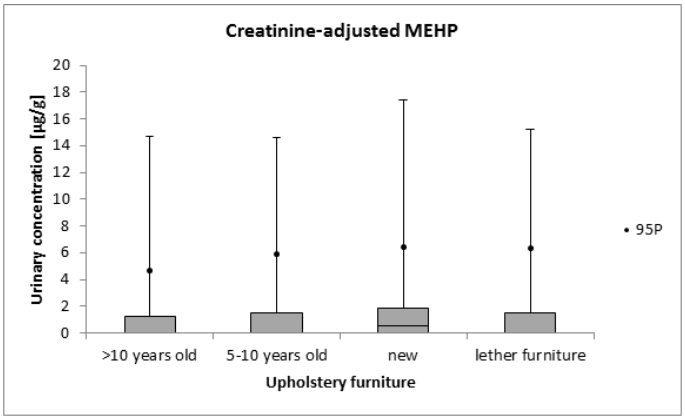


Figure 110. Distribution of urinary creatinine-adjusted MEHP concentrations [µg/g] among participants who owned upholstered furniture older than 10 years (n=96), 5-10 years old (n=164), new upholstered furniture (n=130) or leather furniture (n=109)

P95 values of creatinine-adjusted and creatinine-unadjusted urinary MCHP levels were very similar, however, the values of participants who owned new upholstery furniture were slightly higher compared to participants who owned older or leather upholstery furniture (Figure 111).

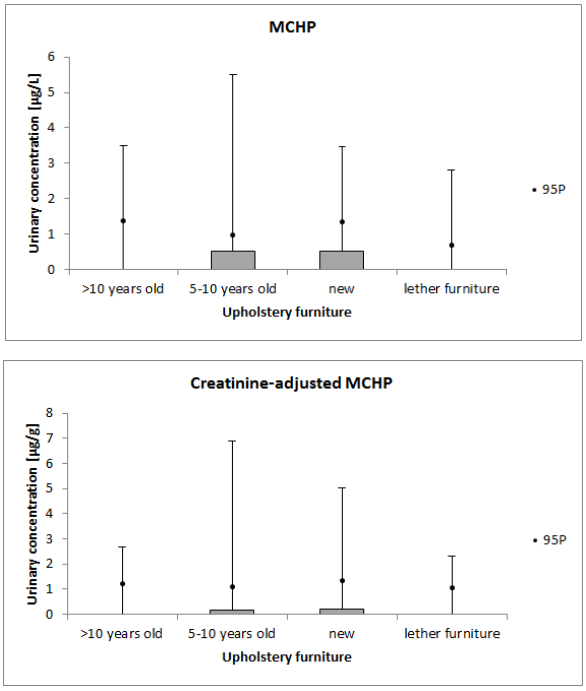


Figure 111. Distribution of urinary creatinine-unadjusted [µg/g] and creatinine-adjusted [µg/l] MCHP concentrations among participants who owned upholstered furniture older than 10 years (n=96), 5-10 years old (n=170 and 164, respectively), new upholstered furniture (n=133 and 130, respectively) or leather furniture (n=109)

The exposure of participants to creatinine-adjusted 3cx-MPP decreased with decreasing age of the upholstery furniture (Figure 115).

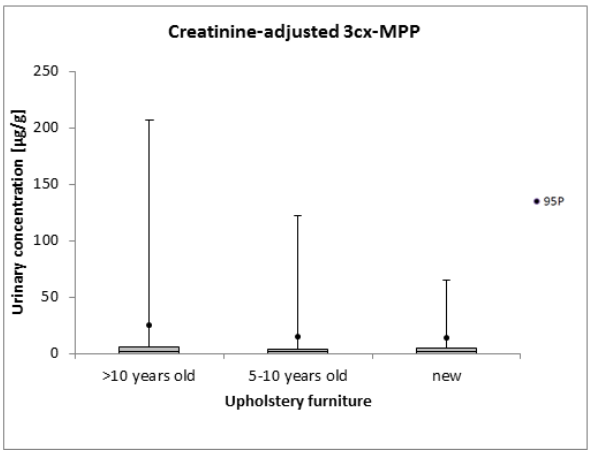


Figure 112. Distribution of urinary creatinine-unadjusted 3cx-MPP [µg/g] concentrations among participants who owned upholstered furniture older than 10 years (n=96), 5-10 years old (n=164), new upholstered furniture (n=130) or leather furniture (n=109)

Functional sports wear

No significant differences were identified.

3.1.7.13 Use of handicraft materials

Regarding the use of handicraft materials, differences in questionnaires existed: adults and elderly people were asked if they use handicraft materials either never, 1-2 times/month or 1-2 times/week, whereas children were asked if they use handicraft materials either never, 1-2 times/month, 1-2 times/week or more than 2 times/week. Therefore, the groups of Children I and II and Adults and Elderly People were investigated separately.

Table 86. Frequency of the use of handicraft materials among children (n=234), and adults and elderly people (n=238)

	Frequency of the use of handicraft materials			
	never	***1-2 x/month***	***1-2 x/week***	***>2 x/week***
Children (n=234)	48 (21%)	92 (39%)	70 (30%)	24 (10%)
Children I (n=30)	*0 (0%)*	*11 (37%)*	*19 (63%)*	*0 (0%)*
Children II (n=204)	*48 (23%)*	*81 (40%)*	*51 (25%)*	*24 (12%)*
Adults and Elderly (n=328)	206 (63%)	103 (31%)	19 (6%)	Not asked
Adults (n=262)	*156 (60%)*	*87 (33%)*	*19 (7%)*	*Not asked*
Elderly People (n=66)	*50 (76%)*	*16 (24%)*	*0 (0%)*	*Not asked*

Among children (n=234), a statistically significant difference (Kruskal-Wallis test) was found between the use of handicraft materials and creatinine-adjusted MnBP (p=0.043). Children who used handicraft materials more often showed lower MnBP exposure than children who used handicraft materials less often (Figure 113).

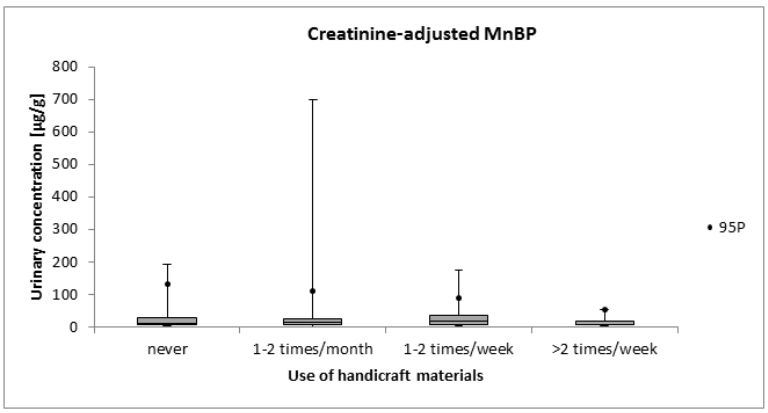


Figure 113. Distribution of creatinine-adjusted MnBP [µg/g] among children from the Children I and Children II group who used handicraft materials never (n=46), 1-2 times per month (n=89), 1-2 times per week (n=70) and more than 2 times per week (n=23)

3.1.7.14 Playing behaviour among children

Among both groups of children, the duration of daily use of television (TV), video game consoles (VGC) and/or personal computers (PC) were surveyed, as was the daily duration of play with plastic toys. Sample size distributions are listed in Table 87.

Table 87. Durations of the use of television, video game consoles and/or personal computers and durations of play with plastic toys among children from the groups of Children I and Children II

Population group	Use of TV, VGC and/or PC		Duration of play with plastic toys	
	Duration	n (%)	Duration	n (%)
Children I	0-1 h/d	17 (61%)	0-1 h/d	16 (52%)
	>1 h/d	11 (39%)	>1 h/d	15 (48%)
Children II	0-1 h/d	61 (32%)	0-1 h/d	158 (78%)
	1-2 h/d	75 (39%)	>1 h/d	44 (22%)
	>2 h/d	57 (29%)		

Abbreviations: d, day; h, hour(s); n, sample size; PC, personal computers; TV, television; VGC, video game consoles.

Among the group of Children I (n=27-31 concerning creatinine-adjusted and creatinine-unadjusted metabolite levels), no statistically significant associations could be identified for either the use of TV, VGC and/or PC, or for the duration of play with toys.

Among the Children II group, 61 children (32%) reported use TV, VGC and/or PC <1 h/d, 75 children (39%) 1-2 h/d and 57 children (29%) >2 h/d (Table 87). Kruskal-Wallis tests discovered significant differences between the different groups concerning the duration of the use of TV, VGC and/or PC and phthalate metabolite concentrations for creatinine-unadjusted MEP (p=0.017), 5OH-MEHP (p=0.027), 5cx-MEPP p= (0.038) and for creatinine-adjusted and creatinine-unadjusted MEHP p= (0.037 and 0.007, respectively). Regarding to the medians, exposure to the named urinary metabolites increased with increased duration of use. As regards the daily duration of play with plastic toys, Mann-Whitney U tests identified significant differences for creatinine-unadjusted urinary MiBP (p=0.029), as well as for creatinine-adjusted 5OH-MEHP (p=0.049) and 5oxo-MEHP (p=0.032), with the children who reported playing more than two hours with plastic toys per day being less exposed to these phthalate metabolites (Figure 114). However, the suboptimal sample size distribution, as well as the relatively high significances must be considered.

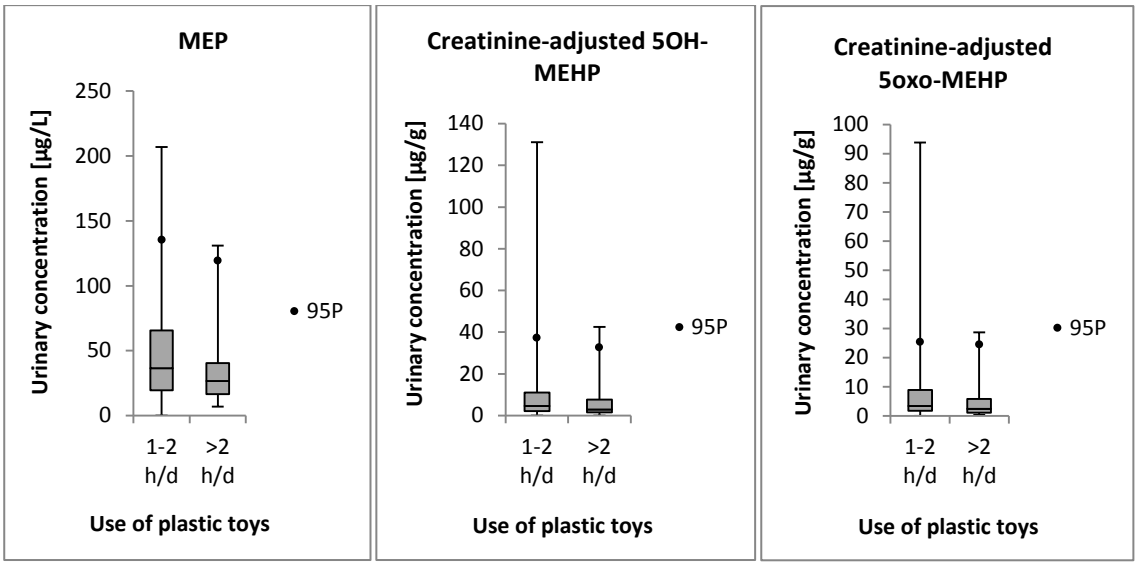


Figure 114. Distributions of urinary creatinine-unadjusted MEP [µg/l] and creatinine-adjusted 5OH-MEHP and 5oxo-MEHP [µg/g] among children from the group of Children II who played with plastic toys 1-2 hours per day (n=158 and 153, respectively) and more than 2 hours per day (n=44)

3.1.8 Summarised results for each phthalate and its corresponding metabolite(s)

Table 88. Result summary for DEP / MEP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MEP	n.d.-447 (15.7; 308) (31)	n.d.-463 (19.5; 108) (220)	n.d.-1087 (31.9; 400) (272)	n.d.-2105 (38.0; 1188) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MEP	n.d.-336 (20.0; 331) (30)	n.d.-1645 (20.7; 114) (215)	n.d.-1276 (28.6; 335) (269)	n.d.-3394 (31.7; 1102) (69)
Daily Intake				
Volume-based DI of DEP [µg/kg bw/d]	n.d.-18.5 (0.65; 12.8) (31)	n.d.-14.6 (0.70; 3.5) (219)	n.d.-41.6 (1.3; 14.3) (269)	n.d.-80.3 (1.4; 40.1) (71)
Creatinine-based DI of DEP [µg/kg bw/d]	n.d.-10.1 (0.53; 9.9) (30)	n.d.-8.9 (0.61; 3.1) (214)	n.d.-48.7 (0.9; 11.2) (267)	n.d.-130 (1.2; 37.5) (69)
RfD [µg/kg bw/d]	800	800	800	800
DI exceedances of AL [%]	0	0	0	0
Reference Values [µg/l]	110	110	440	440
Scenario Exposure Calculations				
SEC based on mean levels in food [µg/kg bw/d]	0.03-0.16 (0.07; 0.16) (25)	0.006-0.57 (0.05; 0.26) (205)	0.003-0.36 (0.03; 0.06) (296)	0.001-0.12 (0.03; 0.08) (59)
SEC based on maximum levels in food [µg/kg bw/d]	0.13-0.82 (0.31; 0.79) (25)	0.03-1.6 (0.22; 0.69) (205)	0.01-0.68 (0.09; 0.23) (296)	0.01-0.22 (0.07; 0.16) (59)
Parameters				
Age	Significant increase with increasing age among the total study population.			
Sex	Females more highly exposed than males in the Children I group for creatinine-adjusted and -unadjusted MEP, and in the group of Adults for creatinine-adjusted MEP.			
Residential area	Higher exposure in participants from (sub)urban areas among the total population.			
Occupation: current employment	Significantly higher MEP exposure in unemployed adult females.			
Workplace: construction works	Significantly higher creatinine-adjusted MEP levels in participants from the Adults group at whose workplaces construction work had been done.			

continued

Current place of residence	Higher exposure in participants from the groups of Children I (adjusted MEP) and Children II (adjusted and unadjusted MEP) living in apartments.
Changed flooring at place of residence	Higher exposure to creatinine-adjusted MEP in the group of Elderly People at whose place of residence floorings had been replaced.
Upholstery furniture	Slightly higher exposure to creatinine-unadjusted MEP in participants with new upholstery furniture.
Use of TV, VGC and/or PC	Significant increase of creatinine-unadjusted MEP (medians) with increasing duration of use of TV, VGC and/or PC among the group of Children II.

Abbreviations: AL, acceptable level of exposure; DI, daily intake; n, sample size; PC, personal computer; P95, 95th percentile; RfD, Reference Dose; SEC, Scenario Exposure Calculations; TV, television; VGC, video game consoles.

Table 89. Result summary for DnBP / MnBP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MnBP	2.0-69.6 (26.5; 65.0) (31)	n.d.-87.7 (12.0; 47.2) (220)	n.d.-73.7 (7.9; 40.7) (272)	n.d.-84.5 (10.4; 57.0) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MnBP	6.1-516 (33.0; 371) (30)	n.d.-699 (12.0; 73.1) (215)	n.d.-78.4 (6.5; 35.3) (269)	n.d.-98.4 (11.7; 53.9) (69)
Daily Intake				
Volume-based DI of DnBP [µg/kg bw/d]	0.07-2.6 (0.99; 2.4) (31)	0.0-2.5 (0.40; 1.6) (219)	0.0-2.4 (0.28; 1.4) (269)	0.0-2.9 (0.35; 1.9) (71)
Creatinine-based DI of DnBP [µg/kg bw/d]	0.15-14.7 (0.84; 10.2) (30)	0.0-18.6 (0.34; 1.8) (214)	0.0-2.0 (0.24; 1.1) (267)	0.0-2.6 (0.35; 1.9) (69)
RfD / RfD AA [µg/kg bw/d]	100	100	100	100
TDI [µg/kg bw/d]	10	10	10	10
DI exceedances of AL [%]	3[a]	0.5[a]	0	0
Reference Values [µg/l]	45	45	40	40
Scenario Exposure Calculations				
SEC based on mean levels in food [µg/kg bw/d]	0.37-2.2 (0.71; 2.1) (25)	0.03-4.3 (0.45; 2.0) (205)	0.08-2.7 (0.33; 0.74) (296)	0.08-0.85 (0.23; 0.58) (59)
SEC based on maximum levels in food [µg/kg bw/d]	11.6-56.6 (25.4; 55.2) (25)	0.94-139 (16.1; 78.5) (205)	0.86-100 (9.5; 28.6) (296)	0.64-31.3 (8.9; 22.8) (59)
Parameters				
Age	Significant differences between different age groups among the total study population.			
Sex	Females more highly exposed to adjusted and unadjusted MnBP than males in the Children I group and in the Adults group for creatinine-adjusted and -unadjusted MnBP.			
Allergies	Significantly higher creatinine-adjusted MnBP levels in participants from the group of Adults who did not suffer from allergies.			
Smoking behaviour	Significantly higher creatinine-unadjusted MnBP levels in non-smokers from the Adults group.			
Occupation: employment position	Significant differences between MnBP levels and employment positions in males from the group of Adults.			
Handicraft materials	Significant decrease of creatinine-adjusted MnBP with increased use of handicraft materials in children from both groups (Children I and II).			

[a] *exceedance of TDI of creatinine-based DI*
Abbreviations: AL, acceptable level of exposure; crea, creatinine; DI, daily intake; n, sample size; P95, 95th percentile; RfD, Reference Dose; RfD AA, Reference Dose for Anti-Androgenicity; SEC, Scenario Exposure Calculations; TDI, Tolerable Daily Intake.

Table 90. Result summary for DiBP / MiBP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MiBP	5.6-177 (53.6; 156) (31)	n.d.-207 (35; 131) (220)	n.d.-248 (24.3; 109) (272)	2.5-152 (25.7; 111) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MiBP	17.5-494 (70.2; 461) (30)	n.d.-1086 (31.1; 213) (215)	n.d.-497 (21.2; 104) (269)	4.6-241 (27.3; 152) (69)
Daily Intake				
Volume-based DI of DiBP [µg/kg bw/d]	0.25-7.9 (2.4; 6.9) (31)	0.0-7.1 (1.3; 4.7) (219)	0.0-11.6 (0.99; 4.6) (269)	0.08-5.3 (1.0; 4.4) (71)
Creatinine-based DI of DiBP [µg/kg bw/d]	0.52-16.7 (2.3; 14.2) (30)	0.0-34.3 (1.1; 7.0) (214)	0.0-16.0 (0.78; 3.4) (267)	0.15-8.7 (0.96; 4.9) (69)
TDI [µg/kg bw/d]	10	10	10	10
RfD [µg/kg bw/d]	100	100	100	100
RfD AA [µg/kg bw/d]	200	200	200	200
DI exceedances of AL [%]	13[a]	2[a]	0.37[b]	0
Reference Values [µg/l]	130	130	110	110
Scenario Exposure Calculations				
SEC based on mean levels in food [µg/kg bw/d]	0.14-1.9 (0.44; 1.5) (25)	0.03-2.0 (0.28; 1.1) (205)	0.05-1.4 (0.26; 0.58) (296)	0.08-0.8 (0.27; 0.55) (59)
SEC based on maximum levels in food [µg/kg bw/d]	0.74-5.2 (1.7; 4.8) (25)	0.07-10.8 (1.0-4.3) (205)	0.17-6.3 (0.71; 1.5) (296)	0.22-1.9 (0.72; 1.5) (59)
Parameters				
Age	Significant differences between different age groups of the total study population.			
Sex	Females more highly exposed than males of the Adults group for (un)adjusted MiBP.			
Allergies	Significantly higher creatinine-adjusted MiBP levels in participants from the group of Adults who did not suffer from allergies.			
Intake of pharmaceuticals	Positive correlations between creatinine-adjusted and -unadjusted MiBP levels and the number of pharmaceuticals consumed per day in the group of Elderly People.			
Occupation: working sectors	Significant differences between different working sectors and MiBP levels in participants from the group of Adults.			
Duration of playing with plastic toys	Significantly lower MiBP exposure in participants from the group of Children II with higher duration of play with plastic toys (>2 h/d).			

[q] *exceedance of TDI of creatinine-based DI*
[b] *exceedances of TDI for creatinine-based and volume-based DI, respectively*
Abbreviations: AL, acceptable level of exposure; crea, creatinine; DI, daily intake; n, sample size; P95, 95th percentile; RfD, Reference Dose; RfD AA, Reference Dose for Anti-Androgenicity; SEC, Scenario Exposure Calculations; TDI, Tolerable Daily Intake.

Table 91. Result summary for DnPeP / MnPeP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MnPeP	n.d.-<LOQ (n.d.; <LOQ) (31)	n.d.-4.5 (n.d.; <LOQ) (220)	n.d.-2.9 (n.d.; <LOQ) (272)	n.d.-2.0 (n.d.; n.d.) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MnPeP	n.d.-2.3 (n.d.; <LOQ) (30)	n.d.-3.4 (n.d.; <LOQ) (215)	n.d.-2.2 (n.d.; <LOQ) (269)	n.d.-2.0 (n.d.; n.d.) (69)
Daily Intake	Not estimated.			
Reference Values [µg/l]	Not estimated.			
Scenario Exposure Calculations	Not estimated.			
Parameters	No statistically significant differences / associations were found.			

Abbreviations: n, sample size; P95, 95th percentile; SEC, Scenario Exposure Calculations.

Table 92. Result summary for DCHP / MCHP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MCHP	n.d.-2.3 (n.d.; <LOQ) (31)	n.d.-5.5 (n.d.; 1.3) (220)	n.d.-3.5 (n.d.; 1.4) (272)	n.d.-1.0 (n.d.; <LOQ) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MCHP	n.d.-1.2 (n.d.; <LOQ) (30)	n.d.-6.9 (n.d.; <LOQ) (215)	n.d.-5.2 (n.d.; <LOQ) (269)	n.d.-<LOQ (n.d.; <LOQ) (69)
Daily Intake	Not estimated.			
Reference Values [µg/l]	1.5	1.5	1.5	1.5
Scenario Exposure Calculations	Not estimated.			
Parameters				
Allergies	Significantly higher creatinine-adjusted and -unadjusted MCHP levels in participants from the group of Adults who did not suffer from allergies.			
Contact with cleaning products	Significantly higher MCHP exposure in participants who had no contact with cleaning products.			
Upholstery furniture	Slightly higher MCHP exposure (creatinine-adjusted and -unadjusted) in participants with new upholstery furniture.			

Abbreviations: n, sample size; P95, 95th percentile; SEC, Scenario Exposure Calculations.

Table 93. Result summary for BBzP / MBzP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MBzP	n.d.-53.3 (5.3; 45.3) (31)	n.d.-57.1 (2.6; 20.6) (220)	n.d.-40.2 (1.4; 9.8) (272)	n.d.-16.6 (1.3; 12.7) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MBzP	n.d.-66.5 (7.0; 64.1) (30)	n.d.-52.9 (2.5; 25.7) (215)	n.d.-33.5 (1.3; 7.1) (269)	n.d.-14.3 (1.4; 12.4) (69)
Daily Intake				
Volume-based DI of BBzP [µg/kg bw/d]	0.0-2.2 (0.22; 1.9) (31)	0.0-1.8 (0.09; 0.78) (219)	0.0-1.2 (0.05; 0.38) (269)	0.0-0.61 (0.05; 0.46) (71)
Creatinine-based DI of BBzP [µg/kg bw/d]	0.0-2.1 (0.21; 1.9) (30)	0.0-1.3 (0.08; 0.77) (214)	0.0-1.0 (0.04; 0.23) (267)	0.0-0.46 (0.05; 0.40) (69)
TDI [µg/kg bw/d]	500	500	500	500
RfD [µg/kg bw/d]	200	200	200	200
RfD AA [µg/kg bw/d]	330	330	330	330
DI exceedances of AL [%]	0	0	0	0
Reference Values [µg/l]	25	25	10	10
Scenario Exposure Calculations				
SEC based on mean levels in food [µg/kg bw/d]	0.02-0.22 (0.04; 0.17) (25)	0.0-0.39 (0.02; 0.12) (205)	0.003-0.32 (0.02; 0.04) (296)	0.001-0.1 (0.01; 0.07) (59)
SEC based on maximum levels in food [µg/kg bw/d]	0.38-4.2 (1.6; 4.0) (25)	0.04-8.3 (0.91; 4.3) (205)	0.07-5.1 (0.61; 2.0) (296)	0.03-2.5 (0.59; 1.9) (59)
Parameters				
Age	Significant decrease with increasing age among the total study population.			
Sex	Females more highly exposed to creatinine-adjusted and -unadjusted MBzP than males of the Children I group.			
Regional differences	Significantly higher exposure to creatinine-adjusted and -unadjusted MBzP in participants from East Austria compared to participants from West Austria.			
Intake of pharmaceuticals	Positive correlations between creatinine-adjusted MBzP levels and the number of pharmaceuticals consumed per day among the group of Elderly People. Significantly higher exposure to creatinine-adjusted MBzP among participants from the Elderly People group who consumed capsules daily.			
Occupation: current employment	Significantly higher MBzP exposure among unemployed females from the Adults group.			
Changed flooring at place of residence	Significantly higher exposure to MBzP (creatinine-unadjusted) in participants from the Children I group whose flooring had been replaced at their place of residence.			

Abbreviations: AL, acceptable level of exposure; crea, creatinine; DI, daily intake; n, sample size; P95, 95th percentile; RfD, Reference Dose; RfD AA, Reference Dose for Anti-Androgenicity; SEC, Scenario Exposure Calculations; TDI, Tolerable Daily Intake.

Table 94. Result summary for DEHP / MEHP, 5OH-MEHP, 5oxo-MEHP, and 5cx-MEPP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MEHP	n.d.-11.2 (<LOQ; 10.1) (31)	n.d.-20.1 (<LOQ; 8.0) (220)	n.d.-17.2 (n.d.; 3.6) (272)	n.d.-11.8 (n.d.; 6.6) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MEHP	n.d.-17.4 (1.3; 14.5) (30)	n.d.-23.2 (0.94; 8.5) (215)	n.d.-6.1 (n.d.; 3.4) (269)	n.d.-11.1 (n.d.; 6.6) (69)
Urinary concentrations [µg/l] of 5OH-MEHP	<LOQ-40.4 (10.8; 34.3) (31)	n.d.-80.0 (4.0; 27.4) (220)	n.d.-46.6 (1.8; 10.7) (272)	n.d.-76.2 (3.3; 31.1) (72)
Creatinine-adjusted urinary concentrations [µg/g] of 5OH-MEHP	2.5-99.4 (17.5; 85.6) (30)	n.d.-131 (31.1; 213) (215)	n.d.-28.6 (1.6; 9.6) (269)	n.d.-71.9 (2.9; 31.0) (69)
Urinary concentrations [µg/l] of 5oxo-MEHP	<LOQ-26.2 (8.7; 21.4) (31)	n.d.-57.3 (3.0; 19.8) (220)	n.d.-29.3 (1.2; 7.9) (272)	n.d.-55.4 (1.6; 20.1) (72)
Creatinine-adjusted urinary concentrations [µg/g] of 5oxo-MEHP	1.8-62.3 (12.9; 60.0) (30)	n.d.-93.9 (3.3; 24.8) (215)	n.d.-18.0 (<LOQ; 6.3) (269)	n.d.-52.3 (1.6; 17.4) (69)
Urinary concentrations [µg/l] of 5cx-MEPP	2.3-57.4 (22.6; 52.5) (31)	2.6-102 (15.5; 56.5) (220)	n.d.-219 (7.8; 29.0) (272)	1.0-134 (10.0; 80.5) (72)
Creatinine-adjusted urinary concentrations [µg/g] of 5cx-MEPP	7.1-135 (5.2; 30.7) (30)	2.7-179 (15.0; 67.3) (215)	n.d.-131 (6.0; 24.3) (269)	1.8-150 (9.2; 71.3) (69)
Daily Intake				
Volume-based DI of DEHP[a] [µg/kg bw/d]	0.19-6.6 (2.3; 5.7) (31)	0.14-11.2 (1.1; 5.0) (219)	0.0-10.8 (0.54; 2.3) (269)	0.04-12.2 (0.66; 6.3) (71)
Creatinine-based DI of DEHP[a] [µg/kg bw/d]	0.39-11.2 (2.4; 11.1) (30)	0.09-15.2 (0.94; 5.2) (214)	0.0-7.5 (0.39; 1.6) (267)	0.10-9.8 (0.62; 6.1) (69)
Volume-based DI of DEHP[b] [µg/kg bw/d]	0.26-9.1 (3.3; 7.7) (31)	0.19-15.5 (1.5; 6.9) (219)	0.0-14.9 (0.75; 3.2) (269)	0.06-16.9 (0.91; 8.7) (71)
Creatinine-based DI of DEHP[b] [µg/kg bw/d]	0.54-15.6 (3.3; 15.4) (30)	0.13-21.1 (1.3; 7.2) (214)	0.0-10.4 (0.53; 2.2) (267)	0.14-13.6 (0.86; 8.5) (69)
TDI [µg/kg bw/d]	50	50	50	50
RfD [µg/kg bw/d]	20	20	20	20
RfD AA [µg/kg bw/d]	30	30	30	30
DI exceedances of AL [%]	0	0.47[c]	0	0
Reference Values [µg/l]				
Σ all DEHP metabolites	100	100	50	50
Σ 5OH-MEHP + 5oxo-MEHP	50	50	20	20
5OH-MEHP	30	30	15	15
5oxo-MEHP	20	20	10	10
5cx-MEPP	60	60	35	35
Scenario Exposure Calculations				
SEC based on mean levels in food [µg/kg bw/d]	1.5-6.1 (2.5; 5.9) (25)	0.18-16.1 (1.4; 7.5) (205)	0.26-10.6 (1.1; 2.1) (296)	0.25-3.2 (0.78; 2.3) (59)
SEC based on maximum levels in food [µg/kg bw/d]	7.3-82.3 (16.6; 65.3) (25)	0.72-118 (11.3; 37.8) (205)	1.7-51.4 (7.5; 16.8) (296)	1.9-34.6 (7.2; 17.3) (59)
Parameters				
Age	Significant decrease of 5oxo-MEHP, 5OH-MEHP and 5cx-MEPP with increasing age among the total study population.			
Sex	Females more highly exposed than males in the group of Adults for creatinine-adjusted and -unadjusted 5oxo-MEHP and 5OH-MEHP, and for unadjusted 5cx-MEPP.			
Regional differences	Significantly higher exposure among participants from East Austria compared to those from West Austria for all investigated creatinine-adjusted and -unadjusted DEHP metabolites.			
Residential area	Significant higher exposure in participants from (sub)urban areas than those from rural areas for creatinine-adjusted 5oxo-MEHP and 5OH-MEHP, as well as for creatinine-unadjusted 5cx-MEHP.			
BMI	Significant increase of creatinine-unadjusted 5OH-MEHP and 5cx-MEHP with increasing BMI among the total study population.			
Hypertension	Significantly higher creatinine-adjusted and -unadjusted 5cx-MEHP and 5OH-MEHP exposure, as well as unadjusted 5oxo-MEHP exposure among participants from the group of Elderly People who suffered from hypertension.			
Allergies	Significantly higher creatinine-adjusted 5oxo-MEHP levels in participants from the group of Adults who did not suffer from allergies.			

continued

Intake of pharmaceuticals	Positive correlations between creatinine-adjusted MEHP, 5OH-MEHP and 5cx-MEPP levels and the number of pharmaceuticals consumed per day in the group of Elderly People, as well as significant higher creatinine-adjusted and -unadjusted MEHP exposure at consumption levels of >4 pharmaceuticals per day. Among participants from the group of Adults, slight but significantly higher MEHP exposure (adjusted and unadjusted) who consumed pharmaceuticals daily. Significantly higher exposure to creatinine-adjusted 5cx-MEPP among participants from the Elderly People group who consumed film tablets daily.
Nutrition	For logarithmic DEHP metabolites, statistically significant results were observed for the food types rice/pasta, brown bread, almonds/nut/peanuts, butter/oils, tab water/mineral water, French fries and microwave popcorn, although a clear conclusion could only be made for the frequency of the consumption of French fries and microwave popcorn, which were associated with higher DEHP metabolite exposure.
Smoking behaviour	Significantly higher creatinine-adjusted and -unadjusted 5cx-MEHP levels in non-smokers from the group of Adults.
Occupation: current employment	Significantly higher MEHP, 5oxo-MEHP and 5cx-MEPP exposure in unemployed females from the Adults group.
Occupation: employment position	Significant differences between 5cx-MEPP levels and employment positions in males from the Adults group.
Occupation: working sectors	Significant differences between different working sectors and 5oxo-MEHP and 5cx-MEPP levels in participants from the group of Adults.
Contact with cleaning products	Significantly higher MEHP exposure (adjusted and unadjusted levels) in participants who had contact with cleaning products.
Contact with chemicals	Significantly higher 5cx-MEPP exposure (creatinine-unadjusted levels) in participants who had no contact with chemicals.
Current place of residence	Significantly higher exposure to creatinine-adjusted MEHP, 5oxo-MEHP, 5OH-MEHP and 5cx-MEPP, and to creatinine-unadjusted MEHP in participants from the Children I group living in apartments.
Changed flooring at place of residence	Significantly higher exposure to creatinine-unadjusted 5oxo-MEHP, 5OH-MEHP and 5cx-MEHP in participants from the Children I group whose flooring had been replaced at their place of residence. Higher exposure to creatinine-unadjusted 5oxo-MEHP and 5cx-MEPP in participants from the group of Elderly People whose flooring had not been replaced at their place of residence.
Upholstery furniture	Slightly higher creatinine-adjusted MEHP exposure in participants with new upholstery furniture.
Use of TV, VGC and/or PC	Significant increase of creatinine-unadjusted MEHP, 5OH-MEHP and 5cx-MEPP (medians) with increasing duration of use of TV, VGC and/or PC among participants of the group of Children II.
Duration of playing with plastic toys	Significant lower creatinine-adjusted 5oxo-MEHP and 5OH-MEHP exposure in participants from the group of Children II with higher duration of playing with plastic toys (>2 h/d).

[a] based on F_{UE}s derived from Koch et al. (2005)
[b] based on F_{UE}s derived from Anderson et al. (2011)
[c] exceedance of creatinine-based DI based on F_{UE}s derived from Anderson et al. (2011)
Abbreviations: AL, acceptable level of exposure; crea, creatinine; DI, daily intake; n, sample size; PC, personal computers; PS; P95, 95th percentile; RfD, Reference Dose; RfD AA, Reference Dose for Anti-Androgenicity; SEC, Scenario Exposure Calculations; TDI, Tolerable Daily Intake; TV, television; VGC, video game consoles.

Table 95. Result summary for DnOP / MnOP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MnOP	n.d.-<LOQ (n.d.; <LOQ) (31)	n.d.-3.4 (n.d.; <LOQ) (220)	n.d.-2.0 (n.d.; <LOQ) (272)	n.d.-<LOQ (n.d.; <LOQ) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MnOP	n.d.-2.3 (n.d.; 1.8) (30)	n.d.-3.6 (n.d.; <LOQ) (215)	n.d.-1.3 (n.d.; <LOQ) (269)	n.d.-1.0 (n.d.; <LOQ) (69)
Daily Intake	Not estimated.			
Reference Values [µg/l]	Not estimated.			
Scenario Exposure Calculations	Not estimated.			
Parameters	No statistically significant differences / associations were found.			

Abbreviations: n, sample size; P95, 95th percentile; SEC, Scenario Exposure Calculations.

Table 96. Result summary for DiNP / MiNP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MiNP	n.d.-12.7 (n.d.; 5.1) (31)	n.d.-5.4 (n.d.; 1.7) (220)	n.d.-5.4 (n.d.; 1.4) (272)	n.d.-2.4 (n.d.; 0.95) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MiNP	n.d.-12.3 (n.d.; 5.6) (30)	n.d.-5.7 (n.d.; 1.7) (215)	n.d.-44.5 (n.d.; 1.2) (269)	n.d.-5.5 (n.d.; 1.0) (69)
Daily Intake	Not estimated			
TDI [µg/kg bw/d]	150	150	150	150
RfD AA [µg/kg bw/d]	1500	1500	1500	1500
Reference Values [µg/l]	Not estimated.			
Scenario Exposure Calculations				
SEC based on mean and maximum levels in food [µg/kg bw/d]	0.02-0.37 (0.12; 0.36) (25)	0.002-0.91 (0.05; 0.27) (205)	0.001-0.07 (0.01; 0.03) (296)	0.002-0.04 (0.01; 0.03) (59)
Parameters				
Sex	Females more highly exposed than males among participants from the group of Adults for creatinine-adjusted and -unadjusted MiNP.			
Regional differences	Significantly higher exposure among participants from East Austria compared to those from West Austria for creatinine-adjusted and -unadjusted MiNP.			

Abbreviations: n, sample size; P95, 95th percentile; RfD AA, Reference Dose for Anti-Androgenicity; SEC, Scenario Exposure Calculations; TDI, Tolerable Daily Intake.

Table 97. Result summary for DiDP / MiDP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l] of MiDP	n.d.-<LOQ (n.d.; <LOQ) (31)	n.d.-1.0 (n.d.; <LOQ) (220)	n.d.-0.91 (n.d.; <LOQ) (272)	n.d.-1.1 (n.d.; <LOQ) (72)
Creatinine-adjusted urinary concentrations [µg/g] of MiDP	n.d.-<LOQ (n.d.; n.d.) (30)	n.d.-2.2 (n.d.; <LOQ) (215)	n.d.-3.1 (n.d.; <LOQ) (269)	n.d.-4.4 (n.d.; 1.3) (69)
Daily Intake	Not estimated.			
TDI [µg/kg bw/d]	150	150	150	150
Reference Values [µg/l]	Not estimated.			
Scenario Exposure Calculations				
SEC based on mean and maximum levels in food [µg/kg bw/d]	0.03-0.44 (0.09; 0.41) (25)	0.002-0.91 (0.05; 0.27) (205)	0.001-0.32 (0.02; 0.12) (296)	0.0-0.18 (0.01; 0.51) (59)
Parameters	No statistically significant differences / associations were found.			

Abbreviations: n, sample size; P95, 95th percentile; SEC, Scenario Exposure Calculations; TDI, Tolerable Daily Intake.

Table 98. Result summary for 3cx-MPP

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l]	<LOQ-14.2 (22.6; 11.8) (31)	n.d.-62.5 (<LOQ; 17.2) (220)	n.d.-188 (<LOQ; 19.0) (272)	n.d.-38.4 (<LOQ; 16.2) (72)
Creatinine-adjusted urinary concentrations [µg/g]	<LOQ-40.5 (5.2; 30.7) (30)	n.d.-206 (<LOQ; 16.9) (215)	n.d.-122 (<LOQ; 17.6) (269)	n.d.-36.2 (<LOQ; 21.3) (69)
Parameters				
BMI	Significant increase of creatinine-unadjusted 3cx-MPP with increasing BMI among the total study population.			
Hypertension	Significantly higher creatinine-adjusted and -unadjusted 3cx-MPP exposure in participants from the group of Adults without self-reported hypertension (however, not ideal sample size distribution). Significantly higher creatinine-unadjusted 3cx-MPP exposure in participants with hypertension from the group of Elderly People.			
Intake of pharmaceuticals	Positive correlations between creatinine-adjusted and -unadjusted 3cx-MPP levels and the number of pharmaceuticals consumed per day in participants from the group of Elderly People, as well as significantly higher exposure at consumption levels of >4 pharmaceuticals per day. Significantly higher exposure to creatinine-adjusted and unadjusted 3cx-MPP among participants from the Elderly People group who consumed film tablets daily.			
Current place of residence	Significant creatinine-adjusted and -unadjusted 3cx-MPP levels in participants from the group of Adults living in homes constructed before 1945.			
Upholstery furniture	Slight but significantly lower creatinine-adjusted 3cx-MPP exposure in participants with new upholstery furniture.			

Abbreviations: n, sample size; P95, 95th percentile.

3.2 BISPHENOL A

3.2.1 Description of the study population

The study population used for BPA analysis is very similar to the study population for phthalate analysis. In some few cases, only BPA concentrations were measured in urine samples and vice versa for phthalates. However, in most of samples, both BPA and phthalate metabolites were analysed, but because of slight differences in study population, the population used for BPA analysis is described separately.

Table 99. Data Children I (BPA analysis)

	All	Males	Females
SEX[1]	31 (100%)	16 (52%)	15 (48%)
AGE [years] (range; mean±SD)[1,2]	6-8; 7±0.5	6-8; 7±0.5	6-8; 7±0.6
FEDERAL STATE (n=29)[1,3]			
Vienna	4 (14%)	2 (13%)	2 (14%)
Burgenland	7 (24%)	3 (20%)	4 (29%)
Lower Austria	5 (17%)	3 (20%)	2 (14%)
Styria	1 (4%)	0 (0%)	1 (7%)
Salzburg	12 (41%)	7 (47%)	5 (36%)
REGION (n=29)[1,3]			
East Austria	17 (59%)	8 (53%)	9 (64%)
West Austria	12 (41%)	7 (47%)	5 (36%)
RESIDENTAL AREA (n=28)[1,4]			
urban	7 (25%)	3 (22%)	4 (29%)
suburban	4 (14%)	2 (14%)	2 (14%)
rural	17 (61%)	9 (64%)	8 (57%)
ANTHROPOMETRIC CHARACTERISTICS			
Bodyheight [cm] (n=31)[1,2] (range; mean±SD)	118-141; 128±6	120-141; 129±5	118-141; 128±7
Bodyweight [kg] (n=31)[1,2] (range; mean±SD)	21-39; 28±4	23-33; 27±3	21-39; 28±6
WC [cm] (n=31)[1,3] (range; mean±SD)	50-68; 59±4	55-65; 60±3	50-68; 58±5
HC [cm] (n=31)[1,2] (range; mean±SD)	62-81; 70±5	62-80; 71±5	63-81; 69±5
AC [cm] (n=31)[1,2] (range; mean±SD)	50-75; 62±6	54-70; 62±5	50-75; 62±6

Abbreviations: AC, abdominal circumference; HC, hip circumference; n, sample size; SD, standard deviation; WC, waist circumference.
[1] In some cases, sample sizes differ due to missing values in participants' questionnaires. Additionally, sex of one sample is unknown.
[2] n(female)=15; n(male)=16
[3] n(female)=14; n(male)=15
[4] n(female)=14; n(male)=14

Table 100. Data of Children II (BPA analysis)

	All	Males	Females
SEX	221 (100%)	122 (55%)	99 (45%)
AGE [years] (range; mean±SD)	7-15; 11±1.7	7-15; 11±1.8	8-14; 11±1.7
FEDERAL STATE (n=206)[1,3]			
Vienna	62 (30%)	32 (28%)	30 (33%)
Burgenland	54 (26%)	33 (29%)	21 (23%)
Lower Austria	31 (15%)	16 (14%)	15 (16%)
Styria	7 (4%)	3 (3%)	4 (4%)
Upper Austria	23 (11%)	12 (10%)	11 (12%)
Tyrol	29 (14%)	18 (16%)	11 (12%)
REGION (n=221)			
East Austria	170 (77%)	92 (75%)	78 (79%)
West Austria	51 (23%)	30 (25%)	21 (21%)
RESIDENTAL AREA (n=203)[1,4]			
urban	52 (26%)	25 (22%)	27 (29%)
suburban	20 (10%)	12 (11%)	8 (9%)
rural	131 (64%)	74 (67%)	57 (62%)
ANTHROPOMETRIC CHARACTERISTICS			
Bodyheight [cm] (n=221) (range; mean±SD)	116-187; 150±12.0	124-187; 150±12.7	116-172; 149±11
Bodyweight [kg] (n=221) (range; mean±SD)	24-91; 45±14	24-91; 46±15	24-77; 44±13
WC [cm] (n=220)[1,2] (range; mean±SD)	49-90; 67±9	53-88; 68±9	49-90; 66±8
HC [cm] (n=220)[1,2] (range; mean±SD)	64-111; 83±10	64-111; 83±10	66-111; 82±10
AC [cm] (n=220)[1,2] (range; mean±SD)	53-106; 74±11	53-103; 74±11	54-106; 73±10

Abbreviations: AC, abdominal circumference; HC, hip circumference; n, sample size; SD, standard deviation; WC, waist circumference.
[1] In some cases, sample sizes differ due to missing values in participants' questionnaires.
[2] n(female)=99; n(male)=121
[3] n(female)=92; n(male)=114
[4] n(female)=92; n(male)=111

Table 101. Data Adults (BPA analysis)

	All	Males	Females
SEX	275 (100%)	112 (40.7%)	163 (59.3%)
AGE [years] (range; mean±SD)	18-65; 39.2±13.5	18-64; 40.7±12.9	18-65; 38.2±13.9
FEDERAL STATE (n=271)[1,3]			
Vienna	28 (10%)	14 (13%)	14 (9%)
Burgenland	51 (19%)	27 (24%)	24 (15%)
Lower Austria	30 (11%)	15 (14%)	15 (9%)
Styria	29 (11%)	13 (12%)	16 (10%)
Upper Austria	15 (6%)	4 (4%)	11 (7%)
Salzburg	22 (8%)	10 (9%)	12 (7%)
Tyrol	94 (35%)	27 (24%)	67 (42%)
Vorarlberg	2 (<1%)	0 (0%)	2 (1%)
REGION (n=274)[4]			
East Austria	142 (52%)	71 (63%)	71 (44%)
West Austria	132 (48%)	41 (37%)	91 (56%)
RESIDENTAL AREA (n=273)[1,5]			
urban	107 (39%)	49 (44%)	58 (36%)
suburban	42 (15%)	19 (17%)	23 (14%)
rural	124 (46%)	44 (39%)	80 (50%)
ANTHROPOMETRIC CHARACTERISTICS			
Bodyheight [cm](n=272)[1,2] (range; mean±SD)	145-194; 171±9	158-194; 178±7	145-182; 166±7.1
Bodyweight [kg] (n=272)[1,2] (range; mean±SD)	42-123; 72±15	55-123; 83±13	42-109; 65±11
BMI [kg/m^2] (n=272)[1,2] (range; mean±SD)	16.3-39.2; 25±4	19.2-39.2; 26±4	16.3-39; 24±4
WC [cm] (n=262)[1,6] (range; mean±SD)	60-120; 83±13	72-120; 92±11	60-113; 76±11
HC [cm] (n=272)[1,2] (range; mean±SD)	59-128; 100±9	89-121; 103±7	59-128; 98±10
AC [cm] (n=272)[1,2] (range; mean±SD)	66-129; 90±12	75-129; 95.8±11	66-127; 86±10
WHR (n=262)[1,6] (range; mean±SD)	0.62-1.2; 0.8±0.09	0.75-1.04; 0.89±0.07	0.62-1.2; 0.78±0.08

Abbreviations: AC, abdominal circumference; BMI, body mass index; HC, hip circumference; n, sample size; SD, standard deviation; WC, waist circumference; WHR, waist-to-hip ratio.
[1] In some cases, sample sizes differ due to missing values in participants' questionnaires.
[2] n(female)=161; n(male)=111
[3] n(female)=161; n(male)=110
[4] n(female)=162; n(male)=112
[5] n(female)=161; n(male)=112
[6] n(female)=161; n(male)=107

Table 102. Data Elderly People (BPA analysis)

	All	Males	Females
SEX	66 (100%)	30 (45.5%)	36 (54.5%)
AGE [years] (range; mean±SD)	64-79; 71.0±4.3	64-79; 70.9±4.5	65-79; 71.1±4.3
FEDERAL STATE (n=66)			
Vienna	13 (20%)	4 (13%)	9 (25%)
Burgenland	2 (3%)	2 (7%)	0 (0%)
Lower Austria	9 (14%)	3 (10%)	6 (17%)
Styria	6 (9%)	3 (10%)	3 (8%)
Upper Austria	4 (6%)	4 (13%)	0 (0%)
Salzburg	18 (27%)	8 (27%)	10 (28%)
Tyrol	14 (21%)	6 (20%)	8 (22%)
REGION (n=65)[1,2]			
East Austria	30 (46%)	12 (41%)	18 (50%)
West Austria	35 (54%)	17 (59%)	18 (50%)
RESIDENTAL AREA (n=64)[1,3]			
urban	42 (66%)	16 (55%)	26 (74%)
suburban	11 (17%)	5 (17%)	6 (17%)
rural	11 (17%)	8 (28%)	3 (9%)
ANTHROPOMETRIC CHARACTERISTICS			
Bodyheight [cm] (n=65)[1,2] (range; mean±SD)	139-186; 166±11	162-186; 174±6	139-176; 159±8
Bodyweight [kg] (n=65)[1,2] (range; mean±SD)	54-112; 77±13	67-112; 82±11	54-103; 72±12
BMI [kg/m²] (n=65)[1,2] (range; mean±SD)	21.6-44.6; 28±5	21.6-34.5; 27±4	22.3-44.6; 29±5
WC [cm] (n=65)[1,2] (range; mean±SD)	72-123; 95±11	83-123; 99±10	72-122; 92±12
HC [cm] (n=65)[1,2] (range; mean±SD)	90-162; 106±11	93-162; 105±13	90-137; 107±10
AC [cm] (n=65)[1,2] (range; mean±SD)	77-129; 101±11	88-129; 102±10	77-125; 100±12
WHR (n=65)[1,2] (range; mean±SD)	0.65-1.1; 0.89±0.09	0.65-1.1; 0.95±0.09	0.74-1.0; 0.85±0.06

Abbreviations: AC, abdominal circumference; BMI, body mass index; HC, hip circumference; n, sample size; SD, standard deviation; WC, waist circumference; WHR, waist-to-hip ratio.
[1] In some cases, sample sizes differ due to missing values in participants' questionnaires.
[2] n(female)=36; n(male)=29
[3] n(female)=35; n(male)=29

3.2.2 Urinary BPA concentrations

Total BPA concentrations [µg/l] were analysed in 2013 by on-line SPE-HPLC-MS/MS. The limit of detection (LOD) of BPA is 2.5 µg/l. If total BPA levels of more than 10 µg/l were measured, analysis were additionally performed to measure the respective free BPA concentration and identify possible contaminations of the samples. Total BPA was measured by the enzymatic scission of β-glucuronidase, whereas free BPA was measured without enzymatic scission.

Additionally, analysed BPA concentrations in urine were creatinine-adjusted (the method of creatinine adjustment is described in Chapter 2.5.1) to recognise differences

in individual renal function, body mass, sex and age. Urinary creatinine levels of each sample were provided by the IfEW, which analysed the creatinine content photometrically in urine.

Urinary BPA concentrations [µg/l] in children, adults and elderly people are illustrated in Table 103. Table 104 shows the creatinine-adjusted BPA concentrations [µg/g] in the population groups.

Table 103. Concentrations of creatinine-unadjusted BPA [µg/l] in Austrian children, adults and elderly people

[µg/l]	**Children I**	**Children II**	**Adults**	**Elderly People**
n	32	221	275	66
range	n.d.-14.8	n.d.-12.9	n.d.-16.9	n.d.-6.5
mean±SD	2.4±3.7	0.47±1.5	0.41±1.7	0.31±1.1
median	n.d.	n.d.	n.d.	n.d.
25th percentile	n.d.	n.d.	n.d.	n.d.
75th percentile	4.1	n.d.	n.d.	n.d.
95th percentile	11.9	2.9	n.d.	3.2
DR [%]	50.0	17.6	11.3	10.6
LOD	2.5	2.5	2.5	2.5

Abbreviations: DR, detection rate; LOD, limit of detection; n, sample size; n.d., not detected; SD, standard deviation.

Table 104. Concentrations of creatinine-adjusted BPA [µg/g] in Austrian children, adults and elderly people

[µg/g]	**Children I**	**Children II**	**Adults**	**Elderly People**
n	30	218	273	63
range	n.d.-20.0	n.d.-21.2	n.d.-11.9	n.d.-5.0
mean±SD	3.1±4.6	0.45±1.8	0.36±1.4	0.26±0.90
median	n.d.	n.d.	n.d.	n.d.
25th percentile	n.d.	n.d.	n.d.	n.d.
75th percentile	5.0	n.d.	n.d.	n.d.
95th percentile	15.2	2.4	2.3	2.6
DR [%]	40.0	17.4	10.9	11.1

Abbreviations: DR, detection rate; n, sample size; n.d., not detected; SD, standard deviation.

Generally, children showed higher BPA exposure than adults and elderly people. Thus, a decrease of BPA exposure with increasing age was identified. The distributions of BPA exposure in all study population groups for un-adjusted as well as creatinine-adjusted urinary BPA are shown in Figure 115 and in Figure 116, respectively. However, BPA levels were very low, and additionally, BPA was detected in the group of Children I in 50% of all samples, declining to about 11% in elderly people. Thus, exposure to BPA in this study population was low.

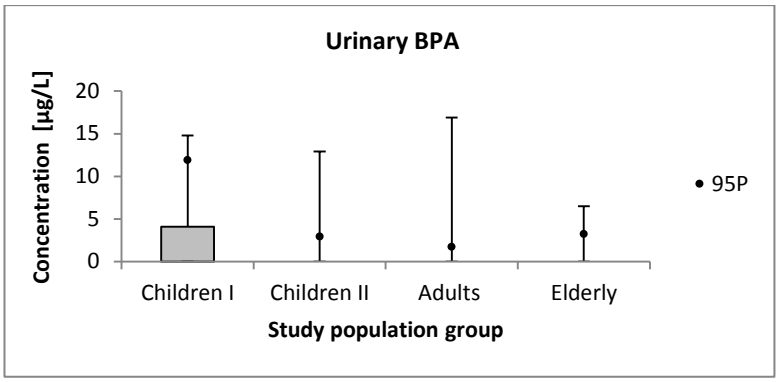


Figure 115. Creatinine-unadjusted BPA [µg/l] in the groups of Children I (n=32), Children II (n=221), Adults (n=275) and Elderly People (n=66)

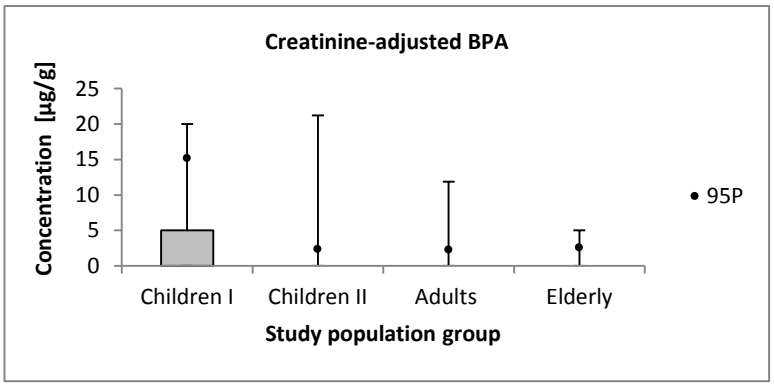


Figure 116. Creatinine-adjusted BPA [µg/g] in the groups of Children I (n=30), Children II (n=218), Adults (n=273) and Elderly People (n=63)

3.2.3 Comparison with other study results

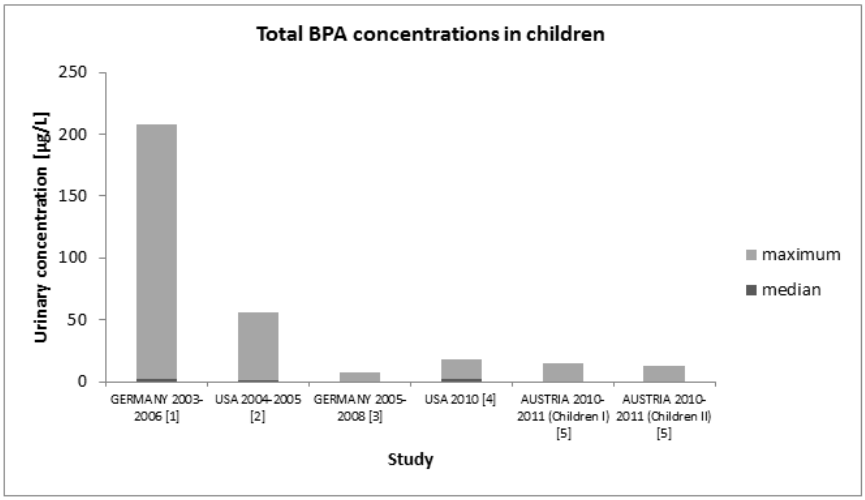
3.2.3.1 International studies

Urinary concentrations of total and/or free BPA, and/or creatinine-adjusted BPA in several population groups as derived from various studies are shown in Table 142 and Table 143 (Appendix B.2) (tables are not comprehensive).

Median total BPA concentrations in the urine of children were generally low in all listed studies. In a study conducted in the USA between 1998 and 2003, the highest BPA levels (medians) were identified in children aged 3-4 years (n=198) born to African-American and Dominican women (Perera et al., 2012). Compared to results from Austrian children, exposure was lower in both groups (Children I and Children II), respectively (Figure 117).

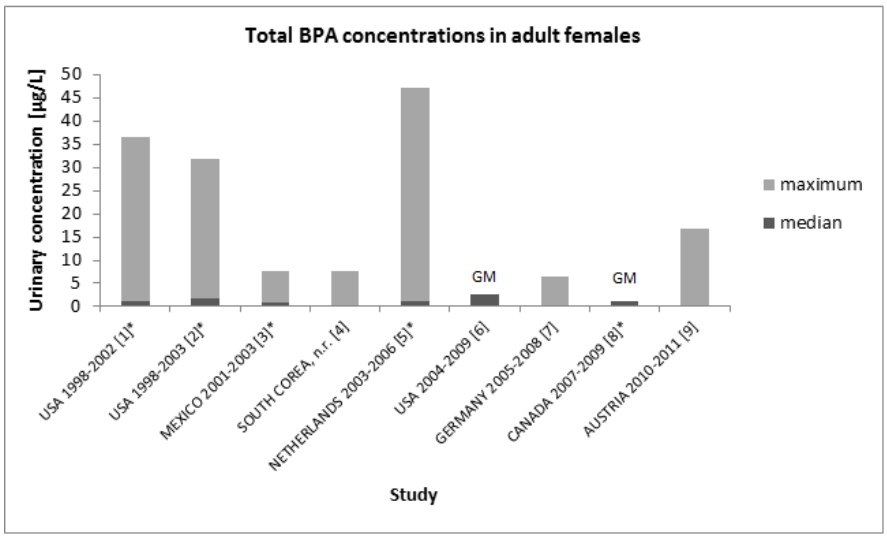
Among adults, several investigations were conducted on women, especially during pregnancy (Figure 118). Median BPA levels were lower in Austrian women compared

the results of other studies. The highest maximum level of urinary BPA was found in pregnant women aged 18-41 years in 2003-2006 from the Netherlands (n=100), where one woman showed a BPA concentration of 46 µg/l (Ye et al., 2008). The maximum level of urinary BPA in Austrian women (n=163) from the present study was at 16.9 µg/l, whereby for example in a comparable population of German women (n=31) the maximum levels were lower (Völkel, Kiranoglu and Fromme, 2008). In male and female adults, exposures to BPA (median levels) were lower in Austrian samples compared to adults from other countries (Figure 119).



References: [1] Becker et al. (2009); [2] Wolff et al. (2007); [3] Völkel, Kiranoglu and Fromme (2008); [4] Rudel et al. (2011); [5] this study.

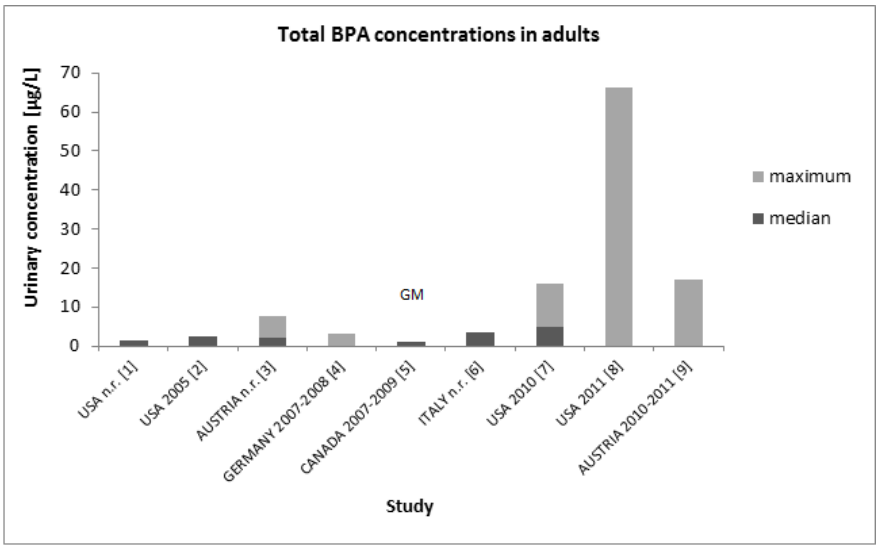
Figure 117. Median and maximum creatinine-unadjusted BPA concentrations [µg/l] in different study populations of children between 2003 and 2011 from several countries compared to results of the present study



* pregnant women

References: [1] Wolff et al. (2008); [2] Perera et al. (2012); [3] Cantonwine et al. (2010); [4] Kim et al. (2003); [5] Ye et al. (2008); [6] Braun et al. (2012); [7] Völkel, Kiranoglu and Fromme (2008); [8] Arbuckle et al. (2014); [9] this study.

Figure 118. Median and maximum creatinine-unadjusted BPA concentrations [µg/l] in different study populations of adult females between 1998 and 2011 from several countries compared to results of the present study



References: [1] Calafat et al. (2005); [2] Ye et al. (2011); [3] Schöringhumer and Cichna-Markl (2007) (mean); [4] Völkel, Kiranoglu and Fromme (2008); [5] Bushnik et al. (2010); [6] Galloway et al. (2010); [7] Rudel et al. (2011); [8] Liao and Kannan (2012); [9] this study.

Figure 119. Median and maximum creatinine-unadjusted BPA concentrations [µg/l] in different study populations of adults between <2005 and 2011 from several countries compared to results of the present study

3.2.3.2 National studies

A study on BPA exposure in male and female children aged 6-11 years and women aged 38 years (mean) was performed by the EAA in 2009. In the total study population (n=25), only four samples showed total BPA concentrations in urine above the LOD, which leads to an overall detection rate of 16%. (Hohenblum and Hutter, 2011) Compared with results from the present study, BPA was found in urine samples of 11% of participants from the group of Adults and 50% of participants from the group of Children I. Maximum values were slightly higher in the present study compared to those of the study from 2009. However, the different study populations and the small sample size in the previous study should be considered.

3.2.4 Daily Bisphenol A Intake

3.2.4.1 Calculation

The estimation of the daily intake (DI) of BPA is similar to the calculations made for phthalates (Chapter 3.1.5). Based on analysed urinary total BPA concentrations, volume-based DIs according to Koch et al. (2012b) and creatinine-based DIs according to Frederiksen et al. (2013) were calculated with the following formulas:

Volume-based model (Koch et al., 2012b):

$$\textbf{Daily BPA Intake}\ [\mu\mathbf{g/kg\ bw/d}] = \frac{\mathrm{UC}\ [\mu\mathrm{g/l}] * \mathrm{UV_{24h}}\ [\mathrm{l/d}]}{\mathrm{F_{UE}} * \mathrm{bw}\ [\mathrm{kg}]}$$

UC	Urinary concentration - analysed total BPA concentration excreted via urine
UV_{24h}	24h urinary volume
F_{UE}	urinary molar excretion fraction of BPA
bw	bodyweight

Creatinine-based model (Frederiksen et al., 2013):

$$\textbf{Daily BPA Intake}\ [\mu\mathbf{g/kg\ bw/d}] = \frac{\mathrm{UE_{crea}}\ [\mu\mathrm{g/g}] * \mathrm{CE_{smoothed}}\ [\mathrm{g/d}]}{\mathrm{F_{UE}} * \mathrm{bw}\ [\mathrm{kg}]}$$

UE_{crea}	urinary excretion of total BPA per creatinine
$CE_{smoothed}$	smoothed creatinine excretion: reference values for the urinary creatinine excretion based on bodyheight and gender (children) and bodyweight (adults, elderly people)
F_{UE}	urinary molar excretion fraction of BPA
bw	bodyweight

Urinary concentration (UC):

In this study, total BPA concentrations were analysed in urine in µg/l.

24-h urinary volume (UV_{24h}):

Reference values for urinary volume excreted per day are shown in Table 59.

Urinary excretion per creatinine (UE_{crea}):

Total BPA levels were analysed in urine in µg/l. Urinary creatinine levels were provided by the IfEW of each participant. The procedure of the estimation of concentrations of BPA excretion per creatinine is described in Chapter 2.5.1.

Smoothed creatinine excretion ($CE_{smoothed}$):

Similar to the calculation of daily phthalate intake, for the estimation of the DIs of BPA, 24h urinary creatinine excretion reference values are necessary (cf. 3.1.5.1). For children, reference values published in Remer, Neubert and Maser-Gluth (2002) were

used, and the reference values of 18 mg/kg bw/d (for females) and 23 mg/kg bw/d (for males) were used for adults and elderly people (Koch, Drexler and Angerer, 2003).

Molar fraction values (F_{UE}):

F_{UE} is the amount of urinary excreted BPA within 24 h after an oral application and was determined in various metabolism studies in humans. The F_{UE} of BPA is set to 1 because nearly 100% of administered BPA is excreted via urine as glucuronide- or sulphate-conjugate within 24 h. (Koch et al., 2012b)

3.2.4.2 Acceptable levels of exposure

For BPA, the U.S. EPA has set out a RfD of 50 µg/kg bw/d (U.S. EPA, 2012b). Since 2014, a temporary new TDI of 5 µg/kg bw/d has been set out by the EFSA (EFSA, 2014a).

3.2.4.3 Results

The estimated volume-based and creatinine-based daily BPA intakes for each study population group are shown in Table 105 and Table 106, respectively.

Table 105. Volume-based daily BPA intakes (ranges, medians, 95th percentiles) [µg/kg bw/d] in Austrian children, adults and elderly people

	DI BPA (volume-based) [µg/kg bw/d]			
Population group	*Sample size (n)*	*Range*	*Median*	*95th percentile*
Children I	32	n.d.-0.37	0.016	0.300
Children II	221	n.d.-0.32	n.d.	0.055
Adults	272	n.d.-0.44	n.d.	0.045
Elderly People	65	n.d.-0.12	n.d.	0.073

Table 106. Creatinine-based daily BPA intakes (ranges, medians, 95th percentiles) [µg/kg bw/d] in Austrian children, adults and elderly people

	DI BPA (creatinine-based) [µg/kg bw/d]			
Population group	*Sample size (n)*	*Range*	*Median*	*95th percentile*
Children I	30	n.d.-0.38	n.d.	0.280
Children II	218	n.d.-0.45	n.d.	0.042
Adults	271	n.d.-0.27	n.d.	0.049
Elderly People	63	n.d.-0.09	n.d.	0.057

3.2.4.3.1 Comparison with acceptable levels of exposure

Compared with ALs (TDI and RfD), all samples showed daily BPA intakes (volume-based and creatinine-based) far below the RfD of 50 µg/kg bw/d and the temporary TDI of 5 µg/kg bw/d.

3.2.4.3.2 Differences between study population groups

As shown in Figure 120 and Figure 122, DIs for BPA decreased with increasing age. Children showed higher DIs compared to younger adults and elderly people. Differences between the study population groups were statistically significant for both volume-based and creatinine-based daily BPA intakes (Kruskal-Wallis test; p=0.000). Relative cumulative frequencies are illustrated in Figure 121 for creatinine-based daily BPA intake and in Figure 123 for volume-based daily BPA intake.

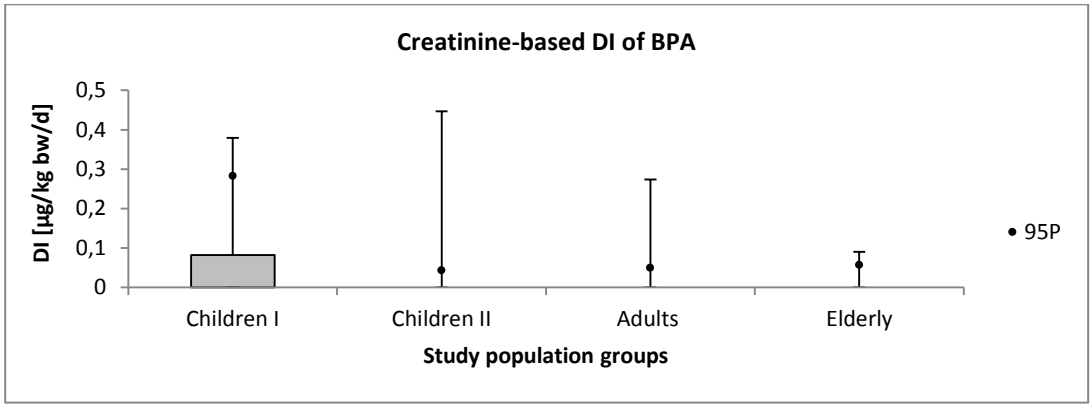


Figure 120. Distribution of creatinine-based daily BPA intake [µg/kg bw/d] in the groups of Children I (n=31), Children II (n=218), Adults (n=271) and Elderly People (n=63)

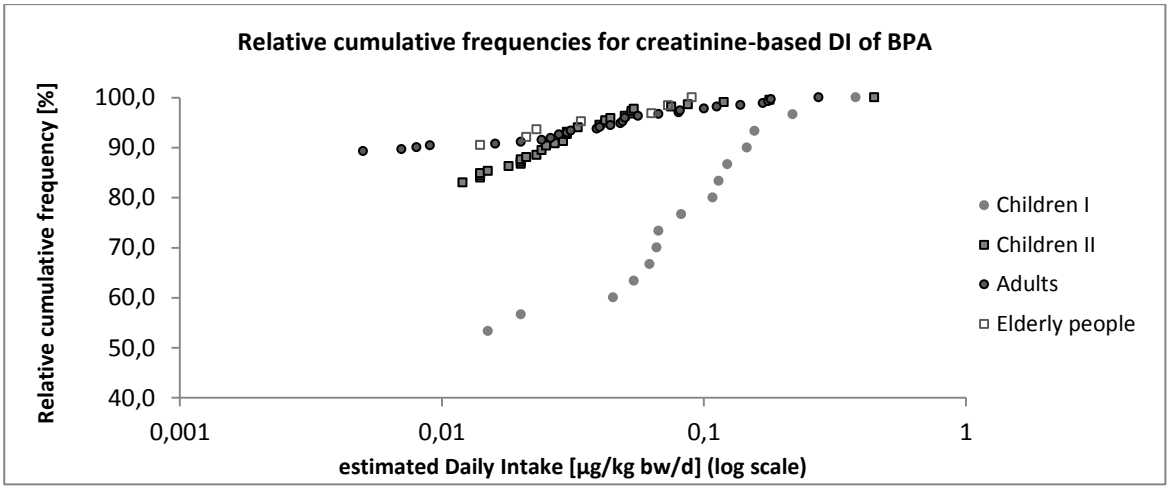


Figure 121. Relative cumulative frequencies [%] for creatinine-based daily BPA intakes [µg/kg bw/d] among the groups of Children I (n=31), Children II (n=218), Adults (n=271) and Elderly People (n=63)

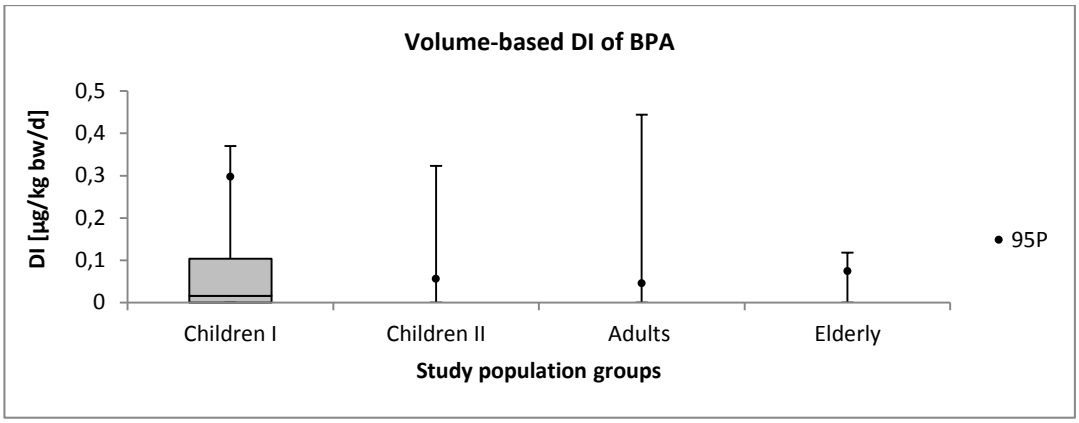


Figure 122. Distribution of volume-based daily BPA intake [µg/kg bw/d] in the groups of Children I (n=32), Children II (n=221), Adults (n=272) and Elderly People (n=65)

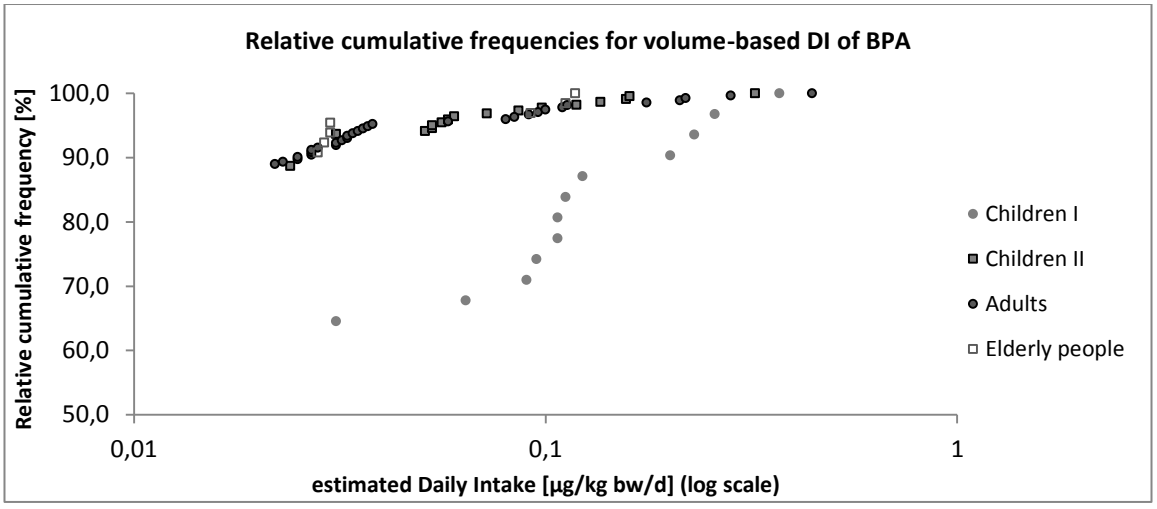


Figure 123. Relative cumulative frequencies [%] for volume-based daily BPA intakes [µg/kg bw/d] among the group of Children I (n=32), Children II (n=221), Adults (n=272) and Elderly People (n=65)

3.2.4.3.3 Associations with several selected parameters

Sex

Among the different study population groups, no statistically significant differences between males and females were identified.

Age

After the performance of Spearman correlation tests, significant correlations were found between age and volume-based daily BPA intake (n=221; r=0.148, p=0.05) and creatinine-based BPA intake (n=218; r=0.149, p=0.05) among the group of Children II, and between age and volume-based daily BPA intake (n=272; r=-0.161, p=0.01) and creatinine-based BPA intake (n=271; r=-0.153, p=0.05) in the group of Adults.

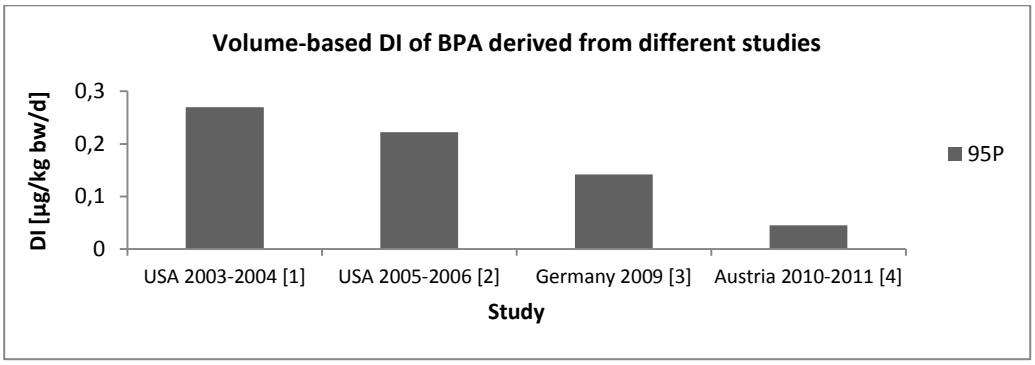
Geographical distribution

Among adults, significant differences (Mann-Whitney U tests) were observed between volume-based daily BPA intake (n=271; p=0.007) as well as creatinine-based daily BPA intake (n=270; p=0.014) and the geographical distribution (East Austria (n=140) and West Austria (n=131-132)). Samples from West Austria showed higher BPA exposure compared to samples from East Austria.

3.2.4.3.4 Comparison with other study results

Several studies have investigated daily BPA intakes in various populations (Table 107).

Compared to results derived from studies in the USA and Germany, participants from the group of Adults from the present study exhibited multiple lower P95 values (Figure 124). However, the different sampling years and countries must be considered.



[1] Lakind and Naiman (2008); [2] Lakind and Naiman (2011); [3] Koch et al. (2012b); [4] this study (adults)

Figure 124. 95th percentiles of volume-based daily BPA intakes [µg/kg bw/d] in U.S.-American children and adults (age 6-60+ years; n=2488 [1]; n=2535 [2]), German adults (age 20.5-28.7; n=60) and Austrian adults (age 18-65 years; n=272)

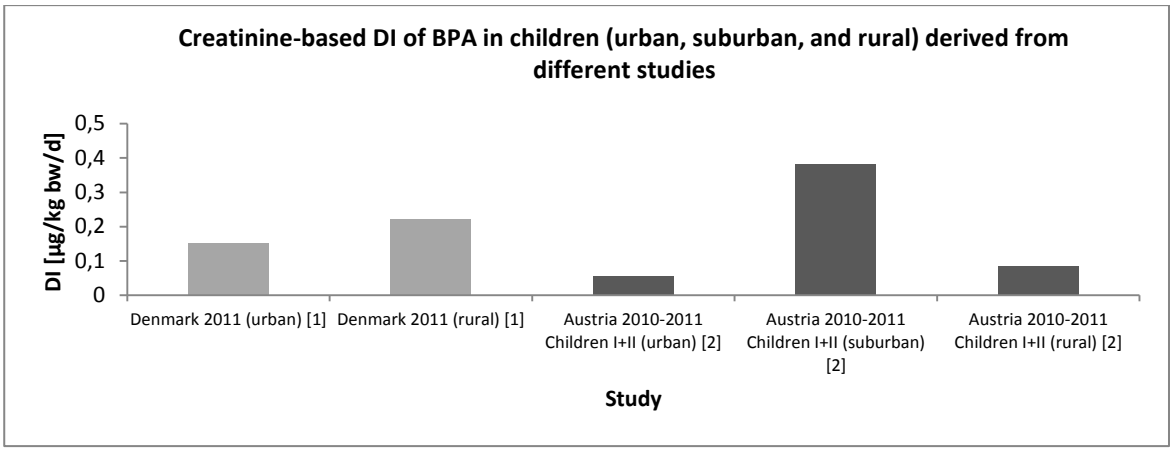
Among children from urban as well as rural areas of Denmark and Austria, 95th percentiles of daily BPA intake were lower in Austrian children (including Children I and Children II as one group). Similar to findings from Denmark, Austrian children from rural areas showed slightly higher BPA intakes than children from urban areas (Figure 125). Distinctively, P95 values in Austrian children from suburban areas were multiple higher compared to all other groups.

Table 107. Estimated daily BPA intakes (ranges, medians, 95th percentiles) [µg/kg bw/d] from selected studies

Study / population	Year(s)	Sample size (n)	Daily BPA intake [µg/kg bw/d] range (median; P95)	Reference
Germany				
Male and female German students from Environmental Specimen Bank (aged 20.5-28.7 years) *volume-based*	2009	60	0.009-0.302 (0.037; 0.142)	Koch et al. (2012b)
Denmark				
Male and female Danish children (aged 6-11 years) from urban and rural area, respectively *creatinine-based*	2011	74 (urban) 67 (rural)	*Urban:* 0.27 (max) (0.04; 0.15) *Rural:* 11.4 (max) (0.04; 0.22)	Frederiksen et al. (2013)
Female Danish women (aged 31-52 years) from urban and rural area, respectively *creatinine-based*	2011	75 (urban) 69 (rural)	*Urban:* 0.35 (max) (0.03; 0.122) *Rural:* 0.95 (max) (0.04; 0.24)	Frederiksen et al. (2013)
USA				
Males and females from NHANES 2003-2004 (aged 6-60+) *volume-based*	2003-2004	2488	(0.05; 0.27) 0.047 (GM)	Lakind and Naiman (2008)
Males and females from NHANES 2005-2006 (aged 6-60+ years) *volume-based*	2005-2006	2535	0.035 (GM) 0.222 (P95)	Lakind and Naiman (2011)
Asia				
Male and female school children (aged 8-11) from Shanghai (China) *volume-based*	2011	144	0.03-8.64 (0.21) µg/d	Wang et al. (2012a)
Male and female school children (aged 12-15) from Shanghai (China) *volume-based*	2011	115	0.06-19.56 (1.02) µg/d	Wang et al. (2012a)
Male and female children and adolescents (aged <20) from 7 Asian countries[1] *volume-based*	2006-2007 (Korea), 2010	47	0.03-13.6 (1.16) µg/d	Zhang et al. (2011)
Male and female adults (aged *>20) from 7 Asian countries*[1] *volume-based*	2006-2007 (Korea), 2010	259	0.08-51.2 (2.21) µg/d	Zhang et al. (2011)

Abbreviations: GM, geometric mean; max, maximum; NHANES, National Health and Nutrition Examination Survey; P95, 95th percentile.

[1] China, India, Japan, Korea, Kuwait, Malaysia, Vietnam.



[1] Frederiksen et al. (2013); [2] this study

Figure 125. 95th percentiles of creatinine-based daily BPA intakes [µg/kg bw/d] in Danish children (age 6-11; n (urban) = 74, n (rural) = 67) and Austrian children (age 7-15 years; n (urban) = 58), n (suburban) = 23), n (rural) = 146)

3.2.4.4 Discussion

Daily BPA intakes (DIs) were calculated based on analysed urinary total BPA concentrations with creatinine-based and volume-based calculation models according to Frederiksen et al. (2013) and Koch et al. (2012b), respectively.

Generally, daily BPA intakes were low. The highest individual volume-based DI was observed in a participant from the group of Adults (0.44 µg/kg bw/d) and the highest individual creatinine-based DI in a child from the Children II group (0.45 µg/kg bw/d. Additionally, no available acceptable exposure level (RfD: 50 µg/kg bw/d, TDI: 5 µg/kg bw/d) was exceeded by any participant. Although the exposure to BPA was low in the present study population, the higher exposure in children compared to adults deserves particular attention, because of the fact that children are a very vulnerable group.

Between the different study population groups, statistically significant differences were observed, whereby the daily intakes decreased with increasing age. Thus, children are more highly exposed than adults. Additionally, among the group of Adults significant differences were found between East and West Austria, whereby participants from West Austria showed higher DIs.

In comparison to the results of other studies investigating exposure to children, DIs of BPA were lower in the present study than those of studies from other countries. Independent of the country of origin, BPA exposure seems to have been decreasing in recent years, which could be due to the reduced use.

3.2.5 Reference values for the Austrian population

As described for phthalates (Chapter 3.1.4), urine samples with creatinine concentrations between 0.3 and 3 g/l (EAG, 2005) were used for the derivation of reference values for BPA. Data based on urinary BPA concentrations of 222 children (age 6-15 years; 101 females, 121 males) and 300 adults (age 18-81; 173 females, 127 males) are shown in Table 108:

Table 108. Data used as a basis for the derivation of reference values for urinary BPA [µg/l] of the general population in Austria

BPA (LOD: 1.3) [µg/l]

Population group	*n*	*Median*	*P95*	*Range*	*DR [%]*	*CI-PP95*
6-15 years	222	0.0	3.8	n.d.-14.8	20.7	2.9-8.3
18-81 years	300	0.0	1.3	n.d.-16.9	10.7	1.3-4.5

Abbreviations: CI-PP95, confidence interval of 95th population percentile; DR, detection rate; LOD, limit of detection; n, sample size; n.d., not detected; P95, 95th percentile. *Notes:* LOD=LOQ/2.

The reference values for the Austrian population based on total BPA in the urine of children and adults are listed in Table 109. The reference value for children is more than two times higher than the value for adults.

Table 109. Reference values for urinary BPA in children and adults in Austria

Population	Reference values for BPA
Children, 6-15 years of age, 2010-2011	4 µg/l
Adults, 18-81 years of age, 2010-2011	1.5 µg/l

3.2.5.1 Comparison with reference values derived from Germany

Table 110. Reference values for BPA in children (3-5 years and 6-14 years) and adults (20-29 years) in Germany (EAG, 2012)

Population	Reference value for BPA [µg/l]	Study year(s)
Children (3-5 years)	30	2003-2006
Children (6-14 years)	15	2003-2006
Adults (20-29 years)	7	1995-2009

For BPA, reference values have been published for the German population by the HBM-commission of the EAG as shown in Table 110. It must be considered for the comparison of the reference values from Germany and Austria, however, that

investigated age groups and periods of sampling differ. For both Austrian children and adults, derived reference values were a multitude lower than values derived from Germany.

3.2.5.2 Comparison with HBM-values

The HBM-commission of the EAG has set out a HBM-I-value for total BPA (free and conjugated) for children at 1.5 mg/l (=1500 µg/l), and for adults at 2.5 mg/l (=2500 µg/l). No HBM-II-values are currently established (EAG, 2012, 2013b) For adults and for children, the derived Austrian reference values of 1.5 µg/l and 4 µg/l are far below the HBM-I-value and thus, no action should be necessary because there is no expectation of adverse health effects. However, the current HBM-I-values are based on the former EFSA TDI for BPA of 50 µg/kg bw/d. In 2014, a new temporary TDI of 5 µg/kg bw/d was set out by the EFSA, and possible correction of the current HBM-I-value should be considered in future.

3.2.6 Associations with selected parameters

3.2.6.1 Age

The total study population (n=593) was classified into several age groups: 6-10 years (20%), 11-15 years (23%), 18-24 years (7%), 25-50 years (27%), 51-64 years (12%) and ≥65 years (11%). Figure 126 illustrates the distribution of different age groups among the total study population:

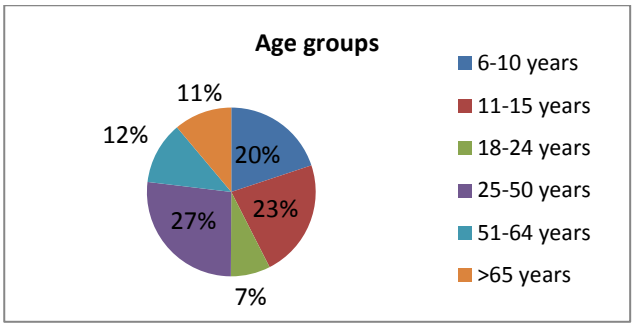


Figure 126. Distribution of age groups (BPA) (n=593)

Following the performance of Kruskal-Wallis tests at a significance level of 0.05, significant differences were identified between the different age groups and urinary BPA concentrations [µg/l] (p=0.011), as well as creatinine-adjusted BPA concentrations [µg/g] (p=0.014). Maximum and P95 values are shown in Figure 127 and Figure 128.

Higher BPA levels were observed in younger children than in older children. BPA levels increased with increasing age of participants, from children to those belonging to the age group of 51-64 years. In the group of Elderly People, lower levels were found again, which were also lower than the levels of children.

Table 111. Significant correlations (Spearman's correlation) between urinary BPA concentrations [µg/l], as well as creatinine-adjusted BPA concentrations [µg/g], and age in the total study population and the different study population groups

Age [years]	n	BPA [µg/l]	n	Creatinine-adjusted BPA [µg/g]
All samples	*593*	*-0,167***	*584*	*-0,166***
Children I	31	No correlations	30	No correlations
Children II	221	0.166*	218	0.148*
Adults	275	-0.161**	273	-0.157**
Elderly People	66	No correlations	63	No correlations

* Correlation is significant at 0.05 level.
** Correlation is significant at 0.01 level.

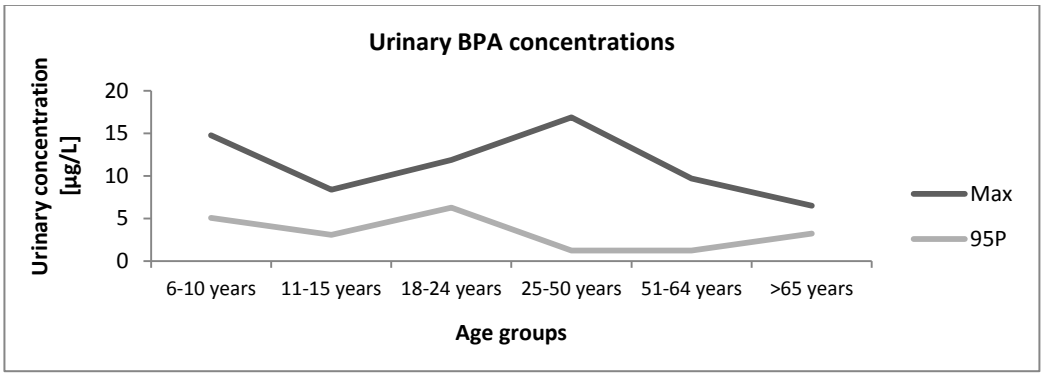


Figure 127. Maximums and 95th percentiles of urinary BPA concentrations [µg/l] in the age groups 6-10 years (n=118), 11-15 years (n=134), 18-24 years (n=45), 25-50 years (n=159), 51-64 years (n=71) and >65 years (n=66)

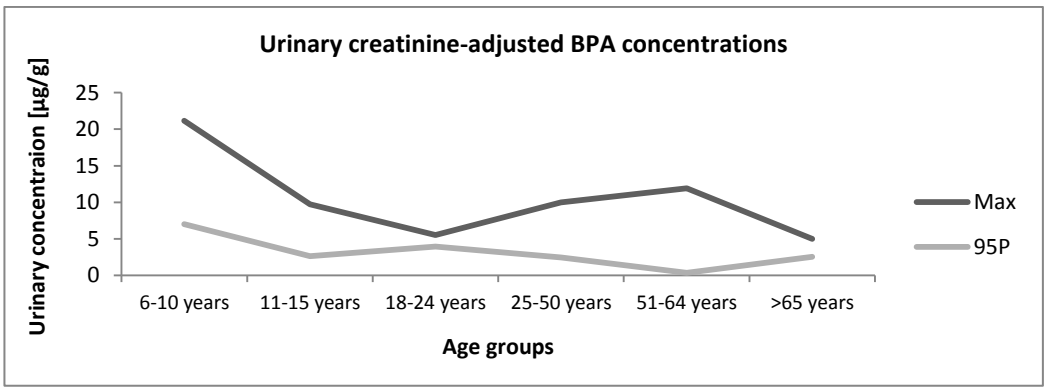


Figure 128. Maximums and 95th percentiles of urinary creatinine-adjusted BPA concentrations [µg/g] in the age groups 6-10 years (n=116), 11-15 years (n=132), 18-24 years (n=45), 25-50 years (n=158), 51-64 years (n=70) and >65 years (n=63)

3.2.6.2 Sex

No significant differences were identified between sexes among the total study population.

3.2.6.3 Regional differences

In the group of Adults, significant differences were observed between the distribution of East to West Austria and urinary BPA concentration [µg/l] (p=0.006), as well as creatinine-adjusted BPA concentrations [µg/g] (p=0.013) when performing Mann-Whitney U tests. Comparing maximum and P95 values, an east-west-decline was identified, whereby BPA exposure was higher in East Austria.

3.2.6.4 Residential area

Similar to investigations of phthalate metabolite exposure, potential differences were assessed between participants from (sub)urban and rural areas regarding BPA exposure. 237 participants (44.5%) were from (sub)urban areas and 295 participants (55.5%) were from rural areas. For BPA, no significant differences were found between the different living areas.

3.2.6.5 Diseases/disorders

Among the groups of Adults and Elderly People, occurrences of several diseases and/or disorders were surveyed. The distribution of diseases/disorders in both study population groups was very similar to those of the phthalate metabolite analysis. Thus, Figure 76 also reflects the distribution of diseases/disorders from BPA investigations.

Between urinary BPA concentrations and the occurrence of diseases/disorders, no significant associations could be identified.

3.2.6.6 Allergies

The distribution of participants with and without self-reported allergies is illustrated in Table 112. Following the performance of Mann-Whitney U tests, significant differences were observed between both investigated groups in the study population group of Children II for creatinine-unadjusted BPA and creatinine-adjusted BPA (p=0.003). Children without allergies showed higher BPA exposure than children with self-reported allergies.

Table 112. Distribution of participants with self-reported allergies and without allergies among the groups of Children I, Children II, Adults and Elderly People (BPA analysis)

Population group	Reported allergies	No reported allergies
Children I (n=26)	2 (8%)	24 (92%)
Children II (n=176)	41 (22%)	135 (78%)
Adults (n=224)	52 (23%)	172 (77%)
Elderly People (n=46)	9 (20%)	37 (80%)

3.2.6.7 Intake of pharmaceuticals

No statistically significant differences or associations between urinary BPA levels and intake of pharmaceuticals were observed.

3.2.6.8 Smoking behaviour

Regarding to the smoking behaviour in the groups of Adults and Elderly People, no statistically significant differences or associations with urinary BPA levels were found.

3.2.6.9 Nutrition

Table 113 illustrates the frequencies of food intake among the total study population.

For statistical analysis, in some cases two categories of food intake frequency were used to make comparisons possible. A statistically significant difference was identified between unadjusted BPA and no or only infrequent consumption of soft drinks (Mann-Whitney U test; p=0.043); participants who reported no intake or an infrequent intake (n=324) showed slightly higher BPA levels in urine compared to participants with a frequent consumption of soft drinks (n=235). Additionally, statistically significant differences were also identified between coffee consumption and both creatinine-unadjusted BPA (p=0.007) and creatinine-adjusted BPA (p=0.008). Participants with no or an infrequent coffee intake (n=294-299) showed higher BPA intakes compared to participants with a frequent coffee intake (n=263-267).

Table 113. Frequencies of intake of different food types among the total study population (n=563-575) in relation to investigations of urinary BPA concentrations

Food group	Total n	Intake		
		Never / not frequently	***Normal*** *(1-3 times/week)*	***Frequently*** *(4 times/week to >4 times/d)*
Rice, pasta	561	149 (27%)	347 (62%)	65 (11%)
Bread, brown	550	91 (16%)	142 (26%)	317 (58%)
Bread, white	548	156 (29%)	260 (47%)	132 (24%)
Bread, wholemeal	541	179 (33%)	203 (38%)	159 (29%)
Potatoes	566	146 (26%)	352 (62%)	68 (12%)
Vegetables	568	77 (13%)	226 (40%)	265 (47%)
Fruits, fresh	568	43 (8%)	145 (25%)	380 (67%)
Fruit pulp	548	406 (74%)	105 (19%)	37 (7%)
Milk, milk drinks	567	120 (21%)	147 (26%)	300 (53%)
Meat (beef, pork)	569	180 (32%)	322 (56%)	67 (12%)
Poultry	567	229 (40%)	312 (55%)	26 (5%)
Sausages, cold meat	559	130 (23%)	243 (44%)	186 (33%)
Fish	565	297 (53%)	251 (44%)	17 (3%)
Eggs	567	229 (40%)	282 (50%)	56 (10%)
Legumes	568	415 (73%)	139 (24%)	14 (3%)
Almonds, peanuts, nuts	573	360 (63%)	150 (26%)	63 (11%)
Butter, oils	555	104 (19%)	146 (26%)	305 (55%)
Pastries, cakes	566	161 (28%)	323 (57%)	82 (15%)
Chocolate, sweets	568	130 (23%)	234 (41%)	204 (36%)
Fruit or vegetable juices	561	195 (35%)	175 (31%)	191 (34%)
Soft drinks	559	324 (58%)	137 (24%)	98 (18%)
Carbonated beverages	567	234 (41%)	151 (27%)	182 (32%)
Tea	558	210 (38%)	159 (28%)	189 (34%)
Coffee	566	259 (46%)	40 (7%)	267 (47%)
Tab water, mineral water	564	32 (6%)	46 (8%)	486 (86%)
Alcoholic beverages				
Alcoholic beverages: Children I	25	25 (100%)	0 (0%)	0 (0%)
Alcoholic beverages: Children II	209	202 (97%)	5 (2%)	2 (1%)
Alcoholic beverages: Adults	266	106 (40%)	121 (45%)	39 (15%)
Alcoholic beverages: Elderly People	60	24 (40%)	18 (30%)	18 (30%)
Canned food	563	436 (77%)	113 (20%)	14 (3%)
Fast Food, Take Away	557	466 (84%)	76 (13%)	15 (3%)
French fries	567	465 (82%)	87 (15%)	15 (3%)
Microwave popcorn	560	501 (89%)	48 (9%)	11 (2%)
Beverages in TetraPak	553	359 (65%)	136 (25%)	58 (10%)
Beverages in PET	561	323 (58%)	131 (23%)	107 (19%)
Beverages in plastic containers	564	467 (83%)	52 (9%)	45 (8%)

3.2.6.10 Occupation

For all investigated occupation-related parameters (current employment, job sector, workplace, construction work at workplace, flooring, wall covering and contact with chemicals/cleaning products/biocides), no statistically significant differences could be identified.

3.2.6.11 Place of resistance

Current place of residence

Statistically significant differences were identified only among the group of Adults, where 135 (51%) participants lived in houses and 128 (49%) in apartments. Following the performance of Mann-Whitney U tests, differences existed between place of residence and BPA exposure (p=0.009) and creatinine-adjusted BPA exposure (p=0.001), whereby higher BPA exposure was found among adults living in apartments.

Use of a laundry dryer

Among the group of Adults, statistically significant differences were found between the use of a laundry dryer at the participant's place of residence and creatinine-unadjusted BPA (p=0.040) and creatinine-adjusted BPA (p=0.046) after performing Mann-Whitney U tests. Adults who reported using a laundry dryer at their homes (n=205; 76%) showed higher BPA exposure than adults who reported not using a laundry dryer (n=65; 24%).

3.2.7 Summarised results

In Table 114, a result summary of BPA analysis is illustrated describing the assessed exposure, the calculated daily BPA intake, the derived reference values for the Austrian population, the scenario exposure calculations and the significant associations and/or differences between BPA exposure and selected parameters:

Table 114. Result summary for BPA

	Children I range (median; P95) (n)	**Children II** range (median; P95) (n)	**Adults** range (median; P95) (n)	**Elderly People** range (median; P95) (n)
Exposure				
Urinary concentrations [µg/l]	n.d.-14.8 (n.d.; 11.9) (32)	n.d.-12.9 (n.d.; 2.9) (221)	n.d.-16.9 (n.d.; 1.7) (275)	n.d.-6.5 (n.d.; 3.2) (66)
Creatinine-adjusted urinary concentrations [µg/g]	n.d.-20.0 (n.d.; 15.2) (30)	n.d.-21.2 (n.d.; 2.4) (218)	n.d.-11.9 (n.d.; 2.3) (273)	n.d.-5.0 (n.d.; 2.6) (63)
Daily Intake				
Volume-based DI [µg/kg bw/d]	n.d.-0.37 (0.016; 0.30) (32)	n.d.-0.32 (n.d.; 0.06) (221)	n.d.-0.44 (n.d.; 0.05) (272)	n.d.-0.12 (n.d.; 0.07) (65)
Creatinine-based DI [µg/kg bw/d]	n.d.-0.38 (n.d.; 0.28) (30)	n.d.-0.45) (n.d.; 0.04) (218)	n.d.-0.27 (n.d.; 0.05) (271)	n.d.-0.09 (n.d.; 0.06) (63)
RfD [µg/kg bw/d]	50	50	50	50
Temporary TDI [µg/kg bw/d]	5	5	5	5
DI exceedances of AL [%]	0	0	0	0
Reference Values [µg/l]	4	4	1.5	1.5
Scenario Exposure Calculations				
SEC based on mean levels in food [µg/kg bw/d]	0.03-2.8 (0.44; 2.5)	0.001-6.0 (0.25; 1.9)	0.001-2.1 (0.09; 0.71)	0.002-0.9 (0.01; 0.31)
SEC based on maximum levels in food [µg/kg bw/d]	0.14-11.8 (0.96; 8.9)	0.04-11.3 (0.86; 4.9)	0.09-3.5 (0.64; 2.0)	0.18-2.7 (0.54; 1.6)
Parameters				
Age	Significant decrease of BPA exposure (creatinine-adjusted and -unadjusted levels) with increasing age.			
Regional differences	In the group of Adults, significant east-west decline for creatinine-unadjusted BPA was observed.			
Allergies	Significantly higher BPA exposure (adjusted and unadjusted) in the Children I group without self-reported allergies.			
Nutrition	Slightly, yet significantly higher BPA exposure (creatinine-unadjusted levels) in participants who consumed soft drinks either never or infrequently. Significantly higher exposure (creatinine-adjusted and -unadjusted) in participants who consumed coffee either never or not often.			
Current place of residence	Significantly higher BPA exposure (adjusted and unadjusted) in participants from the group of Adults living in apartments.			
Use of laundry dryer	Significantly higher exposure to BPA (creatinine-unadjusted) in the group of Adults who used a laundry dryer at their homes.			

[a] *exceedance of TDI of creatinine-based DI*

Abbreviations: AL, acceptable level of exposure; crea, creatinine; DI, daily intake; n, sample size; P95, 95th percentile; RfD, Reference Dose; SEC, Scenario Exposure Calculations; TDI, Tolerable Daily Intake.

3.3 SCENARIO EXPOSURE CALCULATIONS

Based on the surveyed Food Frequency Questionnaires (FFQ) and 24h-recalls provided by the IfEW, scenario exposure calculations (SEC) were performed to estimate of the *potential* phthalate and BPA intake via food ingestion. Therefore, the frequency of intakes and the amounts of consumed food were compared with phthalate and BPA concentrations of different food groups, respectively, which were reported in literature.

The FFQ contained 33 questions about the frequency of consumption of various foodstuffs (Table 115). The participants were able to choose between the answers “never”, “1-3 times per month”, “1 time per week”, “2-3 times per week”, “4-6 times per week”, “1 time per day”, “2-3 times per day” and “4 times per day or more often” to describe their frequency of usual food intake. For each participant and food group, the mean daily consumption frequency was calculated: never (0 times/day), 1-3 times per month (0.07 times/day), 1 time per week (0.14 times/day), 2-3 times per week (0.36 times/day), 4-6 times per week (0.71 times/day), 1 time per day (1 time/day), 2-3 times per day (2.5 times/d) and 4 times per day or more often (4 times/day).

Participants provided 24h-recalls for three consecutive (in children) or two non-consecutive days (in adults and elderly people), respectively. Therefore, consumption of all food and beverages were documented at delivered sheets by the IfEW as detailed as possible. Portion sizes were weighed or gauged by the participants themselves. Reported amounts of food intake (portion size) were sorted by food type for each study population group[15], and the calculated means were used for further estimations (shown in Table 118 to Table 122).

3.3.1 Approach

1. Literature research of available data on phthalate and BPA levels in various foodstuffs (in relation to the FFQ food types) and preparation of tables containing mean (or median) and maximum concentrations.
2. Derivation of mean and maximum amounts of food consumption for the investigated population provided from the individual data of the 24-h recalls.

[15] The population group of Children II was divided in two additional age groups (7-11 and 12-15), because of the presumption of different amounts of food intake in this both age groups.

3. Estimation of the individual uptake of phthalates and BPA through food; reported frequencies of intake of different food types (provided from FFQ) were converted into frequency of intake per day.
4. Calculation of intakes per day [µg/d] and intakes per bodyweight per day [µg/kg bw/d] for each food group (coded with FFQ1-FFQ33) for several phthalates (DMP, DEP, DiBP, DnBP, BBzP, DEHP, DiNP and DiDP) as well as for BPA for mean and maximum concentrations levels in food, respectively. Additionally, the sum of all phthalates was calculated.
5. Investigation of differences between study population groups.
6. Cumulative Risk Assessment for phthalates (estimation of Hazard Indices).
7. Comparison of selected estimated phthalate and BPA intakes via food derived from the SEC and daily intakes derived from analysed phthalate metabolites and BPA in urine with Spearman's correlation (2-tailed).

3.3.2 Investigated food groups

Table 115 shows the investigated food groups (coded by FFQ1-FFQ33) from surveyed FFQ:

Table 115. Food groups in the FFQ

Food groups in the FFQ		
FFQ1 **Rice, Noodles**	FFQ12 **Sausages, cold meat**	FFQ23 **Tea**
FFQ2 **Brown bread**	FFQ13 **Fish**	FFQ24 **Coffee**
FFQ3 **White bread**	FFQ14 **Eggs**	FFQ25 **Tab / mineral water**
FFQ4 **Wholemeal bread**	FFQ15 **Legumes**	FFQ26 **Alcoholic beverages**
FFQ5 **Potatoes**	FFQ16 **Almonds, peanuts, nuts**	FFQ27 **Preserves (canned food)**
FFQ6 **Vegetables**	FFQ17 **Butter, oil**	FFQ28 **Fast Food, Take Away**
FFQ7 **Fruits fresh**	FFQ18 **Pastries, cakes**	FFQ29 **French fries**
FFQ8 **Compote, fruit pulp**	FFQ19 **Chocolate, sweets**	FFQ30 **Microwave popcorn**
FFQ9 **Milk and milk drinks**	FFQ20 **Fruit or vegetable juices**	FFQ31 **Juices in TetraPak**
FFQ10 **Meat (beef or pork)**	FFQ21 **Soft drinks**	FFQ32 **Beverages in PET**
FFQ11 **Poultry**	FFQ22 **Carbonated drinks**	FFQ33 **Beverages in plastic cup for Take Away**

3.3.3 Phthalate and BPA levels in food

A literature research was performed to collect available data on phthalate and BPA concentrations in various foodstuffs. Therefore, scientific studies, reports and other publications and data were gathered by internet research and online publication databases searching via appropriate key words[16]. Collected data were compiled in an Excel file. Because of the availability of data from different countries all over the world, as well as from investigations that occurred within the last decades, decisions had to be made for choosing data for calculations. If available, data from studies performed in Austria, Germany or other countries of the EU, as well as more recent studies were preferred. However, uncertainties exist, which will be discussed below (Chapter 3.3.7).

Phthalate and BPA concentrations in foodstuff are given in µg/kg food. For beverages, a density of 1 was expected. Selected BPA and phthalate levels in food are listed in Table 116 and Table 117 , respectively. In Appendix C, complete collected data are shown.

Table 116. BPA concentrations (maximums and means) [µg/kg] in various foodstuffs derived from several studies used for scenario exposure calculations

Food group	Packaging	BPA [µg/kg] *max (mean)*	References / Comments
FFQ1 Rice, pasta			
Rice	n.r.	n.d.	Cao et al., 2011
Pasta	n.r.	n.d.	Cao et al., 2011
FFQ2 Bread, brown	n.r.	1.73	Cao et al., 2011
FFQ3 Bread, white	n.r.	0.4	Cao et al., 2011
FFQ4 Bread, wholemeal	No data available, therefore values from “FFQ2 Bread, brown” was used		
FFQ5 Potatoes	n.r.	0.82 (0.41)	Cao et al., 2011 *(mean concentrations of baked with skin, and peeled and boiled potatoes were used)*
FFQ6 Vegetables	n.r.	399.0 (n.d.)	Cao et al., 2011 *(mean value)*; Sungur, Köroğlu and Ozkan, 2014 *(maximum value; mushrooms in glass)*
FFQ7 Fruits	n.r.	0.57 (n.d.)	Cao et al., 2011
FFQ8 Compote, fruit pulp	No data available, therefore “FFQ7 Fruits” were used		
FFQ9 Milk and milk drinks	TetraPak	2.64 (1.82)	Casajuana and Lacorte, 2004 *(In Austria, milk is mainly in TetraPak available)*
FFQ10 Meat (beef, pork)			
Beef	n.r.	n.d.	Cao et al., 2011
Pork	n.r.	n.d.	Cao et al., 2011
FFQ11 Poultry	fresh	0.35 (0.28)	Schlecter et al., 2010

[16] Used key words were for example “phthalate”, “phthalic acid esters”, “bisphenol A”, “food” or “food content”.

continued

FFQ12 Sausages, cold meat	n.r.	0.48	Cao et al., 2011
FFQ13 Fish	fresh	0.48 (0.16)	Goodson, Summerfield and Cooper, 2002; Cao et al., 2011
FFQ14 Eggs	n.r.	n.d.	Cao et al., 2011
FFQ15 Legumes	Can	37.0 (25.2)	Goodson, Summerfield and Cooper, 2002; Braunrath et al., 2005 *(only data for canned legumes available; mean value was used from investigations in Europe)*
FFQ16 Almonds, peanuts, nuts	n.r.	n.d.	Cao et al., 2011
FFQ17 Butter, oil	Can, glass, plastic	7.7 (1.9)	Liao and Kannan, 2013
FFQ18 Pastries, cakes	n.r.	n.d.	Cao et al., 2011
FFQ19 Chocolate, sweets	Plastic	1.0	Sajiki et al., 2007
FFQ20 Fruit or vegetable juices	Paper box	82.6 (66.7)	Sungur, Köroğlu and Ozkan, 2014
FFQ21 Soft drinks	Can	4.0 (0.49)	Cunha et al., 2011
FFQ22 Carbonated beverages	Values used from “FFQ21 Soft drinks” and “FFQ25 Tab water / mineral water”		
FFQ23 Tea	n.r.	n.d.	Cao et al., 2011
FFQ24 Coffee	n.r.	0.22	Cao et al., 2011
FFQ25 Tab water / mineral water	PC, HDPE, PET, can, glass	8.8 (n.d.)	BCS, 2010b
FFQ26 Alcoholic beverages			
Wine	glass	0.74	Cao et al., 2011
Beer	Can, glass	1.5 (0.17)	Braunrath et al., *2005 (investigations from Austria in canned beer);* BCS, 2010a *(beer bottled in glass)*
FFQ27 Canned food	Can	551 (21.2)	Sungur, Köroğlu and Ozkan, 2014 *(maximum value; tuna);* Braunrath et al., 2005 *(mean value; canned soups from Austria)*
FFQ28 Fast Food, Take Away	n.r.	33.0 (5.5)	*Mean values were derived from concentrations published in* Cao et al., 2011 and Goodson, Summerfield and Cooper, 2002
FFQ29 French fries	n.r.	1.1	Cao et al., 2011
FFQ30 Microwave popcorn	n.r.	n.d.	Cao et al., 2011
FFQ31 Juices in TetraPak	Paper box	82.6 (66.7)	Sungur, Köroğlu and Ozkan, 2014
FFQ32 Beverages in PET			
Soft drinks	PET	0.018 (0.002)	BCS, 2010a
Mineral water	PET	n.d.	BCS, 2010b
FFQ33 Beverages in plastic cup for Take Away	No data available		

Abbreviations: BPA, Bisphenol A; max, maximum; n.d., not detected; n.r., not reported.

Table 117. Phthalate concentrations (maximum, mean/median) [µg/kg] in various foodstuffs derived from several studies used for scenario exposure calculations

Food Group	Pack-aging	DMP [µg/kg] max (mean)	DEP [µg/kg] max (mean)	DiBP [µg/kg] max (mean)	DnBP [µg/kg] max (mean)	BBzP [µg/kg] max (mean)	DEHP [µg/kg] max (mean)	DiNP [µg/kg] max (mean)	DiDP [µg/kg] max (mean)	References / Comments
FFQ1 Rice, pasta										
Flour or noodles	n.k.	5.8 (0.0, median)	4.86 (0.72, median)	326 (19.1, median)	360 (10.0)	0.56 (0.0, median)	762 (9.22, median)			Guo et al., 2012; missing values from Wormuth et al., 2006. Data from China was used.
Rice	n.k.	0.41 (0.12, median)	1.45 (0.83, median)	70.8 (6.21, median)	360 (10.0)	0.64 (0.0, median)	378 (19.2, median)			Guo et al., 2012; missing values from Wormuth et al., 2006. Data from China was used.
FFQ2 Bread, brown	n.k.	0.0	17.4 (6.0)	232.0 (60.0)	5130 (32.0)	440.0 (0.0)	1960 (68.0)	0.0		Wormuth et al., 2006; missing values from Bradley et al., 2013
FFQ3 Bread, white	No data available, therefore values from "FFQ2 Bread, brown" were used									
FFQ4 Bread, wholemeal	No data available, therefore values from "FFQ2 Bread, brown" were used									
FFQ5 Potatoes	n.k.	0.0	9.0 (9.0)	5.0 (5.0)	0.0	0.0	80.0 (76.0)	0.0		Wormuth et al., 2006; missing values from Bradley et al., 2013
FFQ6 Vegetables	n.k.	4.6 (0.0, median)	2.0 (0.0, median)	13.0 (1.0, median)	17.0 (1.7, median)	26.0 (0.0, median)	1413 (0.0, median)	0.0		Wormuth et al., 2006; missing values from Bradley et al., 2013
FFQ7 Fruits	n.k.	0.0	0.0	52.0 (30.0)	50.0 (28.0)	0.0	120 (69.0)	0.0		Wormuth et al., 2006; missing values from Bradley et al., 2013
FFQ8 Compote, fruit pulp	No data available, therefore data from "FFQ7 Fruits" were used									
FFQ9 Milk and milk drinks	n.k.	28.0 (0.0)	10.0 (0.0)	16.0 (0.0)	30.0 (15.0)	0.5	27.0 (calculated mean: 20.0)	10.0		Wormuth et al., 2006, Sørensen, 2006, Peters, 2006, Bradley et al., 2013
FFQ10 Meat (beef, pork)	n.k.	25.0 (2.0, median)	1.4 (0.0, median)	9.7 (2.0, median)	15.0 (1.5, median)	18.0 (0.0, median)	433 (44.5, median)	10.0	10.0	Fierens et al., 2012, Peters, 2006
FFQ11 Poultry	n.k.	0.0	10.0 (5.0)	60.0 (30.0)	200 (100)	30.0 (15.0)	700 (285)	0	10.0	Wormuth et al., 2006, Bradley et al., 2013, Peters, 2006
FFQ12 Sausages, cold meat	n.k.	0.5	40.0	18.0	170.0 (4.0)	2.0	329.0	10.0	10.0	Bradley et al., 2013, Peters, 2006, Wormuth et al., 2006
FFQ13 Fish	n.k.	43.0 (0.0, median)	9.3 (0.6, median)	13.0 (0.0, median)	12.5 (0.0, median)	8.0 (0.0, median)	5932 (86.0, median)			Fierens et al., 2012; missing value from Bradley et al., 2013
FFQ14 Eggs	n.k.	0.5	0.5	5.0		0.5	10.0	10.0	10.0	Peters, 2006
FFQ15 Legumes	No data available, therefore values from "FFQ6 Vegetables" are used									

continued

Food Group	Pack-aging	DMP [µg/kg] max (mean)	DEP [µg/kg] max (mean)	DiBP [µg/kg] max (mean)	DnBP [µg/kg] max (mean)	BBzP [µg/kg] max (mean)	DEHP [µg/kg] max (mean)	DiNP [µg/kg] max (mean)	DiDP [µg/kg] max (mean)	References / Comments
FFQ16 Almonds, peanuts, nuts	n.k.	21.0 (0.0)	23.3 (7.5)	232 (45.0)	17460 (218)	21.0 (0.0)	(366.7, calculated mean)	0.0		Wormuth et al., 2006, Bruns-Weller and Pfordt, 2000
FFQ17 Butter, oil										
Oil, fats	n.k.	32.0 (0.0, median)	154 (0.0, median)	53.0 (0.0, median)	203 (0.0, median)	1127 (12.5, median)	1827 (101.5, median)	72.0	10.0	Fierens et al., 2012, Guo et al., 2012, Peters, 2006
Butter	n.k.	32 (0.0, median)	154 (0.0, median)	53 (0.0, median)	203 (0.0, median)	1127 (12.5, median)	1827 (101.5, median)	72.0	10.0	Peters, 2006
FFQ18 Pastries, cakes	n.k.	58.9 (23.5) (12.9, median)	1.97 (1.17) (1.32, median)	20.0 (7.0)	420 (130)	88.0 (28.0)	1100 (547)	0.0		Wormuth et al., 2006, Guo et al., 2012 *Cakes, buns, puddings*
FFQ19 Chocolates, sweets										
Candy	n.k.	20.5 (7.59) (2.08, median)	3.14 (1.51) (1.11, median)	76.2 (25.6) (0.5, median)	83.3 (0.0, median)	2.58 (0.86) (0.0, median)	172 (57.3) (0.0, median)			Guo et al., 2012 *Data for "Candy" and "Confectionary" were used because both were evaluated in 24h-recalls*
Confectionary	n.k.	0.0	5.6 (0.0)	69.0 (12.0)	7890 (75.0)	37.0 (0.0)	640 (278)	0.0		Wormuth et al., 2006 *Data for "Candy" and "Confectionary" were used because both were evaluated in 24h-recalls*
FFQ20 Fruit or vegetable juices	n.k.	0.0	0.0	0.0	20.0 (0.0)	0.0	60.0 (20.0)	0.0	10.0	Wormuth et al., 2006; missing values from Peters, 2006
FFQ21 Soft drinks	PET	166 (60.6)	10.0 (1.1)	3.82 (0.92)	190 (5.0)	0.0	136 (17.1)	0.0		Bosnir et al., 2007 *(soft drinks preserved with orthophosphoric acid)*; missing values from Wormuth et al., 2006, Guo et al., 2012
FFQ22 Carbonated beverages										
Mineral water	PET	0.0	1.0 (0.11)			0.0	50.0 (8.8)			Bosnir et al., 2007
Soft drinks	PET	166 (60.6)	10.0 (1.1)	3.82 (0.92)	190 (5.0)	0.0	136 (17.1)	0.0		Bosnir et al., 2007 *(soft drinks preserved with orthophosphoric acid)*; missing values from Wormuth et al., 2006, Guo et al., 2012
FFQ23 Tea	n.k.	0.0	0.0	6.0 (6.0)	0.0	0.0	10.0 (8.0)	0.0		Wormuth et al., 2006
FFQ24 Coffee	n.k.	0.0	0.0	6.0 (6.0)	0.0	0.0	10.0 (8.0)	0.0		Wormuth et al., 2006

continued

Food Group	Pack-aging	DMP [µg/kg] max (mean)	DEP [µg/kg] max (mean)	DiBP [µg/kg] max (mean)	DnBP [µg/kg] max (mean)	BBzP [µg/kg] max (mean)	DEHP [µg/kg] max (mean)	DiNP [µg/kg] max (mean)	DiDP [µg/kg] max (mean)	References / Comments
FFQ25 Table water / mineral water										
Water	Glass	0.02	0.02	0.03	0.23		0			Montuori et al., 2008 *Water bottled in glass (for table water)*
Mineral water	PET	0.0	1.0 (0.11)	0.32	50.0 (13.0)	0.0	50.0 (8.8)			Bosnir et al., 2007; missing values from Montuori et al., 2008, Serodio and Nogueira, 2006
FFQ26 Alcoholic beverages										
Wine	Glass	0.46 (0.23)	4.22 (2.48)	107.0	2.21 (1.34)	4.29 (2.15)	4.75 (8.44)			Carrillo, Martinez and Tena, 2008; missing values from Guo et al., 2012 *Wine bottled in glass with one-piece cork stoppers*
Beer	n.k.	0.0	0.0	0.0	70.0 (23.0)	0.0	110 (41.0)	0.0		Wormuth et al., 2006
Spirits	n.k.	0.0	0.0	0.0	10.0 (0.0)	10.0 (0.0)	30.0 (0.0)	0.0		Wormuth et al., 2006
FFQ27 Canned food	Can		-	-		-	-			Bradley et al., 2013 *Canned vegetables*
FFQ28 Fast Food, Take Away	n.k.	6.1 (0.0, median)	5.3 (0.0, median)	114 (4.3, median)	65 (3.2, median)	14 (0.6, median)	308 (35, median)			Fierens et al., 2012 *Snacks*
FFQ29 French fries	No data available, therefore values from "FFQ5 Potatoes" were used									
FFQ30 Microwave popcorn	No data available									
FFQ31 Juices in TetraPak	No data available, therefore values from "FFQ20 Fruit or vegetable juices" are used									
FFQ32 Beverages in PET										
Water	PET	0.06	0.22	0.32	0.23	0.002	0.0			Montuori et al., 2008; missing values from Casajuana and Lacorte, 2003
Mineral water	PET	0.0	1.0 (0.11)		50.0 (11.3)	0.0	50.0 (8.8)			Bosnir et al., 2007
Soft drinks	PET	166 (60.6)	10.0 (1.1)	3.82 (0.92)	190 (5.0)	0.0	136 (17.1)	0.0		Bosnir et al., 2007; missing values from Wormuth et al., 2006 and Guo et al., 2012 *Soft drinks preserved with orthophosphoric acid*
FFQ32 Beverages in plastic containers	No data available									

continued

Food Group	Pack-aging	DMP [µg/kg] max (mean)	DEP [µg/kg] max (mean)	DiBP [µg/kg] max (mean)	DnBP [µg/kg] max (mean)	BBzP [µg/kg] max (mean)	DEHP [µg/kg] max (mean)	DiNP [µg/kg] max (mean)	DiDP [µg/kg] max (mean)	References / Comments
OTHERS										
Cottage cheese	n.k.	0.5	0.5	1500	780	25.0	890	660	10.0	Peters, 2006
(Hard) cheese	n.k.	0.0	7.0 (2.33)	0.0	300 (56.0)	39.0 (14.0)	1230 (496)	0.0	10.0	Wormuth et al., 2006; missing values from Peters, 2006
Yoghurt	n.k.	35 (11.7)	0.0	0.0	0.0	0.0	90.0 (51.0)	2.5	2.5	Wormuth et al., 2006; missing values from Sørensen, 2006
Offal	n.k.		-	6.0	-	-	-			Bradley et al., 2013
Cereals	n.k.	1.4 (0.0, median)	558 (0.5, median)	1054 (8.7, median)	61 (4.6, median)	14 (1.5, median)	1073 (63.0, median)			Fierens et al., 2012; missing value from Bradley et al., 2013
Seafood, fish	n.k.	16.8 (0.3)	8.5 (2.54)	25.0 (1.0)	380.0 (8.0)	5.0 (2.0)	290.0 (13.0)	35.0 (0.4)		Wormuth et al., 2006

Abbreviations: BBzP, butyl benzyl phthalate; DEHP, di-2-ethylhexyl phthalate; DEP, diethyl phthalate; DiBP, di-isobutyl phthalate; DiDP, di-isodecyl phthalate; DiNP, di-isononyl phthalate; DMP, dimethyl phthalate; DnBP, di-*n*-butyl phthalate; max, maximum; n.k., not known; PET, polyethylenterephthalate.

3.3.4 Amounts of food consumption

For ASNS, 24h-recalls were collected from almost all participants mostly on two non-consecutive days for adults and elderly people, and three consecutive days for children. The participants documented (in the ideal case) all food and beverages consumed by weighing or gauging the masses. Based on these recalls, the approximate intakes (amounts of consumption) per portion [g] were calculated for each food group for this sample (Table 118 - Table 122). The benefit of the calculation from these data was that mean intakes of this population were available and could be used for scenario exposure calculations, which should minimise the possible error.

If the data was not normally distributed, median values were used for SEC.

3.3.5 Calculation

Calculations were performed according to the following formula of SEC of phthalate and BPA intake, respectively, for each single food group (FFQx):

$$\textbf{Phthalate or BPA intake}\ [\mu\,\textbf{g/kg bw/d}] = \frac{(\mathrm{Freq_{intake}}[\mathrm{times/d}] * \mathrm{Consumption}\ [\mathrm{g}] * \mathrm{c_{food}}[\mu\,\mathrm{g/kg}])}{\mathrm{bw}\ [\mathrm{kg}]}$$

$Freq_{Intake}$	Frequency of intake of a food type (FFQx) per day
Consumption	Amount of mean consumption of a food type (FFQx)
c_{food}	Phthalate / BPA concentration (maximum and minimum) in foodstuff
bw	Bodyweight

Table 118. Consumption of various foodstuff (mean±SD, median, range) [g] among the Children I group (age 6-8) (n=29) derived from 24h-recalls for 3 consecutive days (n=87)

	Amount	mean±SD	Median	Min	Max
FFQ1 Rice/Noodles	35	108.3±56.7	112	15	254
Rice	22	99.2±51.9	112	20	250
Noodles	13	123.7±63.1	110	15	254
FFQ2 Bread, brown	69	50.6±17.0	50	15	100
FFQ3 Bread, white	59	46.8±22.3	61.3	20	125
FFQ4 Bread, wholemeal	15	48.7±25.6	50	20	100
FFQ5 Potatoes	27	109.9±49.3	70	63	228
FFQ6 Vegetables	74	51.8±32.6	50	12	207
FFQ7 Fruits fresh	75	106.1±40.3	125	20	159
FFQ8 Compote, fruit pulp	2	172±0.0	172	172	172
FFQ9 Milk, milk drinks	93	211.2±66.1	200	19	375
FFQ10 Meat (beef or pork)	18	107.7±41.4	110	53	200
FFQ11 Poultry	10	118.3±30.7	113	53	160
FFQ12 Sausages, cold meat	69	31.7±31.3	25	8.3	200
FFQ13 Fish	10	82.4±52.2	77	30	199
FFQ 14 Eggs	12	61.9±9.4	65	32.5	65
FFQ15 Legumes	4	50±35.6	40	20	100
FFQ16 Almonds, peanuts, nuts	3	12.7±15.1	6	2	30
FFQ17 Butter, oil	91	7.3±4.6	7.5	0.2	22
Butter	50	9.1±4.1	10	4	22
Oil	31	3.8±3.4	2.65	0.2	10
Margarine	10	9.0±4.6	10	5	20
FFQ18 Pastries, cakes	43	68.4±37.0	64	20	210
FFQ19 Chocolate, sweets	92	21.1±16.9	20	1.4	100
FFQ20 Fruit or vegetable juices	61	191.7±84.5	190	30	500
FFQ21 Soft drinks	35	238.1±96.0	250	100	500
Soft drinks carbonated	30	227.8±91.2	225	100	500
Soft drinks not carbonated	5	300.0±111.8	250	250	500
FFQ 22 Carbonated beverages[1]	45	232.0±94.5	220	100	500
FFQ23 Tea	18	233.9±49.8	200	190	300
FFQ24 Coffee	1	171	171	171	171
FFQ25 Tab / mineral water	215	219.6±96.1	220	50	650
Tab water	200	218.1±95.6	220	50	650
Mineral water	15	240.3±103.7	220	100	500
FFQ26 Alcoholic beverages	0				
FFQ27 Preserves	4	45.0±10.0	50	30	50
FFQ28 Fast Food, Take Away	6	167.3±145.0	106	20	350
FFQ29 French fries	9	116.4±43.5	116	58	175
FFQ30 Popcorn	3	40.0±8.7	45	30	45
FFQ31 Juices in TetraPak	11	309.1±126.1	250	150	500
FFQ32 Beverages in PET[2]	19	230.5±97.3	220	100	500
FFQ33 Beverages in plastic container for Take Away[3]		300			

Abbreviations: Max, maximum; Min, minimum; PET, polyethylene terephthalate; SD, standard derivation.
[1] mineral water carbonated and soft drinks carbonated
[2] all data of mineral water and of soft drinks known to be bottled in PET (e.g. Coca Cola, Almdudler, Sprite, Mezzo Mix) were used
[3] no information from 24h-recalls available, therefore a mean value was used for possible volumes of common plastic containers (derived from: http://www.plastikbecher.de/index.php?cat=HEISSGETRAENKEBECHER)

Table 119. Consumption of various foodstuff (mean±SD, median, range) [g] among the Children II group (age 8-11) (n=87) derived from 24h-recalls for 3 non-consecutive days

	Amount	mean±SD	Median	min	max
FFQ1 Rice/Noodles	119	114.9±56.1	110	10	254
Rice	51	92.6±46.2	60	30	250
Noodles	68	131.6±57.4	137	10	254
FFQ2 Bread, brown	307	51.4±17.8	50	15	140
FFQ3 Bread, white	266	53.0±18.5	61.3	10	125
FFQ4 Bread, wholemeal	71	45.6±20.6	50	15	140
FFQ5 Potatoes	98	119.5±64.7	132	15	420
FFQ6 Vegetables	270	67.5±42.1	60	4	207
FFQ7 Fruits fresh	259	100.8±54.8	125	2	301
FFQ8 Compote, fruit pulp	12	131.6±35.9	113	84	172
FFQ9 Milk, milk drinks	247	226.0±90.9	200	15	750
FFQ10 Meat (beef or pork)	93	104.4±67.2	110	9.8	418
FFQ11 Poultry	42	83.0±39.2	91.5	18	160
FFQ12 Sausages, cold meat	326	39.0±34.0	27	5	202.5
FFQ13 Fish	32	85.4±48.4	64	10	199
FFQ 14 Eggs	35	67.8±20.8	60	32.5	130
FFQ15 Legumes	4	50.0±0.0	50	50	50
FFQ16 Almonds, peanuts, nuts	10	27.6±20.9	25	2	50
FFQ17 Butter, oil	319	6.8±4.7	5	0.33	32.3
Butter	169	8.4±4.4	10	2.5	30
Oil	135	4.6±4.3	3.2	0.33	32.3
Margarine	15	9.1±4.3	10	5	22
FFQ18 Pastries, cakes	194	68.7±35.8	64	6.33	190
FFQ19 Chocolate, sweets	344	25.6±23.9	16.5	1.4	120
FFQ20 Fruit or vegetable juices	223	199.1±107.3	150	20	750
FFQ21 Soft drinks	172	310.9±160.3	250	100	1500
Soft drinks carbonated	128	305.2±131.8	250	100	1000
Soft drinks not carbonated	44	327.3±224.8	250	100	1500
FFQ 22 Carbonated beverages[1]	236	302.3±144.1	250	62.5	1000
FFQ23 Tea	114	241.4±103.9	200	100	1000
FFQ24 Coffee	3	198.3±67.9	190	135	270
FFQ25 Tab / mineral water	823	252.7±134.2	250	50	2000
Tab water	715	245.7±129.0	250	20	2000
Mineral water	108	298.9±157.9	250	62.5	1000
FFQ26 Alcoholic beverages	1	125	125	125	125
FFQ27 Preserves	11	78.2±70.2	50	10	200
FFQ28 Fast Food, Take Away	17	150.5±87.1	120	20	350
FFQ29 French fries	27	91.7±32.9	90	58	175
FFQ30 Popcorn	13	32.3±20.2	30	15	90
FFQ31 Juices in TetraPak	22	228.4±77.6	250	125	500
FFQ32 Beverages in PET[2]	126	298.9±152.3	250	62.5	1000
FFQ33 Beverages in plastic containers[3]		300			

Abbreviations: Max, maximum; Min, minimum; PET, polyethylene terephthalate; SD, standard derivation.
[1] mineral water carbonated and soft drinks carbonated
[2] all data of mineral water and of soft drinks known to be bottled in PET (e.g. Coca Cola, Almdudler, Sprite, Mezzo Mix) were used
[3] no information from 24h-recalls available, therefore a mean value was used for possible volumes of common plastic containers (derived from: http://www.plastikbecher.de/index.php?cat=HEISSGETRAENKEBECHER)

Table 120. Consumption of various foodstuff (mean±SD, median, range) [g] among the Children II group (age 12-15) (n=86) derived from 24h-recalls for 3 non-consecutive days

	Amount	mean±SD	Median	min	max
FFQ1 Rice/Noodles	61	159.5±61.2	170	60	385
Rice	24	115.9±38.5	112	60	171
Noodles	37	187.8±56.6	170	110	385
FFQ2 Bread, brown	143	54.5±19.2	50	30	140
FFQ3 Bread, white	153	51.6±16.7	61.3	20	83
FFQ4 Bread, wholemeal	17	57.4±16.6	60	25	100
FFQ5 Potatoes	27	154.9±59.6	141	63	280
FFQ6 Vegetables	113	77.8±61.6	60	10	370
FFQ7 Fruits fresh	106	116.8±40.0	125	25	301
FFQ8 Compote, fruit pulp	3	88.7±81.1	84	10	172
FFQ9 Milk, milk drinks	111	215.7±71.4	200	20	500
FFQ10 Meat (beef or pork)	49	115.1±58.9	111	45	320
FFQ11 Poultry	30	100.3±52.9	101	20	253
FFQ12 Sausages, cold meat	190	38.3±29.1	27	9.8	150
FFQ13 Fish	16	92.7±48.6	97	30	199
FFQ 14 Eggs	14	70.7±19.8	65	60	130
FFQ15 Legumes	4	156.5±96.4	163	50	250
FFQ16 Almonds, peanuts, nuts	6	41.3±22.5	30	20	70
FFQ17 Butter, oil	122	7.6±4.9	5.6	0.5	22
Butter	47	8.6±4.3	10	5	22
Oil	68	6.2±4.3	5.6	0.5	19.5
Margarine	7	13.7±8.0	10	5	22
FFQ18 Pastries, cakes	96	73.7±40.5	64	14	180
FFQ19 Chocolate, sweets	141	32.1±33.8	20	1.4	200
FFQ20 Fruit or vegetable juices	84	284.4±161.0	250	75	1000
FFQ21 Soft drinks	173	331.4±182.4	250	50	1000
Soft drinks carbonated	129	336.9±188.5	250	100	1000
Soft drinks not carbonated	44	315.2±164.1	250	50	1000
FFQ 22 Carbonated beverages[1]	173	340.7±212.8	250	100	1500
FFQ23 Tea	36	216.1±34.5	200	150	300
FFQ24 Coffee	15	215.3±72.0	200	50	300
FFQ25 Tab / mineral water	360	293.1±183.5	250	75	1500
Tab water	316	285.0±166.1	250	75	1500
Mineral water	44	351.6±274.0	250	150	1500
FFQ26 Alcoholic beverages	2	265.0±91.9	265	200	330
Beer	1	330	330	330	330
Other alcoholic beverages	1	200	200	200	200
FFQ27 Preserves	5	64.0±49.3	100	10	100
FFQ28 Fast Food, Take Away	34	214.4±114.3	187	20	350
FFQ29 French fries	30	129.0±36.5	130	30	175
FFQ30 Popcorn	5	60.0±28.1	45	30	90
FFQ31 Juices in TetraPak	8	406.3±129.4	500	250	500
FFQ32 Beverages in PET[2]	61	383.4±262.3	250	150	1500
FFQ33 Beverages in plastic containers[3]		300			

Abbreviations: Max, maximum; Min, minimum; PET, polyethylene terephthalate; SD, standard derivation.
[1] mineral water carbonated and soft drinks carbonated
[2] all data of mineral water and of soft drinks known to be bottled in PET (e.g. Coca Cola, Almdudler, Sprite, Mezzo Mix) were used
[3] no information from 24h-recalls available, therefore a mean value was used for possible volumes of common plastic containers (derived from: http://www.plastikbecher.de/index.php?cat=HEISSGETRAENKEBECHER)

Table 121. Consumption of various foodstuff (mean±SD, median, range) [g] among the Adults group (n=270) derived from 24h-recalls for mostly two non-consecutive days (n=535)

	Amount	mean±SD	Median	min	max
FFQ1 Rice/Noodles	171	126.7±63.9	112	10	500
Rice	86	100.5±43.9	112	10	277.9
Noodles	85	153.3±70.0	170	20	500
FFQ2 Bread, brown	420	57.8±24.0	50	10	210
FFQ3 Bread, white	227	55.4±25.0	61.3	10	156.3
FFQ4 Bread, wholemeal	145	58.0±27.3	50	2	150
FFQ5 Potatoes	132	129.7±56.6	141	35	407
FFQ6 Vegetables	715	65.9±46.3	56	3	300
FFQ7 Fruits fresh	616	123.1±72.1	125	2	660
FFQ8 Compote, fruit pulp	14	157.6±96.1	140.8	30	400
FFQ9 Milk, milk drinks	531	60.2±90.6	20	10	750
FFQ10 Meat (beef or pork)	144	114.6±54.9	111	9.8	345
FFQ11 Poultry	92	118.5±55.4	111	20	316.3
FFQ12 Sausages, cold meat	327	43.4±40.2	34.5	5	250
FFQ13 Fish	57	111.8±53.2	124	5	250
FFQ 14 Eggs	59	61.7±21.1	60	10	195
FFQ15 Legumes	27	63.1±34.0	52	17	150
FFQ16 Almonds, peanuts, nuts	49	31.2±35.4	30	2	250
FFQ17 Butter, oil	542	9.0±8.0	7.6	0.3	90
Butter	228	12.0±8.6	12.5	2.5	90
Oil	286	5.6±5.0	5.3	0.3	47.8
Margarine	28	18.6±9.3	12.5	5	37.5
FFQ18 Pastries, cakes	276	85.5±55.6	64	5	320
FFQ19 Chocolate, sweets	377	32.5±38.7	38.7	1.4	300
FFQ20 Fruit or vegetable juices	237	262.3±139.4	250	10	1000
FFQ21 Soft drinks	105	412.5±195.0	400	100	1000
Soft drinks carbonated	86	371.1±166.8	330	100	1000
Soft drinks not carbonated	19	552.6±213.7	500	250	1000
FFQ 22 Carbonated beverages[1]	445	441.5±196.5	500	100	1500
FFQ23 Tea	294	383.1±310.0	250	100	2500
FFQ24 Coffee	645	197.3±78.2	180	25	900
FFQ25 Tab / mineral water	1388	448.1±234.3	500	30	1500
Tab water	1021	443.7±245.5	500	30	1500
Mineral water	367	460.6±199.5	500	125	1500
FFQ26 Alcoholic beverages	222	361.3±367.5	250	20	2500
Beer	106	592.3±413.6	500	200	2500
Wine	84	163.7±84.9	125	125	500
Spirits	9	36.1±35.9	20	20	125
Liqueur	3	20.0±0.0	20	20	20
Other alcoholic beverages	20	164.8±117.3	125	40	500
FFQ27 Preserves	27	78.1±56.5	64	10	200
FFQ28 Fast Food, Take Away	29	183.9±115.2	190	20	350
FFQ29 French fries	22	101.7±43.1	97	62	250
FFQ30 Popcorn	6	45.0±36.7	30	15	90
FFQ31 Juices in TetraPak	230	264.8±140.3	250	10	1000
FFQ32 Beverages in PET[2]	462	448.3±199.5	500	100	1500
FFQ33 Beverages in plastic containers[3]		300			

Abbreviations: Max, maximum; Min, minimum; PET, polyethylene terephthalate; SD, standard derivation.
[1] mineral water carbonated and soft drinks carbonated
[2] all data of mineral water and of soft drinks known to be bottled in PET (e.g. Coca Cola, Almdudler, Sprite, Mezzo Mix) were used
[3] no information from 24h-recalls available, therefore a mean value was used for possible volumes of common plastic containers (derived from: http://www.plastikbecher.de/index.php?cat=HEISSGETRAENKEBECHER)

Table 122. Consumption of various foodstuff (mean±SD, median, range) [g] among the Elderly People group (n=69) derived from 24h-recalls for 1-2 non-consecutive days, respectively (n=135)

	Amount	Mean±SD	Median	Min	Max
FFQ1 Rice/Noodles	16	127.8±38.0	114.5	60	170
Rice	7	68.6±22.7	60	60	120
Noodles	9	150.0±30.0	170	110	170
FFQ2 Bread, brown	123	49.3±9.9	50	5	75
FFQ3 Bread, white	55	46.1±21.1	61.3	10	83
FFQ4 Bread, wholemeal	43	50.2±6.7	50	30	60
FFQ5 Potatoes	55	123.7±32.5	141	63	228
FFQ6 Vegetables	128	76.2±49.6	75	3	225
FFQ7 Fruits fresh	168	93.8±52.4	125	2	250
FFQ8 Compote, fruit pulp	8	132.9±60.6	131.5	50	229
FFQ9 Milk, milk drinks	158	69.6±113.3	20	2.5	750
FFQ10 Meat (beef or pork)	32	109.9±46.8	111	26	220
FFQ11 Poultry	19	129.7±55.9	125	50	316.3
FFQ12 Sausages, cold meat	96	35.9±24.5	34.5	9.8	150
FFQ13 Fish	21	119.9±63.7	151	13	285
FFQ 14 Eggs	14	58.6±8.4	60	30	65
FFQ15 Legumes	11	69.8±31.4	73	15	101
FFQ16 Almonds, peanuts, nuts	13	18.8±9.6	15	10	30
FFQ17 Butter, oil	170	9.3±6.5	10	0.4	40
Butter	75	11.3±5.1	12.5	2.5	30
Oil	74	5.8±5.0	5.6	0.4	25
Margarine	21	14.1±9.3	12.5	2.5	40
FFQ18 Pastries, cakes	95	64.3±46.6	47	4	210
FFQ19 Chocolate, sweets	64	24.3±28.0	14	1.4	160
FFQ20 Fruit or vegetable juices	29	222.8±164.6	250	10	1000
FFQ21 Soft drinks	9	258.3±100.0	250	125	500
Soft drinks carbonated	9	258.3±100.0	250	125	500
Soft drinks not carbonated	0				
FFQ 22 Carbonated beverages[1]	68	349.6±184.7	250	125	1000
FFQ23 Tea	94	357.5±197.7	250	180	1000
FFQ24 Coffee	158	184.0±41.3	180	22.5	270
FFQ25 Tab / mineral water	299	384.8±199.4	250	70	1500
Tab water	240	390.0±201.4	330	70	1500
Mineral water	59	363.5±191.1	250	125	1000
FFQ26 Alcoholic beverages	100	274.5±174.7	250	20	1000
Beer	42	412.1±166.2	330	200	1000
Wine	44	177.3±83.3	125	50	500
Spirits	2	20.0±0.0	20	20	20
Liqueur	1	20	20	20	20
Other alcoholic beverages	11	207.3±116.8	200	80	500
FFQ27 Preserves	3	134.3±30.1	125	110	168
FFQ28 Fast Food, Take Away	1	127	127	127	127
FFQ29 French fries	3	91.7±27.4	97	62	116
FFQ30 Popcorn	0				
FFQ31 Juices in TetraPak	26	228.8±168.6	250	100	1000
FFQ32 Beverages in PET[2]	68	349.6±184.7	250	125	1000
FFQ33 Beverages in plastic containers[3]		300			

Abbreviations: Max, maximum; Min, minimum; PET, polyethylene terephthalate; SD, standard derivation.
[1] mineral water carbonated and soft drinks carbonated
[2] all data of mineral water and of soft drinks known to be bottled in PET (e.g. Coca Cola, Almdudler, Sprite, Mezzo Mix) were used
[3] no information from 24h-recalls available, therefore a mean value was used for possible volumes of common plastic containers (derived from: http://www.plastikbecher.de/index.php?cat=HEISSGETRAENKEBECHER)

3.3.6 Results

3.3.6.1 Phthalates

In total, phthalate intakes of 585 participants were investigated for the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59). Participants with more than five missing items in their FFQ were eliminated from calculation. In the following, calculated phthalate intake via food and identified exceedances of acceptable levels of exposure, differences between study population groups, estimated hazard indices and comparisons with DIs derived from analysed urinary phthalate metabolites will be reported and discussed.

3.3.6.1.1 Calculated intake through various foodstuffs

Children I

Table 123. Calculated phthalate intakes [µg/kg bw/d] through various foodstuffs in the group of Children I (n=25)

[µg/kg bw/d]	Phth mean				Phth max			
	range	***mean±SD***	***median***	***P95***	***range***	***mean±SD***	***median***	***P95***
DMP	0.0-2.3	0.57±0.66	0.27	2.1	0.14-7.1	2.0±1.9	1.4	6.7
DEP	0.03-0.16	0.08±0.03	0.07	0.16	0.13-0.82	0.37±0.18	0.31	0.79
DiBP	0.14-1.9	0.51±0.34	0.44	1.5	0.74-5.2	1.9±0.97	1.7	4.8
DnBP	0.37-2.2	0.83±0.44	0.71	2.1	11.6-56.6	27.7±12.4	25.4	55.2
BBzP	0.02-0.22	0.05±0.04	0.04	0.17	0.38-4.2	1.9±0.97	1.6	4.0
DEHP	1.5-6.1	2.7±1.2	2.5	5.9	7.3-82.3	19.6±14.1	16.6	65.3
DiNP	0.02-0.37	0.16±0.09	0.12	0.36	0.02-0.37	0.16±0.09	0.12	0.36
DiDP	0.03-0.44	0.13±0.12	0.09	0.41	0.03-0.44	0.13±0.12	0.09	0.41
Sum	*2.5-10.1*	*5.1±2.3*	*4.2*	*10.1*	*24.3-155*	*53.7±27.4*	*48.5*	*133*

Abbreviations: max, maximum; Phth, phthalate; P95, 95th percentile; SD, standard derivation.

From 29 participants, 24h-recalls from three consecutive days were available for the estimation of mean food intake. 25 children from the Children I group provided FFQs with at least no more than five missing items and available bodyweights. Several calculated phthalate intakes through various food types are shown in Table 123.

Children II

For the determination of mean amounts of food intake for performing SEC, the study population group of Children II was divided into two age groups, because of presumably differing amounts of food intake: children aged 7-11 years (n=129) and

children aged 12-15 years (n=82), whereof 128 participants from the age group 7-11, and 78 participants from the age group 12-15 provided complete 24h-recalls for three consecutive days, which were then used for estimation of mean intake of various food types. For SEC, all samples of the Children II group were investigated. 205 children provided documentation of bodyweight and no more than five missing items in their FFQs. Table 124 shows the calculated phthalate intakes through food:

Table 124. Calculated phthalate intake [µg/kg bw/d] through various foodstuffs in the group of Children II (age 7-15) (n=205)

[µg/kg bw/d]	Phth mean				Phth max			
	range	***mean±SD***	***median***	***P95***	***range***	***mean±SD***	***median***	***P95***
DMP	0.001-7.5	0.63±0.91	0.28	2.5	0.01-20.5	1.9±2.5	0.9	6.9
DEP	0.006-0.57	0.08±0.09	0.05	0.26	0.03-1.6	0.28±0.26	0.22	0.69
DiBP	0.03-2.0	0.40±0.36	0.28	1.1	0.07-10.8	1.4±1.4	1.0	4.3
DnBP	0.03-4.3	0.62±0.61	0.45	2.0	0.94-139	24.0±23.8	16.1	78.5
BBzP	0.0-0.39	0.03±0.06	0.02	0.12	0.04-8.3	1.4±1.4	0.91	4.3
DEHP	0.18-16.1	2.2±2.4	1.4	7.5	0.72-118	15.5±15.6	11.3	37.8
DiNP	0.0-0.45	0.7±0.08	0.04	0.25	0.0-0.45	0.7±0.08	0.04	0.25
DiDP	0.002-0.91	0.09±0.12	0.05	0.27	0.002-0.91	0.09±0.12	0.05	0.27
Sum	*0.33-27.0*	*4.1±4.1*	*2.9*	*12.3*	*2.2-281*	*45.0±42.0*	*32.3*	*133*

Abbreviations: max, maximum; Phth, phthalate; P95, 95th percentile; SD, standard derivation.

Adults

Table 125. Calculated phthalate intake [µg/kg bw/d] through various foodstuffs in the group of Adults (n=296)

[µg/kg bw/d]	Phth mean				Phth max			
	range	***mean±SD***	***median***	***P95***	***range***	***mean±SD***	***median***	***P95***
DMP	0.0-1.6	0.16±0.23	0.07	0.58	0.01-4.5	0.46±0.63	0.24	1.6
DEP	0.003-0.36	0.03±0.02	0.03	0.06	0.01-0.68	0.10±0.06	0.09	0.23
DiBP	0.05-1.4	0.29±0.16	0.26	0.58	0.17-6.3	0.82±0.52	0.71	1.5
DnBP	0.08-2.7	0.38±0.23	0.33	0.74	0.86-100	12.1±9.2	9.5	28.6
BBzP	0.003-0.32	0.02±0.02	0.02	0.04	0.07-5.1	0.81±0.61	0.61	2.0
DEHP	0.26-10.6	1.2±0.77	1.1	2.1	1.7-51.4	8.7±5.2	7.5	16.8
DiNP	0.001-0.07	0.02±0.01	0.01	0.03	0.001-0.07	0.02±0.01	0.01	0.03
DiDP	0.001-0.32	0.04±0.04	0.02	0.12	0.001-0.32	0.04±0.04	0.02	0.12
Sum	*0.46-15.9*	2.1±1.2	*1.9*	*3.9*	*3.0-157*	23.0±15.0	*19.5*	*47.5*

Abbreviations: max, maximum; Phth, phthalate; P95, 95th percentile; SD, standard derivation.

Among the group of Adults, 270 participants provided 24h-recalls for two non-consecutive days, while five participants provided only one single day. The time span between the first and the second surveyed day was between 6 and 46 days (18±7 days). 296 adults provided no more than five missing items in their FFQs as well as available bodyweights, and were used for SEC (results are shown in Table 125). For comparisons with creatinine-adjusted DIs, 257 adults were investigated who provided all necessary parameters.

Elderly People

59 participants from the group of Elderly People provided FFQs with no more than five missing items. 24h-recalls were surveyed on two non-consecutive days, whereby the time span between surveyed days was 6 to 53 days (18±7 days).

Table 126. Calculated phthalate intake [µg/kg bw/d] through various foodstuffs in the group of Elderly People (n=59)

[µg/kg bw/d]	Phth mean				Phth max			
	range	***mean±SD***	***median***	***P95***	***range***	***mean±SD***	***median***	***P95***
DMP	0.001-0.28	0.05±0.07	0.02	0.22	0.01-0.79	0.16±0.19	0.09	0.63
DEP	0.001-0.12	0.03±0.02	0.03	0.08	0.01-0.22	0.08±0.04	0.07	0.16
DiBP	0.08-0.8	0.3±0.14	0.27	0.55	0.22-1.9	0.72±0.34	0.72	1.5
DnBP	0.08-0.85	0.27±0.14	0.23	0.58	0.64-31.3	9.8±6.3	8.9	22.8
BBzP	0.001-0.10	0.02±0.02	0.01	0.07	0.03-2.5	0.75±0.51	0.59	1.9
DEHP	0.25-3.2	0.96±0.54	0.78	2.3	1.9-34.6	8.4±5.3	7.2	17.3
DiNP	0.002-0.04	0.01±0.008	0.01	0.03	0.002-0.04	0.01±0.008	0.01	0.03
DiDP	0.0-0.18	0.02±0.03	0.01	0.51	0.0-0.18	0.02±0.03	0.01	0.51
Sum	*0.43-5.3*	1.7±0.82	*1.5*	*3.4*	*3.0-62.1*	19.9±11.5	*18.6*	*50.9*

Abbreviations: max, maximum; Phth, phthalate; P95, 95th percentile; SD, standard derivation.

3.3.6.1.2 Differences between population groups, and comparison with acceptable levels of exposure

Differences between population groups were identified. Additionally, calculated phthalate intakes were compared with acceptable exposure levels (ALs) in order to identify possible exceedances, similar to investigations of daily intakes (cf. Chapter 3.1.5). ALs for selected phthalates can be found in Table 8. In the following, results for

calculations with maximum and mean levels of phthalates in various foodstuffs will be discussed.

DMP (Dimethyl phthalate)

Between the different study population groups (Children I, Children II, Adults and Elderly People), significant differences for DMP (for both maximum and mean exposure levels in food) existed (Kruskal-Wallis test; p=0.000). Median DMP intakes per day decreased with increasing age between the Children I group (1.4 µg/kg bw/d (maximum exposure levels) and 0.27 µg/kg bw/d (mean exposure levels)) and the group of Elderly People (0.09 µg/kg bw/d (maximum exposure levels) and 0.02 µg/kg bw/d (mean exposure levels)) in relation to maximum and mean exposure levels in food. P95 values of the Children I and the Children II group were similar and also decreased with age. Maximum DMP exposures differed notably between both groups of children, whereas children from the Children II group showed a higher exposure than children from the Children I group (based on maximum exposure levels in food: 7.1 and 20.5 µg/kg bw/d; based on mean exposure levels in food: 2.3 and 7.5 µg/kg bw/d). In summary, children show higher DMP exposures per kg of bodyweight per day compared to adults and elderly people (Figure 129). For DMP, no acceptable exposure levels exist.

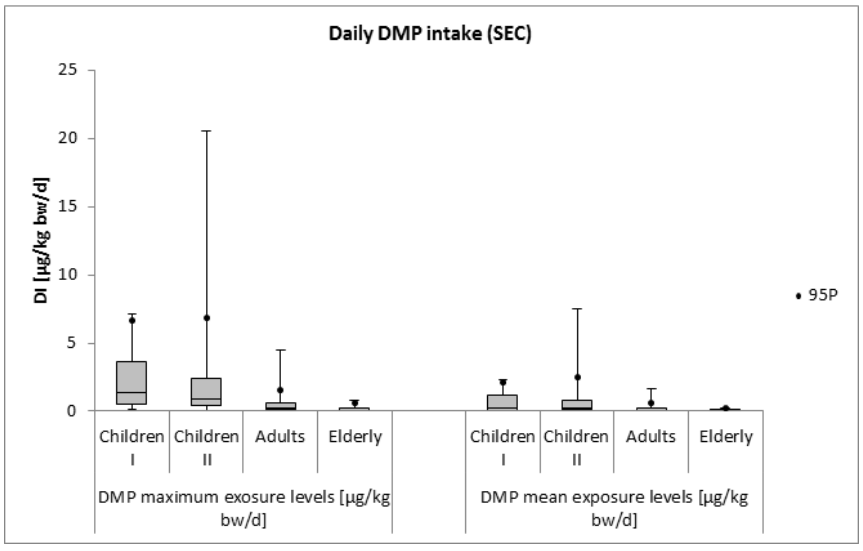


Figure 129. Distributions of estimated DMP intakes [µg/kg bw/d] performed by Scenario Exposure Calculation based on maximum and mean exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

DEP (Diethyl phthalate)

Calculated DEP intakes are shown in Figure 130. The median DEP intakes per day decreased with increasing age, whereby levels in the groups Adults and Elderly People are very similar (decrease from 0.07 µg/kg bw/d in the Children I group to 0.03 µg/kg bw/d in the group of Adults and Elderly People based on mean exposure levels in food, and from 0.31 g/kg bw/d in the Children I group to 0.07 µg/kg bw/d in the group of Elderly People based on maximum exposure levels in food). For the 95th percentiles of DEP intakes based on calculation with maximum exposure levels in food, a decrease was also identified with increasing age from 0.79 µg/kg bw/d in the Children I group to 0.16 µg/kg bw/d in the group of Elderly People. For intakes based on mean exposure levels in food, no decreases were identified, but children showed slightly higher exposures than adults and elderly people. Generally, calculated DEP exposure levels were low. Similar to findings in DMP, participants from the Children II group showed higher maximum DEP intakes per day compared to participants from the Children I group (based on maximum exposure levels in food: 0.82 g/kg bw/d (Children I) and 1.6 µg/kg bw/d (Children II); based on mean exposure levels in food: 0.16 g/kg bw/d (Children I) and 0.57 µg/kg bw/d (Children II)), as well as compared to the groups of Adults and Elderly People. Differences between the population groups were statistically significant (Kruskal-Wallis test; p=0.000).

The RfD of DEP set out by the U.S. EPA is 800 µg/kg bw/d. The calculated exposures were very low compared to this acceptable exposure level. Therefore, no exceedances for DEP exist.

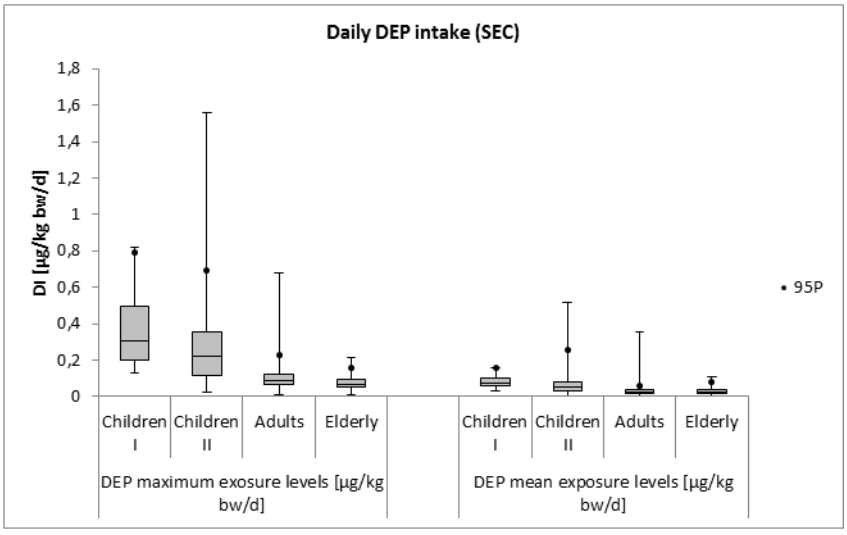


Figure 130. Distributions of estimated DEP intakes [µg/kg bw/d] performed by Scenario Exposure Calculation based maximum and mean exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

DiBP (Di-isobutyl phthalate)

Statistically significant differences existed between all population groups for DiBP (Kruskal-Wallis test; p=0.000). In the groups of Adults and Elderly People, P95 and median DiBP levels were similar. As shown in Figure 131, decreases of these levels were observed in line with an increasing age. A decrease of maximum DiBP intakes with age was also identified when comparing the groups of Children II (10.8 µg/kg bw/d (based on maximum exposure levels) and 2.0 µg/kg bw/d (based on mean exposure levels based), respectively), Adults (6.3 and 1.4 µg/kg bw/d, respectively) and Elderly People (1.9 and 0.8 µg/kg bw/d, respectively). In the group of Children II, higher maximum intakes were observed compared to the Children I group, especially for levels calculated based on maximum exposure levels in food.

The EFSA did not set out a TDI for DiBP, but for DnBP (10 µg/kg bw/d), which is used as TDI for DiBP. An exceedance of the TDI existed for the maximum DiBP intake value of 10.8 µg/kg bw/d in one child (4.0%) of the group of the Children II based on calculation with maximum exposure levels in food.

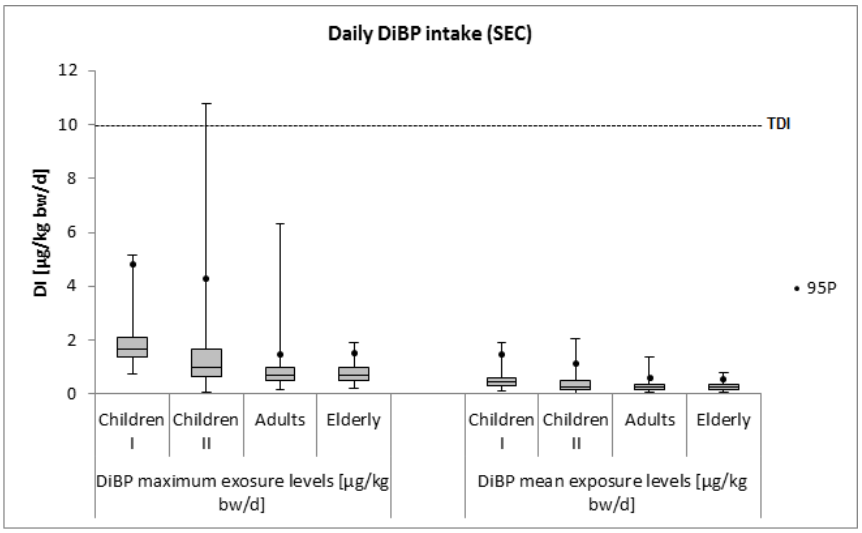


Figure 131. Distributions of estimated DiBP intakes [µg/kg bw/d] performed by Scenario Exposure Calculation based on maximum and mean exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

DnBP (Di-*n*-butyl phthalate)

Median DnBP intakes per bodyweight per day decreased with increasing age (Figure 132). Consistent results were found for the 95th percentiles, but only for intakes estimated based on mean exposure levels in food. In relation to maximum values (for both intakes based on maximum and mean exposure levels) and P95 values (based on

maximum exposure levels), participants from the Children I group showed lower DnBP intakes per bodyweight compared to the Children II group. Differences between population groups were statistically significant with p=0.000.

The RfD and RfD AA for DnBP were both 100 µg/kg bw/d and the TDI was 10 µg/kg bw/d. TDI exceedances of DnBP intake based on calculations with maximum exposure levels in food existed among all population groups, and took account of the median value (25.4 µg/kg bw/d), the P95 value (55.2 µg/kg bw/d) and the maximum value (56.6 µg/kg bw/d) of DnBP intake among the group of Children I, the median value (16.1 µg/kg bw/d), the P95 value (78.5) and the maximum value (139 µg/kg bw/d) in 150 participants (73.2%) in the group of Children II, the P95 value (28.5 µg/kg bw/d) and the maximum value (100 µg/kg bw/d) in the group of Adults, as well as the 95P value (22.8 µg/kg bw/d) and the maximum value (31.3 µg/kg bw/d) in the group of Elderly People (25 exceedances of maximums (42.3%)). Although the RfD and the RfD AA are 10 times higher than the TDI, exceedances also existed for the maximum DnBP intake in two children (0.98%) from the group of Children II, and in one participant from the Adult group (0.34%). Estimated DnBP intakes based on mean exposure levels in food did not exceed any acceptable exposure level.

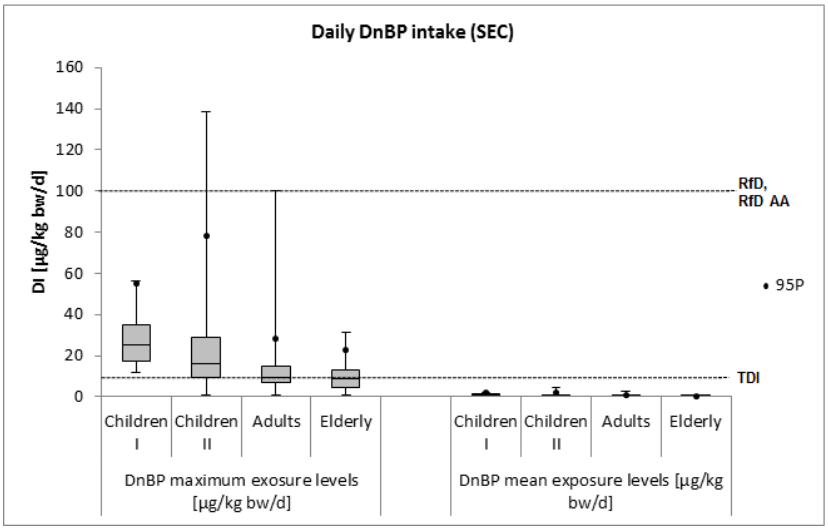


Figure 132. Distributions of estimated DnBP intakes [µg/kg bw/d] performed by Scenario Exposure Calculation based on maximum and mean exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

BBzP (Butyl benzyl phthalate)

Median BBzP intakes per day also increased with increasing age (see Figure 133 and Figure 134). However, median intakes were generally low and therefore relatively

similar. Also, declines in the 95th percentiles of BBzP intake existed, but based on estimations with mean exposure levels in food, slightly higher intakes were calculated for elderly people (0.07 µg/kg bw/d) compared to younger adults (0.04 µg/kg bw/d). Additionally, based on estimations with maximum exposure levels in food, the 95th percentile of BBzP intake in the group of Children I (4.0 µg/kg bw/d) was slightly lower than in the Children II group (4.3 µg/kg bw/d). Maximum BBzP intakes declined with age from the group of Children II to the group of Elderly People. Participants from the Children I group showed lower maximum calculated intakes than participants from the groups of Children II and Adults. Differences between study population groups were statistically significant (p=0.000).

No exceedances of any investigated acceptable exposure level were identified.

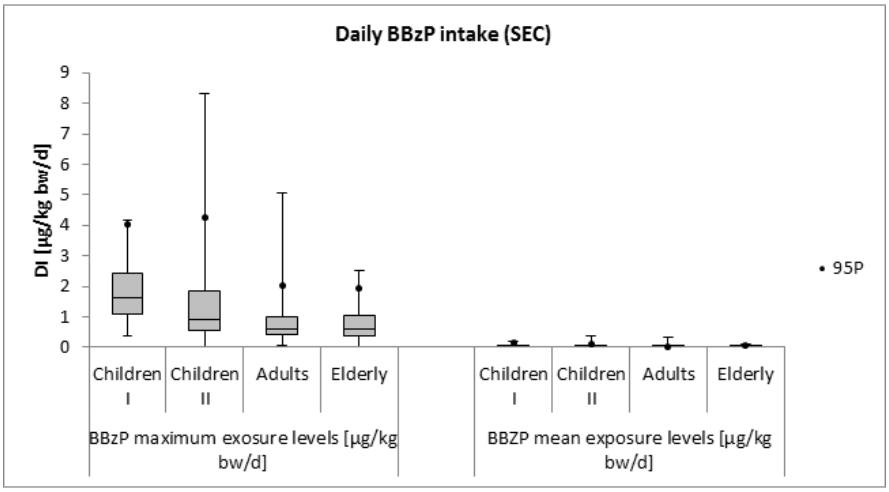


Figure 133. Distributions of estimated BBzP intakes [µg/kg bw/d] performed by Scenario Exposure Calculation based on maximum and mean exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

A more detailed graphic presentation of estimated BBzP intakes based on mean exposure levels is illustrated in Figure 134:

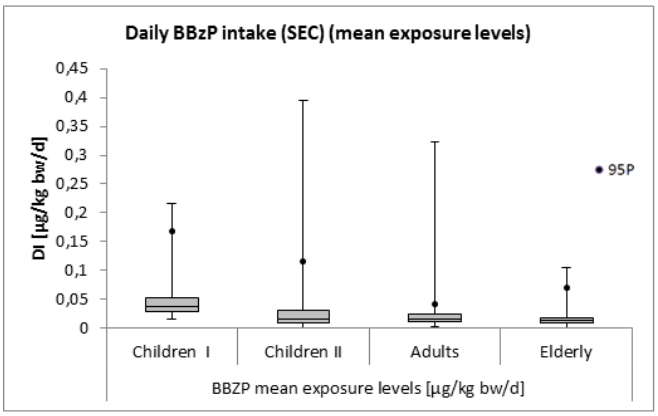


Figure 134. Distributions of estimated BBzP intake s[µg/kg bw/d] performed by Scenario Exposure Calculation based on mean exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

DEHP (Di-2-ethylhexyl phthalate)

Figure 135 shows the estimated DEHP intakes per bodyweight per day based on calculations with maximum and mean exposure levels in food, respectively. Between the different study population groups, statistically significant differences existed (Kruskal-Wallis test; p=0.000). Based on calculations with maximum exposure levels in food, medians and 95th percentiles of DEHP intakes decreased with increasing age. However, 95th percentiles of DEHP intake in the group of Elderly People (17.3 µg/kg bw/d) were slightly higher than in the group of Adults (16.8 µg/kg bw/d). Estimated maximum DEHP intakes in the Children I group (82.3 µg/kg bw/d) were lower compared to the Children II group (118 µg/kg bw/d), but a decline with age existed among both children and elderly people. Based on calculations with minimum exposure levels, median DEHP intake also decreased with age. 95th percentiles decreased with increasing age from 7.5 µg/kg bw/d in the group of Children II, and 2.3 µg/kg bw/d in the group of Elderly People. However, children from the Children I group showed lower DEHP intakes (5.9 µg/kg bw/d) compared to children from the Children II group. Findings were similar for maximum DEHP intake, which amounted to 6.1 µg/kg bw/d in the Children I group, 16.1 µg/kg bw/d in the Children II group, 10.6 µg/kg bw/d in the group of Adults and 3.2 µg/kg bw/d in the group of Elderly People.

The TDI for DEHP was set at 50 µg/kg bw/d, the RfD at 20 g/kg bw/d and the RfD AA at 30 µg/kg bw/d. Exceedances of these ALs existed for intakes based on calculations with maximum levels in food, but not for intakes based on mean levels. In both groups of children, the 95th percentile and maximum values of DEHP intake, as well as the maximum intakes in adults, exceeded all investigated ALs. In elderly people,

exceedances of RfD and RfD AA existed for maximum DEHP intake. Detailed frequencies and percentages of exceedances of ALs for maximum levels are shown in Table 127:

Table 127. Amount (percentage) of exceedances of TDI, RfD and RfD AA of maximum DEHP intake based on maximum exposure levels in food for the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

	TDI *(50 µg/kg bw/d)*	**RfD** *(20 µg/kg bw/d)*	**RfD AA** *(30 µg/kg bw/d)*
Children I	1 (4.0%)	8 (32.0%)	2 (8.0%)
Children II	6 (2.9%)	48 (23.4%)	19 (9.3%)
Adults	1 (0.34%)	7 (2.4%)	3 (1.0%)
Elderly People	0 (0%)	2 (3.4%)	1 (1.7%)

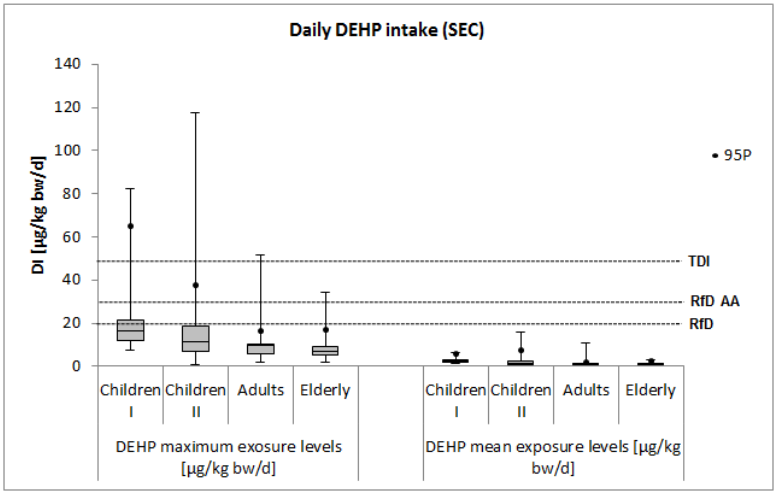


Figure 135. Distributions of estimated DEHP intakes [µg/kg bw/d] performed by Scenario Exposure Calculation based on maximum and mean exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

DiNP (Di-isononyl phthalate)

As discussed above, DiNP levels in food were not available for 20% of all food types. Therefore, DiNP intakes were already underestimated. Figure 136 shows estimated DiNP intake based on scenario exposure calculations with mean and maximum exposure levels, respectively, which were equal in the case of DiNP. The calculated exposures were low. Median and 95th percentile levels decreased with increasing age, similar to findings from other phthalates. Maximum DiNP levels also decreased with increasing age, except for participants from the Children I group, which showed lower levels than the older participants from the Children II group.

Neither the TDI of 150 µg/kg bw/d, nor the RfD AA of 1500 µg/kg bw/d were exceeded by any participant.

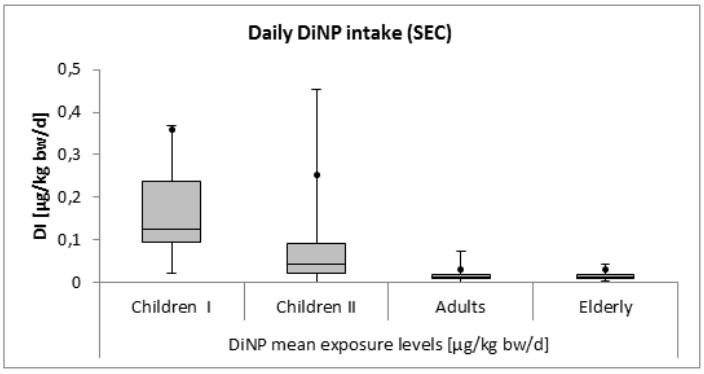


Figure 136. Distribution of estimated DiNP intakes [µg/kg bw/d] performed by Scenario Exposure Calculation based on mean/maximum exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

DiDP (Di-isodecyl phthalate)

For DiDP, levels in food provided from literature were only available for a few food types (meat, poultry, eggs, butter/oil and fruit/vegetable juices). Therefore, calculated DiDP intakes were underestimated and inaccurate. Medians, 95th percentiles and maximum levels of estimated DiDP intake per bodyweight per day for children, adults and elderly people are shown in Figure 137 for the sake of completeness.

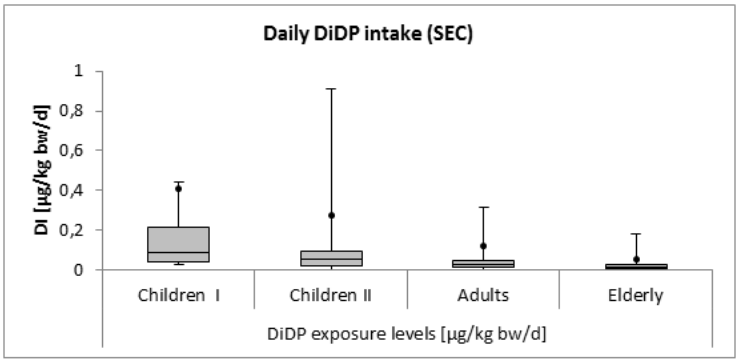


Figure 137. Distribution of estimated DiDP intakes [µg/kg bw/d] performed by Scenario Exposure Calculation based on mean/maximum exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

Sum of phthalates

The sum of all investigated phthalates (DMP, DEP, DiBP, DnBP, BBzP, DEHP, DiNP and DiDP) was estimated for all study population groups based on mean and maximum exposure levels in food, respectively. Phthalate intakes based on mean exposure

levels were a multitude lower compared to intakes based on maximum exposure levels (Figure 138). Figure 139 shows the phthalate intakes per bodyweight per day based on calculation with mean exposure levels in food. Medians increased with decreasing age from 48.5 µg/kg bw/d in the group of Children I to 18.6 µg/kg bw/d in the group of Elderly People, as similarly shown in individual phthalates above. 95th percentiles of phthalate intake were similar in both groups of children (133 µg/kg bw/d), and also decreased with increasing age, whereby elderly people (50.9 µg/kg bw/d) showed slightly higher levels than younger adults (47.5 µg/kg bw/d). Participants from the Children II group showed the highest maximum phthalate intake of 281 µg/kg bw/d compared to other study population groups. There was also a decline in phthalate intake with age, although children from the Children I group showed lower maximum levels than participants from the Children II and the Adults group. Based on mean exposure levels, the distributions of phthalate intakes were similar to those discussed above. However, median phthalate levels were higher in elderly people compared to younger adults and children from the Children II group. The highest maximum intakes existed among the group of Children II (27.0 µg/kg bw/d). Compared with results of calculation based on maximum exposure levels in food, the maximum level of phthalate intake was about 10 times lower.

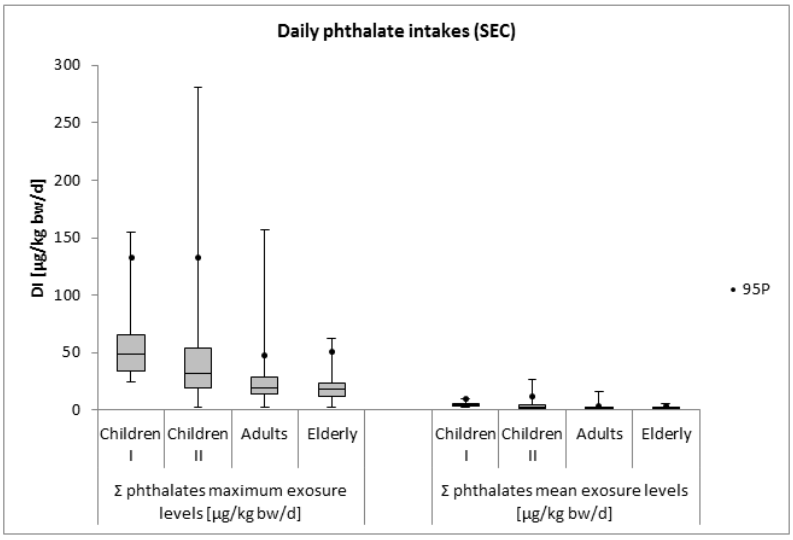


Figure 138. Distribution of estimated phthalate intakes (Σ of DMP, DEP, DiBP, DnBP, BBzP, DEHP, DiNP and DiDP) [µg/kg bw/d] performed by Scenario Exposure Calculation based on maximum and mean exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

Detailed graphical presentation of estimated daily total phthalate intake based on calculations with mean exposure levels in food in children, adults and elderly people can be found in Figure 139:

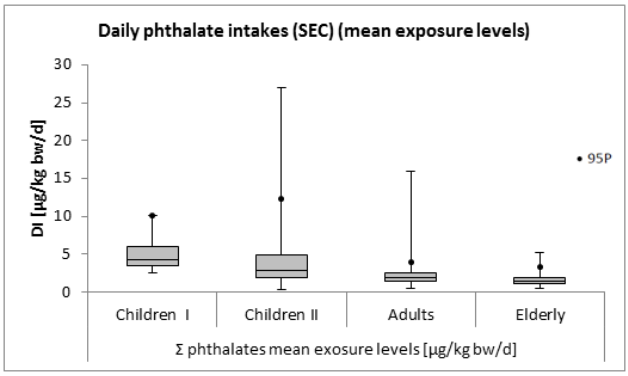


Figure 139. Distribution of estimated phthalate intakes (Σ of DMP, DEP, DiBP, DnBP, BBzP, DEHP, DiNP and DiDP) [µg/kg bw/d] performed by Scenario Exposure Calculation based on mean exposure levels in food in the groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59)

3.3.6.1.3 Hazard Index

As discussed in Chapter 3.1.6, the Hazard Index (HI) is used for cumulative risk assessment. The HI calculation procedure is described in the named chapter. Exceedances of the value 1 indicate the existence of cause for concern.

Table 128 shows estimated HIs based on TDI, RfD and RfD AA for children, adults and elderly people based on calculated daily phthalate intake levels (mean and maximum exposure levels in food, respectively). By the use of maximum phthalate levels in various foodstuffs provided from the literature, different numbers of exceedances of investigated ALs existed, especially among children and for the TDI, where among the group of Children I (n=26) 100% of all calculated HIs exceeded the TDI. In contrast, for HIs based on calculations with mean exposure levels in food, no exceedances were observed. Compared with HIs derived from the daily phthalate intake from analysed urinary phthalate metabolites (which can be found in Table 73), HIs derived from SEC differed substantially, except for HIs based on RfD and RfD AA among the groups Children II and Adults based on mean exposure levels in food, which were similar.

Table 128. Hazard Indices (HIs) for Austrian children, adults and elderly people derived from Scenario exposure calculations based on mean and maximum phthalate exposure levels in food, respectively

	Children I (n=25) range (median; P95)	Children II (n=205) range (median; P95)	Adults (n=296) range (median; P95)	Elderly (n=59) range (median; P95)
	Based on maximum exposure levels in food			
HI (TDI)[1]	1.4-7.7 (3.0; 7.2)	0.12-16.7 (1.9; 9.3)	0.15-11.5 (1.2; 3.4)	0.13-3.9 (1.1; 2.7)
n>1 [%]	100	80.5	64.2	59.3
HI (RfD)[2]	0.49-4.7 (1.1; 3.8)	0.05-7.4 (0.74; 2.9)	0.1-3.3 (0.48; 1.1)	0.11-1.9 (0.48; 1.2)
n>1 [%]	57.7	36.1	7.1	5.1
HI (RfD AA)[3]	0.36-3.3 (0.84; 2.7)	0.04-5.3 (0.55; 2.2)	0.07-2.5 (0.35; 0.82)	0.07-1.3 (0.35; 0.89)
n>1 [%]	26.9	22.0	2.4	3.4
	Based on mean exposure levels in food			
HI (TDI)[1]	0.11-0.52 (0.16; 0.47)	0.01-0.96 (0.10; 0.47)	0.02-0.62 (0.08; 0.18)	0.02-0.23 (0.07; 0.13)
n>1 [%]	0	0	0	0
HI (RfD)[2]	0.08-0.34 (0.13; 0.33)	0.01-0.87 (0.08; 0.41)	0.01-0.57 (0.06; 0.12)	0.01-0.18 (0.05; 0.12)
n>1 [%]	0	0	0	0
HI (RfD AA)[3]	0.06-0.23 (0.09; 0.22)	0.01-0.59 (0.05; 0.28)	0.01-0.39 (0.04; 0.08)	0.01-0.12 (0.03; 0.08)
n>1 [%]	0	0	0	0

Abbreviations: HI, Hazard Index; n, sample size; P95, 95th percentile; RfD, Reference Dose; RfD AA, Reference Dose for Anti-Androgenicity; TDI, Tolerable Daily Intake.

[1] based on DEHP, DnBP, DiBP, BBzP and DiNP.

[2] based on DEHP, DEP, DnBP, DiBP and BBzP.

[3] based on DEHP, DnBP, DiBP, BBzP and DiNP.

3.3.6.1.4 Comparison of daily intakes

The comparison of DIs based on measured urinary phthalate metabolites and phthalate intake based on calculated scenario exposure could potentially be subject to uncertainties and limitations. Detailed information on individually consumed food in relation to time of urine sample collection was not available. Additionally, comparisons between DIs and 24h-recalls could not be performed, because urine samples were collected before the respective 24h-recalls were provided. Therefore, it was not possible to associate food intake and phthalate metabolite excretion. Nevertheless, comparisons were made, but should be regarded with some suspicion.

The comparison of the creatinine-based DIs of DEHP, DEP, DiBP, DnBP and BBzP [µg/kg bw/d] with calculated scenario exposures [µg/kg bw/d] of the total study population (n=545) produced several statistically significant correlations, which are listed in Table 129.

Table 129. Correlations (Spearman's correlation) between creatinine-based daily intakes (DIs) of DEHP, DEP, DiBP, DnBP and BBzP [µg/kg bw/d] and corresponding exposure levels [µg/kg bw/d] estimated by scenario exposure calculations (SEC) among the total study population (age 7-81; n=545)

		Creatinine-based DI				
		DEHP[1]	*DEP*	*DiBP*	*DnBP*	*BBzP*
DI estimated from SEC (based on maximum and mean exposure levels in food)	*DEHP*[1] *max*	0.321**				
	DEHP[1] *mean*	0.255**				
	DEP max		-0.123**			
	DEP mean		-0.091**			
	DiBP max			0.106*		
	DiBP mean			0.112**		
	DnBP max				No correlation	
	DnBP mean				No correlation	
	BBzP max					0.125**
	BBzP mean					0.095*

* Correlation is significant at 0.01 level.

** Correlation is significant at 0.05 level.

[1] Creatinine-based daily DEHP intake was calculated using F_{UE}s derived from Koch et al. (2005).

Performing Spearman's correlation for each study population group separately revealed a statistically significant correlation (r=0.155; p=0.05) between calculated DEHP intakes via foodstuffs and creatinine-based daily DEHP intake in the group of Children II (n=205). No correlations were found between calculated daily intakes via food and creatinine-based DI for all investigated phthalates among the group of Children I (n=25), nor in the groups of Adults (n=257) or Elderly People (n=58). It must be noted, however, that the sample size of the group of Children I was small.

3.3.6.2 Bisphenol A

3.3.6.2.1 Calculated intake through various foodstuffs

The SEC for BPA was performed similar to calculations for phthalates.

Table 130. Calculated BPA intake [µg/kg bw/d] through various foodstuffs in the groups of Children I (age 6-8) (n=26), Children II (age 7-15) (n=210), Adults (age 18-65) (n=296) and Elderly People (age 64-81) (n=59)

[µg/kg bw/d]	BPA mean				BPA max			
	range	***mean±SD***	***median***	***P95***	***range***	***mean±SD***	***median***	***P95***
Children I	0.03-2.8	0.62±0.69	0.44	2.5	0.14-11.8	1.6±2.2	0.96	8.9
Children II	0.001-6.0	0.47±0.74	0.25	1.9	0.04-11.3	1.4±1.7	0.86	4.9
Adults	0.001-2.1	0.18±0.26	0.09	0.71	0.09-3.5	0.79±0.55	0.64	2.0
Elderly People	0.002-0.9	0.07±0.14	0.01	0.31	0.18-2.7	0.63±0.45	0.54	1.6

Abbreviations: BPA, Bisphenol A; max, maximum; P95, 95th percentile; SD, standard derivation.

Table 130 provides estimated BPA intakes for all study population groups based on mean and maximum exposure levels in foods, respectively.

3.3.6.2.2 Differences between study population groups and comparison with acceptable levels of exposure

Statistically significant differences were identified between the different study population groups (Children I, Children II, Adults and Elderly People) for BPA intake per day based on maximum and mean exposure levels in food (Kruskal-Wallis test; p=0.000). Distributions of medians, 95th percentiles and maximum values are shown in Figure 140 (based on maximum levels) and Figure 141 (based on mean levels). BPA intakes decreased with increasing age. The TDI set out by the EFSA, which was valid until 2013, as well as the RfD set out by the U.S. EPA of 50 µg/kg bw/d were not exceeded by any participant. The new temporary TDI set out by EFSA in 2014 of 5 µg/kg bw/d was exceeded in several cases, especially for BPA intakes based on maximum exposure levels: among the group of Children I, one sample (11.8 µg/kg bw/d) and among the group of Children II, 13 samples (6%) based on maximum exposure levels exceeded the temporary TDI. Based on calculations with mean exposure levels, one child from the group of Children II exceeded the temporary TDI.

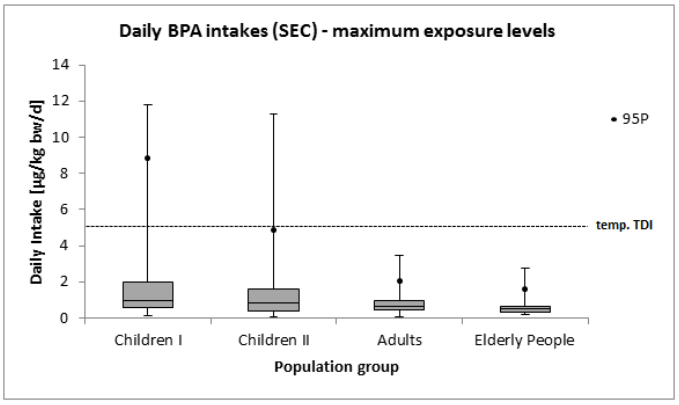


Figure 140. Distribution of estimated BPA intake [µg/kg bw/d] performed by Scenario Exposure Calculation based on maximum exposure levels in foodstuffs in the groups of Children I aged 6-8 (n=26), Children II aged 7-15 (n=210), Adults aged 18-65 (n=296) and Elderly People aged 64-81 (n=59)

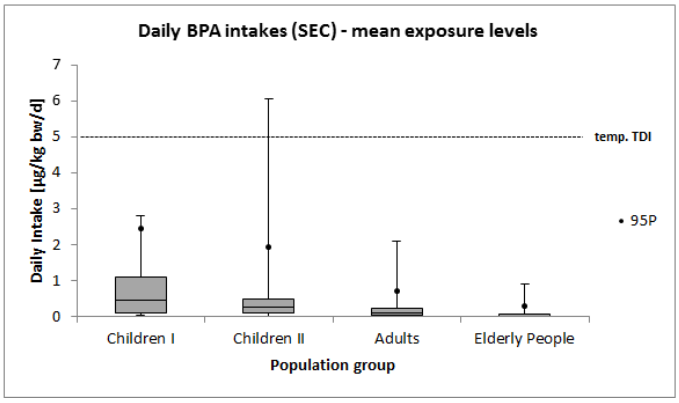


Figure 141. Distribution of estimated BPA intake [µg/kg bw/d] performed by Scenario Exposure Calculation based on mean exposure levels in foodstuffs in the groups of Children I aged 6-8 (n=26), Children II aged 7-15 (n=210), Adults aged 18-65 (n=296) and Elderly People aged 64-81 (n=59)

3.3.6.2.3 Comparison with daily intakes

As similarly discussed regarding phthalates (cf. Chapter 3.3.6.1.4), the comparison of DIs based on urinary BPA concentrations and daily BPA intake based on SEC could be subject to limitations and uncertainties. However, a statistically significant negative correlation was found between the daily BPA intake derived from SEC based on maximum exposure levels in food and the creatinine-based daily BPA intake derived from urinary concentrations among the group of Adults (n=262) (Spearman's correlation, r=-0.132, p=0.05). Although a significant correlation existed, it was only observed in one study population group and was a negative correlation. Thus, there is a discrepancy between daily intakes derived from BPA concentrations measured in urine samples and daily intakes derived from theoretical estimation by performing a SEC.

3.3.7 Uncertainties and limitations

The calculation of scenario exposures to phthalates and BPA via foodstuffs is a theoretical estimation of possible or probable intake. Thus, no exact calculation can be made and uncertainties may occur. In the following, potential sources of uncertainty will be discussed in brief.

Data collection

Data on food intake was collected from participants via 24h-recalls and FFQs. Information was provided by self-reporting of the participants, which have led to over-

or under-reporting. Additionally, portion sizes stated at 24h-recalls may be vague or entries have been neglected. In FFQs, consumed food may be misremembered, and items may be missing because of information not provided by the participants. Therefore, all participants who provided more than five missing items in their FFQ have been excluded from calculations. Additionally, surveyed food types are not complete, e.g. milk products were not included.

Phthalate and BPA levels in food

Phthalate and BPA concentrations found in different foodstuffs were provided from a multitude of scientific studies. Uncertainties may exist because:

- in many studies, only small sample sizes were investigated,
- data were collected from studies all over the world, whereby source, processing, etc. of foodstuff may differ between the countries,
- it is not possible to consider different legislations, as well as the use of phthalates and BPA in different countries, which may influence concentrations in food,
- some studies were performed years ago; therefore differences in concentrations compared with the latest results may exist,
- studies were available for most but not for all derived food types[17], and
- the decision of data's use for calculation was based on the following considerations: data from Austria, Germany or other EU states as well as latest publications were preferred.

Amounts of food consumption

Amounts of consumed food were estimated for all study population groups based on the information provided from the 24h-recalls. Compositions of complete meals were not considered.

[17] No phthalate levels were available for white bread, wholemeal bread, compote/fruit pulp, legumes, French fries and juices in TetraPak; however, data from similar food types were used in these cases. No data nor alternative data were available for microwave popcorn or beverages in plastic cups, which were not considered for further calculation. For DiNP, levels in food were missing in 20% of food types (excluding the food types named above), and for DiDP, levels were only available for meat, poultry, eggs, butter/oil and fruit/vegetable juices. BPA levels in food were not available for wholemeal bread and compote/fruit pulp, for which data from similar food types were instead used as alternative. Beverages in plastic cups for take-away were not considered for further calculation because of missing data and no available alternative data.

Absorption rates

Absorption rates of 100% has been assumed.

3.3.8 Discussion

Scenario exposure calculations (SEC) were performed for several phthalates as well as for BPA to estimate the theoretical uptake of these substances through food. Oral exposure via foodstuffs is the major exposure route for phthalates and BPA, in addition to exposure through dermal contact and inhalation. For calculations, reported frequency of intakes of various food types of the participants from their individual Food Frequency Questionnaire (FFQ), and maximum and mean exposure levels in food provided from a multitude of scientific studies and reports were used. Although it has been assumed that the use of maximum exposure levels in food would be not plausible, it was performed in order to constitute a maximum exposure scenario to identify if such a high exposure would result in the existence of cause of concern. SEC is theoretical calculation and therefore uncertainties and limitations exist which may lead to under- or overestimations, e.g. because of self-reported food intake by the participants, subjective decisions for the use of exposure levels in food, the non-consideration of complete meals in the uptake, or the partial lack of available data. However, it was attempted to perform an accurate investigation of phthalate and BPA intake via food, to identify differences between study population groups and to compare estimated results with daily intakes derived from analysed urinary metabolites.

Phthalates

Among the group of phthalates, DMP, DEP, DiBP, DnBP, BBzP, DEHP, DiNP, DiDP, as well as their sum were investigated based on maximum and mean exposure levels in food, respectively. Differences between the study population groups of Children I (n=25), Children II (n=205), Adults (n=296) and Elderly People (n=59) were statistically significant at a significance level of 0.05 (Kruskal-Wallis tests). For the investigated phthalates[18], median and 95th percentile levels [µg/kg bw/d] decreased with increasing age. These results support findings from other studies, which showed that children are more exposed than adults. Additionally, the results match with urinary phthalate metabolite concentrations analysed in this study, where decreases in exposure with

[18] For DiNP, results have to be considered carefully, because exposure levels in food were only available for 20% of all food types. For DiDP, only few data on exposure levels in food were available, therefore no conclusions were able to be made.

increasing age were also found, except for DEP. Measured urinary MEP concentrations increased with increasing age, which was contrary to results derived from SEC in relation to its parent compound. One explanation for this (by ignoring possible deviance between calculated intakes and factual intakes could be that exposure of DEP via dermal contact and inhalation are also important routes, because DEP is widely used in cosmetics, personal care products, perfumes, textile dyes, modelling clay, or polish and wax blends, whereby cosmetics, for example are mainly used by adults and not by children. A decline with increasing age also existed for the sum of all investigated phthalates. Nevertheless, differences in sample sizes among the four study population groups must be considered.

Daily intakes derived from SEC were compared to several acceptable exposure levels (ALs): the Tolerable Daily Intake (TDI) set out by the EFSA, and the Reference Dose (RfD) set out by the U.S. EPA and the Reference Dose for Anti-Androgenicity (RfD AA) established by Kortenkamp and Faust (2010). For all investigated phthalates based on calculations with mean exposure levels in food, no exceedances of any of named ALs were observed. Based on calculations with maximum exposure levels in food, several exceedances were identified for DiBP, DnBP and DEHP[19]. Similar to SEC, identified exceedances of ALs by creatinine-based DIs derived from analysed phthalate metabolite concentrations in urine were in regards to DiBP, DnBP and DEHP. However, percentages of exceedances of both SEC and DIs were different and thus difficult to compare.

For cumulative risk assessment, Hazard Indices (HIs) were calculated based on TDI, RfD and RfD AA. A HI above 1 indicates the cause for concern. Based on mean exposure levels in food, there were no HIs above the upper limit identified, whereas based on maximum exposure levels in food a high number of HI exceedances was

[19] For DiBP, one participant (4%) of the group of Children II exceeded the TDI of 10 µg/kg bw/d. Exceedances of the RfD and the RfD AA (both set out at 100 µg/kg bw/d) were identified in two children from the Children II group (<1%) and in one adult (<0.5%), and exceedances of the TDI (10 µg/kg bw/d) for all participants from the group of Children I (100%), 150 participants from the group of Children II (~73%), 136 participants from the group of Adults (~46%) and 25 participants from the group of Elderly People (~42%). One participant of the group of Children I (4%), six participants of the group of Children II (~3%) and one participant of the group of Adults (<0.5%) exceeded the TDI for DEHP (set out at 50 µg/kg bw/d). The RFD of DEHP (20 µg/kg bw/d) was exceeded by eight children from the Children I group (32%), by 48 children of the Children II group (~23%), by seven participants from the Adults group (~2%) and by two participants from the group of Elderly People (~3%). The RfD AA (30 µg/kg bw/d) was exceeded by two children from the group Children I (8%), by 19 children from the group Children II (~9%), by three participants from the group of Adults (1%) and by one elderly person (~2%).

observed, which decreased with increasing age. Compared with HIs derived from daily intakes from analysed phthalate metabolite concentrations in the urine of the study population, the number of HI values above 1 was considerably higher for SEC results. Similar to investigations of exceeded ALs, HIs were difficult to compare.

Nevertheless, possible statistical correlations between daily phthalate intakes calculated from SEC, and creatinine-based DIs calculated from measured urinary phthalate metabolites were investigated by performing Spearman correlations. Statistically significant positive correlations were found among the total study population (n=595) mostly at a significance level of 0.01 for DEHP, DiBP and BBzP. No correlation was found for DnBP. For DEP, a statistically significant negative correlation was identified, which supports the assumption that the main routes of exposure are through dermal contact and inhalation, as discussed above.

The use of maximum exposure levels derived from several studies investigating phthalate content in various foodstuffs for SEC lead to a high theoretical oral phthalate exposure and resulted in the existence of cause of concern. Calculations based on mean exposure levels in food resulted in a relatively low exposure to phthalates, and lead to the presumption that the exposure via food at these exposure levels would be safe. However, it must be considered that SECs are theoretical estimations with existing uncertainties and limitations, and that the oral route of exposure contains more than exposure via foodstuffs (e.g. exposure via pharmaceuticals), as well as that dermal contact and inhalation also play a role in exposure. Although there are difficulties in the comparison of results of SEC and results of analysed urinary phthalate metabolite concentrations[20], similar trends were shown: the decline of exposure levels and HIs in the participants with increasing age for almost all investigated phthalates, exceedances of ALs of the same three phthalates (DiBP, DnBP and DEHP), and significant correlations between DIs derived from SEC and creatinine-based DIs resulting from analysed phthalate metabolites.

Bisphenol A

Similar to phthalates, BPA was investigated based on maximum and mean exposure levels in food, respectively. Calculated intakes per bodyweight per day were low, especially for results based on mean exposure levels. Between the groups Children I (n=26), Children II (n=210), Adults (n=296) and Elderly People (n=59), statistically

[20] It has to be noted, that spontaneous urine samples were taken at one single day, which also limits comparison with theoretical scenario exposure calculations.

significant differences existed: BPA intakes decreased with increasing age; the median and 95th percentile BPA intake of participants from the Children I group were 44 times and eight times higher than the median in the group of Elderly People, respectively, based on mean exposure levels in food. Based on maximum levels in food, the median was about two times and the 95th percentile about six times higher. The maximum calculated BPA intake amounted to 11.8 µg/kg bw/d and was found in the study group of Children I. No exceedances of the former TDI of 50 µg/kg bw/d existed, but of the new temporary TDI of 5 µg/kg bw/d set out by EFSA in 2014, which was exceeded by two children, one from the group of Children I and one from the group of Children II for BPA intakes based on maximum exposure levels in food, and by one child from the group of Children II for intakes based on mean exposure levels. Compared with daily intakes derived from urinary BPA concentrations, daily intakes derived from SEC did not match very well. One single but negative statistically significant correlation was observed in only one single study population group (Adults), and additionally, DIs calculated by SEC were much higher compared to DIs derived from urinary concentrations.

4 DISCUSSION AND CONCLUSION

In the context of the Austrian Study on Nutritional Status (ASNS) performed by the Department of Nutritional Sciences (IfEW) of the University of Vienna, phthalate metabolites and bisphenol A concentrations in urine samples of 595 children, adults and elderly people were analysed. Based on the measured exposure, investigations were performed based with the aid of surveyed ASNS data in order to evaluate the exposure to the Austrian population, to establish reference values for the investigated substances, to assess possible associations with several selected parameters such as age, sex, anthropometric data, occurrences of various diseases, lifestyle, nutrition and occupation, and to perform scenario exposure calculations as well as cumulative risk assessment estimations. In the following, the investigated substances will be discussed in relation to the study aims described in Chapter 1.2, and afterwards limitations of the study will be reviewed.

4.1 Phthalates

Phthalates, a group of man-made chemicals mainly used as plasticisers in polyvinyl production, are widely used in a multitude of common consumer products, which contributes to human exposure. These substances are suspected to contribute to several adverse health effects in animals and humans, especially regarding their endocrine activities and their toxicity to reproduction. (EC, 2011f; Hauser and Calafat, 2005; Kortenkamp et al., 2011) Generally, phthalates can be divided into low molecular weight phthalates (e.g. DEP, DnBP, DiBP, DnPeP, DCHP and BBzP), which are primarily used in personal care products, cosmetics, lacquers, coatings, varnishes or pharmaceuticals, and high molecular weight phthalates (e.g. DEHP, DnOP, DiNP and DiBP), which are primarily used in flooring, wall covering, medical devices and food contact materials (Hauser and Calafat, 2005). Humans can be exposed to phthalates through oral uptake (via food, pharmaceuticals, nutritional supplements or toys), uptake via inhalation (via house dust, indoor air), through dermal uptake (via clothing, cosmetics, toys, dust or cleaning products), and intravenous uptake (via medical devices) (Schettler et al., 2006).

4.1.1 Exposure to the Austrian population

The analysis of 14 phthalate metabolite concentrations in urine samples (MEP, MnBP, MiBP, MCHP, MnPeP, MBzP, MEHP, 5oxo-MEHP, 5OH-MEHP, 5cx-MEPP, MnOP, 3cx-MPP, MiNP and MiDP)[21] was performed by HPLC-MS/MS in 2012.

Phthalate metabolites were detected in almost all samples, with most of the metabolites of low molecular weight phthalates and one high molecular weight phthalate (DEHP) present in the majority of the samples. In contrast, the metabolites of high molecular weight phthalates (except DEHP metabolites) were detected in only a small number of samples. However, in the case of DiNP and DiDP no accurate conclusion can be made regarding exposure because the analysed primary metabolites MiNP and MiDP are not adequate biomarkers for exposure assessment. The findings are interesting compared in relation the development of phthalate use reported by industries, which has indicated a shift on the European market during the last decade from low to high molecular weight phthalates (ECPI, 2010b). As previously claimed, the results of the present study can be underestimated due to the lacking knowledge of exposure to the high molecular weight phthalates DiNP and DiBP.

Among the three highest phthalate metabolite levels illustrated in Table 131, MiBP was present in all study population groups. MEP and MnBP were present in the majority of the groups, and the DEHP metabolite 5cx-MEPP was present in both children groups.

Table 131. Urinary metabolites [µg/l] with highest levels of exposure (median, P95) among the various study population groups

Population group	1. (median; P95) [µg/l]	2. (median; P95) [µg/l]	3. (median; P95) [µg/l]
Children I (n=31)	**MiBP** (53.6; 153)	**MnBP** (26.5; 65.0)	**5cx-MEPP** (22.6; 52.5)
Children II (n=220)	**MiBP** (35.0; 131)	**MEP** (19.5; 108)	**5cx-MEPP** (15.5; 56.5)
Adults (n=272)	**MEP** (31.9; 400)	**MiBP** (24.3; 109)	**MnBP** (7.9; 40.7)
Elderly People (n=72)	**MEP** (38.0; 1188)	**MiBP** (25.7; 111)	**MnBP** (10.4; 57.0)

[21] MEP, monoethyl phthalate; MnBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MCHP, mono cyclohexyl phthalate; MnPeP, mono-n-pentyl phthalate; MBzP, mono-benzyl phthalate; MEHP, mono-2-ethylhexyl phthalate; 5oxo-MEHP, mono-2-ethyl-5-oxohexyl phthalate; 5OH-MEHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; 5cx-MEPP, mono-5-carboxy-2-ethylpentyl phthalate; MnOP, mono-n-octyl phthalate; 3cx-MPP, 3-carboxy-mono-propyl phthalate; MiNP, mono-isononyl phthalate; MiDP, mono-isodecyl phthalate.

Among all assessed phthalate metabolites, the highest urinary levels were detected for MEP with a maximum concentration of 2105 µg/l in a female participant of the group of Elderly People, and a P95 value of 1188 µg/l.

The use of spontaneous urine samples includes the problem of possible variations in urine volumes and in substance concentrations between the various voids of a single day. Thus, creatinine adjustments of analysed urinary phthalate metabolite concentrations were performed.

In general, the majority of urinary phthalate metabolite concentrations were significantly higher in children and adolescents compared to younger adults and elderly people, which is in agreement with results from other studies (e.g. Silva et al., 2004; Wittassek and Angerer, 2008). However, elderly people showed higher levels of several urinary phthalate metabolites than younger adults, which were partially comparable with levels in the group of Children II. This might be explained by variations in metabolic capacities related to age or sex, along with the additionally influencing factors of nutrition or lifestyle (NRC, 2008). A possible explanation for the higher exposure of children is the more frequent contact to phthalate-containing products such as toys, school supplies, paints or plastic gloves, as well as indoor dust and food (Wormuth et al., 2006). In addition, factors such as physiology, developmental stage, and behaviour can contribute to a higher exposure to several phthalates (NRC, 2008). A notable exception among the urinary metabolites is MEP. The highest MEP levels were found in elderly people followed by younger adults; this could be due to the more likely use of cosmetics, personal care products and other consumer products containing MEP by younger adults and elderly people compared to children and adolescents (Heudorf, Mersch-Sundermann and Angerer, 2007). Additionally, because MEP is widely used in pharmaceuticals (Hauser and Calafat, 2005), the more frequent intake among adults, and especially among elderly people, may also have an important impact on MEP exposure. Compared with results from other studies, most metabolites were lower in the present study. Generally, findings matched most with results from Denmark in 2011 (Frederiksen et al., 2013). According to previous studies performed in several European countries, phthalate exposure has decreased within the last decade, which may be due to stricter legislations and changes in the use of phthalates as plasticisers in consumer products.

Also similar to findings from other studies (e.g. Silva et al., 2004), females generally showed higher exposures to several phthalates than males (among the group of Children I, significant differences were identified for the metabolites MEP and MnBP,

and among the group of Adults for MEP, MnBP, MiBP, MBzP, MiNP and all secondary DEHP metabolites). As noted above, these findings might be explained by various metabolic capacities differing inter-individually in relation to sex, age and demographic factors (NRC, 2008), different body composition or different distributions of substances within the organism (Klaasen, 2013), as well as differences in lifestyle related to e.g. nutrition, pharmaceutical intake, use of cosmetics or the use of other consumer products.

For all DEHP metabolites and the metabolite MBzP, significant east-west declines in Austria were identified among the total study population (n=595). East-west declines also exist for adipositas prevalence among the study population investigated in the Austrian Study on Nutritional Status (Elmadfa et al., 2012), which also included participants from the present study. Thus, possible indications exist that exposure to DEHP and BBzP contribute to overweight, or that nutrition has an important impact on phthalate exposure. However, because of the epidemiologic data, a reasonable conclusion cannot be given. Additional geographic differences comprised significant differences between residential areas. Participants from urban areas showed higher MEP and 5oxo-MEHP exposure, whereas in rural areas, 5cx-MEPP exposure was higher.

4.1.2 Daily intakes

The estimations of individual DEP, DnBP, DiBP, BBzP and DEHP intakes were based on two different calculation models published in Koch et al. (2007) for urinary volume excretion and urinary creatinine excretion, and were compared with various existing acceptable levels of exposure. Estimated daily phthalate intakes naturally complied with respective urinary phthalate metabolite concentrations; thus, values decreased with increasing age and increased again among elderly people. Additionally, comparable to findings discussed above, daily DEP intakes were higher in participants from the groups of Adults and Elderly People compared to both groups of children. In general, daily intakes derived from the creatinine-based calculation model were lower compared to those derived from the volume-based model, especially in relation to the medians. However, in some cases, 95th percentiles from the creatinine-based model were higher.

Currently, only a few studies investigating daily phthalate intakes in different populations exist. In comparison to results from other European countries (e.g. Frederiksen et al., 2013; Koch et al., 2007, 2011; Koch, Drexler and Angerer, 2003;

Wittassek et al., 2007), estimated daily phthalate intakes were lower in the present study.

Exceedances of acceptable levels of exposure existed mainly for Tolerable Daily Intakes (TDI) set out by the EFSA. Generally, the TDIs for the majority of phthalates are lower than the Reference Dose (RfD) set out by the U.S. EPA and the Reference Dose for Anti-Androgenicity (RfD AA) established by Kortenkamp and Faust (2010). Exceptions are BBzP and DEHP, which have higher TDIs. Differences in various acceptable levels of exposure are due to the use of different endpoints when deriving the values. A few exceedances of the TDI were identified for creatinine-based DnBP and DiBP intakes, especially among children from both groups (Children I and Children II). In participants from the group of Adults, only one single exceedance each existed for volume-based and creatinine-based daily DiBP intake, respectively. Daily intakes of DEP showed no exceedances of the only available acceptable level, the RfD of 800 µg/kg bw/d. However, in some participants, daily DEP intakes were high, especially in the group of Elderly People with a maximum level of 130 µg/kg bw/d. Additionally, no exceedances existed for daily BBzP intakes. Although the exceedances were observed in only a very small number of participants, the findings show that there is some cause for concern regarding health risks.

The calculation of daily DEHP intake was based on two different metabolism studies from Koch et al. (2005), and from Anderson et al. (2011), respectively, which derived different molar fraction values (F_{UE})[22] for the DEHP metabolites MEHP, 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP. The use of these two separate calculations with different F_{UE}s had the aim of identifying differences in results and addressing the importance of detailed knowledge regarding the metabolism and elimination of phthalates. F_{UE}s derived from Anderson et al. (2011) were lower than the F_{UE}s published in Koch et al. (2005), which leads to higher estimated daily DEHP intakes (about 1.4-fold higher). In the present study, generally no exceedances of any investigated acceptable level of exposure (TDI, RfD or RfD AA) were found for daily DEHP intakes based on urinary creatinine excretion and F_{UE}s derived from Anderson et al. (2011), where one child out of 214 from the Children II group exceeded the RfD of 20 µg/kg bw/d, which shows the significant influence of F_{UE}s on daily intakes. However, regardless of the phthalate, investigations on metabolism and elimination were performed exclusively on adults. For children and elderly people, data on F_{UE}s or other important data are still missing, and

[22] Molar fraction: molar ratio of phthalate metabolite concentrations eliminated via urine and the concentration of the parent phthalate (Koch et al., 2007).

for assessments, data derived from studies on adults are used. Children might be more sensitive, and this may contribute to biased results.

4.1.3 Cumulative Risk Assessment

A cumulative risk assessment for combined phthalate exposure was performed using the dose-addition concept of the Hazard Index (HI) approach for the evaluation of the overall potential for non-carcinogenic effects according to Kortenkamp and Faust (2010), which allows the assumption of adverse health effects resulting from simultaneous exposure. Individual HIs were calculated based on TDI and RfD AA, respectively. Generally, cause for concern exists for HIs exceeding a value of 1. Similar to the discussion for daily phthalate intakes, HIs based on TDI were in general higher, because of lower TDI levels compared to the corresponding RfD AA levels.

HIs decreased with increasing age between children and adults, and increased again in elderly people to levels approximating those of the children from the Children II group. Exceedances of the HI level of 1 existed only for the TDI-based HIs, but not for RfD AA-based, whereby the exceedances of TDI-based were exhibited especially in children. Exceedances of the TDI-based HIs were seen in all study population groups, with a maximum rate of 13% in the group of Children I. These results indicate a potential cause for concern, especially for children as a vulnerable population group. In comparison with results from previous studies, which are generally rare due to the fact that cumulative risk assessment has only relatively recently received the attention of the scientific community, results from the present study match with findings from comparable Danish population groups with regards to TDI-based HIs.

Additionally, it should be mentioned that the majority of the investigated phthalate metabolites are in a statistically significant positive correlation with each other (cf. Table 53), especially all DEHP metabolites, MBzP, MiBP, MiBP, MCHP and 3cx-MPP. This indicates that humans who are more highly exposed to a specific phthalate are also more highly exposed to several other phthalates, which demonstrates out the importance of cumulative risk assessment.

4.1.4 Associations with collected parameters

Apart from the significant differences between age groups, sex and geographical factors discussed above, several statistically significant differences and associations were also identified for diverse selected parameters which will be discussed in this section. Generally, findings should be treated with a certain degree of caution, since

the present epidemiological data do not demonstrate clear relationships. In addition to phthalates, humans are exposed to a multitude of other chemical substances which might also have negative impacts on health or lead to similar effects in humans. However, a multitude of our findings are in concordance with findings from other studies and can contribute to the identification of potential relationships between the diverse parameters and phthalate exposure.

Anthropometric data

In relation to several anthropometric data including body mass index (BMI), waist circumference (WC), abdominal circumference (AC), hip circumference (HC) and waist-to-hip ratio (WHR), diverse results were shown. In the group of Elderly People, 5OH-MEHP, 5cx-MEPP and 3cx-MPP exposures increased with increasing BMI. Whether these findings are an indication for the contribution of phthalate exposure to the development of overweight and adipositas in elderly people or are related to nutrition cannot be deduced from the present epidemiological data. Additionally, significant associations were identified for neither children nor adults. In relation to the other named body size measurement parameters, several statistically significant positive and/or negative correlations were identified in every study population group, but with partially contradictory results. Negative correlations between some phthalates and WC, AC, HC and/or WHR were mainly observed in the group of Adults, whereas positive correlations were found in the groups of Children II and Elderly People. In the group of Children I, both negative and positive correlations were found. However, results are inconsistent, difficult to interpret and should be treated with caution as a result of, for example, the non-consideration of co-variables.

In the available literature, several studies exist which have investigated various study populations for potential relationships between body size measurements, and thus for instance the occurrence of obesity, and urinary phthalate metabolite concentrations, obtaining varying results[23]. Due to the diversity of results obtained not only from the

[23] For example, Wang et al. (2013) observed positive associations between BMI or WC and several phthalate metabolites in the urine in Chinese children, although after the use of models employing sex and age as co-variables, significant associations only remained for MEHP and MEP (Wang et al., 2013). In African-American and Hispanic U.S.-American children, Teiltelbaum et al. (2012) reported positive associations between MEP as well as the sum of low molecular weight phthalates and BMI as well as WC (Teitelbaum et al., 2012). Another study in U.S.-Americans found associations between increasing BMI and WC and several phthalate metabolites in adult males and adolescent females. Contrarily, MEHP was inversely related to BMI in adolescent and adult females. No associations were found in children, but several inverse relationships were found in elderly individuals. However, the authors claimed that their

present study, but from other studies in different population groups as well, no definitive conclusion can be reached regarding associations between an exposure to phthalates and body size. Thus, further and more detailed investigations should be conducted with consideration of, for example, confounding variables.

Hypertension

An interesting discovery was made regarding potential associations between urinary phthalate metabolite exposure and self-reported hypertension among participants from the group of Elderly People. 62% of these participants reported suffering from hypertension, which was related to significantly higher exposures to 5oxo-MEHP, OH-MEHP, 5cx-MEPP (and therefore all secondary DEHP metabolites that were investigated) and 3cx-MPP. Currently almost no studies are available which investigate phthalate exposure and possible associations with hypertension and blood pressure. A study conducted on U.S.-American children and adolescents aged 6-19 years published by Trasande et al. (2013a) showed associations between dietary DEHP exposure and higher systolic blood pressure. As discussed in the named study, phthalates have short half-lives, but the development of hypertension is a chronic process. However, phthalates can induce oxidative stress, which can lead to changes in arteries. Additionally, they might have an influence on insulin resistance development, resulting in the production of microvascular changes, and therefore potentially causing higher blood pressure. (Trasande et al., 2013a) Results from the group of Elderly People may suggest these findings as well. However, this might be an interesting matter for further investigations.

Allergies

Several studies have reported significant associations between phthalate exposure, primarily due to house dust, and the occurrence of asthma and allergies, especially in children (e.g. Bornehag et al., 2004; Hsu et al., 2012; Jaakkola and Knight, 2008; Kolarik et al., 2008).

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study had limitations (Hatch et al., 2008). Additionally correlations between abdominal obesity as well as insulin resistance, and several urinary phthalate metabolites were observed in U.S-American males (Stahlhut et al., 2007). Contrarily, Trasande et al. (2013b) found no significant associations in several different ethnic subgroups of children and adolescents from an U.S.-American population (Trasande et al., 2013b).

In the present study, no associations were identified between urinary phthalate metabolite concentrations and allergies in children. In adults, statistically significant associations were obtained in relation to self-reported allergies (asthma, rhinitis, dermatitis) for MCHP, 5oxo-MEHP, MnBP and MiBP. However, our findings were contradictory to results from other studies, because adults with self-reported allergies showed significantly lower levels of the named phthalate metabolites. Limitations included the sample size distribution, of which only 23% of adults reported to suffer from allergies, and the non-specification of allergy types. Although the observed differences were statistically significant, no decisive conclusion can be made.

Consumption of pharmaceuticals

Pharmaceuticals are an important source of phthalates such as DEP, DnBP, DiBP and DEHP (FDA, 2012; Fromme et al., 2009; Hauser and Calafat, 2005; Kelley et al., 2012). Additionally, BBzP is used in the packaging of medical products (ECHA, 2009b).

Significant associations were found between the daily consumption of pharmaceuticals and urinary MEHP levels in the group of Adults, as well as between the daily consumption of more than four pharmaceuticals and MEHP, as well as 3cx-MEHP, in the group of Elderly People. Additionally in elderly individuals, significant correlations were identified between amounts of pharmaceuticals consumed daily and MBzP, MiBP, 3cx-MPP and all four creatinine-adjusted DEHP metabolites. Regarding the application type of pharmaceuticals, significantly higher exposure levels were observed among participants from the group of Elderly People to (not) creatinine-adjusted 3cx-MPP and creatinine-adjusted 5cx-MEPP in association with the daily consumption of film tablets, as well as to creatinine-adjusted MBzP in association with the daily consumption of capsules.

These findings demonstrate that the consumption of pharmaceuticals, especially in higher amounts and/or higher frequencies, contribute to the exposure to several phthalates. Notably, no statistically significant associations were found for DEP, which is reported to be widely used in pharmaceuticals. However, both the highest MEP exposure and the greatest consumption of pharmaceuticals were observed in elderly people, which leads to the assumption that pharmaceuticals may contribute to MEP exposure in the elderly. The findings also indicate that the application type of pharmaceuticals contributes to the exposure to several phthalates.

Nutrition

For the statistical investigation of potential associations between phthalate metabolite exposure and the consumption of different food types as surveyed by Food Frequency Questionnaires (FFQ), linear models were used. For logarithmic DEHP metabolites, several statistically significant associations were observed at a significance level of 0.05. However, only for the food types of 'French fries' and 'microwave popcorn' were higher DEHP metabolite exposure levels shown in association with more frequent consumption. Regarding low molecular weight phthalate metabolites (MEP, MnBP, MiBP, MnPeP, MCHP and MBzP), no statistically significant associations could be identified. Generally, the investigation of the influence of nutrition on phthalate metabolite exposure is difficult to perform based on spontaneous urine samples and FFQs. However, the findings appear to indicate the contribution of, in particular, the frequent consumption of French fries and microwave popcorn to exposure to DEHP. Nevertheless, further and more detailed investigations would be necessary to prove this conclusively.

Tobacco smoke

Slight but significant differences were found between smokers and non-smokers in the adult population group, whereby smokers were less heavily exposed to urinary MnBP and 5cx-MEPP. Decisive conclusions regarding the influence of smoking behaviour on the exposure to several phthalates cannot be made based on the present data or the statistical results.

Occupation

Investigations of phthalate metabolite exposure and several parameters related to occupation were conducted only for the group of Adults, which constitute the main employed group among the total study population. Among females from the group of Adults, significant differences in phthalate metabolite exposure were identified between employed and unemployed participants, whereby unemployed females were more highly exposed to the DEHP metabolites MEHP, 5oxo-MEHP and 5cx-MEPP, as well as to MBzP and creatinine-adjusted MEP. Explanations for these findings might include the different lifestyles of employed and unemployed females or the possibility of a higher exposure in unemployed females as a result of increased exposure to house dust in the home. However, because of the lack of further detailed information regarding lifestyle, no exact conclusion could be made. Among adult males, differences existed between various occupations (skilled worker/craftsman, self-employee,

company or public employee and company or public employee in a leading position) in relation to exposure to MnBP and 5cx-MEPP, which indicates that the type of occupation might contribute to the exposure to certain phthalates. Differences were also found between different working sectors in relation to 5oxo-MEHP, 5cx-MEPP, MiBP and creatinine-adjusted MnBP. Generally, students constituted the group most highly exposed to all named phthalates. However, although statistically significant differences between the different working sectors existed, explanations for these differences cannot be proposed because of the suboptimal sample size distribution and the lack of data regarding details about the places of employment and possible exposure routes.

In regards to the workplace, a statistically significant relationship was identified between construction works and MEP. Participants at the workplaces of whom construction works had been performed within the last five years exhibited a significantly higher exposure to MEP.

Contact with cleaning products

Among the group of Adults, statistically significant higher MEHP exposure was identified in participants who had frequent contact with cleaning products. In the case of MCHP, significant findings were also observed that were inverse to those related to MEHP. However, the low detection rates of MCHP must be considered. In previous investigations, phthalates were detected in cleaning products; Dodson et al. (2012) reported several phthalates in stain removers (DEP), laundry bleach (DEP), car interior cleaners (BBzP), dryer sheets (DEP, DnBP, DEHP), carpet cleaners (DEP), polish/wax (DEP, DnBP), toilet bowl cleaners (DEP) and tub and tile cleaners (DnBP). Although results from the present study seem to indicate positive associations between MEHP exposure und the use of cleaning products, detailed and confident conclusions could not be made as a result of the less than optimal sample size distribution (only 15 participants out of 150 had contact with cleanings products) and the lack of knowledge regarding the type of cleaning products with which participants were in contact. Additionally, the use of DEHP, which is the parent phthalate of the detected MEHP, seemed to be rare in cleaning products (cf. Dodson et al. (2012)).

Place of residence

In both groups of children (Children I and Children II), but not in the groups of Adults or Elderly People, significantly higher exposures to several phthalate metabolites were identified for participants living in apartments rather than in houses: urinary

concentrations of creatinine-adjusted MEP and of all creatinine-adjusted DEHP metabolites (MEHP, 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP) were higher in children from the Children I group who lived in apartments, and urinary concentrations of MEP were also higher in children from the Children II group who lived in apartments. House dust is an important source of phthalate exposure, especially among children. Participants from the group of Adults living in homes constructed before 1945 exhibited significantly higher exposure to 3cx-MPP than adults living in homes constructed after 1945. However, no clear explanation for this can be given, because on the one hand exact descriptions of the places of residence were not available, and on the other hand, the phthalate source cannot be identified because of the fact that 3cx-MPP is a metabolite of three different phthalates. Nevertheless, findings in children and adults suggest that the type of residence has an important impact on phthalate exposure.

In regards to floorings at the participants' respective places of residence, slightly yet statistically significant higher levels of MnBP exposure were identified in the total study population for participants living in homes where floorings had not been changed within the last 5 years.

Among the total study population, participants who reported owning new upholstery furniture showed significantly higher exposure to MEP, creatinine-adjusted MEHP, as well as creatinine-adjusted and not-adjusted MCHP compared to participants who reported owning older upholstery furniture. In the case of MEP and creatinine-adjusted MEHP, participants who owned leather furniture were exposed to a degree similar to that of participants who owned new upholstery furniture. Regarding creatinine-adjusted 3cx-MPP exposure, statistically significant differences were also observed in relation to the age of upholstery furniture; however, P95 values were similar for all age groups of furniture. These findings suggest that new upholstery furniture might contribute to increased exposure, especially to MEP and MEHP, which could be due to migration out of the material into the air and house dust.

Use of handicraft materials

In children (both the Children I and Children II groups), statistically significant differences were observed between frequency of the use of handicraft materials and creatinine-adjusted MnBP. However, results were contrary to those which were expected: children who used handicraft materials less frequently showed a higher exposure to MnBP than children who used these materials more frequently, which could be a change finding. Thus, no exact conclusion could be made.

Playing behaviour among children

Among the group of Children II, statistically significant higher exposure levels to not-creatinine-adjusted MiBP, creatinine-adjusted 5OH-MEHP and 5oxo-MEHP were observed in children who played 1-2 h per day with plastic toys compared to children who played more. These statistical findings could be due to the suboptimal sample size distribution (only 44 children out of 222 played more than two hours per day with plastic toys). A reasonable conclusion could therefore not be drawn. The statistical analysis of the phthalate metabolite exposure and the duration of the use of TV, PS and/or PC within the same study population group showed statistically significant associations for the creatinine-adjusted metabolites MEP, 5OH-MEHP, 5cx-MEPP and MEHP, as well as additionally for not-creatinine-adjusted MEHP, whereby in regards to medians the exposure increased with increased duration of use.

4.1.5 Reference values and their comparison with HBM values

Reference values in Human Biomonitoring are determined based on exposure data and describe the level of exposure a population or a population group has been subjected to. The estimation follows the IUPAC guideline (Poulsen, Holst and Christensen, 1997), which defines reference values within the 95% confidence interval of the 95th population percentile of measured urinary phthalate metabolite concentrations of a representative sample. (Bader and Lichtnecker, 2003; EAG, 2011). Thus, reference values were derived for the Austrian children and adults from 2010-2011 based on the urinary levels of several phthalate metabolites. It should be noted, however, that reference values are statistically derived values and are subject to change as a result of their dependence on various factors such as age, sex, geographic region, study sample or lifestyle (Bader and Lichtnecker, 2003; EAG, 2009).

Based on derived data shown in Table 56, reference values were estimated for the metabolites of DEP, DnBP, DiBP, BBzP, DEHP and DCHP, respectively for children aged 6-15 years and adults aged 18-81 years (Table 57). For most investigated phthalate metabolites, reference values for children are approximately two times higher compared to reference values for adults. Exceptions include MnBP and MiBP, for which the reference values are more similar, and MEP, for which adults exhibit values nearly four times higher.

Compared to the available reference values of corresponding phthalate metabolites for German children (age 4-14 years) from 2003-2006 and adults (20-29 years) from 2006

and 2008, values of the Austrian population are several times lower. Additionally, for almost all DEHP metabolites (except 5cx-MPP), the reference values of the Austrian children were similar to those of German adults. Nevertheless, it must be considered that these differences not only arise because of the comparison of two different countries, but also because of the somewhat differently constructed age groups and the different sampling periods.

For DEHP based on its secondary metabolites 5oxo-MEHP and 5OH-MEHP, the HBM-I-values set out by the HBM-commission of 500 µg/l for children aged 6-13 years, 300 µg/l for females in childbearing years and 750 µg/l for males older than 14 years are not exceeded by the reference values for the named DEHP metabolites derived from the present study population (50 µg/l for Austrian children and 20 µg/l for Austrian adults). Thus, there are currently no expectations of adverse health effects and therefore no need for action in the Austrian population concerning DEHP exposure.

4.1.6 Scenario exposure calculations

Based on the surveyed Food Frequency Questionnaires (FFQ) and 24-h recalls from the ASNS, estimates were made in order to investigate theoretical potential daily phthalate intakes through food consumption. Mean and maximum phthalate levels derived from several studies for various food stuffs were collected and used for calculations. Further, mean intakes of different food groups were estimated for the present population based on data from 24-h recalls.

However, the scenario exposure calculations made exhibit several uncertainties and limitations, such as uncertainties regarding food intake as a result of potential under- or over-reporting by participants, incomplete coverage of all food types (e.g. milk products were missing), the non-consideration of complete meals or lacking exact knowledge concerning phthalate content of consumed food.

For the investigated phthalates DMP, DEP, DnBP, DiBP, BBzP, DEHP, DiNP and DIDP, statistically significant differences existed between the population groups (Children I, Children II, Adults and Elderly People) and daily intakes [µg/kg bw/d], with exposures increasing with increasing age for all metabolites. Results for DiNP should be considered carefully, however, because available studies only provided DiNP levels for 20% of all investigated food types. For DiDP, only sparse data on exposure levels in food were available and thus, no accurate conclusions can be made. The results suggest that children are more highly exposed than adults, which is similar to findings from the present study based on measured urinary phthalate metabolite concentrations

and findings from other studies (e.g. Silva et al., 2004; Wittassek and Angerer, 2008). An exception is the estimated exposure to DEP, which has been found to be higher in adults and elderly people than in children. In this regard it must be considered that dermal contact and inhalation are important DEP exposure routes due its wide use in cosmetics, personal care products, perfumes and textile dyes, and that cosmetics, for example, are mainly used by adults, but not by younger children. Furthermore, an additional explanation for higher exposure levels in children may be that children generally exhibit higher food intakes per bodyweight.

Compared with median daily intakes based on measured phthalate metabolites in urine, daily intakes derived from SEC based on mean exposure levels were similar to median volume- and creatinine-based DIs for most investigated phthalates (DnBP, BBzP and DEHP), with median daily intakes derived from SEC based on maximum exposure levels being higher. Higher median volume- and creatinine-based daily intakes were established for DiBP and DEP. However, between DIs derived from SEC and DIs derived from calculations based on urinary metabolite concentrations, statistically positive correlations existed for DEHP, DiBP and BBzP, in most cases at a significance level of 0.01. For DnBP, no significant correlation was identified, and for DEP negative correlations were found. This could be explained by the use of cosmetics and personal care products as a major source of DEP exposure. These findings suggest the suitability of SEC based on mean exposure levels with real daily intakes estimated based on urinary phthalate metabolite concentrations, and more importantly, that nutrition is a major source for a multitude of phthalates.

4.1.7 Findings discussed for each phthalate metabolite

MEP

Monoethyl phthalate (MEP) is the metabolite of the low molecular weight phthalate diethyl phthalate (DEP), which is used in personal care products, cosmetics, food packing materials and pharmaceuticals (Hauser and Calafat, 2005).

MEP was found in the highest concentrations among all investigated phthalates with a P95 value of 1188 µg/l in the group of Elderly People, and was found in about 99% of all samples. MEP was the only metabolite that showed increased urinary exposure levels with increased age. Additionally, females were more highly exposed than males, especially among young children and adults. These findings are similar to findings from other studies and could be explained by the more frequent use of cosmetics and personal care products with increasing age. Differences were also identified in relation

to the residential areas in which participants lived, with persons from (sub)urban areas exhibiting higher exposure levels than those from rural areas. MEP exposure also differed in the group of Elderly People in relation to the change of flooring at their places of residence, with participants who had not changed their floorings within the last five years exhibiting higher levels. Additionally, participants with new upholstery furniture showed a slightly higher MEP exposure. Regarding employment circumstances, higher MEP exposure was associated with construction work, and women who were employed exhibited lower exposure levels than unemployed women. The statistically significant associations match with the use of MEP in consumer products.

As an acceptable exposure level, only a RfD of 800 µg/kg bw/d is available for DEP, which was not exceeded by any participant. The highest evaluated daily intake of 130 µg/kg bw/d was about 6-fold lower than the RfD. Thus, although exposure is generally high, especially compared to other phthalates, there should be no cause for concern.

MnBP

Mono-n-butyl phthalate (MnBP) is the major metabolite of di-n-butyl phthalate (DnBP), a low molecular weight phthalate mainly used as a plasticiser in PVC products, as well as in film coatings, adhesives and printing inks (ECB, 2003c). In the EU, DnBP is prohibited in cosmetics, intermediate packaging of medical products, toys and childcare articles, and in materials containing fatty food (EC, 2009c, 2011c, 2011e; European Parliament, 2009). It is classified according to the CLP as toxic for reproduction category 1B, and as very toxic to aquatic life (Aquatic Acute 1) (ECHA, 2013k).

Similar to the majority of phthalate metabolites, the highest MnBP exposure was found in children, and the exposure decreased with increasing age. Depending on the study population group, detection rates ranged between 97% and 100%. In the group of Elderly People, exposures increased again nearly to the levels of the Children II group, which could be due to different rates of absorption, metabolism, distribution and elimination at different ages. Females exhibited higher MnBP exposure compared to males among younger children and adults. Several statistically derived significant associations could not be explained or are difficult to trace back to measured urinary MnBP concentrations, such as the lower exposure to MnBP in smokers, in adults without allergies and in connection with frequent use of handicraft materials in children. Additionally, statistically significant differences in MnBP exposure for various

employment positions in adult males could not be explained in detail due to the lack of knowledge concerning particular working circumstances.

Acceptable exposure levels for DnBP are 100 µg/kg bw/d (RfD and RfD AA set out by the U.S. EPA) and 10 µg/kg bw/d (TDI set out by the EFSA). For estimated volume-based daily intakes, no exceedance of any acceptable level existed. However, for creatinine-based daily intakes, exceedances of the TDI were observed in the group of Children I (3%) and the group of Children II (0.5%). Although only a few participants exceeded the TDI, there is some cause for concern, especially regarding children.

MiBP

Mono-isobutyl phthalate (MiBP) is the metabolite and biomarker for di-isobutyl phthalate (DiBP) exposure, a low molecular weight phthalate used in PVC floorings, wall coverings, suitcases, curtains, footwear, lacquers for wooden furniture and in flooring (Danish EPA, 2011). The EU has banned the use of DiBP in the immediate packaging of medical products, toys and childcare articles, as well as in cosmetic products (EC, 2009c, 2011c; European Parliament, 2009), and classified DiBP as toxic for reproduction category 1B at a concentration limit of ≥25% and category 2 at a concentration limit of 5-25% (ECHA, 2009c, 2013d).

Depending on the study group, MiBP was detected in 96% to 100% of the samples, which was very similar to MnBP. In children (from both Children groups), MiBP was found in the highest amounts of all investigated phthalates. Similar to the majority of the investigated phthalate metabolites, exposures decreased with increasing age, with participants from the group of Elderly People exhibiting slightly higher exposure than those from the group of Adults. Similar to MEP and MnBP, adult females were more highly exposed to MiBP than males. In elderly people, significant associations were identified between MiBP exposure and the amount of pharmaceuticals consumed per day, which suggests that pharmaceuticals are an important source of phthalate intake. The statistically significant higher exposure of adults without allergies could not be reasonably explained, and could be a result of statistical effects. Additionally, significant differences were shown in adults working in different sectors, but due to the lack of detailed information on working circumstances, no further conclusions could be drawn.

The RfD AA for DiBP, established by Kortenkamp and Faust (2010), is 200 µg/kg bw/d. For DiBP, neither a TDI nor a RfD is available. Thus, because of its similarity to DnBP, a TDI of 10 µg/kg bw/d, and a RfD of 100 µg/kg bw/d were used. The highest daily

intakes were found in children. Exceedances of the TDI existed for children from the groups Children I (13%) and Children II (2%) for creatinine-based daily intakes, and for participants from the group of Adults (0.4%) for creatinine- and volume-based daily intakes, respectively. Among all investigated daily phthalate intakes, the highest rate of exceedances existed for DiBP. This indicates cause for concern, especially in the case of children.

MnPeP

Mono-n-pentyl phthalate (MnPeP) is the metabolite of the low molecular weight phthalate di-n-pentyl phthalate (DnPeP). DnPeP is mainly used as a plasticiser in PVC products. However, production volumes in Europe are low. (HSDB, 2009a) MnPeP has CMR properties and is therefore a SVHC and classified according to CLP regulation as toxic to reproduction category 1B and as very toxic to aquatic life (ECHA, 2013i; 2013j). In the EU, the use of DnPeP in cosmetics and toys is prohibited (ECHA, n.r.).

Exposure to MnPeP in the present study population is very low. In only 3% to 7% of the samples was MnPeP detected, depending on the study population group, with the lowest detection rate found in the group of Elderly People and the highest in the group of Children I. However, the maximum urinary MnPeP found in the group of Children II was 4.5 µg/l, and therefore also low, which reflects the limited use of DnPeP in consumer products.

For DnPeP, no acceptable exposure level exists. Furthermore, no daily intake was calculated because of generally very low exposure. Thus, for DnPeP no cause for concern exists due to the low exposure of the Austrian population.

MCHP

Mono-cyclohexyl phthalate (MCHP) is the metabolite of di-cyclohexyl phthalate (DCHP), which is used as a plasticiser for nitrocellulose, ethylcellulose, vinyl acetate, vinyl chloride resins (METI, 2003), various PVC products, paints and inks, but also in materials for food packaging (Hass et al., 2012). DCHP is not classified according to the CLP, and currently no EU legislation applies to it. However, DCHP is listed as a potential endocrine disruptor (Danish EPA, 2013).

MCHP was detected in only a minor number of samples, with the lowest detection rate found in the group of Children I (3%) and the highest in the group of Adults (36%). Additionally, exposure to it was very low, with the maximum urinary concentration of 5.5 µg/l exhibited by a child. Contrary to the majority of the phthalate metabolites

investigated, no trends in exposure in relation to age or sex could be identified. Nevertheless, statistically derived associations were found between urinary MCHP exposure and adults without allergies, as well as higher MCHP exposure in participants without contact with cleaning products. These findings were statistically significant; however, no conclusion could be drawn. A positive association with the presence of new upholstery furniture could possibly be explained by the potential migration of substances out of the material. However, such associations must be handled with care, especially because of the lack of knowledge concerning the detailed composition of the individual pieces of furniture and the possible content of phthalates in the materials.

Daily intakes were not estimated for DCHP because of the very low exposure of the Austrian population.

MBzP

Mono-benzyl phthalate (MBzP) is the metabolite and biomarker for the low molecular weight phthalate butyl benzyl phthalate (BBzP). BBzP is mainly used in polymer products, especially PVC floorings, as well as in leather and textile coating, such as upholstery or bags, and is also used in wall coverings, medical product packaging, printing inks, adhesives and paints. In recent years, the use of BBzP has decreased as a result of its replacement by alternatives such as DiNP, DEHT, and DINCH. (ECHA, 2009b) Similar to several other phthalates, BBzP is classified as toxic to reproduction category 1B and as very toxic to aquatic life according to the CLP regulation (ECHA, 2013f). In the EU, its use is banned in plasticised materials, toys and childcare articles (EC, 2008; ECHA, 2009b), cosmetics (European Parliament, 2009), in single-use materials containing fatty foods and in contact materials for infant feeding formulas (EC, 2011e).

Although the use of BBzP is still decreasing and is strictly regulated, MBzP was detected in the majority of the investigated samples (86%-100%). Exposure was highest in young children and decreased with increasing age. Similar to findings from other phthalates, females were more highly exposed than males in the Children I group. Additionally, a significant east-west decline was observed. In the group of Elderly People, MBzP exposure correlated positively with the number of pharmaceuticals consumed per day, which may indicate that pharmaceuticals are also an important source of exposure. Similar to findings related to MEP, employed females exhibited significantly less exposure to MBzP. In the group of Children I, participants who had changed floorings at their home had a higher exposure to MBzP, which may

result from the use of PVC floorings. However, no definitive relationship can be established based on the available data, but this could represent a reasonable explanation.

Acceptable exposure levels for BBzP are generally high compared to other phthalates. The TDI is set out at 500 µg/kg bw/d, the RfD at 200 µg/kg bw/d and the RfD AA at 330 µg/kg bw/d. No participant exceeded any of the available acceptable exposure levels. Additionally, the estimated daily intakes were very low. Thus, there should be no cause for concern in Austria regarding BBzP.

MEHP, 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP

Mono-2-ethylhexyl phthalate (MEHP), mono-2-ethylhydroxyhexyl phthalate (5OH-MEHP), mono-2-ethyl-5-oxohexyl phthalate (5oxo-MEHP) and mono-5-carboxy-2-ethylpentyl phthalate (5cx-MEPP) are the primary and secondary metabolites of the high molecular phthalate di-2-ethylhexyl phthalate (DEHP). DEHP is mainly used as a plasticiser in PVC materials, and is thus found in a multitude of common consumer products. Furthermore, it is also used in non-polymer products such as adhesives, printing inks, lacquers and paints. (ECB, 2008) According to CLP legislation, DEHP is classified as toxic to reproduction category 1 (ECHA, 2014b). In the EU, its use is banned in immediate medical product packaging (EC, 2011c), childcare articles and toys (EC, 2009c), cosmetic products (European Parliament, 2009), as well as in food contact materials for single-use and containing fatty foods (EC, 2011e). In addition to the phthalates DnBP, DiBP and BBzP, DEHP is listed in Appendix XIV of the EU regulation No 1907/2006, which currently undergo new authorisation in order to remove that substance from the European market in the future. After its sunset date in February 2015, DEHP will only be allowed to be temporarily produced and/or used after special authorisation. (ECHA, 2013c; LFU, 2012)

The primary metabolite MEHP was detected in only a portion of the investigated urine samples (36-66%, depending on the population group), whereas the three secondary metabolites were found in the majority of the samples (93-100%). Among all DEHP metabolites, the highest urinary levels were found for 5cx-MEPP, which was additionally found to be the third highest metabolite of all investigated phthalates in children. Significant decreases with increasing age were identified for all secondary metabolites, with elderly people exhibiting slightly higher median and P95 levels than younger adults. These findings are similar to those concerning several other phthalate metabolites. The higher exposure of females compared to males from the group of

Adults for the secondary metabolites showed also similarity to other phthalate metabolites. The exposure to all DEHP metabolites followed a significant east-west decline, and participants from (sub)urban areas were more highly exposed to the secondary metabolites than participants from rural areas. The significant increase of exposure to 5OH-MEHP and 5cx-MEHP with increasing BMI might suggest that food intake plays an important role in phthalate exposure. Additionally, significant associations were found between the secondary metabolites and the occurrence of hypertension in the group of Elderly People. However, it must be considered that hypertension is very common among the elderly and that this disease develops chronically. A contribution of DEHP exposure to the development of hypertension cannot be excluded, but further investigations are necessary. Similar to findings concerning other phthalate metabolites, significantly higher creatinine-adjusted 5oxo-MEHP levels were found among the group of Adults in participants without self-reported allergies. As discussed above, the findings could also be the results of mere statistical coincidence. Significant relationships were identified regarding the intake of pharmaceuticals. In the group of Elderly People, the creatinine-adjusted secondary DEHP metabolites were significantly positively correlated with the number of pharmaceuticals consumed daily, as well as creatinine-adjusted and not-adjusted MEHP with the consumption of more than four different pharmaceuticals per day. Similar findings were identified among the group of Adults, with a higher MEHP exposure being significantly associated with the daily consumption of pharmaceuticals. These findings suggest that pharmaceuticals might contribute significantly to the DEHP exposure in younger adults and the elderly. Concerning nutrition, the logarithmic DEHP metabolites (MEHP, 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP) were significantly correlated with the more frequent consumption of French fries and microwave popcorn. Thus, the consumption of these food types appears to contribute to DEHP exposure. However, making a definitive conclusion is difficult in part due to the use of single spontaneous urine samples and Food Frequency Questionnaires; more detailed investigations are necessary. Regarding smoking behaviour, a significant difference was found in relation to 5cx-MEPP in participants from the Adults group, where non-smokers were found to be more highly exposed than smokers, which could not be explained. Concerning occupation, significantly higher levels of exposure to MEHP, 5oxo-MEHP and 5cx-MEPP were exhibited by unemployed females, and significant differences existed between different employment positions and 5cx-MEPP, as well as between different working sectors and 5oxo-MEHP and 5cx-MEPP in adults, which is similar to findings pertaining to several other phthalate metabolites. Thus, occupation seemed to be an important contributor to DEHP exposure. However, detailed

conclusions cannot be made because of the lack of specific occupational data. With respect to places of residence, children from the Children I group who lived in apartments were more highly exposed to all creatinine-adjusted DEHP metabolites than children who lived in houses, which might be a result of dust exposure varying in relation to the place of residence. Additionally in this study population group, significant differences were also found for all secondary DEHP metabolites concerning replaced floorings at the children's homes, with children being more highly exposed where floorings had been replaced. Contrarily, in the group of Elderly People, participants who reported changed floorings at their homes were significantly less exposed to 5oxo-MEHP and 5cx-MEPP. These significant differences could be due to the materials used for floorings. However, findings were contrary in the two different study population groups. Participants who owned new upholstery furniture showed slightly, yet significantly higher MEHP exposure compared to participants who owned older ones.

Acceptable levels of exposure for DEHP are 50 µg/kg bw/d (TDI), 30 µg/kg bw/d (RfD AA) and 20 µg/kg bw/d (RfD). Creatinine- and volume-based daily intakes were estimated based on all investigated metabolites, with two different calculations being performed in relation to the two different published molecular fraction values (F_{UE}) from Koch et al. (2005) and Anderson et al. (2011), respectively. Daily DEHP intakes based on F_{UE}s from Koch et al., which were lower, exceeded all available acceptable exposure levels. Daily intakes based on F_{UE}s from Anderson et al. showed exceedances among the group of Children II (0.5%). Although the number of exceedances was low, there is still some cause for concern, especially for children.

MnOP

Mono-n-octyl phthalate (MnOP) is the metabolite and biomarker of the high molecular weight phthalate di-n-octyl phthalate (DnOP). DnOP is used primarily as a plasticiser in flooring, cables, adhesives and cosmetics, but also as a dye carrier, for example in the production of PVC, cellulose ester or polystyrene resins (Taylor and Bittner, 1997). DnOP is not classified according to CLP regulation (ECHA, 2014a), but its use is prohibited in the EU in toys and childcare articles that may be placed into the mouth by children (EC, 2009).

Exposure to MnBP was very low in the investigated population. It was detected in only 6% to 13% of the investigated urine samples, depending on the study population group. The highest urinary concentration was found in a child from the Children I group at 3.4 µg/l. Thus, exposure to DnOP in Austria seems to be currently irrelevant.

MiNP

Mono-isononyl phthalate (MiNP) is the primary metabolite of di-isononyl phthalate (DiNP), a high molecular weight phthalate used in products such as medical devices, floorings, foot wear, coatings, building and construction materials, wall coverings, toys and food contact materials, and is also used as a substitute for DEHP (ECHA, 2010b). DiNP is not classified according CLP regulation (ECHA, 2014d), but is banned in the EU in toys and childcare articles (EC, 2009c), food contact materials for single-use, materials containing fatty foods, and in infant and follow-on formulas (EC, 2011e).

MiNP is not an accurate biomarker for DiNP exposure due to its excretion via urine in a fraction of only a few percentages. Thus, the secondary oxidized metabolites 7OH-mono-methyloctyl phthalate (OH-MiNP), 7oxo-methyloctyl phthalate (oxo-MiNP) and 7carboxy-mono-methylheptyl phthalate (cx-MiNP) are used as biomarkers in human biomonitoring studies. Due to the fact that accurate standards of the secondary metabolites were not available at the time of analysis, only MiNP was measured. Thus, an investigation of the exposure to the parent compound DiNP was not possible. However, the primary metabolite MiNP was found in small quantities in up to 18% of the samples, depending on the study population group. The highest urinary concentration of 12.7 µg/l was measured in a participant from the group of Children I.

Adult females were more highly exposed to MiNP than males, which is comparable to the case of other phthalate metabolites, and a significant east-west decline was also identified. Thus, the exposure seems to behave in a manner similar to that of other phthalates. Nevertheless, investigation of all DiNP metabolites, especially the secondary ones, would be of great importance, not only because of the increasing use of DiNP, especially as an alternative to DEHP, in many consumer products.

MiDP

Mono-isodecyl phthalate (MiDP) is the primary metabolite of di-isodecyl phthalate (DiDP), which is used as a plasticiser in PVC products such as coatings, floorings, wall coverings, roofings, foot wear, wires, cables, car undercoatings, paints and lacquers (ECB, 2003b). DiDP is not classified according to CLP (ECB, 2003b). In the EU, its use is banned in toys and childcare articles that can be placed into the mouth (EC, 2009c), in single-use food contact materials and materials containing fatty foods, as well as in infant and follow-up formulas (EC, 2011e). Similar to DiNP, accurate biomarkers for exposure include its primary metabolite MiDP and its secondary metabolites 6-hydroxy-mono-isodecyl phthalate (oxo-MiDP) and mono-carboxyl-isooctyl phthalate (cx-MiDP).

At the time of chemical analysis, standards for the secondary metabolites were not available, which made the measurement of only MiDP in urine samples possible. Thus, an accurate exposure assessment was not possible.

Nevertheless, MiDP was detected in up to 24% of the samples, depending on the study population group. However, if detected, the levels of MiDP in urine were very low, with the highest concentration at 1.1 µg/l in a participant from the group of Elderly People. Daily intakes were not estimated due to the lack of knowledge concerning secondary metabolite levels. Additionally, no statistically associations with any investigated parameter could be identified for MiDP.

For the assessment of the DiDP exposure of the Austrian population, the analysis of all metabolites would be necessary, and thus, further investigation of this phthalate is needed.

3cx-MPP

3-carboxy-mono-propyl phthalate (3cx-MPP) is the metabolite of three different phthalates: DnBP, DnOP and DiNP. Therefore, regarding measured urinary concentrations, no conclusion can be made concerning the definitive parent compound.

3cx-MPP was found in the majority of the samples at detection rates between 58% in the group of Adults and 100% in the group of Children I. P95 levels increased with increasing age between children and adults. In elderly people, the P95 level was lower again, similar to the P95 level of the Children II group.

Statistically significant associations were found for 3cx-MPP exposure and BMI, which increased with increasing BMI. Additionally, exposure to 3cx-MPP was significantly higher in elderly people with self-reported hypertension, as well as being significantly associated with the number of pharmaceuticals consumed daily and the consumption of more than four different pharmaceuticals per day. Regarding places of residence, significant 3cx-MPP levels were identified in adults living in homes built before 1945, and slight, yet statistically significant lower 3cx-MPP exposure was found in participants who owned new upholstery furniture.

4.1.8 Conclusion

Fourteen different urinary phthalate metabolites were investigated in an Austrian study population of 595 participants consisting of children, adults and elderly people.

Generally, the total study population was exposed to several phthalate metabolites, with low molecular weight phthalates metabolites and the metabolites of the high molecular weight phthalate DEHP being detected in either all or at least the majority of the investigated urine samples. Thus, the study population was consistently exposed to phthalates through various routes of exposure. In accordance with findings from several previous international studies, the most highly exposed population group for the majority of phthalate metabolites, except for MEP which was found in higher concentrations among adults and elderly people, was the group of children. This finding is also consistent with findings from other studies, and the increased exposure of adults might be due to their more frequent use of cosmetics and personal care products when compared to children. Overall, the present study could identify children as a vulnerable group. Although the exposure to various phthalate metabolites is lower in Austria compared to the results of investigations conducted in other countries, some exceedances of diverse acceptable exposure levels (especially exceedances of the Tolerable Daily Intake (TDI)) were identified, mainly among children. The greater exposure among children was also shown in the cumulative risk assessment of several phthalates (DEHP, DnBP and DiBP) in relation to the TDI, whereby certain Hazard Index exceedances were identified. Thus, the exposure of children to phthalates must be reduced.

Additionally, several parameters were identified to contribute to the level of phthalate metabolite exposure, such as the ingestion of pharmaceuticals among the elderly, construction works at the workplaces of employed adults, the different residence types (apartments vs. houses) or the frequency of consumption of French fries or microwave popcorn. However, results must be considered with a degree of caution, since the surveyed parameters were derived epidemiologically, which can include certain limitations. Statistically significant associations could be first indications and suggest existing data, but further investigations focused on specific findings would be beneficial.

The derivation of reference values for the Austrian population, which was performed in the context of this study for the first time for Austria based on a relatively large population group, contributes greatly to the national and international risk assessment for phthalates. In comparison with reference values from Germany, Austrian children and adults exhibited lower reference values, which leads to the conclusion that Austrians were less exposed than Germans. The derivation of reference values for other countries, especially in Europe, would be beneficial for an exposure assessment on a European level, as well as for cross-national comparisons.

4.2 Bisphenol A

BPA is an industrial chemical mainly used as a monomer for the production of polycarbonates (PC) and epoxy resins. It is further used as an additive in PVC products, thermal paper, can coatings (European Communities, 2008) and several other products. BPA can migrate from BPA-containing products into the environment leading to human exposure through different routes of entry (Kuwabo et al., 2009). BPA is an endocrine-disrupting chemical and can lead to various adverse health effects (ECHA, 2011).

4.2.1 Exposure to the Austrian population

Total (free and conjugated) urinary BPA concentrations were measured in 595 urine samples by on-line column-switching HPLC-MS/MS in 2013. The individual samples sizes for each population group differed slightly compared to those from the phthalate metabolite analysis due to the varied availabilities of urine samples for the two analyses.

BPA was detected in only a marginal number of samples, with the highest detection rates being exhibited by children (50% in the Children I group, 17.6% in the Children II group, 11.3% in the group of Adults and 10.6% in the group of Elderly People). Additionally, children were more highly exposed to BPA than adults and elderly people, and thus a decrease was shown with increasing age, which is comparable to the exposure to the majority of investigated phthalate metabolites. However, urinary BPA concentrations were very low; the highest levels were found in an adult for not-creatinine-adjusted BPA (17 µg/l) and in a child of the group of Children II for creatinine-adjusted BPA (21 µg/g). As with the exposure to phthalates, different behaviour and lifestyles, physiology or developmental stages (NRC, 2008), as well as higher food consumption per bodyweight in children compared to adults are all reasonable explanations for the age-related differences. However, no statistically significant differences were observed based on sex.

Compared to results from previous international studies, the exposure to BPA was lower in the present study population, especially related to the median urinary total BPA levels and the detection rates. Thus, the exposure to BPA is generally low in the Austrian population and should not be a cause for concern.

4.2.2 Daily Intakes

The estimation of the daily BPA intake occurred according to the calculation procedures published in Koch et al. (2012b) for volume-based DI and those published in Frederiksen et al. (2013) for creatinine-based DI. Daily BPA intakes for both calculation models were generally low. The highest levels were found in participants from the Children I group. Similar to the trends observed regarding urinary BPA concentrations, DI values decreased with increasing age. However, participants from the group of Elderly People exhibited higher DIs than participants from both the Adults group and the group of Children II. These findings were similar to findings for the majority of phthalate metabolite concentrations. Generally, daily intakes were low. Thus, neither the RfD of 50 µg/kg bw/d set out by the U.S. EPA (U.S. EPA, 2012b), nor the temporary TDI of 5 µg/kg bw/d set out by the EFSA (EFSA, 2014a) were exceeded by any study participant. Additionally, positive levels of BPA in urine were found in only a minority of the samples (11% of the participants from each of the groups of Adults and Elderly People, but in 50% of the Children I group). In comparison with results from other studies, participants from the present study showed lower daily intakes for the most part. However, Austrian children from (sub)urban areas had higher DI levels (P95) than children from Denmark (Frederiksen et al., 2013) living in either urban or rural areas. The findings do indicate, however, that in Austria BPA exposures were very low, and based on the investigated population there should not be cause for concern. Nevertheless, the possible effects of BPA at low doses should be considered, especially because of the higher exposure of children, who are a vulnerable group. Additionally, divergent opinions exist regarding the hazardousness of BPA. The French Agency for Food, Environmental and Occupational Health and Safety (ANSES), for example, has claimed the need to determine the significance of warning signals observed during several studies conducted on the low-dose effects of BPA. Additionally, it was advised that the increase of the TDI's safety factor should be debated. (AFSSA, 2010)

4.2.3 Associations with selected parameters

After statistical analysis was conducted, several significant associations and differences were observed. However, statistically derived findings should be considered with caution as there is a possibility of findings being mere chance, but also because BPA exposure was altogether very low.

Age

For both creatinine-adjusted and not-creatinine-adjusted total BPA, significant differences existed between the different age groups. As discussed above, between children and adults, urinary BPA levels decreased with increasing age. In a manner similar to the findings of phthalate metabolite levels in urine, BPA levels in participants from the group of Elderly People were again higher, being comparable to the concentrations of children from the Children II group. Possible explanations for these age-related differences include differences in lifestyle, physiology, etc., as discussed above.

Regional differences

In the group of Adults, an east-west decline existed for not-creatinine-adjusted BPA. This finding showed also a resemblance to findings from investigations of phthalate metabolite exposure, and may suggest that nutrition has a high impact on exposure. As discussed above, an east-west decline was also found in association with overweight and adipositas (Elmadfa et al., 2012). However, based on the available data from this study and from the ASNS, no exact conclusion can be made concerning this possible connection.

Allergies

In the group of Children I, children who did not suffer from self-reported allergies exhibited significantly higher BPA exposure than participants who reported suffering from allergies.

Associations between BPA exposure and the occurrence of allergies and asthma have been investigated in several studies, with different results. For example, prenatal exposure to BPA has been found to be inversely associated with wheezing in five-year-old children, exposure at the age of three years found positively associated with wheezing in five-year old-children, and exposure in seven-year-old children has also been associated with wheezing (Donohue et al., 2013). Investigations in the USA have shown significant associations between urinary BPA concentrations and allergic asthma in females (Vaidya and Kulkarni, 2012). Another study reported that exposure to BPA at an early age does not necessarily exacerbate allergic inflammation in adulthood (Bauer et al., 2012). Nevertheless, there might be some indications for potential relationships between allergies such as allergic asthma and BPA exposure. However, findings from the present study indeed indicate statistically significant

differences between children with and without self-reported allergies, but on the one hand the sample size distribution was suboptimal, and on the other no detailed information on the type of allergy reported has been given. Thus, results are not clear and therefore no conclusions can be drawn.

Nutrition

The investigation of total BPA exposure and possible associations with the consumption of food showed some statistically significant, but not very reasonable results: participants of the total study population who reported either no or an infrequent consumption of soft drinks as well as no or an infrequent consumption of coffee were more highly exposed to BPA. Additionally, although canned food is a major food source of BPA exposure, a frequent consumption of this food type did not contribute to a higher exposure.

Current place of residence

In the group of Adults, significant differences were found regarding BPA exposure between participants living in houses and those living in apartments, with adults living in apartments being more highly exposed than those adults who lived in houses. These findings are similar to results concerning phthalate metabolite exposure in children, where several phthalate metabolite concentrations were significantly associated with living in apartments. Due to the fact that house dust is an important source of BPA as well as phthalate exposure, potential differences in house dust exposure between apartments and houses could be an explanation for these findings.

Use of laundry dryers

Statistically significantly higher BPA exposure was identified in adults who reported using a laundry dryer at their home. On the one hand, BPA is used in coil coatings of dryers (PlasticsEurope, 2007) and on the other hand it was also detected in laundry detergents (Dodson et al., 2012). Thus, the migration of BPA from laundry dryers and deposits of laundry detergents remaining on clothes into the air and house dust might be possible, and findings from the present study suggest that the use of laundry dryers at the home contribute to total BPA exposure.

4.2.4 Reference values and their comparison with HBM-values

Reference values for BPA, which are defined as statistically derived values for the exposure experienced by a population or population group, were estimated as described in the related chapters above. Because of their statistical derivation, reference values are subject to change depending on several factors including sex, age, geography, chosen sample and lifestyle. (Bader and Lichtnecker, 2003; EAG, 2009, 2011)

Based on measured urinary total BPA concentrations in the Austrian population from 2010-2011, reference values of 4 µg/l in male and female children (aged 6-15 years) and 1.5 µg/l in male and female adults (aged 18-81) were derived, with the values for children being more than two times higher than those of the adult population.

Compared to the available reference values for BPA for German children (aged 6-14 years) from 2003-2006 and adults (20-29 years) from 1995-2009, the derived values of the Austrian population are several times lower, which is also similar to reference values derived for various phthalate metabolites (see above). Again, it must be considered that these differences between populations might also arise because of the comparison of two different countries, different sampling periods and different age groups, particularly regarding the adult populations.

The HBM-commission has set out HBM-I-values for BPA of 1500 µg/l for children and of 2500 µg/l for adults. The reference values derived from the present study population for children and for adults are far below the respective HBM-I-value and thus, no adverse health effects should be expected. However, the current HBM-I-values are based on the former EFSA TDI value for BPA, which was several times higher than the new temporary TDI of 5 µg/kg bw/d.

4.2.5 Scenario exposure calculations

Scenario exposure calculations (SEC) for BPA were performed in a manner similar to that used for phthalates. Intakes [µg/kg bw/d] decreased with increasing age independently of estimations derived from literature based on mean or maximum BPA levels in food. Contrary to findings based on measured urinary BPA concentrations, elderly people showed the lowest BPA exposure compared to the other study population groups and therefore to younger participants, which might be due to differences in physiology and lifestyle, as discussed above. The results of SEC also suggest that nutrition plays a role in exposure to BPA. Compared to DIs calculated on the basis of measured urinary BPA levels, DIs derived from SEC were several times

higher and exceeded the temporary TDI of 5 µg/kg bw/d in children on several occasions, especially based on maximum BPA levels in food. However, SECs were theoretical estimations based on data from literature with certain limitations. Thus, although exceedances existed, there should not be cause for concern because the actual BPA concentrations in urine samples were all far below the acceptable exposure levels. Additionally, only one statistically significant correlation at a significance level of 0.05 was found between BPA intake derived from SEC based on maximum exposure levels and the creatinine-based daily BPA intake derived from measured urinary BPA levels in adults. Contrary to SEC performed for phthalates, which were much more suitable, SEC performed for BPA seemed to not be a particularly accurate method of estimating the theoretical intake via food.

4.2.6 Conclusion

Total BPA concentrations (free and conjugated BPA) were investigated in the urine samples of 595 Austrian participants including children, adults and elderly individuals with a total age range of 6-81 years. The exposure to BPA was generally low, with detection rates between 10.6% in the group of Elderly People and 50% in the group of Children I, and the highest urinary level measured was 17 µg/l from a participant from the Adults group. As with phthalate metabolite exposure, children are also the most vulnerable population group regarding BPA. Nevertheless, median BPA concentrations were below the limit of detection (LOD) in all investigated population groups. Additionally, calculated individual daily BPA intakes did not exceed any acceptable exposure level.

Statistically significant associations were identified between BPA exposure and several surveyed parameters. As discussed above, differences existed between age groups, with children being more highly exposed than older participants. Similar to the findings for several phthalate metabolites, BPA exposure was also identified to be greater for participants from East Austria than for those from West Austria, as well as for participants using laundry dryers at home. Also as in the case of several phthalate metabolites, higher exposure levels were found in adults living in apartments than in those living in houses, which might be due to differences in exposure to house dust.

The derivation of reference values showed exposures to be lower among the Austrian population than the German. As discussed in the chapter on phthalates, the derivation of reference values for other European countries would be beneficial for exposure assessment in Europe and for comparisons on international level.

Although exposure to BPA is low in Austria, special forms of dose-response curves as well as potential adverse effects at low doses should be considered. Regarding dose-response, several studies have shown non-monotonic curves of hormones, which are U-shaped or inverse U-shaped, which is an indication of effects at both low and high levels of exposure resulting from a down-regulation of hormone receptors at higher concentrations or by combinations of two or more monotonic curves via different pathways. For BPA, non-monotonic dose-response curves were reported. (Jekins et al., 2011; Vandenberg et al., 2009) However, controversies exist in the scientific community concerning the dose-response of BPA.

4.3 Limitations

Spontaneous urine samples

In order to evaluate exposure to phthalates and bisphenol A, spontaneous urine samples were used. Generally, in epidemiological studies, 24-h urine samples would be ideal sources for the determination of exposure as well as for the calculation of daily intakes, but they can also be rather difficult to realize, especially in the case of young children. For this reason, most epidemiological studies assess the exposure to many chemicals. (Barr et al., 2005; Koch et al., 2007) The use of spontaneous urine samples leads to the disadvantage of variable urine volumes and substance concentrations from one void to the next, but this can be corrected by creatinine adjustment (Barr et al., 2005). For calculations of daily phthalate and bisphenol A intakes, 24-h urine samples were also optimal, but single urine samples can also be extrapolated to reflect the excretion of a substance throughout the course of an entire day, based on reference values for creatinine and urinary volume excretion (Koch et al., 2011). Thus, urinary metabolite concentrations assessed in the present study based on spontaneous urine samples are given in µg/l as well as creatinine-adjusted in µg/g. Additionally, daily intakes were estimated in light of reference values for creatinine excretion and urinary volume excretion dependent on age, sex, and/or body height.

Determination of DiNP and DiBP exposure

According to their chemical structure, phthalates are metabolised in their hydrolytic monoesters, or further transformed into their oxidative secondary metabolites, as in the cases of DiNP and DiDP. Thus, biomarkers for DiNP include not only the hydrolytic monoester MiNP, but also the oxidised metabolites OH-MiBP, oxo-MiNP, and cx-MiNP, and for DiDP the monoester MiDP and the secondary metabolites OH-MiDP, oxo-MiDP

and cx-MiDP. (Koch and Angerer, 2012) An investigation of the DiNP metabolism conducted by applying a single dose of the labelled substance to a volunteer showed a urinary excretion of about 20% OH-MiNP, 11% cx-MiNP, 11% oxo-MiNP and only 2.2% MiNP after 48 hours (Koch and Angerer, 2007). In the present study, only the primary metabolites MiNP and MiDP were analysed in urine samples because of the lacking availability of analytical standards for the respective secondary metabolites. Thus, the assessment of the exposure to DiNP and DiDP was not possible, which leads, among other things, to underestimations of total phthalate exposure. Because of its widespread use, the assessment in the present study of exposure to DiNP would have been especially beneficial.

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APPENDIX A – Participants' questionnaire

The original questionnaires (in German) of the Austrian Study of Nutritional Status (ASNS) provided from the Department of Nutritional Sciences (IfEW) of the University of Vienna can be found on the digital media attached to this thesis.

APPENDIX B – EXPOSURE TO DIFFERENT POPULATIONS PROVIDED FROM SEVERAL STUDIES

Appendix B.1: PHTHALATE METABOLITE EXPOSURE

In a multitude of scientific studies, exposure to phthalates was investigated in different populations. The following tables show measured phthalate metabolite concentrations in urine samples collected within more than the last two decades all over the world (lists are not exhaustive). Data is sorted by metabolite(s) of the parent compound and time of sample collection.

DEP metabolite

Table 132. Urinary MEP concentrations [µg/l] (usually range and median) in adults published in several studies (sample collection between 1988 and 2011)

Population (n) Sampling year(s), (Reference)	MEP range (median)	DR [%]	LOD	Method
U.S.-American adults (240), males (100) and females (140), age 20-60, taken from NHANES III (spot urine) 1988-1994, (Hoppin, Ulmer and London, 2004)	*Males:* 0.5 – 16150 *Females:* 0.5 – 11192	n.r.	n.r.	HPLC-MS
U.S.-American adults (289), age 20-60, 44% males and 56% females, collected as part of NHANES III 1988-1994, (Blount et al., 2000)	<LOD – 16200 (305)	n.r.	1.0	HPLC-MS/MS
African-American females (46) from Washington, DC, USA, age 35-49 (first morning urine) 1996-1997, (Hoppin et al., 2002)	57.9 – 1042.8 (211.4)	100	1.0	HPLC-APCI-MS/MS
U.S.-American women (382) from New York City, USA during 3rd trimester of pregnancy, age 24±6.2 1998-2002, (Wolff et al., 2008)	<LOD – 44740 (380)	99.5	0.4	On-line HPLC-MS/MS
U.S.-American males (338) who are partners of subfertile couples, age 20-54 (spot urine) 2000-2003, (Duty et al., 2005)	(145) 164 (GM) 1953 (P95)	100	1.21	HPLC-MS/MS
Swedish primipara females (38), 2-3 weeks after delivery, age 23-39 2001, (Högberg et al., 2009)	0.5 - 761 (35)	n.r.	1.0	HPLC-ESI-MS/MS
German subjects (85) from Erlangen, males (32) and females (53), age 7-64 (first morning urine) 2002, (Koch et al., 2003)	5.4 – 2111 (90.2)	100	LOQ=2.0	LC/LC-MS/MS
Dutch pregnant women (100) from Rotterdam, age 18-41 2002-2006, (Ye et al., 2008)	<LOD – 4330 (117)	97	1.0	HPLC-MS/MS
U.S.-American subjects (2697), 47.6% males and 52.4% females, age 6-85, as part of NHANES 2003/2004 2003-2004, (Colacino, Harris and Schlecter, 2010)	3.5 – 46347 (207.9)	>60	0.4	HPLC-MS/MS
US-American pregnant females (137) before and during pregnancy, age 18-45 (spot urine) 2004-2009, (Braun et al., 2012)	*Before:* 98 (GM) *During:* 89 (GM)	n.r.	0.1-1	Online HPLC-MS/MS
Israeli pregnant women (19) from Jerusalem, age 24-41 2006, (Berman et al., 2009)	19.1 – 3410 (165)	100	0.8	HPLC-ESI-MS/MS
French pregnant women (279) from ELFE pilot study 2007, (Zeman et al. 2013)	6.3-1285.9 (43.5)	91.8	LOQ=7	LC-MS/MS
Male and female Canadian subjects (1208), age 20-49 from Canadian Health Measures Survey 2007-2009 2007-2009, (Saravanabhavan et al., 2013)	60.8 (GM)	>99	0.5	UPLC-MS/MS
Chinese subjects (183) from 3 cities in china: Guangzhou (110), Shanghai (24) and Quiqihaer (49), males (84) and females (99), age <10 - >40 (spot urine) 2010, (Guo, Wu and Kannan, 2011)	*f:* n.d. - 1850 (25.2) *m:* n.d. - 1330 (18.4)	100	0.1	HPLC-ESI-MS/MS
Japanese pregnant women (111), age 33±4 (mean±SD), during the 9th and 40th week of gestation (spot urine) n.r., (Suzuki et al., 2012)	(7.75)	100	0.027	HPLC-MS/MS
Italian males (74) and females (83), age 29-47 n.r., (Tranfo et al., 2013)	*f:* (61) *m:* (73.2)	98	3	HPLC-MS/MS
Danish women (145) from urban and rural area, age 31-52 (first morning urine) 2011, (Frederiksen et al., 2013)	3.1-582 (29)	100	0.53	SPE-LC-MS/MS

Abbreviations: APCI, atmospheric-pressure chemical ionisation; DR, detection rate; ELFE, Étude Longitudinale Francaise depuis l'Enfance; ESI, electrospray ionisation; GM, geometric mean; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantitation; MEP, Monoethyl phthalate; MS, mass spectrometry; n, sample size; n.d., not detected; NHANES, National Health and Nutrition Examination Survey; n.r., not reported; P95, 95th percentile; SD, standard deviation; SPE, solid phase extraction; UPLC, ultra-performance liquid chromatography.

Table 133. Urinary MEP concentrations [µg/l] (usually range and median) in children published in several studies (sample collection between 2004 and 2011)

Population (n) Sampling year(s), (Reference)	**MEP** range (median)	**DR** [%]	**LOD**	**Method**
U.S.-American young girls (90), age 6-9 2004-2005, (Wolff et al., 2007)	5.3 - 2580 (83.2) 75.7 (GM)	100	0.4	HPLC-MS/MS
U.S.-American children (379) from New York City, age 6-8, males (80) and females (299) (spot urine) 2004-2008, (Teitelbaum et al., 2012)	*Females:* (168.4) *Males:* (191.2)	>97	n.r.	Online HPLC-MS/MS
Danish healthy girls (725) from Greater Copenhagen area, Denmark, age 5.6-19.1 (first morning urine) 2006-2008, (Frederiksen et al., 2012)	2.2 – 11490 (39)	100	0.53	SPE-ID-LC-MS/MS
Danish healthy boys (555) from Greater Copenhagen area, Denmark, age 6.07-19.83, with (38) and without (517) palpable gynaecomastia (PG) (first morning urine) 2006-2008, (Mieritz et al., 2012)	*With PG:* 9.56 – 817.4 (38.7) *Without PG:* 2.71 – 12655 (36.24)	100	0.53	SPE-ID-LC-MS/MS
Male and female Canadian children (1037), age 6-11 from Canadian Health Measures Survey 2007-2009 2007-2009, (Saravanabhavan et al., 2013)	25.9 (GM)	>99	0.5	UPLC-MS/MS
Male (240) and female (201) Danish children from the Danish Indoor Environment and Children's Health Study, age 3-6 2008-2009, (Langer et al., 2014)	(16.6)	97.1	n.r.	LC-ESI-MS/MS
Egyptian premenstrual females (57) from rural (29) and urban (28) Gharbiah province, age 10-13 (spot urine) 2009, (Colacino et al., 2011)	*Urban:* 9.7 - 7740 (98.8) *Rural:* 3.8 - 4290 (43.2)	n.r.	0.2-1.2	HPLC-ESI-MS/MS
Danish children (143) from urban and rural area, age 6-11 (first morning urine) 2011, (Frederiksen et al., 2013)	4.2 - 211 (20)	100	0.53	SPE-LC-MS/MS

Abbreviations: DR, detection rate; ESI, electrospray ionization; GM, geometric mean; HPLC, high-performance liquid chromatography; ID, isotope dilution; LC, liquid chromatography; LOD, limit of detection; MEP, Monoethyl phthalate; MS, mass spectrometry; n, sample size; PG, palpable gynaecomastia; SPE, solid phase extraction; UPLC, ultra-performance liquid chromatography.

Table 134. Urinary primary and secondary DEHP metabolite concentrations [µg/l] (usually range and median) in adults published in several studies (sample collection between 1988 and 2011)

Population (n) Sampling year(s), (Reference)	MEHP range (median)	5OH-MEHP range (median)	5oxo-MEHP range (median)	5cx-MEPP range (median)	2cx-MMHP range (median)	DR [%]	LOD	Method
U.S.-American adults (289), age 20-60, 44% males and 56% females, from NHANES III (spot urine) 1988-1994, (Blount et al., 2000)	<LOD - 66.6 (2.7) 21.5 (P95)					n.r.	1.2	HPLC-MS/MS
U.S.-American adults (240), males (100) and females (140), age 20-60, from NHANES III (spot urine) 1988-1994, (Hoppin, Ulmer and London, 2004)	*Males:* 0.04-67 *Females:* 0.04-66					n.r.	0.6	HPLC-MS
German students (634), age 20-29, females (326) and males (308) (24h-urine) 1988-2003, (Wittassek et al., 2007b)	<LOD - 129 (7.6)	2.3 - 257 (21.0)	1.8 - 251 (16.7)	1.9 - 340 (26.9)	0.8 - 178 (8.7)	98-100	0.25	LC/LC-MS/MS
African-American females (46) from Washington, DC, USA, age 35-49 (first morning urine) 1996-1997, (Hoppin et al., 2002)	1.0 - 143.9 (7.3)					100	1.2	HPLC-APCI-MS/MS
U.S.-American women (382) from New York City, USA during 3rd trimester of pregnancy, age 24±6.2 1998-2002, (Wolff et al., 2008)	<LOD - 526 (6.0)	<LOD – 2051 (20.0)	<LOD – 1335 (17.0)	<LOD – 2054 (35.0)		90.6-99.5	0.25-0.9	Online HPLC-MS/MS
U.S.-American pregnant women (319), age 18-35, during the 3rd trimester of pregnancy (spot urine) 1999-2006, (Whyatt et al., 2012)	<LOD - 613 5.1 (GM)	1.1 - 1750 23.0 (GM)	0.7 - 1320 19.2 (GM)	3.0 - 1840 40.2 (GM)		84-100	0.3-1.6	Online HPLC-MS/MS
German subjects (19) from Southern Germany, including young children and adults (spot urine) n.r., (Preuss, Koch and Angerer, 2005)	3.7 - 49.9 (9.8)	7.9 - 96.1 (47.5)	8.1 - 72.5 (39.7)	12.8 - 164 (85.5)	6.3 - 87.7 (36.6)	100	0.25	Online HPLC-MS/MS
U.S.-American males (338) who are partners of subfertile couples, age 20-54 (spot urine) 2000-2003, (Duty et al., 2005)	5.2 (median) 134.6 (P95)					75	0.87	HPLC-MS/MS
Dutch pregnant women (100) from Rotterdam, age 18-41 2000-2006, (Ye et al., 2008)	<LOD - 392 (6.9) 82.8 (P95)	4.7 - 494 (14) 86.2 (P95)	2.6 - 514 (14.5) 104 (P95)	2.8 - 421 (18.4) 141 (P95)	3.2 - 67.3 (6.2) 33.4 (P95)	96-100	0.25	HPLC-MS/MS
Swedish primipara females (38), 2-3 weeks after delivery, age 23-39 2001, (Högberg et al., 2009)	2.9 - 57 (9)	1.4 - 126 (15)	0.54 -83 (11)			n.r.	0.95-1.1	HPLC-ESI-MS/MS
Taiwanese pregnant women (100) from Central Taiwan, age 25-35, during 3rd trimester of pregnancy 2001-2002, (Lin et al., 2011)	0.14 - 218 (10.46)	1.29 - 617 (21.74)	0.91 - 645 (20.8)	1.19 - 859 (27.91)	0.09 - 183 (7.04)	100	n.r.	HPLC-MS/MS

continued

Population (n) Sampling year(s), (Reference)	MEHP range (median)	5OH-MEHP range (median)	5oxo-MEHP range (median)	5cx-MEPP range (median)	2cx-MMHP range (median)	DR [%]	LOD	Method
German subjects (85) from Erlangen, males (32) and females (53), age 7-64 (first morning urine) 2002, (Koch et al., 2003)	<LOQ - 177 (10.3)	0.6 - 818 (46.8)	0.5 - 544 (36.5)			98.8-100	LOQ = 0.5	LC/LC-MS/MS
U.S.-American subjects (2697), 47.6% males and 52.4% females, age 6-85, from NHANES 2003-2004, (Colacino, Harris and Schlecter, 2010)	0.6 - 718 (2.1)	0.2 - 3141 (23.1)	0.4 - 1953 (15.9)	0.2 - 2886 (35.3)		>60	0.25-0.9	HPLC-MS/MS
Japanese subjects (36) mostly from Tokyo-Yokohama area, adults (35) and one child (1), males (25) and females (9), age 4-70 2004, (Itoh, Yoshida and Masunaga, 2005)	0.76 - 25.0 (5.1)					100	0.33	HPLC-MS/MS
US-American pregnant females (137) before and during pregnancy, age 18-45 (spot urine) 2004-2009, (Braun et al., 2012)	*Before:* 8.1 (GM) *During:* 9.5 (GM)					n.r.	0.1-1	Online HPLC-MS/MS
German subjects (50) from Munich and nearby rural and suburban areas, males (23) and females (27), age 14-60 (first morning urine) 2005, (Fromme et al., 2007)	*Females*: 0.1 - 16.3 (4.0) *Males:* 1.8 - 11.8 (5.1)	*Females:* 5.1 - 65.6 (17.5) *Males:* 10 - 40.4 (22.7)	*Females:* 3.6 - 61.5 (14.4) *Males:* 7.8 - 26.8 (15.9)	*Females:* 4.1 - 92.4 (25.6) *Males:* 14.7 - 54.1 (24.4)	*Females:* 1.6 - 28.8 (9.1) *Males:* 3.8 - 23.6 (10.2)	95-100	0.25	LC/LC-MS/MS
Israeli pregnant women (19) from Jerusalem, age 24-41 2006, (Berman et al., 2009)	<LOD - 21 (6.8)	1.8 - 70.9 (21.5)	1.7 - 63.8 (17.5)	5.8 - 107 (26.7)		95-100	0.6-1.2	HPLC-ESI-MS/MS
French pregnant women (139-279) from ELFE pilot study 2007, (Zeman et al. 2013)	1.1-768.1 (16.7)	1.1-1597.9 (41.9)	1.5-924.5 (28.5)	3.0-2003.6 (42.7)	1.0-1212.3 (12.3)	90.7-100	LOQ = 1-2	HPLC-MS/MS
Male and female Canadian subjects (1208), age 20-49 from Canadian Health Measures Survey 2007-2009 2007-2009, (Saravanabhavan et al., 2013)	3.7 (GM)	21.4 (GM)	12.8 (GM)			>99	0.2-0.4	UPLC-MS/MS
Chinese subjects (183) from 3 cities in china: Guangzhou (110), Shanghai (24) and Quiqihaer (49), males (84) and females (99), age <10 - >40 (spot urine) 2010, (Guo, Wu and Kannan, 2011)	*Females:* n.d. - 56.9 (1.7) *Males:* n.d. - 207 (2.2)	*Females:* 0.4 - 299 (10.5) *Males:* 0.3 - 1120 (11.9)	*Females:* 0.2 - 111 (7.3) *Males:* 0.3 - 564 (6.9)	*Females:* 1.0 - 864 (30.2) *Males:* 2.1 - 867 (27.4)	*Females:* 1.7 - 851 (18.7) *Males:* n.d. - 646 (18.7)	100	LOQ = 0.1-0.5	HPLC-ESI-MS/MS

continued

Population (n) Sampling year(s), (Reference)	MEHP range (median)	5OH-MEHP range (median)	5oxo-MEHP range (median)	5cx-MEPP range (median)	2cx-MMHP range (median)	DR [%]	LOD	Method
Japanese pregnant women (111), age 33±4 (mean±SD), during the 9th and 40th week of gestation (spot urine) n.r., (Suzuki et al., 2012)	3.71 (median) 7.14 (P75)	7.05 (median) 13.8 (P75)	7.75 (median) 13.0 (P75)			100	0.006- 0.024	HPLC- MS/MS
Italian males (74) and females (83), age 29-47 n.r., (Tranfo et al., 2013)	Females: (2.1) Males: (3.58)	Females: (8.4) Males: (11.6)				74-100	0.45- 0.5	HPLC- MS/MS
Danish women (145) from urban and rural area, age 31-52 (first morning urine) 2011, (Frederiksen et al., 2013)	<LOD-308 (1.7)	1.3-350 (12)	<LOD-237 (6.1)	1.3-356 (8.2)		91-100	0.14- 0.91	SPE-LC- MS/MS

Abbreviations: APCI, atmospheric-pressure chemical ionisation; DEHP, di(2-ethylhexyl) phthalate; DR, detection rate; ELFE, Étude Longitudinale Francaise depuis l'Enfance; ESI, electrospray ionization; GM, geometric mean; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantification; MEHP, mono-(2-ethylhexyl) phthalate; MS, mass spectrometry; n, sample size; n.d., not detected; NHANES, National Health and Nutrition Examination Survey; n.r., not reported; P75, 75th percentile; P95, 95th percentile; SD, standard deviation; SPE, solid phase extraction; UPLC, ultra-performance liquid chromatography; 2cx-MMHP, Mono(2-carboxymethyl-hexyl) phthalate; 5cx-MEPP, mono-(2-ethyl-5-carboxypentyl) phthalate; 5OH-MEHP, mono-(2-ethyl-5-hydroxyl) phthalate; 5oxo-MEHP, mono-(2-ethyl-5-oxohexyl) phthalate.

Table 135. Urinary primary and secondary DEHP metabolite concentrations [µg/l] (usually range and median) in children published in several studies (sample collection between 2001 and 2011)

Population (n) Sampling year(s), [Reference]	MEHP range (median)	5OH-MEHP (MEHHP) range (median)	5oxo-MEHP (MEOHP) range (median)	5cx-MEPP (MECPP) range (median)	2cx-MMHP (MCMHP) range (median)	DR [%]	LOD	Method
German children (254), age 3-14, males (114) and females (140), from GerES IV (first morning urine) 2001-2002, (Becker et al., 2004)	0.74 - 226 (7.18)	1.86 - 2590 (52.1)	<0.5 - 1420 (41.4)			n.r.	LOQ = 0.5	LC/LC-MS/MS
German children (599), age 3-14 from GerES IV (first morning urine) 2003-2006, (Becker et al., 2009)	319 (max) (6.7)	3640 (max) (46)	2490 (max) (36.3)	4490 (max) (61.4)	1080 (max) (20.4)		LOQ = 0.25	LC/LC-MS/MS
U.S.-American young girls (90), age 6-9 2004-2005, (Wolff et al., 2007)	0.6 - 110 (3.2)	1.4 - 1699 (25.9)	1.3 - 1070 (17.8)	5.9 - 2260 (53.2)		94.4-100	0.25-0.9	HPLC-MS/MS
U.S.-American children (379) from New York City, age 6-8, males (80) and females (299) (spot urine) 2004-2008, (Teitelbaum et al., 2012)	*f:* (5.7) *m:* (6.7)	*f:* (59.1) *m:* (76.6)	*f:* (36.2) *m:* (50.7)	*f:* (97.8) *m:* (126.9)		>97	n.r.	Online HPLC-MS/MS
Danish healthy girls (725) from Greater Copenhagen area, Denmark, age 5.6-19.1 (first morning urine) 2006-2008, (Frederiksen et al., 2012)	0.2 - 307 (4.7)	1.1 - 2968 (47)	<LOD - 1585 (24)	0.9 - 1462 (28)		99.9-100	0.14-0.91	SPE-ID-LC-MS/MS
Danish healthy boys (555) from Greater Copenhagen area, Denmark, age 6.07-19.83, with (38) and without (517) palpable gynaecomastia (PG) (first morning urine) 2006-2008, (Mieritz et al., 2012)	*With PG:* 1.3 – 35.97 (4.86) *Without PG:* 0.47 – 58.29 (5.05)	*With PG:* 7.99 – 392.0 (39.94) *Without PG:* 2.64 – 893.0 (47.36)	*With PG:* 1.3 – 193.9 (21.53) *Without PG:* 1.15 – 385.6 (25.6)	*With PG:* 5.33 – 182.1 (23.41) *Without PG:* 2.3 – 462.5 (27.39)		100	0.14-0.91	SPE-ID-LC-MS/MS
Male and female Canadian children (1037), age 6-11 from Canadian Health Measures Survey 2007-2009 2007-2009, (Saravanabhavan et al., 2013)	3.3 (GM)	31.3 (GM)	19.9 (GM)			>99	0.2-0.4	UPLC-MS/MS
Male (240) and female (201) Danish children from the Danish Indoor Environment and Children's Health Study, age 3-6 2008-2009, (Langer et al., 2014)	(4.7)	(33.2)	(17.6)	(34.5)		84.4-100	n.r.	LC-ESI-MS/MS
Egyptian premenstrual females (57) from rural (29) and urban (28) Gharbiah province, age 10-13 (spot urine) 2009, (Colacino et al., 2011)	*Urban:* 0.9 - 26.8 (4.7) *Rural:* 0.85 - 24.8 (3.5)	*Urban:* 1.1 - 263 (29.1) *Rural:* 2.6 - 104 (23.0)	*Urban:* 0.5 - 173 (18.8) *Rural:* 1.0 - 107 (16.0)	*Urban:* 4.1 - 492 (58.0) *Rural:* 9.5 - 398 (60.9)		n.r.	0.2 - 1.2	HPLC-ESI-MS/MS
Danish children (143) from urban and rural area, age 6-11 (first morning urine) 2011, (Frederiksen et al., 2013)	<LOD – 222 (2.0)	2.1 – 347 (23)	0.86 – 258 (12)	2.1 – 550 (15)		92-100	0.14-0.91	SPE-LC-MS/MS

Abbreviations: DEHP, bis(2-ethylhexyl) phthalate; DR, detection rate; ESI, electrospray ionization; GerES IV, German Environmental Survey of Children IV; GM, geometric mean; HPLC, high-performance liquid chromatography; ID, isotope dilution; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantification; max, maximum; MEHP, mono-(2-ethylhexyl) phthalate; MS, mass spectrometry; n, sample size; n.r., not reported; PG, palpable gynaecomastia; SPE, solid phase extraction; UPLC, ultra-performance liquid chromatography; 2cx-MMHP, Mono(2-carboxymethyl-hexyl) phthalate; 5cx-MEPP, mono-(2-ethyl-5-carboxypentyl) phthalate; 5OH-MEHP, mono-(2-ethyl-5-hydroxyl) phthalate; 5oxo-MEHP, mono-(2-ethyl-5-oxohexyl) phthalate.

DnBP metabolite

Table 136. Urinary MnBP concentrations [µg/l] (usually range and median) in adults and children published in several studies (sample collection between 1988 and 2011)

Population (n) Sampling year(s), (Reference)	MnBP range (median)	DR [%]	LOD	Method
ADULTS				
German students (634), age 20-29, females (326) and males (308) (24h-urine) 1988-2003, (Wittassek et al., 2007b)	7.2-2090 (112.0)	100	1.0	LC/LC-MS/MS
U.S.-American pregnant women (319), age 18-35, during the 3rd trimester of pregnancy (spot urine) 1999-2006, (Whyatt et al., 2012)	0.2 – 785 38.0 (GM)	100	0.4 - 1.1	Online HPLC-MS/MS
Taiwanese pregnant women (100) from Central Taiwan, age 25-35, during 3rd trimester of pregnancy 2001-2002, (Lin et al., 2011)	1.41 – 928 (52.39)	100	n.r.	LC-MS/MS
Japanese pregnant women (111), age 33±4 (mean±SD), during the 9th and 40th week of gestation (spot urine) n.r., (Suzuki et al., 2012)	(46.6)	100	0.157	HPLC-MS/MS
French pregnant women (279) from ELFE pilot study 2007, (Zeman et al. 2013)	1.5-912.1 (35.7)	100	LOQ = 2	LC-MS/MS
Male and female Canadian subjects (1208), age 20-49 from Canadian Health Measures Survey 2007-2009 2007-2009, (Saravanabhavan et al., 2013)	20.5 (GM)	>99	0.2	UPLC-MS/MS
Italian males (74) and females (83), age 29-47 n.r., (Tranfo et al., 2013)	Females: (32.5) Males: (41.2)	99	0.8	HPLC-MS/MS
Danish women (145) from urban and rural area, age 31-52 (first morning urine) 2011, (Frederiksen et al., 2013)	1.9-180 (20)	100	1.43	SPE-LC-MS/MS
CHILDREN				
U.S.-American young girls (90), age 6-9 2004-2005, (Wolff et al., 2007)	0.3-363.0 (37.4)	97.8	0.4	HPLC-MS/MS
German children (599), age 3-14 from GerES IV (first morning urine) 2003-2006, (Becker et al., 2009)	1090, max (93.4)	100	1.0	LC/LC-MS/MS
Danish healthy girls (725) from Greater Copenhagen area, Denmark, age 5.6-19.1 (first morning urine) 2006-2008, (Frederiksen et al., 2012)	1.5 - 571 (51)	100	1.4	SPE-ID-LC-MS/MS
Male (240) and female (201) Danish children from the Danish Indoor Environment and Children's Health Study, age 3-6 2008-2009, (Langer et al., 2014)	(80.1)	100	n.r.	LC-ESI-MS/MS
Danish healthy boys (555) from Greater Copenhagen area, Denmark, age 6.07-19.83, with (38) and without (517) palpable gynaecomastia (PG) (first morning urine) 2006-2008, (Mieritz et al., 2012)	*With PG:* 6.78 - 110 (44.28) *Without PG:* 5.68 - 569 (45.14)	100	1.4	SPE-ID-LC-MS/MS
Male and female Canadian children (1037), age 6-11 from Canadian Health Measures Survey 2007-2009 2007-2009, (Saravanabhavan et al., 2013)	33.1 (GM)	>99	0.2	UPLC-MS/MS
Egyptian premenstrual females (57) from rural (29) and urban (28) Gharbiah province, age 10-13 (spot urine) 2009, (Colacino et al., 2011)	*Urban:* 5.0-375.0 (53.3) *Rural:* 3.5-809.0 (47.5)	100	n.r.	HPLC-ESI-MS/MS
Danish children (143) from urban and rural area, age 6-11 (first morning urine) 2011, (Frederiksen et al., 2013)	5.3-144.0 (32.0)	100	1.43	SPE-LC-MS/MS

Abbreviations: DR, detection rate; ELFE, Étude Longitudinale Francaise depuis l'Enfance; ESI, electrospray ionisation; GerES IV, German Environmental Survey of Children IV; GM, geometric mean; HPLC, high-performance liquid chromatography; ID, isotope dilution; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantitation; max, maximum; MnBP, Mono-n-butyl phthalate; MS, mass spectrometry; n, sample size; n.r., not reported; PG, palpable gynaecomastia; SD, standard deviation; SPE, solid phase extraction; UPLC, ultra-performance liquid chromatography.

DiBP metabolite

Table 137. Urinary MiBP concentrations [µg/l] (usually range and median) in adults published in several studies (sample collection between 1988 and 2011)

Population (n) Sampling year(s), (Reference)	MiBP range (median)	DR [%]	LOD	Method
German students (634), age 20-29, females (326) and males (308) (24h urine) 1988-2003, (Wittassek et al., 2007b)	5.4 - 588 (34.5)	100	1.0	LC/LC-MS/MS
U.S.-American women (382) from New York City, USA during 3rd trimester of pregnancy, age 24±6.2 1998-2002 (Wolff et al., 2008)	<LOD - 131 (6.2)	97.4	0.26	Online HPLC-MS/MS
U.S.-American pregnant women (319), age 18-35, during the 3rd trimester of pregnancy (spot urine) 1999-2006, (Whyatt et al., 2012)	<LOD - 374 9.3 (GM)	99.4	0.3 - 1.0	Online HPLC-MS/MS
Swedish primipara females (38), 2-3 weeks after delivery, age 23-39 2001, (Högberg et al., 2009)	0.52 - 130 (16)	n.r.	1.0	HPLC-ESI-MS/MS
Taiwanese pregnant women (100) from Central Taiwan, age 25-35, during 3rd trimester of pregnancy 2001-2002, (Lin et al., 2011)	1.02 - 269 (10.32)	100	n.r.	LC-MS/MS
Dutch pregnant women (100) from Rotterdam, age 18-41 2002-2006, (Ye et al., 2008)	5.3 - 759 (42.1)	100	1.0	HPLC-MS/MS
U.S.-American subjects (2697), 47.6% males and 52.4% females, age 6-85, as part of NHANES 2003/2004 2003-2004, (Colacino, Harris and Schlecter, 2010)	0.2 - 359 (4.9)	>60	0.26	HPLC-MS/MS
US-American pregnant females (137) before and during pregnancy, age 18-45 (spot urine) 2004-2009, (Braun et al., 2012)	*Before pregnancy:* 8.7 (GM) *During pregnancy:* 9.5 (GM)	n.r.	0.1 - 1	Online HPLC-MS/MS
German subjects (50) from Munich and nearby rural and suburban areas, males (23) and females (27), age 14-60 (morning urine) 2005, (Fromme et al., 2007)	*Females:* 15.7 - 163.8 (36.1) *Males:* 23.1 - 119.7 (36.1)	100	1.0	LC/LC-MS/MS
Israeli pregnant women (19) from Jerusalem, age 24-41 2006, (Berman et al., 2009)	<LOD - 69.6 (15.6)	95	0.3	HPLC-ESI-MS/MS
French pregnant women (279) from ELFE pilot study 2007, (Zeman et al. 2013)	5.5 - 932.5 (53.7)	99.3	LOQ = 2	LC-MS/MS
Chinese subjects (183) from 3 cities in china: Guangzhou (110), Shanghai (24) and Quiqihaer (49), males (84) and females (99), age <10 - >40 (spot urine) 2010, (Guo, Wu and Kannan, 2011)	*Females:* n.d. - 791 (51.7) *Males:* n.d. - 664 (70.2)	100	0.1	HPLC-ESI-MS/MS
Danish women (145) from urban and rural area, age 31-52 (first morning urine) 2011, (Frederiksen et al., 2013)	3.7-321 (36)	100	1.1	SPE-LC-MS/MS

Abbreviations: DR, detection rate; ELFE, Étude Longitudinale Francaise depuis l'Enfance; ESI, electrospray ionization; GM, geometric mean; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantification; MiBP, Mono-iso-butyl phthalate; MS, mass spectrometry; n, sample size; NANHES, National Health and Nutrition Examination Survey; n.d., not detected; n.r., not reported; SPE, solid phase extraction.

Table 138. Urinary MiBP concentrations [µg/l] (usually range and median) in children published in several studies (sample collection between 2003 and 2011)

Population (n) Sampling year(s), (Reference)	MiBP range (median)	DR [%]	LOD	Method
German children (599), age 3-14 from GerES IV (first morning urine) 2003-2006, (Becker et al., 2009)	2050, max (88.1)	100	1.0	LC/LC-MS/MS
U.S.-American young girls (90), age 6-9 2004-2005, (Wolff et al., 2007)	0.2 - 144.0 (7.7)	96.7	0.26	HPLC-MS/MS
U.S.-American children (379) from New York City, age 6-8, males (80) and females (299) (spot urine) 2004-2008, (Teitelbaum et al., 2012)	*Females:* (16.8) *Males:* (22.0)	>97%	n.r.	Online HPLC-MS/MS
Danish healthy girls (725) from Greater Copenhagen area, Denmark, age 5.6-19.1 (first morning urine) 2006-2008, (Frederiksen et al., 2012)	4.0 - 1909 (81)	100	1.1	SPE-ID-LC-MS/MS
Danish healthy boys (555) from Greater Copenhagen area, Denmark, age 6.07-19.83, with (38) and without (517) palpable gynaecomastia (PG) (first morning urine) 2006-2008, (Mieritz et al., 2012)	*With PG:* 13.23 - 196.1 (68.5) *Without PG:* 7.46 - 5684 (74.88)	100	1.1	SPE-ID-LC-MS/MS
Male (240) and female (201) Danish children from the Danish Indoor Environment and Children's Health Study, age 3-6 2008-2009, (Langer et al., 2014)	(72.2)	100	n.r.	LC-ESI-MS/MS
Egyptian premenstrual females (57) from rural (29) and urban (28) Gharbiah province, age 10-13 (spot urine) 2009, (Colacino et al., 2011)	*Urban:* 0.7 - 184 (25.4) *Rural:* 1.1 - 258 (17.6)	n.r.	0.2 - 1.2	HPLC-ESI-MS/MS
Chinese subjects (183) from 3 cities in china: Guangzhou (110), Shanghai (24) and Quiqihaer (49), males (84) and females (99), age <10 - >40 (spot urine) 2010, (Guo, Wu and Kannan, 2011)	*Females:* n.d. - 791 (51.7) *Males:* n.d. - 664 (70.2)	100	0.1	HPLC-ESI-MS/MS
Danish children (143) from urban and rural area, age 6-11 (first morning urine) 2011, (Frederiksen et al., 2013)	8.7-598 (54)	100	1.1	SPE-LC-MS/MS

Abbreviations: DR, detection rate; ESI, electrospray ionization; GerES IV, German Environmental Survey for Children IV; ID, isotope ionization; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LOD, limit of detection; max, maximum; MiBP, Mono-iso-butyl phthalate; MS, mass spectrometry; n, sample size; n.d., not detected; n.r., not reported; PG, palpable gynaecomastia; SPE, solid phase extraction.

BBzP metabolite

Table 139. Urinary MBzP concentrations [µg/l] (usually range and median) in children published in several studies (sample collection between 2003 and 2011)

Population (n) Sampling year(s), (Reference)	MBzP range (median)	DR [%]	LOD	Method
German children (599), age 3-14 as part of GerES IV (first morning urine) 2003-2006, (Becker et al., 2009)	468 (max) (18.1)		LOQ = 0.25	LC/LC-MS/MS
U.S.-American young girls (90), age 6-9 2004-2005, (Wolff et al., 2007)	0.1 - 191 (22.2)	98.9	0.11	HPLC-MS/MS
U.S.-American children (379) from New York City, age 6-8, males (80) and females (299) (spot urine) 2004-2008, (Teitelbaum et al., 2012)	*Females:* (28.4) *Males:* (53.8)	>97	n.r.	Online HPLC-MS/MS
Danish healthy girls (725) from Greater Copenhagen area, Denmark, age 5.6-19.1 (first morning urine) 2006-2008, (Frederiksen et al., 2012)	1.7 - 825 (48)	100	1.1	SPE-ID-LC-MS/MS
Danish healthy boys (555) from Greater Copenhagen area, Denmark, age 6.07-19.83, with (38) and without (517) palpable gynaecomastia (PG) (first morning urine) 2006-2008, (Mieritz et al., 2012)	*With PG:* 10.77 – 346.2 (56.79) *Without PG:* 2.99 - 2863 (47.7)	100	1.1	SPE-ID-LC-MS/MS
Male (240) and female (201) Danish children from the Danish Indoor Environment and Children's Health Study, age 3-6 2008-2009, (Langer et al., 2014)	(13.0)	98	n.r.	LC-ESI-MS/MS
Egyptian premenstrual females (57) from rural (29) and urban (28) Gharbiah province, age 10-13 (spot urine) 2009, (Colacino et al., 2011)	*Urban:* 0.2 - 28.1 (2.2) *Rural:* 0.2 - 16.7 (0.4)	n.r.	0.2 - 1.2	HPLC-ESI-MS/MS
German subjects (85) from Erlangen, males (32) and females (53), age 7-64 (first morning urine) 2002, (Koch et al., 2003)	1.2 - 268 (21)	100	LOQ = 0.5	LC/LC-MS/MS
Male and female Canadian children (1037), age 6-11 from Canadian Health Measures Survey 2007-2009 2007-2009, (Saravanabhavan et al., 2013)	21.1 (GM)	>99	0.2	UPLC-MS/MS
Danish children (143) from urban and rural area, age 6-11 (first morning urine) 2011, (Frederiksen et al., 2013)	<LOD-104 (7.0)	97	1.14	SPE-LC-MS/MS

Abbreviations: DR, detection rate; ESI, electrospray ionisation; GerES IV, German Environmental Survey of Children IV; GM, geometric mean; HPLC, high-performance liquid chromatography; ID, isotope dilution; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantitation; max, maximum; MBzP, Mono-benzyl phthalate; MS, mass spectrometry; n, sample size; n.r., not reported; PG, palpable gynaecomastia; SPE, solid phase extraction; UPLC, ultra-performance liquid chromatography.

Table 140. Urinary MBzP concentrations [µg/l] (usually range and median) in adults published in several studies (sample collection between 1988 and 2011)

Population (n) Sampling year(s), (Reference)	MBzP range (median)	DR [%]	LOD	Method
U.S.-American adults (240), males (100) and females (140), age 20-60, taken from NHANES III (spot urine) 1988-1994, (Hoppin, Ulmer and London, 2004)	*Males:* 1.84 - 1015 *Females:* 1.7 - 338	n.r.	n.r.	HPLC-MS
U.S.-American adults (289), age 20-60, 44% males and 56% females, collected as part of NHANES III 1988-1994, (Blount et al., 2000)	4.2 - 1020 (21.2)	n.r.	0.8	HPLC-MS/MS
German students (634), age 20-29, females (326) and males (308) (24h urine) 1988-2003, (Wittassek et al., 2007b)	<LOQ - 687 (7.4)	99.8	0.25	LC/LC-MS/MS
U.S.-American women (382) from New York City, USA during 3rd trimester of pregnancy, age 24±6.2 1998-2002, (Wolff et al., 2008)	5.6 - 135.2 (31.5)	100	0.8	HPLC-APCI-MS/MS
U.S.-American pregnant women (319), age 18-35, during the 3rd trimester of pregnancy (spot urine) 1999-2006, (Whyatt et al., 2012)	<LOD - 668 (22)	99.4	0.11	Online HPLC-MS/MS
U.S.-American males (338) who are partners of subfertile couples, age 20-54 (spot urine) 2000-2003, (Duty et al., 2005)	<LOD - 1110 19.0 (GM)	99.7	0.1 - 1.0	Online HPLC-MS/MS
Swedish primipara females (38), 2-3 weeks after delivery, age 23-39, 2001, (Högberg et al., 2009)	(6.8) 41.3 (P95)	90	0.47	HPLC-MS/MS
Taiwanese pregnant women (100) from Central Taiwan, age 25-35, during 3rd trimester of pregnancy 2001-2002, (Lin et al., 2011)	2.2 - 38 (13)	n.r.	1.0	HPLC-ESI-MS/MS
German subjects (85) from Erlangen, males (32) and females (53), age 7-64 (first morning urine) 2002, (Koch et al., 2003)	<0.25 – 55 (1.23)	64	n.r.	LC-MS/MS
Dutch pregnant women (100) from Rotterdam, age 18-41 2002-2006, (Ye et al., 2008)	1.2 - 268 (21)	100	LOQ = 0.5	LC/LC-MS/MS
U.S.-American subjects (2697), 47.6% males and 52.4% females, age 6-85, as part of NHANES 2003/2004 2003-2004, (Colacino, Harris and Schlecter, 2010)	1.3 - 320 (7.5)	100	0.25	HPLC-MS/MS
US-American pregnant females (137) before and during pregnancy, age 18-45 (spot urine) 2004-2009, (Braun et al., 2012)	0.1 - 1197 (17.4)	>60	0.11	HPLC-MS/MS
German subjects (50) from Munich and nearby rural and suburban areas, males (23) and females (27), age 14-60 (first morning urine) 2005, (Fromme et al., 2007)	*Before pregnancy:* 5.2 (GM) *During pregnancy:* 5.9 (GM)	n.r.	0.1 - 1	Online HPLC-MS/MS
Israeli pregnant women (19) from Jerusalem, age 24-41 2006, (Berman et al., 2009)	2.6 - 149.6 (8.0)	99	0.25	LC/LC-MS/MS
French pregnant women (139) from ELFE pilot study 2007, (Zeman et al. 2013)	0.5 - 71 (5.3)	100	0.3	HPLC-ESI-MS/MS
Male and female Canadian subjects (1208), age 20-49 from Canadian Health Measures Survey 2007-2009 2007-2009, (Saravanabhavan et al., 2013)	1.3-1177.5 (10.1)	98.6	LOQ = 2	LC-MS/MS
Japanese pregnant women (111), age 33±4 (mean±SD), during the 9th and 40th week of gestation (spot urine) n.r., (Suzuki et al., 2012)	9.4 (GM)	>99	0.2	UPLC-MS/MS
Italian males (74) and females (83), age 29-47 n.r., (Tranfo et al., 2013)	(3.57)	98	0.028	HPLC-MS/MS
Danish women (145) from urban and rural area, age 31-52 (first morning urine) 2011, (Frederiksen et al., 2013)	Females: (4.85) Males: (4.45)	94	0.05	HPLC-MS/MS

Abbreviations: APCI, atmospheric-pressure chemical ionisation; DR, detection rate; ELFE, Étude Longitudinale Francaise depuis l'Enfance; ESI, electrospray ionisation; GM, geometric mean; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantitation; MBzP, Mono-benzyl phthalate; MS, mass spectrometry; n, sample size; NHANES, National Health and Nutrition Examination Survey; n.r., not reported; P95, 95th percentile; SD, standard deviation; SPE; UPLC, ultra-performance liquid chromatography.

DnOP metabolite

Table 141. Urinary MnOP concentrations [µg/l] (usually range and median) in adults and children published in several studies (sample collection between 1988 and 2011)

Population (n) Sampling year(s), (Reference)	MnOP range (median)	DR [%]	LOD	Method
ADULTS				
U.S.-American adults (289), age 20-60, 44% males and 56% females, collected as part of NHANES III 1988-1994, (Blount et al., 2000)	<LOD - 30.5 (<LOD)	n.r.	0.9	HPLC-MS/MS
African-American females (46) from Washington, DC, USA, age 35-49 (first morning urine) 1996-1997, (Hoppin et al., 2002)	0.0 - 173.7 (0.5)	>75	0.9	HPLC-APCI-MS/MS
German subjects (85) from Erlangen, males (32) and females (53), age 7-64 (first morning urine) 2002, (Koch et al., 2003)	<LOQ - 5.9 (<LOQ)	Detected in only a small % of samples	LOQ = 1.0	LC/LC-MS/MS
Dutch pregnant women (100) from Rotterdam, age 18-41 2002-2006, (Ye et al., 2008)	<LOD - 39.1 (<LOD)	2	0.5	HPLC-MS/MS
Chinese subjects (183) from 3 cities in china: Guangzhou (110), Shanghai (24) and Quiqihaer (49), males (84) and females (99), age <10 - >40 (spot urine) 2010, (Guo, Wu and Kannan, 2011)	*Females:* n.d. - 0.6 (n.d.) *Males:* n.d. - 4.6 (n.d.)	100	LOQ = 0.25	HPLC-ESI-MS/MS
Danish women (145) from urban and rural area, age 31-52 (first morning urine) 2011, (Frederiksen et al., 2013)	<LOD-0.3	5	0.15	SPE-LC-MS/MS
CHILDREN				
Danish children (143) from urban and rural area, age 6-11 (first morning urine) 2011, [Frederiksen et al., 2013]	<LOD - 2.1 0.05 (mean)	14	0.15	SPE-LC-MS/MS

Abbreviations: APCI, Atmospheric-pressure chemical ionisation; DR, detection rate; ESI, electrospray ionisation; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantitation; MnOP, Mono-n-ocytl phthalate; MS, mass spectrometry; n, sample size; n.d., not detected; NHANES, National Health and Nutrition Examination Survey; n.r., not reported; SPE, solid-phase extraction.

Table 142. Urinary concentrations of free and/or total BPA [µg/l], and/or creatinine-adjusted BPA [µg/l] (usually range and median) in adults published in several studies (sample collection between 1998 and 2011)

Population (n) Sampling year(s), (Reference)	Free BPA [µg/L] range (median)	Total BPA [µg/L] range (median)	BPA normalized against crea [µg/g] range (median)	DR [%]	LOD [µg/L]	Method
U.S.-American pregnant women (367) from New York City, USA during 3rd trimester of pregnancy, age 24±6 1998-2002, (Wolff et al., 2008)		<LOD-35.2 (1.3)		90.8	0.36	On-line SPE-HPLC-MS/MS
African-American and Dominican pregnant women (198) from New York City, USA during 3rd trimester of pregnancy, age 18-35 (spot urine) 1998-2003, (Perera et al., 2012)		<LOD-30.0 (1.8)		n.r.	0.4	SPE-HPLC-ID-MS/MS
Mexican pregnant females (60) in the 3rd trimester of pregnancy from Mexico City: delivered >37 weeks (30), age 27.3±5.9 and delivered ≤37 weeks (30), age 27.7±6.2 (second morning urine) 2001-2003, (Cantonwine et al., 2010)		0.4-6.7 (0.95)	7.5 (max) (1.4)	80	0.4	On-line SPE-HPLC-ID-MS/MS
Japanese female college students (48) n.r., (Ouchi and Watanabe, 2002)	<LOD-0.2		0.1-11.9 (0.77)	a	0.2	Column-switching HPLC-ECD
Japanese males (4) and female (1), age 22-40 (24-h urine for 5 consecutive days) 2002, (Arakawa et al., 2004)		<0.58-13 µg/d (1.3 µg/d)		100	0.38	GC-MS/MS
Korean males (15), age 42.6±2.4, and females (15), age 43±2.7 from Central South Korea n.r., (Kim et al., 2003)	*Males:* 0.28-2.4 (0.58±0.14, mean±SD) *Females:* 0.07-1.7 (0.56±0.1, mean±SD)	*Males:* 0.85-9.8 *Females:* 1.0-7.6		100	MDL: 0.28	RP-HPLC-FD
Japanese male students (36) from Tokyo, age 24.7±3.9 (24-h urine) 2003, (Arakawa et al., 2004)		<0.21-15.0 µg/d (1.2 µg/d)		100	0.38	GC-MS/MS
Dutch pregnant women (100) from Rotterdam, age 18-41 2003-2006, (Ye et al., 2008)		<LOD-46.0 (1.2)	<LOD-22.7 (1.6)	82	0.26	GC-MS/MS
U.S.-American pregnant women (353) at 26th week of gestation, who lived in a home buit before 1979 from Ohio, USA (spot urine) 2003-2006, (Spanier et al., 2012)			2.2, GM	90.4	0.4	On-line SPE-ID-MS/MS
Chinese males (10) and females (10), age 21-39 (sport urine) n.r., (Mao et al., 2004)		*Males:* <LOD-395 (122±138, mean±SD) *Females:* 3-374 (129±122, mean±SD)		60 100	2.7	HPLC-FD

continued

Population (n) Sampling year(s), (Reference)	**Free BPA [µg/L]** range (median)	**Total BPA [µg/L]** range (median)	**BPA normalized against crea [µg/g]** range (median)	**DR [%]**	**LOD [µg/L]**	**Method**
U.S.-American pregnant women (137) before and during pregnancy, age 18-45 (spot urine) 2004-2009, (Braun et al., 2012)		*before:* 2.5, GM *during:* 2.6, GM		n.r.	0.4	On-line column-switching HPLC-MS/MS
U.S.-American males (194) and females (210) from NHANES III callback cohort, age 20-59 (spot urine) n.r., (Calafat et al., 2005)		(1.28)	(1.32)	95	0.1	SPE-ID-GC/MS
German adults (203), age 18-45, archieved samples (first morning urine) 2005, (Völkel, Kiranoglu and Fromme, 2008)	<LOQ	n.d.		n.r.	0.3 (LOQ: 1.25)	On-line column-switching HPLC-MS/MS
Korean males and females (485) from general communities of large cities 2005, (Yang et al., 2009)			(0.64) 20.2, P95	76	0.063	HPLC-MS/MS
U.S.-American male and female adults (8) from Atlanta, Georgia, age 26-58 (24-h urine) 2005, (Ye et al., 2011)		(2.4)	(3.3)	100	0.4	On-line SPE-ID-HPLC-MS/MS
German females (31), age 18-41) 2005-2008, (Völkel, Kiranoglu and Fromme, 2008)	<LOD-2.5	<LOD-6.5		n.r.	0.3	On-line column-switching HPLC-MS/MS
Austrian healthy adults (12) n.r., (Schöringhumer and Cichna-Markl, 2007)	<LOD-0.8 (0.28, mean)	0.2-5.6 (2.0, mean)	*Free:* <LOD-1.0 *Total:* 0.2-5.4	75 100	0.2-1.2	SGIC-HPLC-FD
Austrian dialysis patients (10) n.r., (Schöringhumer and Cichna-Markl, 2007)	<LOD-0.7 (0.36, mean)	0.4-2.6 (1.3, mean)	*Free:* <LOD-3.0 *Total:* 1.2-8.9	90 100	0.2-1.2	SGIC-HPLC-FD
German adults (21), age 19-52 2007-2008, (Völkel, Kiranoglu and Fromme 2008)	<LOD-1.8	<LOD-3.3		n.r.	0.3	On-line column-switching HPLC-MS/MS
Canadian males and females (5476), age 6-79 (spot midstream urine) 2007-2009, (Bushnik et al., 2010)		1.2, GM	1.4, GM	90.7	0.2	HPLC-MS/MS
U.S.-American male and female college students (77), age 18-23, two weeks[b] n.r., (Carwile et al., 2009)			*Week 1:* 1.2, GM *Week 2:* 2.0, GM	88 96	0.2	On-line SPE-ID-HPLC-MS/MS
Italian male and female adults (720), age 20-74 (24-h urine) n.r., (Galloway et al., 2010)		(3.5)		n.r.	0.5	On-line SPE-HPC-MS/MS
Canadian pregnant women (1936) during 1st trimester of pregnancy, age ≥18 (spot urine) 2008-2011, (Arbuckle et al., 2014)		n.d.-140 (0.82)[c] 5.4, P95		87.7	0.2	GC-MS/MS

continued

Population (n) Sampling year(s), (Reference)	Free BPA [µg/L] range (median)	Total BPA [µg/L] range (median)	BPA normalized against crea [µg/g] range (median)	DR [%]	LOD [µg/L]	Method
U.S.-American male and female adults (10) from 5 different families from Greater San Francisco Bay Area, USA, median age 40.5 (evening urine) 2010, (Rudel et al., 2011)		1.0-11 (4.9)		100	1.0	HPLC-ID-MS/MS
U.S.-American healthy males and females (31) from Albany, New York, age 11-66 (spot urine) 2011, (Liao and Kannan, 2012)	<LOQ-18.7 0.7, GM	0.22-66.2 5.4, GM	*Free:* <LOQ-12.8 *Total: 0.09-40.4*	96.8 100	LOQ: 0.01	SPE-HPLC-MS/MS
Israeli adults (246) from 5 different geographical regions, age 24-74 (spot urine) 2011, (Berman et al., 2014)		0.1-200 (3.0)	0.04-177 (2.3)	100	0.1	GC-MS/MS

[a] detection rates: 2% for unconjugated BPA, 100% for total BPA
[b] Week 1(wash-out phase): consumption of cold beverages from stainless steel containers; Week 2 (intervention phase): consumption of cold beverages from polycarbonate bottles
[c] Kaplan-Meier median

Abbreviations: BPA, Bisphenol A; crea, creatinine; DR, detection rate; ECD, electrochemical detection; FD, fluoremetric detection; GC, gas-chromatography; GM, geometric mean; HPLC, high-performance liquid chromatography; ID, isotope dilution; LOD, limit of detection; LOQ, limit of quantification; max, maximum; MDL, minimum detection limit; MS, mass spectrometry; MS/MS, tandem mass spectrometry; n, sample size; n.d., not detected; n.r., not reported; P95, 95th percentile; RP, reverse phase; SD, standard derivation; SGIC, sol-gel immunoaffinity column; SPE, solid phase extraction; 24-h, 24 hours.

Table 143. Urinary concentrations of free and/or total BPA [µg/l], and/or creatinine-adjusted BPA [µg/l] (usually range and median) in children published in several studies (sample collection between 1998 and 2010)

Population (n) Sampling year(s), (Reference)	Free BPA [µg/L] range (median)	Total BPA [µg/L] range (median)	BPA normalized against crea [µg/g] range (median)	DR [%]	LOD [µg/L]	Method
Children (198) of African-American and Dominican women from New York City, age 3-4 (spot urine) 1998-2003, (Perera et al., 2012)		<LOD-90.8 (3.6)		n.r.	0.4	SPE-HPLC-MS/MS
Japanese male and female (94) from suburb of Tokyo, mean age 11.9 (spot urine) 2003, (Yamano et al., 2010)			0.2-8.5 (0.66)	86	0.5	SPE-ID-HPLC-MS/MS
German male and female (599), age 3-14 (morning urine) 2003-2006, (Becker et al., 2009)		205 (max) (2.7) 14.0, P95		99	0.25	GC-MS/MS
U.S.-American female children (90), age 6-9 2004-2005, (Wolff et al., 2007)		<0.3-54.3 (1.8)	3.0, GM	94.4	0.36	HPLC-MS/MS
German children, age 5-6 2005-2008, (Völkel, Kiranoglu and Fromme, 2008)	<LOD-0.9	<LOD-7.5		n.r.	0.3	On-line SPE-HPLC-MS/MS
U.S.-American male and female children (10) from 5 different families from Greater San Francisco Bay Area, USA, age 3-12 (evening urine) 2010, (Rudel et al., 2011)		1.2-16 (2.6)		100	1.0	HPLC-ID-MS/MS

Abbreviations: BPA, Bisphenol A; crea, creatinine; DR, detection rate; GC, gas-chromatography; GM, geometric mean; HPLC, high-performance liquid chromatography; ID, isotope dilution; limit of detection; max, maximum; MS/MS, tandem mass spectrometry; n, sample size; n.r., not reported; SPE, solid phase extraction.

APPENDIX C – LITERATURE ANALYSIS OF PHTHALATE AND BISPHENOL A LEVELS IN VARIOUS FOODSTUFF

Appendix C.1: PHTHALATES

Table 144. Various phthalate contents [µg/kg] measured in different foodstuffs from selected studies sorted by food groups according to the Food Frequency Questionnaire (FFQ)

Food Group	Sample size	Packaging	DMP [µg/kg] range (mean)	DEP [µg/kg] range (mean)	DiBP [µg/kg] range (mean)	DnBP [µg/kg] range (mean)	BBzP [µg/kg] range (mean)	DEHP [µg/kg] range (mean)	DiNP [µg/kg] range (mean)	DiDP [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
FFQ1 Rice, pasta																
Flour or noodles	6	n.k.	n.d.-5.8 (1.03) (n.d., median)	n.d.-4.86 (1.51) (0.72, median)	5.64-326 (68.7) (19.1, median)	5.94-258 (54.5) (12.2, median)	n.d.-0.56 (0.093) (n.d., median)	n.d.-762 (135) (9.22, median)			LOQ: 2-10	GC-MS	2011	China		[14]
Instant noodles	5	n.k.	1.83-90.8 (22.7) (6.6, median)	n.d.-22.4 (5.6) (1.89, median)	3.74-225 (76.6) (3.92, median)	3.72-76.4 (23.9) (7.17, median)	n.d.-2.07 (0.41) (n.d., median)	n.d.-487 (118) (n.d., median)			LOQ: 2-10	GC-MS	2011	China		[14]
Rice	3	n.k.	n.d.-0.41 (0.18) (0.12, median)	0.02-1.45 (0.77) (0.83, median)	1.82-70.8 (26.3) (6.21, median)	1.48-99 (35.3) (5.53, median)	n.d.-0.64 (0.21) (n.d., median)	14-378 (137) (19.2, median)			LOQ: 2-10	GC-MS	2011	China		[14]
Rice, pasta	n.k.	n.k.	0	0.0-17.0 (0.0)	1.5-158 (21.0)	2.0-360 (10.0)	0.0-25.0 (0.0)	0.0-170 (12.0)			n.k.	n.k.	n.k.	n.k.	a	[1]
FFQ2 Bread, brown																
Bread	n.k.	n.k.	0	0.0-17.4 (6.0)	0.0-232.0 (60.0)	7.0-5130 (32.0)	0.0-440.0 (0.0)	26.1-1960 (68.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
	1	n.k.		-	17.0	16.0	8.0	125			1.7-6.1	GC-MS	2007	UK	b	[11]
FFQ3 Bread, white																
No data available																
FFQ4 Bread, wholemeal																
No data available																
FFQ5 Potatoes																
	n.k.	n.k.	0	0.0-9.0 (9.0)	0.0-5.0 (5.0)	0	0	0.0-80.0 (76.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
	n.k.	n.k.		-	-	-	-	-			1.7-6.1	GC-MS	2007	UK	b	[11]

continued

Food Group	Sample size	Packaging	DMP [µg/kg] range (mean)	DEP [µg/kg] range (mean)	DiBP [µg/kg] range (mean)	DnBP [µg/kg] range (mean)	BBzP [µg/kg] range (mean)	DEHP [µg/kg] range (mean)	DiNP [µg/kg] range (mean)	DiDP [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
FFQ6 Vegetables																
Vegetables	n.k.	n.k.	0	0.0-6.67 (6.67)	0	0.0-30.0 (30.0)	0	0.0-140 (140)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
Vegetables, green	n.k.	n.k.		52.0	-	-	-	-			1.7-6.1	GC-MS	2007	UK	b	[11]
Vegetables (except green vegetables)	n.k.	n.k.		-	9.0	4.0	-	35.0			1.7-6.1	GC-MS	2007	UK	b	[11]
Fruits and vegetables	27	n.k.	n.d.-4.6 (n.d., median)	n.d.-2.0 (n.d., median)	n.d.-13.0 (1, median)	n.d.-17.0 (1.7, median)	n.d.-26.0 (n.d., median)	n.d.-1413 (n.d., median)			LOQ: 0,2-145	GC-EI-MS	2009-2010	Belgium		[13]
FFQ7 Fruits, fresh																
Fruits	n.k.	n.k.	0	0	8.0-52.0 (30.0)	16.0-50.0 (28.0)	0	30.0-120 (69.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
Fruits, fresh	n.k.	n.k.		-	-	-	-	-			1.7-6.1	GC-MS	2007	UK	b	[11]
FFQ8 Compote, fruit pulp																
No data available																
FFQ9 Milk and milk drinks																
Milk or milk beverage	10	n.k.	0.17-25.0 (6.18) (2.92, median)	0.066-1.3 (0.5) (0.41, median)	1.18-38.9 (11.9) (8.24, median)	2.38-266 (41.2) (14.0, median)	n.d.-0.23 (0.044) (n.d., median)	n.d.-88.3 (28.5) (19.2, median)			LOQ: 2-10	GC-MS	2011	China		[14]
Milk, raw	18	n.k.				<LOD (=9.0)	<LOD (=4.0)	7.0-30.0	<LOD (=5.0)	<LOD (=5.0)		LC-ESI-MS/MS	EU	n.k.	c	[2]
Milk, pasteurised	4	u.k.				<LOD (=9.0)	<LOD (=4.0)	13.0 – 27.0	<LOD (=5.0)	<LOD (=5.0)		LC-ESI-MS/MS	EU	n.k.	c	[2]
UHT-milk	2	Tetra Brik	1.3-1.75	36.5-72.0		7.3-9.49	1.11-2.93	15.1-24.7			0.06-0.36	GC-MS	Probably Spain	n.k.	c	[3]
	3	Tetra Brik					10.0 – 20.0 (16.7)	n.n. – 40.0 (16.7)			u.k.	GC-MS	Germany	n.k.	d	[4]
Milk, in-bottle-sterilized	2	HDPE	0.97-1.19 (1.08)	70.9-85.3 (78.1)		40.6-50.3 (45.45)	1.23-2.88 (2.055)	23.2-27.2 (25.2)			0.06-0.36	GC-MS	Probably Spain	n.k.	c	[3]
Milk	1	Tetra Brik				n.n.		30.0			n.k.	GC-MS	Germany	n.k.	d	[4]
	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	<LOD (=10)	<LOD (=1)	<LOD (=20)	<LOD (=20)	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
	n.k.	n.k.	0.0-28.0 (0.0)	0.0-10.0 (0.0)	0.0-16.0 (0.0)	0.0-30.0 (15.0)	0	8.5-170.0 (40.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
	n.k.	n.k.		-	-	-	-	-			1.7-6.1	GC-MS	2007	UK	b	[11]
	2	Plastic	0.1	0.2		0.2	1.5	0.6	48.6		0.2-3.7	GC-MS	2011	USA		[12]

continued

Food Group	Sample size	Packaging	DMP [µg/kg] range (mean)	DEP [µg/kg] range (mean)	DiBP [µg/kg] range (mean)	DnBP [µg/kg] range (mean)	BBzP [µg/kg] range (mean)	DEHP [µg/kg] range (mean)	DiNP [µg/kg] range (mean)	DiDP [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
FFQ10 Meat (beef, pork)																
Meat, fresh	3	n.k.	0.36-2.54 (1.2) (0.71, median)	0.67-2.33 (1.72) (2.17, median)	0.37-42.6 (17.9) (10.8, median)	0.73-13.2 (6.91) (6.84, median)	-	36.8-184 (108) (104, median)			LOQ: 2.0-10.0	GC-MS	2011	China		[14]
Meat and meat products	22	n.k.	n.d.-25 (2, median)	n.d.-1.4 (n.d., median)	n.d.-9.7 (2, median)	n.d.-15 (1.5, median)	n.d.-18 (n.d., median)	10-433 (44.5, median)			LOQ: 5.0-145 (high-fat food); 0.2-8.0 (low-fat food)	GC-EI-MS	2009-2010	Belgium		[13]
	n.k.	n.k.	0	0.0-17.6 (0.0)	0.0-53.0 (7.0)	24.0-110.0 (75.0)	0.0-72.0 (0.0)	24.8-760.0 (207.0)	0.0-11.0 (0.0)		n.k.	n.k.	n.k.	n.k.	a	[1]
Pork	4	see notes	(0.33)	(0.55)	(6.3)	(0.7)	(0.23)	(300)			0.2-3.7	GC-MS	2011	USA	e	[12]
Beef	2	see notes	(0.18)	(0.64)	(0.1)	(0.7)	(0.61)	(1.85)			0.2-3.7	GC-MS	2011	USA	f	[12]
Steak	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	<LOD (=10)	<LOD (=1)	<LOD (=20)	<LOD (=20)	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
FFQ11 Poultry																
Poultry	n.k.	n.k.	0	0.0-10.0 (5.0)	0.0-60.0 (30.0)	0.0-200.0 (100.0)	0.0-30.0 (15.0)	285-700 (285)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
	1	n.k.		-	-	-	-	322			1.7-6.1	GC-MS	2007	UK	b	[11]
	6	see notes	(0.15)	(0.41)	(0.1)	(0.7)	(0.66)	(18.6)			0.2-3.7	GC-MS	2011	USA	g	[12]
Chicken	1	n.k.	4.9	24.0	2300	760	11.0	670	390	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
FFQ12 Sausages, cold meat																
Sausages	2	n.k.	n.d.-1.25 (0.62)	0.74-2.43 (1.58)	4.68-12.8 (8.72)	6.99-14.6 (10.8)	n.d.-2.26 (1.13)	82.3-98.3 (90.3)			LOQ: 2-10	GC-MS	2011	China		[14]
	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	<LOD (=10)	<LOD (=1)	640	<LOD (=20)	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
	n.k.	n.k.	0	0	0.0-27.0 (0.0)	1.0-170.0 (4.0)	0.0-5.0 (0.0)	38.0-750.0 (64.0)	0.0-7.0 (0.0)		n.k.	n.k.	n.k.	n.k.	a	[1]
Meat products	1	n.k.		40.0	18.0	15.0	-	329.0			1.7-6.1	GC-MS	2007	UK	b	[11]
Bacon	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	<LOD (=10)	2.0	1320	<LOD (=20)	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
Ham	1	n.k.	1.1	<LOD (=1)	400	260	17.0	3300	230	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
FFQ13 Fish																
Fish	5	see notes	(0.21)	(0.6)	(1.0)	(11.0)	(1.6)	(31.7)			0.2-3.7	GC-MS	2011	USA	h	[12]
	1	n.k.		-	18.0	9.0	9.0	789			1.7-6.1	GC-MS	2007	UK	b	[11]

continued

Food Group	Sample size	Packaging	DMP [µg/kg] range (mean)	DEP [µg/kg] range (mean)	DiBP [µg/kg] range (mean)	DnBP [µg/kg] range (mean)	BBzP [µg/kg] range (mean)	DEHP [µg/kg] range (mean)	DiNP [µg/kg] range (mean)	DiDP [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
Fish and fish products	18	n.k.	n.d.-43 (n.d., median)	n.d.-9.3 (0.6, median)	n.d.-13 (n.d., median)	n.d.-12.5 (n.d., median)	n.d.-8 (n.d., median)	n.d.-5932 (86, median)			LOQ: 5.0-145 (high-fat food); 0.2-8.0 (low-fat food)	GC-EI-MS	2009-2010	Belgium		[13]
Fish, seafood	n.k.	n.k.	0.0-16.78 (0.3)	0.0-8.51 (2.54)	0.15-25.0 (1.0)	5.0-380.0 (8.0)	0.0-5.0 (2.0)	2.3-290.0 (13.0)	0.0-35.0 (0.4)		n.k.	n.k.	n.k.	n.k.	a	[1]
FFQ14 Eggs																
	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	<LOD (=10)	<LOD (=1)	<LOD (=20)	<LOD (=20)	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
	n.k.	n.k.	0	0	0.0-100.0 (50.0)	34.0-100.0 (67.0)	10.0-90.0 (50.0)	283.0-600.0 (442.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
FFQ15 Legumes																
No data available																
FFQ16 Almonds, peanuts, nuts																
Almonds, grated	1	Plastic film				570		800			n.k.	GC-MS	Germany	n.k.	d	[4]
Hazelnuts, grated	1	Plastic film				240		80.0			n.k.	GC-MS	Germany	n.k.	d	[4]
Nutmeg, grated	1	Plastic film				120		220			n.k.	GC-MS	Germany	n.k.	d	[4]
Nuts, nut spreads	n.k.	n.k.	0.0-21.0 (0.0)	0.0-23.3 (7.5)	0.0-232 (45.0)	43.0-17460 (218)	0.0-21.0 (0.0)	143-19860 (810)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
Nuts	n.k.	n.k.		-	49.0	28.0	-	112			1.7-6.1	GC-MS	2007	UK	b	[11]
FFQ17 Butter, oil																
Cooking oil	3	n.k.	0.13-3.26 (1.72) 1.76, median)	n.d.-0.018 (0.006) (n.d., median)	3.45-13.3 (7.2) (4.7, median)	4-17.9 (9.4) (6.2, median)	1.66-18 (10.7) (12.5, median)	47.1-70.9 (60.1) (62.4, median)			LOQ: 2-10	GC-MS	2011	China		[14]
Oil and fats	26	n.k.	n.d.-32 (n.d., median)	n.d.-154 (n.d., median)	n.d.-53 (n.d., median)	n.d.-203 (n.d., median)	n.d.-1127 (12.5, median)	n.d.-1827 (101.5, median)			LOQ: 5.0-145 (high-fat food); 0.2-8.0 (low-fat food)	GC-EI-MS	2009-2010	Belgium		[13]
	n.k.	n.k.		-	41.0	16.0	-	106.0			1.7-6.1	GC-MS	2007	UK	b	[11]
Olive oil	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	<LOD (=10)	340	24000	72.0	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]

continued

Food Group	Sample size	Packaging	DMP [µg/kg] range (mean)	DEP [µg/kg] range (mean)	DiBP [µg/kg] range (mean)	DnBP [µg/kg] range (mean)	BBzP [µg/kg] range (mean)	DEHP [µg/kg] range (mean)	DiNP [µg/kg] range (mean)	DiDP [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
Vegetable oils	n.k.	n.k.	0	0.0-9.25 (5.0)	0.0-67.0 (20.0)	0.0-880.0 (0.0)	0.0-357.0 (0.0)	0.0-2080 (404)	0.0-46.0 (0.0)		n.k.	n.k.	n.k.	n.k.	a	[1]
	3	see notes	(1.2)	(0.1)	(3.2)	(3.5)	(154)	(117)			0.2-3.7	GC-MS	2011	USA	i	[12]
Butter	1	n.k.	<LOD (=1)	5.6	<LOD (=10)	132	17.0	770	<LOD (=20)	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
FFQ18 Pastries, akes																
Cookies, cakes	6	n.k.	3.27-58.9 (23.5) (12-9, median)	0.35-1.97 (1.17) (1.32, median)	24.5-142 (71.2) (55.6, median)	13.7-572 (138) (58.0, median)	n.d.-17 (3.75) (1.13, median)	45.7-750 (189) (86.4, median)			LOQ: 2-10	GC-MS	2011	China		[14]
Cakes, buns, puddings	n.k.	n.k.	0	0	0.0-20.0 (7.0)	0.0-420 (130)	0.0-88.0 (28.0)	102-1100 (547)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
Bakeries, snacks	n.k.	n.k.	0	0	48.0-26.0 (154)	0.0-1170 (11.0)	0.0530 (0.0)	9.4-4420 (214)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
FFQ19 Chocolate, sweets																
Candy	3	n.k.	0.23-20.5 (7.59) (2.08, median)	0.31-3.14 (1.51) (1.11, median)	n.d.-76.2 (25.6) (0.5, median)	n.d.-83.3 (27.8) (n.d., median)	n.d.-2.58 (0.86) (n.d., median)	n.d.-172 (57.3) (n.d., median)			LOQ: 2-10	GC-MS	2011	China		[14]
Confectionery	n.k.	n.k.	0	0.0-5.6 (0.0)	0.0-69.0 (12.0)	0.0-7890 (75.0)	0.0-37.0 (0.0)	78.4-640 (278)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
FFQ20 Fruit or vegetable juices																
Orange juice	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	<LOD (=10)	<LOD (=1)	<LOD (=20)	<LOD (=20)	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
Juices	n.k.	n.k.	0	0	0	0.0-20.0 (0.0)	0	0.0-60.0 (20.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
FFQ21 Soft drinks																
	12	n.k.	n.d.-3.51 (0.43) (0.14, median)	n.d.-13.3 (1.15) (0.03, median)	0.0032-3.82 (0.92) (0.56, median)	n.d.-18.5 (2.06) (0.41, median)	n.d.-0.43 (0.069) (n.d., median)	n.d.-73.1 (7.96) (0.8, median)			LOQ: 2-10	GC-MS	2011	China		[14]
	n.k.	n.k.	0	0	0	0.0-190 (5.0)	0.0-1.0 (0.0)	0.0-80.0 (18.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
	9	PET	17.0-166 (60.6)	0.0-10.0 (1.1)		0.0-60.0 (12.9)	0	0.0-136 (17.1)			0.005	GC-IR	n.k.	Probably Croatia	k	[15]
	14	PET	0.0-233 (62.6)	0.0-200 (17.1)		0.0-133 (21.3)	0	0.0-80 (15.9)			0.005	GC-IR	n.k.	Probably Croatia	l	[15]
	5	PET	0.0-3000 (759.8)	0.0-30.0 (8.6)		0.0-25.0 (9.0)	0.0-27.0 (5.4)	18.0-60.0 (36.6)			0.005	GC-IR	n.k.	Probably Croatia	m	[15]

continued

Food Group	Sample size	Packaging	DMP [µg/kg] range (mean)	DEP [µg/kg] range (mean)	DiBP [µg/kg] range (mean)	DnBP [µg/kg] range (mean)	BBzP [µg/kg] range (mean)	DEHP [µg/kg] range (mean)	DiNP [µg/kg] range (mean)	DiDP [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
	8	PET	18-2666 (500.9)	0		0.0-130 (26.8)	0	0.0-50.0 (15.0)			0.005	GC-IR	n.k.	Probably Croatia	n	[15]
FFQ22 Carbonated beverages																
Mineral water	9	PET	0	0.0-1.0 (0.11)		0.0-50.0 (11.3)	0	0.0-50.0 (8.8)			0,005	GC-IR	n.k.	Probably Croatia		[15]
Mineral water	1	Plastic	<LOD	0.04		0.35	0.17				0.15-0.60	GC-MS	n.k.	Probably Portugal	c	[6]
Also see "FFQ21 Soft drinks"																
FFQ23 Tea																
Tea	n.k.	n.k.	0	0	0.0-6.0 (6.0)	0	0	0.0-10.0 (8.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
Tea, green	1	n.k.	0.22	2.96	107	79.3	3.58	452			LOQ: 2-10	GC-MS	2011	China		[14]
FFQ24 Coffee																
Coffee	n.k.	n.k.	0	0	0.0-6.0 (6.0)	0	0	0.0-10.0 (8.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
Coffee powder	1	n.k.	0.29	n.d.	8.49	14.4	n.d.	n.d.			LOQ: 2.0-10.0	GC-MS	2011	China		[14]
FFQ25 Table water / mineral water																
Tab water	1	n.k.	0.04	0.19		0.52	0.06				0.15-0.60	GC-MS	n.k.	Probably Portugal	c	[6]
	1	n.k.		0.16		0.64	0.05	0.06			n.k.	n.k.	n.k.	n.k.	a	[1]
	1	n.k.		0.2		0.38	0.02	0.05			n.k.	n.k.	n.k.	n.k.	a	[1]
Mineral water, bottled	1	Plastic	<LOD	0.04		0.35	0.17				0.15-0.60	GC-MS	n.k.	Probably Portugal	c	[6]
	5	PET	<LOD	<LOD		<LOD-0.059	<LOD	n.q.			0.002-0.004	GC-MS	n.k.	Spain		[7]
Water, PET bottled																
	71	PET	0.06	0.22	0.32	0.23		<LOQ			LOD: 0.01-0.08; LOQ: 0.02-0.1	GC-MS	n.k.	Italy	j	[8]
	9	PET	0	0.0-1.0 (0.11)		0.0-50.0 (11.3)	0	0.0-50.0 (8.8)			0,005	GC-IR	n.k.	Probably Croatia		[15]
Water, PET bottled after 10 weeks storage	5	PET	<LOD-0.003 (0.002)	0.082-0.355 (0.214)		0.02-0.07 (0.046)	<LOD-0.01 (0.002)	<LOD-0.188 (0.0995)			0.002-0.004	GC-MS	n.k.	Spain		[7]
Water, bottled	1	n.k.	n.d.	n.d.	0.011	0.046	n.d.	0.015			LOQ: 2-10	GC-MS	2011	China		[14]

continued

Food Group	Sample size	Packaging	DMP [µg/kg] range (mean)	DEP [µg/kg] range (mean)	DiBP [µg/kg] range (mean)	DnBP [µg/kg] range (mean)	BBzP [µg/kg] range (mean)	DEHP [µg/kg] range (mean)	DiNP [µg/kg] range (mean)	DiDP [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
Water, PE bottled	3	PE	<LOD	<LOD-0.139 (0.073)		<LOD	<LOD	n.q.			0.002-0.004	GC-MS	n.k.	Spain		[7]
Water, PE bottled after 10 weeks storage	3	PE	0.001-0.005 (0.003)	0.132-0.99 (0.432)		0.025-0.072 (0.046)	<LOD	0.103-0.153 (0.196)			0.002-0.004	GC-MS	n.k.	Spain		[7]
Water, bottled	n.k.	n.k.	0	0	0	0	0	0.0-30.0 (12.0)			n.k.	n.k.	n.k.	n.k.	a	[1]
	142	n.k.	0.07	0.17	0.2	0.21		0.02			LOD: 0.01-0.08	GC-MS	n.k.	Italy	j	[8]
	71	Glass	0.02	0.02	0.03	0.04		<LOQ			LOD: 0.01-0.08; LOQ: 0.02-0.1	GC-MS	n.k.	Italy	j	[8]
FFQ26 Alcoholic beverages																
Wine and beer	4	n.k.	0.25-97.0 (26.0) (3.34, median)	0.016-0.33 (0.12) (0.07, median)	0.37-107 (39.8) (26.0, median)	2.03-557 (156) (31.8, median)	-	0.2-7.03 (3.58) (3.56, median)			LOQ: 2-10	GC-MS	2011	China		[14]
Wine	2	Glass, one-piece cork	<ql-0.46 (0.23)	0.74-4.22 (2.48)		0.46-2.21 (1.335)	<ql-4.29 (2.145)	3.69-4.75 (8.44)			0.0048-0.0288	GC-MS	n.k.	Probably USA		[9]
	2	Glass, agglomerated cork	<ql – 0.4 (0.2)	0.73 – 1.05 (0.89)		0.38 – 1.97 (1.175)	<ql	<ql			0.0048-0.0288	GC-MS	n.k.	Probably USA		[9]
	2	Glass, synthetic stoppers	<ql	<ql – 2.95 (1.475)		0.52-1.02 (0.77)	<ql	5.22-7.4 (6.31)			0.0048-0.0288	GC-MS	n.k.	Probably USA		[9]
	n.k.	n.k.	0	0	0	0.0-660 (148)	0.0-2.0 (1.0)	0.0-20.0 (9.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
	2	Carton	<ql	<ql		1.62-2.22 (1.92)	<ql	2.62-3.9 (3.26)			0.0048-0.0288	GC-MS	n.k.	Probably USA		[9]
	2	Bag-in-box	<ql-0.61 (0.305)	<ql-1.78 (0.89)		0.3-5.37 (2.835)	<ql	<ql			0.0048-0.0288	GC-MS	n.k.	Probably USA		[9]
Beer	n.k.	n.k.	0	0	0	0.0-70.0 (23.0)	0	0.0-110 (41.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
Spirits	n.k.	n.k.	0	0	0	0.0-10.0 (0.0)	0.0-10.0 (0.0)	0.0-30.0 (0.0)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
FFQ27 Canned food																
Vegetables	n.k.	Can		-	-	-	-	-			1.7-6.1	GC-MS	2007	UK	b	[11]

continued

Food Group	Sample size	Packaging	DMP [µg/kg] range (mean)	DEP [µg/kg] range (mean)	DiBP [µg/kg] range (mean)	DnBP [µg/kg] range (mean)	BBzP [µg/kg] range (mean)	DEHP [µg/kg] range (mean)	DiNP [µg/kg] range (mean)	DiDP [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
FFQ28 Fast Food, Take Away																
Snacks	28	n.k.	n.d.-6.1 (n.d., median)	n.d.-5.3 (n.d., median)	n.d.-114 (4.3, median)	n.d.-65 (3.2, median)	n.d.-14 (0.6, median)	n.d.-308 (35, median)			LOQ: 0,2-145	GC-EI-MS	2009-2010	Belgium		[13]
FFQ29 French fries																
	No data available															
FFQ30 Microwave popcorn																
	No data available															
FFQ31 Juices in TetraPak																
	No data available															
FFQ32 Beverages in PET																
Water, PET bottled	5	PET	<LOD	<LOD		<LOD-0.059	<LOD	n.q.			0.002-0.004	GC-MS	n.k.	Spain		[7]
	71	PET	0.06	0.22	0.32	0.23		<LOQ			LOD: 0.01-0.08; LOQ: 0.02-0.1	GC-MS	n.k.	Italy	j	[8]
Water, PET bottled after 10 weeks storage	5	PET	<LOD-0.003 (0.002)	0.082-0.355 (0.214)		0.02-0.07 (0.046)	<LOD-0.01 (0.002)	<LOD-0.188 (0.0995)			0.002-0.004	GC-MS	n.k.	Spain		[7]
Soft drinks	9	PET	17.0-166 (60.6)	0.0-10.0 (1.1)		0.0-60.0 (12.9)	0	0.0-136 (17.1)			0.005	GC-IR	n.k.	Probably Croatia	k	[15]
Soft drinks	14	PET	0.0-233 (62.6)	0.0-200 (17.1)		0.0-133 (21.3)	0	0.0-80 (15.9)			0.005	GC-IR	n.k.	Probably Croatia	l	[15]
Soft drinks	5	PET	0.0-3000 (759.8)	0.0-30.0 (8.6)		0.0-25.0 (9.0)	0.0-27.0 (5.4)	18.0-60.0 (36.6)			0.005	GC-IR	n.k.	Probably Croatia	m	[15]
Soft drinks	8	PET	18-2666 (500.9)	0		0.0-130 (26.8)	0	0.0-50.0 (15.0)			0.005	GC-IR	n.k.	Probably Croatia	n	[15]
Mineral water	9	PET	0	0.0-1.0 (0.11)		0.0-50.0 (11.3)	0	0.0-50.0 (8.8)			0,005	GC-IR	n.k.	Probably Croatia		[15]
FFQ33 Beverages in plastic cups for Take Away																
	No data available															
OHTERS																
Offal	1	n.k.		-	6.0	-	-	-			1.7-6.1	GC-MS	2007	UK	b	[11]
Cereals	47	n.k.	n.d.-1.4 (n.d., median)	n.d.-558 (0.5, median)	n.d.-1054 (8.7, median)	n.d.-61 (4.6, median)	n.d.-14 (1.5, median)	n.d.-1073 (63, median)			LOQ: 0.2-145	GC-EI-MS	2009-2010	Belgium		[13]
	1	n.k.		13.0	81.0	14.0	-	105			1.7-6.1	GC-MS	2007	UK	b	[11]

continued

Food Group	Sample size	Packaging	DMP [µg/kg] range (mean)	DEP [µg/kg] range (mean)	DiBP [µg/kg] range (mean)	DnBP [µg/kg] range (mean)	BBzP [µg/kg] range (mean)	DEHP [µg/kg] range (mean)	DiNP [µg/kg] range (mean)	DiDP [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
Cottage Cheese	1	n.k.	<LOD (=1)	<LOD (=1)	1500	780	25	890	660	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
Hard Cheese	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	<LOD (=10)	<LOD (=1)	<LOD (=20)	<LOD (=20)	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
Cheese	1	n.k.	6.82	1.92	59.1	39.6	1.49	134			LOQ: 2.0-10.0	GC-MS	2011	China		[14]
	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	<LOD (=10)	21	910	31	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
	1	n.k.	<LOD (=1)	<LOD (=1)	<LOD (=10)	76	32	3000	26	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
	1	n.k.	<LOD (=1)	<LOD (=1)	4400	190	50	210	59	<LOD (=20)	1.0-20.0	GC-MS	n.k.	UK		[5]
	n.k.	n.k.	0	0.0-7.0 (2.33)	0	0.0-300 (56.0)	0.0-39.0 (14.0)	41.0-1230 (496)	0		n.k.	n.k.	n.k.	n.k.	a	[1]
Yoghurt	3	n.k.				<LOD (=9)	<LOD (=4)	15.0-37.0	<LOD (=5)	<LOD (=5)		LC-ESI-MS/MS	EU	n.k.	c	[2]
	n.k.	n.k.	0-35 (11.7)	0	0	0	0	0-90 (51)			n.k.	n.k.	n.k.	n.k.	a	[1]
Beverages, bottled in plastic	8	plastic		n.d.	0.3 (mean)	0.7 (mean)	0.1 (mean)	3.9 (mean)			0.2-3.7	GC-MS	2011	Albany, New York State, USA		[12]
	8	plastic				5.8-105.3 (45.9)		3.3-36.3 (18.5)			2.0-5.0	GC-MS	n.k.	Probably Japan	c	[10]

Abbreviations: EI, ESI, electrospray ionization; EU, European Union; GS, gas chromatography; HDPE, high-density polyethylene; IR, infrared spectrometry; LOD, limit of detection; LOQ, limit of quantitation; MS, mass spectrometry; n.d., not detected; n.k., not known; n.q., not quantitated; PE, polyethylene; PET, polyethylene terephthalate; UK, United Kingdom; *References:* [1] Wormuth et al., 2006; [2] Sørensen, 2006; [3] Casajuana and Lacorte, 2004; [4] Bruns-Weller and Pfordt, 2000; [5] Peters, 2006; [6] Serôdio and Nogueira, 2006; [7] Casajuana and Lacorte, 2003; [8] Montuori et al., 2008; [9] Carrillo, Martínez and Tena, 2008; [10] Kato, Yoshimura and Nakazawa, 2002; [11] Bradley et al., 2013; [12] Schecter et al., 2013; [13] Fierens et al., 2012; [14] Guo et al., 2012; [15] Bošnir et al., 2007; *Notes:* a, Meta analysis; b, from 20 collected composite food samples; c, measurements for analytical method development; d, investigation of the Staatl. Lebensmitteluntersuchungsamt Oldenberg (Germany); e, pork bacon (packed in plastic and paper), ham (packed in plastic), sausage links and pork (packed in foam tray and plastic wrap); f, ground beef (packed in plastic and paper), beef (packed in foam try with a pad an plastic wrap); g, turkey bacon (packed in plastic and paper), turkey breast and chicken franks (packed in plastic), groud turkey, groud chicken, chicken drumsticks (packed in foam tray and plastic wrap); h, salmon fillet (packed in foam tray and plastic wrap), tuna and raw shrimp (packed in paper), chopped clams and sardines (packed in metal); I, virgin olive oil (in glass), canola oil and vegetable oil (packed in plastic); j, samples are from 16 different Italian regions; k, soft drinks preserved with orthophosphoric acid; l, soft drinks preserved with Na-benzoate; m, soft drinks preserved with K-sorbate; n, soft drinks preserved with Na-benzoate and K-sorbate.

Appendix C.2: BISPHENOL A

Table 145. Various BPA content [µg/kg] measured in different foodstuffs from selected studies sorted by food groups according to the Food Frequency Questionnaire (FFQ)

Food group	Sample size	Packaging	BPA [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
FFQ1 Rice, pasta									
Rice	1	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
Pasta	2	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
FFQ2 Bread, brown									
	1	n.r.	1.73	0.38	SPE-GC-MS	2008	Canada	a	[1]
FFQ3 Bread, white									
	1	n.r.	0.4	0.38	SPE-GC-MS	2008	Canada	a	[1]
FFQ4 Bread, wholemeal									
	No data available								
FFQ5 Potatoes									
peeled and boiled	1	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
baked with skin	1	n.r.	0.82	0.38	SPE-GC-MS	2008	Canada	a	[1]
canned	1	Can	48.0	2.0	GC-MS	2000	Belgium		[2]
FFQ6 Vegetables									
	16	n.r.	n.d.-1.17 (n.d.)	0.38	SPE-GC-MS	2008	Canada	a, m	[1]
	45	Can, glass, paper, plastic	n.d.-146 (9.0)	LOQ= 0.01	HPLC-MS/MS	2008, 2011, 2012	USA	l	[17]
	6	Glass	19.2-399	n.r.	HPLC-PAD	n.r.	Turkey	Mushroom	[18]
FFQ7 Fruits									
	12	n.r.	n.d.-0.57 (n.d.)	0.38	SPE-GC-MS	2008	Canada	a	[1]
	20	Can, glass, plastic	n.d.-6.5 (0.53)	LOQ= 0.01	HPLC-MS/MS	2008, 2011, 2012	USA	k	[17]
FFQ8 Compote, fruit pulp									
	No data available								
FFQ9 Milk and milk drinks									
Milk	3	n.r.	n.d.	0.2	SPE-GC-MS	2008	Canada	a	[1]
UHT-milk	4	Tetra Pak	0.99-2.64 (1.82)	0.15	SPE-GC-MS	n.r.	Spain		[15]
Milk	4	HDPE	1.17-1.19	0.15	SPE-GC-MS	n.r.	Spain		[15]
	6	Paper box	81.1-156	n.r.	HPLC-PAD	n.r.	Turkey		[18]
FFQ10 Meat (beef, pork)									
Beef	3	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
	1	plastic	0.2	0.2	HPLC-ECD	n.r.	Japan		[16]
Pork	2	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]

continued

Food group	Sample size	Packaging	BPA [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
FFQ11 Poultry									
	3	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
	2	fresh	<LOD-0.35 (<0.28)	0.2	GC-MS	2010	USA		[5]
FFQ12 Sausages, cold meat									
	n.r.	n.r.	0.48	0.38	SPE-GC-MS	2008	Canada	a	[1]
FFQ13 Fish									
Fish, marine	1	fresh	0.48	0.38	SPE-GC-MS	2008	Canada	a	[1]
Fish, fresh water	1	fresh	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
	1	fresh	<LOD	0.2	GC-MS	2010	USA	*Salmon*	[5]
Tuna, fresh	1	plastic	n.d.	0.2	HPLC-ECD	n.r.	Japan		[16]
Fish and seafood	23	Can, plastic	n.d.-47.4 (3.2)	LOQ= 0.01	HPLC-MS/MS	2008, 2011, 2012	USA	*Fish, shrimp, crab, clam*	[17]
FFQ14 Eggs									
	n.r.	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
FFQ15 Legumes									
	2	Can	5.6-23.5 (14.6)	0.38	SPE-GC-MS	2008	Canada	a	[1]
	9	Can	9.0-37.0 (21.4)	2.0	GC-MS	2000	UK, Holland		[2]
	4	Can	<10.0	LOQ< 10	GC-MS	2003-2004	New Zealand, Italy	*Baked beans*	[4]
	3	Can	26.6-65.0 (50.5)	0.2	GC-MS	2010	USA		[5]
	3	Can	26-35 (29)	1.1-7.4	HPLC-FD	n.r.	Germany, Italy	*Beans, lentils* g	[6]
	6	Can	85.1-1859	n.r.	HPLC-PAD	n.r.	Turkey	*Beans*	[18]
FFQ16 Almonds, peanuts, nuts									
	n.r.	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
FFQ17 Butter, oil									
Butter	1	n.r.	0.53	0.38	SPE-GC-MS	2008	Canada	a	[1]
Fat	2	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
Fat and oils	5	Can, glass, plastic	n.d.-7.7 (1.9)	LOQ= 0.01	HPLC-MS/MS	2008, 2011, 2012	USA	*Vegetable, salad, and olive oil*	[17]
FFQ18 Pastries, cakes									
	6	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a, b	[1]
	4	Plastic	1.0-14.0 (3.5, median)	0.2	HPLC-ECD	n.r.	Japan	*Cookies*	[16]
FFQ19 Chocolate, sweets									
	1	Plastic	1.0	0.2	HPLC-ECD	n.r.	Japan	*White chocolate*	[16]
	6	Paper box	36.5-555	n.r.	HPLC-PAD	n.r.	Turkey	*Pudding*	[18]

continued

Food group	Sample size	Packaging	BPA [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
FFQ20 Fruit or vegetable juices									
	2	Can	0.36-0.53 (0.45±0.09)	0.38	SPE-GC-MS	2008	Canada	a	[1]
	6	Can	0.46-0.78 (0.58)	0.2	GC-MS	2010	USA		[5]
	6	Paper box	40.3-82.6 (66.7)	n.r.	HPLC-PAD	n.r.	Turkey		[18]
FFQ21 Soft drinks									
	n.r.	Can	0.32	0.38	SPE-GC-MS	2008	Canada	a	[1]
	9	Can	n.d.	2.0	GC-MS	2000	UK		[2]
	4	Can	<10.0	LOQ< 10	GC-MS	2003-2004	New Zealand		[4]
	4	Can	0.1-0.7	0.1-0.3	HPLC-FD	n.r.	Austria		[6]
	10	PET	<MDL-0.018 (0.002)	MDL= 0.0045	GC-MS	2009	Canada		[7]
	10	Can	0.019-0.21 (0.1)	MDL= 0.0045	GC-MS	2009	Canada		[7]
	10	Glass	0.02-0.21 (0.09)	MDL= 0.0045	GC-MS	2009	Canada		[7]
	22	Can	n.d.-4.0 (0.49)	0.005	GC-MS	n.r.	Portugal		[8]
FFQ22 Carbonated beverages									
Mineral water	See “FFQ25 tab water / mineral water								
Soft drinks	See “FFQ21 Soft drinks”								
FFQ23 Tea									
	1	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
	3	Can	n.d.-14.3	2.0	HPLC-FD	n.r.	Korea		[3]
FFQ24 Coffee									
	n.r.	n.r.	0.22	0.38	SPE-GC-MS	2008	Canada	a	[1]
	5	Can	11.7-136.1 (45.5)	2.0	HPLC-FD	n.r.	Korea		[3]
	15	Can	33-107 (66.2)	LOQ= 10	HPLC-FD	n.r.	Japan	*Decaffeinated instant*	[9]
	15	Can	50-134 (84.0)	LOQ= 10	HPLC-FD	n.r.	Japan	*Non-decaffeinated instant*	[9]
	2	Plastic	0.3-1.0 (0.65)	0.2	HPLC-ECD	n.r.	Japan		[16]
FFQ25 Tab water / mineral water									
	4	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
	17	PC	<MDL-8.8 (1.4)	MDL= 0.5	GC-MS	2008	Canada		[10]
	2	HDPE	<MDL	MDL= 0.5	GC-MS	2008	Canada		[10]
	1	Can	<MDL	MDL= 0.5	GC-MS	2008	France		[10]
	10	Glass	<MDL	MDL= 0.5	GC-MS	2008	Italy, FRA, GER		[10]

continued

Food group	Sample size	Packaging	BPA [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
	20	PET	<MDL	MDL= 0.5	GC-MS	2008	n		[10]
	1	Plastic	n.d.	0.2	HPLC-ECD	n.r.	Japan		[16]
FFQ26 Alcoholic beverages									
Wine	1	Glass	0.74	0.38	SPE-GC-MS	2008	Canada	a	[1]
Beer	5	Can	n.d.-7.0 (<1.4)	2.0	GC-MS	2000	UK		[2]
	1	Can	1.5	0.1	HPLC-FD	n.r.	Austria	g	[6]
	8	Can	0.08-0.54 (0.21)	MDL= 0.0045	GC-MS	2009	Canada		[7]
	8	Glass	<MDL	MDL= 0.0045	GC-MS	2009	Canada		[7]
	8	Can	n.d.-4.7 (1.5)	0.005	GC-MS	n.r.	Portugal		[8]
FFQ27 Canned food									
Vegetables	7	Can	10.0-42.0 (24.7)	2.0	GC-MS	2000	UK, Belgium, Holland, Italy, Canada	d	[2]
	12	Can	n.d.-21.5 (3.1)	3.0	HPLC-FD	n.r.	Korea		[3]
	13	Can	<10.0-24.0 (<16.2)	LOQ< 10	GC-MS	2003-2004	New Zealand, Australia, Italy, Thailand	*Tomatoes, corn, beetroot*	[4]
	3	Can	8.5-28.0 (18.8)	1.9-2.9	HPLC-FD	n.r.	Germany, Italy	*Peas, corn, tomatoes* g	[6]
	15	Can	4.3-92.0 (19.9)	MDL= 0.6	GC-MS	2009	Canada		[11]
	9	Can	<10.0-95.3 (42.5)	LOQ= 10	HPLC-UV	n.r.	Japan, USA, Indonesia, China	*Corn, asparagus mushroom*	[12]
	10	Can	n.d.-76.3 (20.3)	n.r.	HPLC-MS	n.r. (but before1995)	Spain	h	[13]
	12	Can	3.0-78.0 (14.5, median)	0.2	HPLC-ECD	n.r.	Japan	j	[16]
	6	Can	78.2-231	n.r.	HPLC-PAD	n.r.	Turkey	*Corn*	[18]
Fruits	2	Can	1.2-3.24 (2.2)	0.38	SPE-GC-MS	2008	Canada	a	[1]
	9	Can	n.d.-54.6 (8.6)	3.0	HPLC-FD	n.r.	Korea		[3]
	12	Can	<10.0	LOQ< 10	GC-MS	2003-2004	New Zealand, Australia, South Africa, Philippines	*Apricots, peaches, pineapple*	[4]

continued

Food group	Sample size	Packaging	BPA [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
	4	Can	5.0-24 (10.6)	1.2-5.4	HPLC-FD	n.r.	Indonesia, South Africa, Thailand	*Pineapple, peach, lychee, mango* g	[6]
	5	Can	<10	LOQ=10	HPLC-UV	n.r.	China, Australia, Thailand	*Pear, peach, pineapple*	[12]
	3	Can	n.d.	0.2	HPLC-ECD	n.r.	Japan	*Grapes, peach, pineapple*	[16]
Soups	3	Can	22.2-44.4 (31.9)	0.38	SPE-GC-MS	2008	Canada	a	[1]
	15	Can	n.d.-21.0 (5.8)	2.0	GC-MS	2000	UK		[2]
	4	Can	<10.0-20.0 (16.5)	LOQ<10	GC-MS	2003-2004	New Zealand, Australia		[4]
	12	Can	4.5-22.7 (11.1)	0.2	GC-MS	2010	USA		[5]
	4	Can	9.6-37.6 (21.2)	6.3-6.4	HPLC-FD	n.r.	Austria, Thailand	g	[6]
	41	Can	2.0-94.5 (41.5)	MDL=0.6	GC-MS	2009	Canada		[11]
	10	Can	1.0-156 (23.0, median)	0.2	HPLC-ECD	n.r.	Japan		[16]
Fish	1	Can	106	0.38	SPE-GC-MS	2008	Canada	a	[1]
	20	Can	n.d.-44.0 (18.6)	2.0	GC-MS	2000	e	f	[2]
	8	Can	n.d.-117 (43.7)	3.0	HPLC-FD	n.r.	Korea	*Tuna*	[3]
	11	Can	n.d.-125 (39.8)	3.0	HPLC-FD	n.r.	Korea		[3]
	8	Can	<20.0-109 (33.3)	LOQ<10	GC-MS	2003-2004	Canada, Alaska, Thailand	*Salmon, tuna*	[4]
	3	Can	1.7-3.8 (3.0)	0.2	GC-MS	2010	USA	*Tuna*	[5]
	2	Can	2.1-43 (22.6)	0.2-0.4	HPLC-FD	n.r.	Mauritius, Morocco	*Tuna, sardines (in oil)* g	[6]
	15	Can	9.0-534 (137)	MDL=0.6	GC-MS	2009	Canada	*Tuna*	[11]
	5	Can	34.3-105.4	LOQ=7.1	HPLC-FD	2001	Mexico	*Tuna* i	[14]
	4	Can	2.0-23.0 (7.0, median)	0.2	HPLC-ECD	n.r.	Japan	*Tuna*	[16]
	3	Can	1.0-13.0 (3.0 (median)	0.2	HPLC-ECD	n.r.	Japan	*Salmon, mackerel*	[16]
	6	Can	102-551	n.r.	HPLC-PAD	n.r.	Turkey	*Tuna*	[18]
Meat	11	Can	n.d.-51.0 (20.0)	3.0	HPLC-FD	n.r.	Korea		[3]

continued

Food group	Sample size	Packaging	BPA [µg/kg] range (mean)	LOD [µg/kg]	Analytical Method	Collection year	Country	Notes	References
	6	Can	<20.0-98.0 (34.5)	LOQ< 10	GC-MS	2003-2004	New Zealand, Australia, USA		[4]
	2	Can	9.0-10.0 (9.5, median)	0.2	HPLC-ECD	n.r.	Japan	*Beef*	[16]
	2	Can	10.0-20.0 (15.0, median)	0.2	HPLC-ECD	n.r.	Japan	*Pork*	[16]
Poultry	1	Can	4.0	0.2	HPLC-ECD	n.r.	Japan		[16]
FFQ28 Fast Food, Take Away									
	8	n.r.	1.1-10.9 (2.8)	0.38	SPE-GC-MS	2008	Canada	a, c	[1]
	4	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
	2	n.r.	21.0-33.0 (37.5)	2.0	GC-MS	2000	Holland	*Hot dogs*	[2]
FFQ29 French fries									
	1	n.r.	1.1	0.38	SPE-GC-MS	2008	Canada	a	[1]
FFQ30 Microwave popcorn									
	1	n.r.	n.d.	0.38	SPE-GC-MS	2008	Canada	a	[1]
FFQ31 Juices in TetraPak									
	6	Paper box	40.3-82.6 (66.7)	n.r.	HPLC-PAD	n.r.	Turkey		[18]
FFQ32 Beverages in PET									
Soft drinks	10	PET	<MDL-0.018 (0.002)	MDL= 0.0045	GC-MS	2009	Canada		[7]
Mineral water	20	PET	<MDL	MDL= 0.5	GC-MS	2008	n		[10]
FFQ33 Beverages in plastic cup for Take Away									
No data available									

Abbreviations: BPA, Bisphenol A; ECD, electrochemical detection; FD, fluorescence detection; FFQ, Food Frequency Questionnaire; FRA, France; GC, gas chromatography; GER, Germany; HDPE, high-density polyethylene; HPLC, high-performance liquid chromatography; LOD, limit of detection; LOQ, limit of quantitation; MDL, method detection limit; MS, mass spectrometry; n, sample size; n.d., not detected; PAD, photodiode array detector; PC, polycarbonate; PET, polyethylene terephthalate; n.r., not reported; SPE, solid-phase extraction; UV, ultra violet.

References: [1] Cao et al., 2011 ; [2] Goodson, Summerfield and Cooper, 2002; [3] Lim et al., 2009; [4] Thomson and Grounds, 2005; [5] Schlecter et al., 2010; [6] Braunrath et al., 2005; [7] BCS, 2010a; [8] Cunha et al., 2011; [9] Kang and Kondo, 2002; [10] BCS, 2009; [11] BCS, 2010b; [12] Yoshida et al., 2001; [13] Brotons et al., 1995; [14] Munguía-López et al., 2005; [15] Casajuana and Lacorte, 2004; [16] Sajiki et al., 2007; [17] Liao and Kannan, 2013; [18] Sungur, Köroğlu and Özkan, 2014.

Notes: a, food composite samples from a diet study; b, cake, cookies, donuts, croissants, muffins, pie; c, frozen entrees, French fries, hamburger, chickenburger, hot dogs, beef chow mein, prepared and fast food sandwiches; d, sliced carrots in salt water, baby carrots in sugared salt water, chopped tomatoes with garlic, sweetcorn in water; e, Portugal, USA, Seychelles, Canada, South Africa, Thailand, Denmark; f, sardines, red salmon, tuna, pilchards, mackerel; g, from Austrian supermarket; h, peas, artichokes, mixed vegetables, green beans, corn, mushrooms, asparagus, palm hearts, peppers, tomatoes; i; Measurement at different storage times (0-360 days) in epoxy resin can coatings. Reported BPA concentrations in the table are from 90 days storage time; j; beans, corn, asparagus, mushrooms, tomatoes, palm heart, olives; k, apple, pear, pineapple, peach, grape, orange, banana, raisin, yellow melon, mixed fruits; l, broccoli, cabbage, carrot, celery, cucumber, mushroom, onion, potato, green pepper, radish, pumpkin, beans, lettuce, peanut, spinach, mixed vegetables; m, broccoli, carrots, cauliflowers, celery, cucumbers, lettuce, mushrooms, onions, peppers, rutabagas, tomatoes, spinach, asparagus, Brussels sprouts, corn chips; n, Canada, Germany, France, Poland, USA, Italy.

Appendix D: Control charts

Appendix D.1: PHTHALATE ANALYSIS

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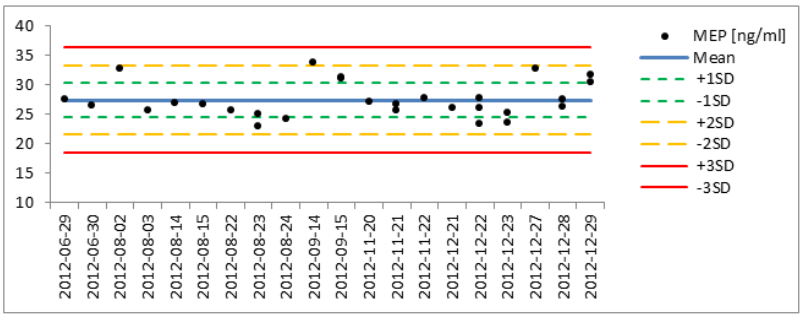

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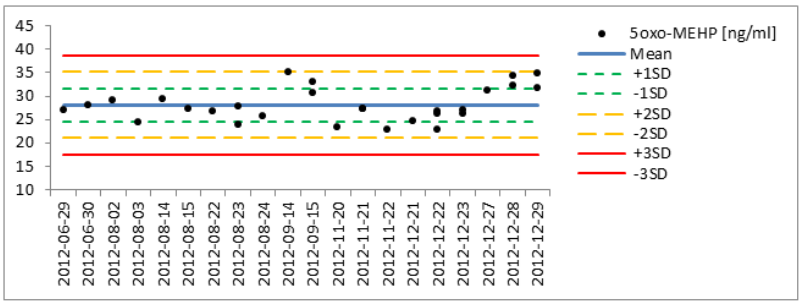

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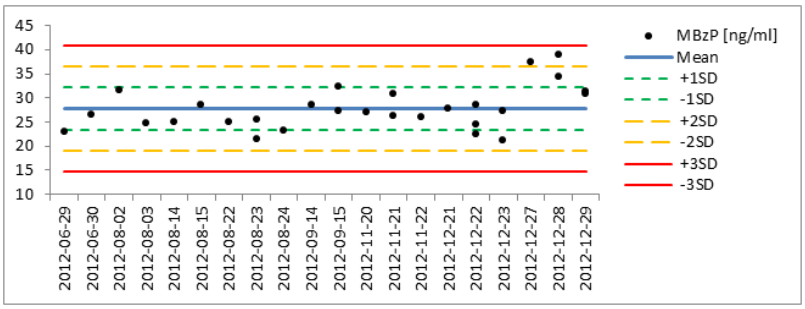

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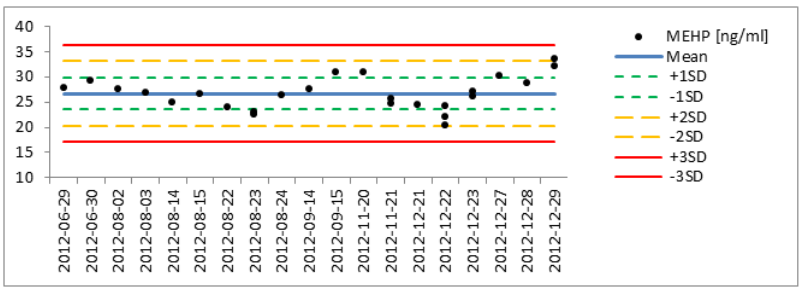

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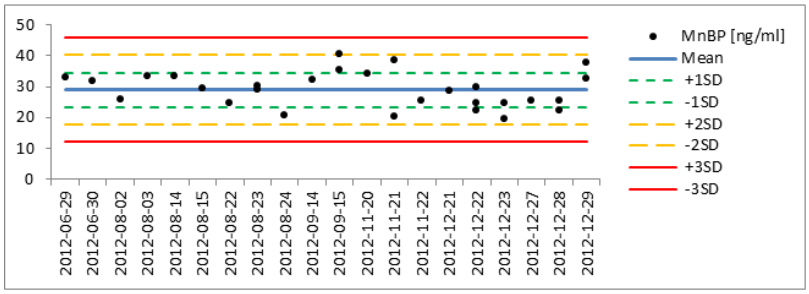

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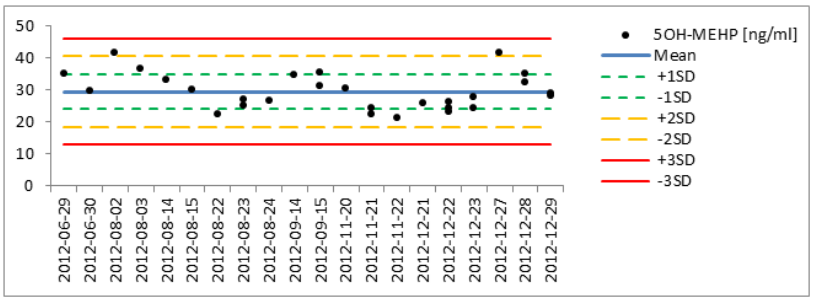

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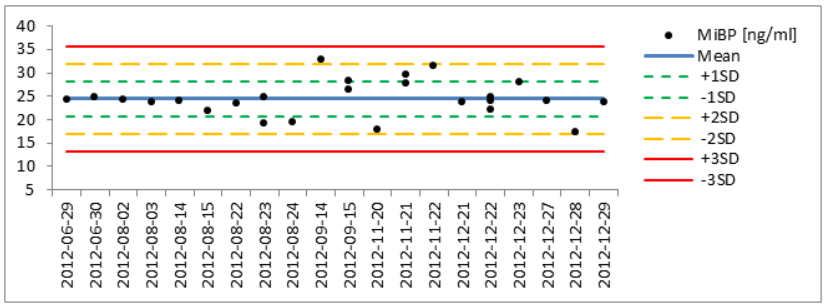

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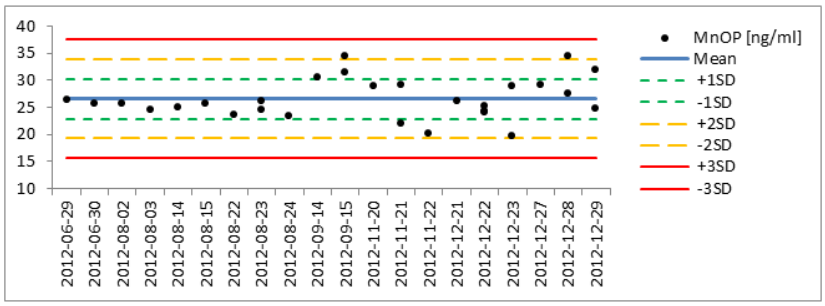

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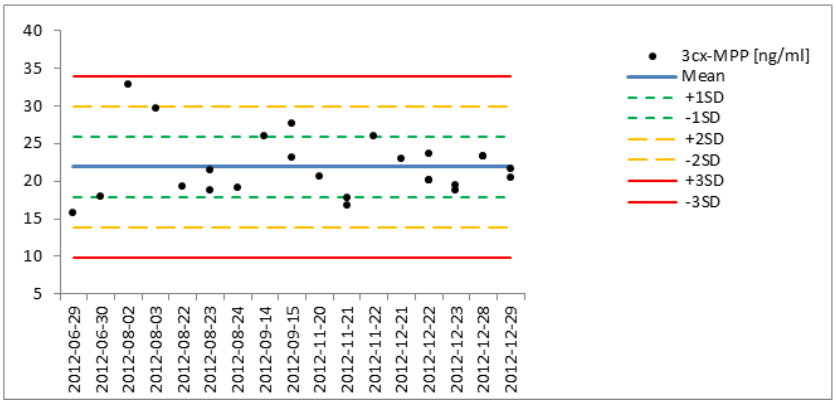

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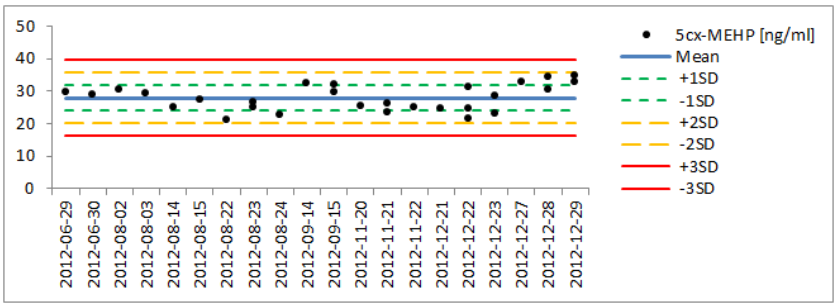

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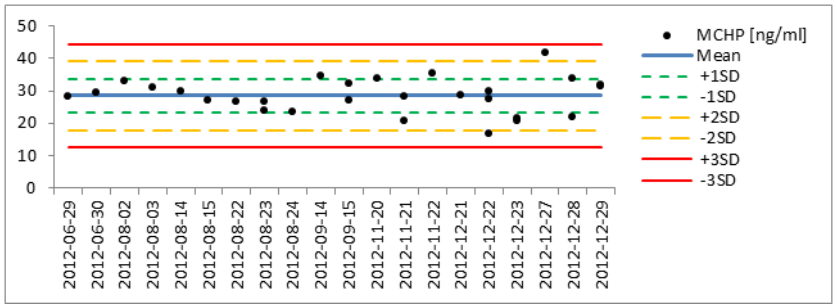

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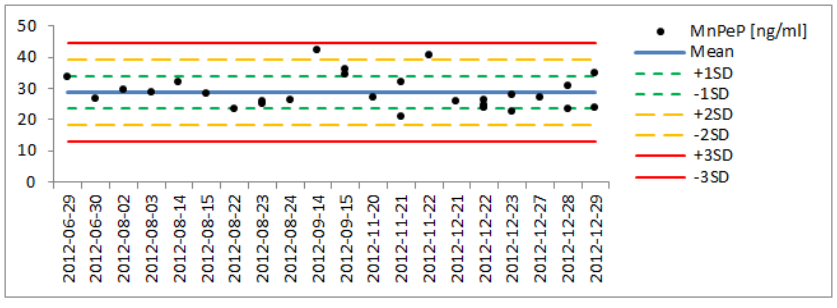

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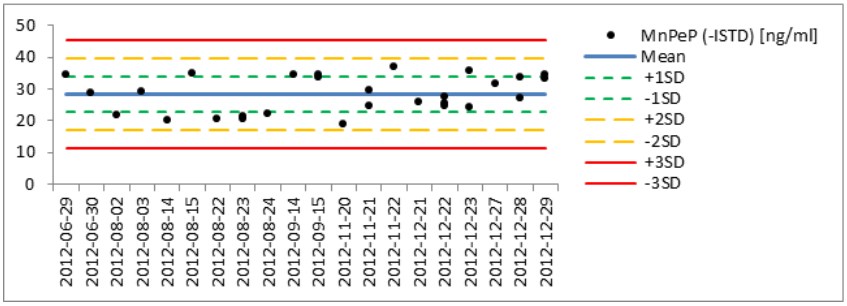

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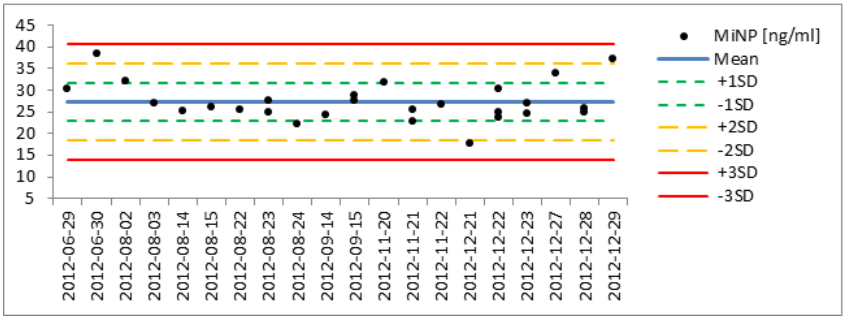

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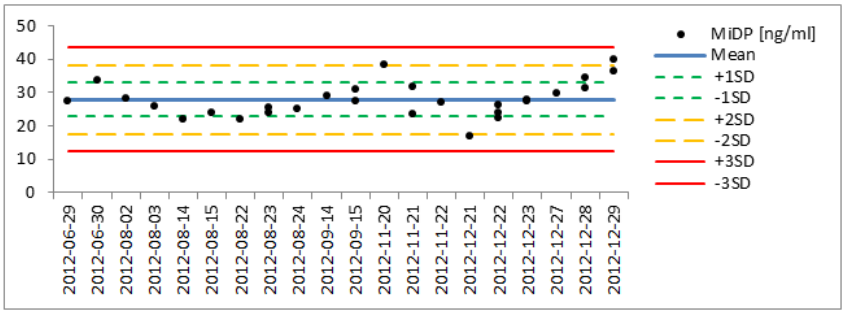
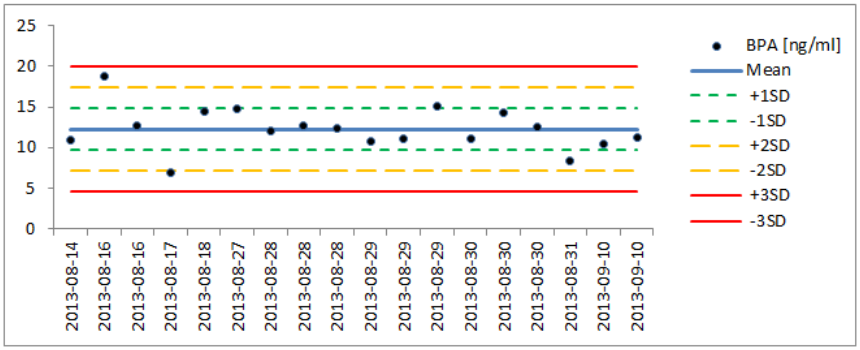


Appendix D.2: BPA ANALYSIS



CURRICULUM VITAE

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Education

Since 2013	Postgraduate Master studies of Toxicology at the Medical University Vienna
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2011 – 2013	Master studies of Environmental Management and Ecotoxicology at the University of Applied Sciences Technikum Wien
2005 – 2010	Master studies of Nutritional Sciences focused on “Nutrition and Environment” at the Department of Nutritional Sciences at the University of Vienna
1997 – 2005	Grammar school Weiz
1993 – 1997	Elementary school Weiz

Internships

04 / 2013	Research internship at the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance of the Ruhr University Bochum
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07-09 / 2009	Research internship at the Research Institute of Child Nutrition (FKE), Dortmund
06 / 2009	Internship at the Austrian Agency for Health and Food Safety (AGES)
02 / 2009	Internship at the University of Vienna, Department of Nutritional Sciences
09/2007	Internship at the University of Vienna, Department of Nutritional Sciences

Professional experience

11/2014 –	Environment Agency Austria, Organic Analysis
2012 – 2014	Self-employment: PhD studies of Natural Sciences in the field of Life Sciences at the Department of Nutritional Sciences at the University of Vienna and the Environment Agency Austria
03/2009-07/2010	Tutor of the course „Lifestyle and Nutrition Associated Diseases and Dietetics" at the University of Vienna

Fellowships

2012-2014	DOC-fFORTE Fellowship of the Austrian Academy of Sciences

Publications

Kanzler, S.; Hartmann, C.; Gruber, A.; Lammer, G.; Wagner, K.-H. (2014). Salt as a public health challenge in continental European convenience and ready meals. *Public Health Nutr., 1-8, doi: 10.1017/S1368980014000731.*