# Risk assessment of phthalates based on aggregated exposure from foods and personal care products and comparison with biomonitoring data

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## Abstract

Phthalates are a group of diesters of phthalic acid and have been widely used by the industry as plasticisers giving flexibility and durability to polyvinyl chloride (PVC) plastics. Commonly their uses vary from plasticisers in food contact materials and toys to emulsifying agents in personal care products. Phthalates are not covalently bound to PVC, thus they can migrate into the air, skin, water, food and the environment. The omnipresence of phthalates results in human exposure via multiple pathways such as dermal, oral and inhalation for prolonged periods. There is evidence that phthalates can induce disruption in oestrogenic activity, reproductive, developmental and liver toxicity both in experimental animals and potentially in humans. The aim of this technical report is to summarise the activities of the fellow performed at the Norwegian Institute of Public Health (NIPH). The goals of the work programme were collecting concentration levels on five specific phthalates from the scientific literature and combining them with consumption/use data reported in a biomonitoring study part of a Horizon 2020 project (EuroMix), and finally, estimate the aggregate phthalate exposure from food and personal care products and compare them with the measured phthalate levels in urine samples collected in the biomonitoring study.

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## 1.      Introduction

Phthalates are diesters of phthalic acid and have been widely used in the industry as plasticisers giving flexibility and durability to polyvinyl chloride (PVC) plastics. Commonly their uses range from plasticisers in plastics, including food contact materials and toys, as emulsifying agents and solvents in personal care products (PCPs), to excipients used in the pharmaceutical industry. This widespread use leads to a ubiquitous, constant and virtually unavoidable exposure in humans. Phthalates can migrate into the air, water and foodstuff, and humans can be exposed via multiple pathways such as dermal, oral and inhalation.

The phthalate plasticiser global market currently stands at approximate 5.5 million metric tonnes per year (OECD, 2018). The biggest market being the People's Republic of China accounting for 45% of all use, followed by Europe and the USA with a combined 25% use. There is evidence in the literature that phthalates can induce disruption in oestrogenic activity, reproductive, developmental and liver toxicity both in experimental animals and in humans (Gray et al., 2000; Heudorf et al., 2007; Lyche et al., 2009; Chen et al., 2014). Di-2-ethylhexyl phthalate (DEHP), one of the most widely used phthalates, has been found to cause liver carcinogenicity in rodents and has also been classified by IARC as possibly carcinogenic to humans (Category 2B). Although, it is disputed if the mechanism involved (peroxisome proliferation) is relevant for humans (IARC, 2013). Even if phthalates were authorised for use as food contact materials in the European Union (EU) in 2011 (EC 10/2011), for the aforementioned reasons, DBP, DEHP and DIBP should not be placed on the market in the EU after July 2020 individually or in any combination, in concentrations equal or greater than 0.1% by weight of plasticised material (EU 2018/2005). Thus, various phthalate substitutes have emerged such as di (isononyl)cyclohexane-1,2-dicarboxylate (DINCH), tributyl *O*-acetylcitrate, triethyl 2-acetylcitrate, trihexyl *O*-acetylcitrate (Schutze et al., 2012; Kim et al., 2019).

In order to evaluate qualitatively or quantitatively the likely human exposure of biological, chemical and physical agents via food and PCPs, exposure assessment was performed. In exposure assessments the magnitude, frequency and duration of human exposure to a chemical agent is modelled and the different exposure pathways, as inhalation, ingestion of water or food and dermal contact for PCPs are taken into account. Exposure is a crucial aspect in risk assessment since if there is no exposure; even a serious health hazard can be classified as a non-risk. In order to estimate chemical exposure, occurrence, product concentration data and use/consumption data are needed. A very popular tool to estimate exposure is probabilistic exposure assessment. Probabilistic analyses use more complicated modelling approaches than the deterministic (point estimates) and rely on distributions of data as input in place of single values. The outcome is a distribution of possible exposure estimates and assists in characterising variability and uncertainty providing an insight into the overall picture in the population. In this way, the outcome is influenced at a lesser degree from possible outliers leading to overestimation or underestimation of the actual exposure. The use of statistical methods, i.e. Monte Carlo simulations, also provides greater credibility in comparison with deterministic approaches and/or expert judgement, which may be led by subjectivity. Even though probabilistic methods can provide a more reliable exposure estimate, it should be mentioned that availability of consumption and exposure data is paramount and limited concentration data can lead to a higher uncertainty in the final exposure estimate.

A biomonitoring study (BM) was performed in Norway between September 2016 and November 2017 as part of the EuroMix project financed by H2020 programme. The study included males and females, who recorded their food consumption (including weights), and cosmetic use and collected all 24 h urine for two non-consecutive days (Husøy et al., 2019). The consumption data from this study along with the concentration data from the literature were used for the probabilistic exposure estimates for five phthalates for males and females on both days. The selected phthalates were di(2-ethylhexyl) phthalate (DEHP), di-iso-nonyl phthalate (DINP), diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP) and butyl-benzyl-phthalate (BBP).

## 2.      Description of work programme

### 2.1.    Aims

The main aims of this work were to estimate the exposure of a sample of the Norwegian population to the most important phthalates recorded in the EuroMix biomonitoring study (DEHP, DINP, DBP, BBP and DEP) and the phthalate substitute DINCH. Finally, the risk characterisation had to be determined for each phthalate. In order to achieve the main goal, the following tasks were performed;

1) Identifying the most important phthalate sources and exposure pathways.
2) Collecting concentrations of phthalates and DINCH in food and PCPs.
3) Performing aggregate probabilistic exposure modelling for the most important phthalates.
4) Comparing the modelling outcome with the two 24-h urine measurements of phthalate and DINCH metabolites.
5) Discussing the potential impact on the risk characterisation after comparing the aggregate exposure with the reference values provided by EFSA in their 2019 opinion on phthalates (under public consultation).

## 2.2. Activities/methods

### 2.2.1. Biomonitoring study

A biomonitoring study was performed in Norway between September 2016 and November 2017 as part of the EuroMix project financed by H2020 programme. The study included 144 participants (44 males and 100 females) participating the first study day and of these 140 participants (43 males and 97 females) completed the second study day. There was a 2- to 3-week interval between the sampling and during the two study sessions. The participants gave detailed weighted records on the food consumed and personal care products usage. All urine was collected for both study days and blood samples were taken at the end of each 24-h period. A detailed description of the EuroMix BM study can be found in the paper published by Husøy et al. (2019). The phthalates measured in the urine with the highest concentrations were the metabolites sums of DEHP, DBP, DEP, DINP and BBP.

### 2.2.2. Systematic literature search

A systematic literature search was performed in October 2019 in order to collect concentration data on phthalates in foods and PCPs. The search included DBP, BBP, DEHP, DEP, DINP and DINCH for the period 2010–2019. The databases used were Web of Science and PubMed. An additional search was completed at the end of November 2019 for the abovementioned compounds starting from 2008; including databases such as Embase, Cochrane, Medline and Web of Science. The retrieved papers were organised in an EndNote 9 file to ensure traceability, and duplicates were removed. Finally, the phthalate concentrations in food and PCP item/category were extracted to an excel table, where information on the country of origin, type of analytical method, number of samples and the type of descriptive data (median, mean, minimum, maximum) were also collected.

### 2.2.3. Data analysis

The collected concentrations were weighted by adjusting the phthalate concentrations with the number of samples tested in each respective study, and finally, lower bound (LB), middle bound (MB) and upper bound (UB) phthalate concentrations were calculated using R (3.6.4 version). Summary data were calculated, such as P50, P5 and P95 quantiles, mean, standard deviation, minimum, maximum and when possible the geometric mean and geometric standard deviation, for LB, MB and UB for each phthalate using R. The P5, P50 and P95 were used for the probabilistic exposure estimates. For the exposure estimates of the five phthalates the consumption data from the EuroMix study were combined with the concentration data from the literature using the following equation (1).

$$\text{Diet exposure} = \sum \frac{x \times C}{BW} \left[ \frac{\mu g}{\text{kg bw day}} \right], \tag{1}$$

where C is the concentration of phthalates in foods ($\mu$g/g); x is the gram food eaten (g/day), and BW is the body weight (kg).

Whereas for the exposure estimates from PCPs, the following equation (2) was used.

$$\text{Dermal exposure} = \sum \frac{C \times PCP_{fr} \times PCP_{a} \times ABS \times R_{f}}{BW} \left[ \frac{\mu g}{\text{kg bw day}} \right] \tag{2}$$

where C is the concentration of DEHP in PCPs ($\mu$g/g); $PCP_{fr}$ is the frequency of application (application/day); $PCP_{\alpha}$ is the amount per application (g/application); ABS is the dermal absorption factor (non-dimensional); $R_{f}$ is the retention factor for rinse-off products (non-dimensional) which were taken from SCCS (2016), and BW is the body weight (kg).

The individual exposure estimates for each phthalate were modelled using 1,000 Monte Carlo interactions, and the triangular type of distribution was based on the P5, P50 and P95 as parameters values. Triangular distributions were used due to the limited availability of concentration data in foods. Triangular distribution is a continuous probability shaped as a triangle and with the Pert distribution, can be used when minimum, maximum and the mode are available (Borek et al., 2014) and is being used in the phthalate exposure estimation (Martinez et al., 2017).

In order to compare the exposure estimates with the phthalate levels found in the urine, the reported phthalate metabolite concentration in the urine were back calculated (μg/kg bw) to external exposure of their respective parent compounds by taking into account toxicokinetic parameters such as absorption and the % excretion represented by the measured phthalate metabolites in the urine.

Further statistical analysis was performed by calculating the linear regression between middle bound and urine for males and females on both days. Two-way ANOVA tests were used to calculate any correlation between the sexes and the 2 days with the levels of phthalates found in the biomonitoring study. In addition, one-way ANOVA tested any significant within day correlation variations in the levels of phthalates for males and females on both days. All calculations were made using R version 3.6.4.

## 3.    Conclusions

The fellow has completed the objectives specified in the project proposal. By accomplishing this, the fellow gained experience in writing a project protocol, performing systematic literature review and acquired practical experience with probabilistic exposure modelling both for single and aggregate exposure. Moreover, the fellow gained theoretical and practical experience in R, along with statistical methods for data treatment. As the part of the results (dietary exposure) was presented at a conference in January 2020 organised by the Norwegian society for Pharmacology and Toxicology at Beitostølen. Phthalate exposure was estimated for food, PCPs and their aggregate and was compared with the measured phthalate metabolites found in the urine. Additionally, their risk was characterised not only for the individual compounds but also for the mixture. The outcome of these activities is going to be published in a peer review journal and the manuscript currently is in preparation. Additionally, part of the results (dietary exposure) were used as a chapter in the fellow's PhD thesis titled 'New developments in harmonised risk assessment of emerging chemical hazards: Chemical mixtures' for the University of Parma, which was the sending institute.

An objective that was amended during the fellowship was the use of the Monte Carlo Risk Assessment tool (MCRA). Due to data protection issues, the fellow was able to use the tool only for training purposes. This did not affect the work outcome since the objectives were met by using R. Additionally the COVID-19 pandemic did not significantly hinder the work progress, since there were frequent online interdepartmental meetings. Overall, the fellow did not have any adjustment issues; he integrated at the NIPH and collaborated well with colleagues from the Section of Toxicology and Risk Assessment.

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## Abbreviations

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| BBP | butyl-benzyl-phthalate |
| BW | body weight |
| DBP | di-*n*-butyl phthalate |
| DEHP | di(2-ethylhexyl) phthalate |
| DEP | diethyl phthalate |
| DINCH | di(isononyl)cyclohexane-1,2-clicarboxylate |
| DINP | di-iso-nonyl phthalate |
| EU-FORA | European Food Risk Assessment Fellowship Programme |
| IARC | International Agency for Research on Cancer |
| LB | lower bound |
| MB | middle bound |
| MCRA | Monte Carlo Risk Assessment |
| NIPH | Norwegian Institute of Public Health |
| OECD | Organisation for Economic Co-operation and Development |
| PCPs | personal care products |
| PVC | polyvinyl chloride |
| SCCS | Scientific Committee on Consumer Safety |
| UB | upper bound |