QUANTIFYING THE HEALTH-RELEVANCE OF DIOXINS AND RELATED COMPOUNDS –CHALLENGES AND CONSTRAINTS

Rappolder M[1]*, Conrad A[1]

[1]Federal Environment Agency (UBA), Corrensplatz 1, 14195 Berlin, Germany

Introduction

The World Health Organization estimates that approximately 25 % of all premature deaths are caused by environmental stressors[1]. Some of the most toxic environmental stressors that have been studied extensively in the last decades are dioxins and related compounds: Results of animal studies, in vitro methods and epidemiological surveys revealed a spectrum of various effects. Besides dioxins, people are exposed to various other health-relevant environmental stressors, such as noise and particulate matter. This poses the question of how to quantify the health risks associated with the exposure to dioxins and related compounds especially in comparison to other environmental stressors.

Quantifying the health-relevance of dioxins and related compounds and comparing it consistently to those of other stressors has gained increased scientific interest. Moreover, this information is vital for policy-makers who have to decide if action is needed and how to prioritize measures as well as to monitor the success of actions. Usually, the health-relevance of environmental stressors is quantified by means of the Environmental Burden of Disease (EBD) approach which includes the calculation of summary measures of population health which are appropriate for comparing different health risks. One of the most common measures is the Disability Adjusted Life Year (DALY) which summarizes effects on mortality and morbidity. Ideally, the EBD/DALY concept allows for comparing the healthy life years lost due to different risk factors. Moreover, also the benefit of specific mitigation measures can by quantified and communicated as health-gains in DALYs.

Unfortunately, the results of EBD/DALY calculations are affected by several inconsistencies and uncertainties. This is especially the case for dioxins and related compounds. Taking the multinational project EBoDE (Environmental Burden of Disease in the European Region)[2] as an example, we demonstrate how to use the EBD/DALY approach for quantifying dioxin-related health risks. Furthermore, we discuss the most important uncertainties and suggest further research for overcoming these limitations.

Materials and methods

In EBoDE the burden of disease due to following nine stressors was analyzed: PCDD/F and dl-PCB, benzene, formaldehyde, lead, environmental noise, ozone, particulate matter, radon, and second-hand smoke. The main objective of EBoDE was to estimate the environmental burden of disease due to these stressors in a comparable way across six European countries (Belgium, Finland, France, Germany, Italy, and the Netherlands). EBoDE aimed for considering all health endpoints that are associated with the environmental stressors with sufficient evidence.

The health impacts due to the specific stressors were quantified in Disability Adjusted Life Years (DALYs) combining effects on mortality (live years lost due to premature death) and morbidity (loss of healthy life years due to disability) using WHO disability weights reflecting the severity of a disease on a scale from 0 to 1. For estimating the EBD related to dioxins, data on the population's exposure, the associated health effects, and corresponding dose-response functions are needed. All EBoDE estimates refer to the year 2004. National population data were taken from EUROSTAT. EBoDE used intake data calculated with WHO-TEFs from 1998. As an exception, the TEQ_{1998} was converted from TEQ_{2005} by 10 % addition for the Netherlands.

Exposure: Dietary intake accounts for more than 90 % of the exposure to dioxins. The dose taken significantly differs by age, because of different consumption habits and bodyweight. For comparability, EBoDE estimates were based on average daily intakes of adults. The intake data were available for five countries (Belgium[3], Finland[4] Germany[5], Italy[6], and the Netherlands[7]) from national surveys based on average food consumptions and dioxin/dl-PCB levels in representative food samples. As an exception, the French daily intake was calculated from adult blood concentration (27.7 WHO-TEQ pg/g blood fat[8]) using the US EPA equation[9] for converting body burden into daily intake:

$$\text{Intake [pg TEQ/kg BW d]} = \frac{\text{body burden [pg TEQ/kg bw]} \times \ln(2)}{\text{half-life [d]} \times \text{fraction absorbed}}$$

Assumptions: body fat: 25 %; half-life: 2,593 days; fraction absorbed: 80 %

Health outcomes and dose-response functions: For several non-cancer effects – such as effects on the immune system, the endocrine system, reproductive functions, as well as developmental effects – no appropriate dose-response functions and/or well defined health endpoints as well as disability weights were available for dioxins. Therefore only the health endpoint "all cancer" could be addressed for this stressor in EBoDE. A non-threshold linear dose-response model for cancer was applied considering an oral slope factor of 1×10^{-3} per pg TEQ/kg bw/d of dioxin intake proposed by US EPA[10]. All cancer cases were assumed to be fatal.
Burden of disease modeling: The general approach for estimating the dioxin-related cases and resulting DALYs was based on WHO methods[11] and is described in the EBoDE report2. The loss of life years was calculated considering the specific life expectancy in the participating countries.

Results and discussion
Exposure: The daily intake of PCDD/F and dl-PCB for adults in the participating six countries exhibits a high variation and ranges from 1.0 to 2.3 pg TEQ/kg bw/d (Fig 1). This variation can be explained by actual differences in food consumption and dioxin contamination of food across regions. However, differences between countries may also be due to not fully harmonized methods. Highest exposures resulted for France and Italy. One reason could be that in France the daily intake was re-calculated from blood concentrations in a small sample. In Italy the intake data were derived in the period from 1997 to 2003 and may include also years with higher intakes.

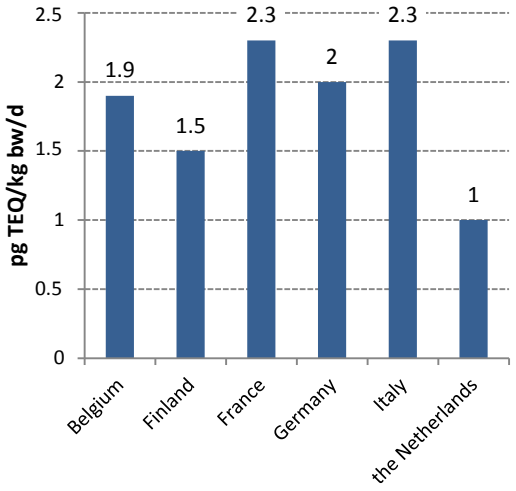

Fig 1: Daily intake of PCDD/F and dl-PCB (results as close as possible to the year 2004)

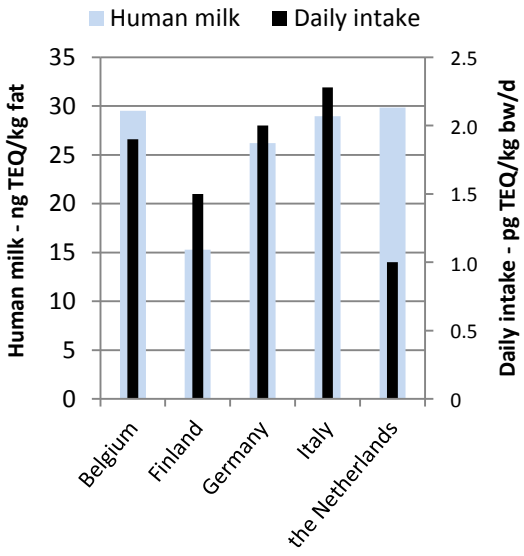

Fig 2: Comparison of daily intake and human milk - results from the 3rd WHO human milk study 2001-2003 (Sum of PCDD/F and dl-PCB)

For elucidating uncertainties within the exposure data daily intakes were compared to results of the 3rd WHO human milk study (Fig 2). This evaluation was not possible for France, as this country did not participate in the human milk study. The comparison indicates a fair agreement between intake estimated and levels in human milk. This, however, was not the case for the Netherlands where a substantial inconsistency between daily intake

and human milk was observed. Therefore, an underestimation of the Dutch daily intake in comparison to the other countries cannot be excluded.

Health outcome and dose response function: For PCDD/F and dl PCB an average of 30 fatal cancer cases per 1 million people was estimated, ranging from 14 (Netherlands) to 33 (France and Italy) (Fig 3). As mentioned above, several known non-cancer effects of PCDD/F and dl-PCB could not be considered due to methodological constraints.

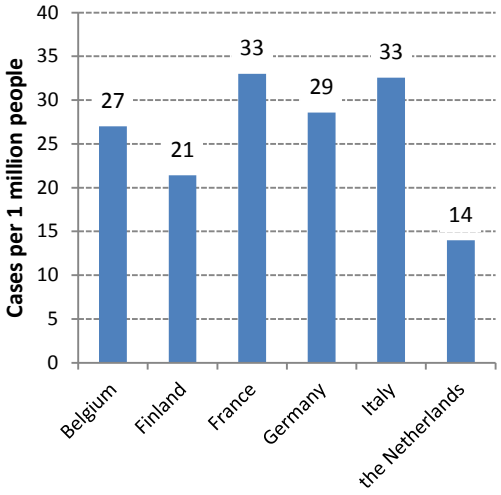

Fig 3: Estimated death per year and 1 million people due to cancer caused by PCDD/F and dl-PCB

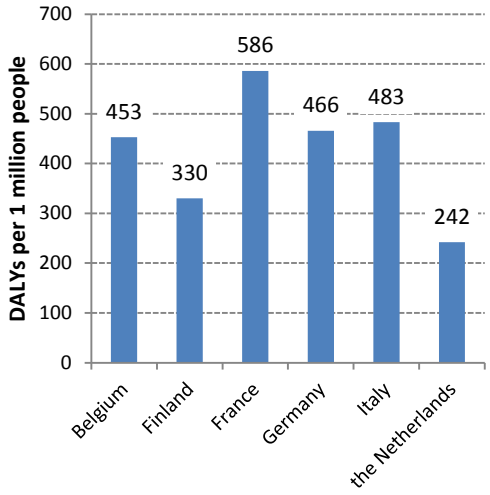

Fig 4: Estimated DALYs per year and 1 million people due to exposure of PCDD/F and dl-PCB

Environmental burden of disease: The EBD due to PCDD/F and dl-PCB was on average 482 DALYs per million people, ranging from 242 (Netherlands) to 583 (France) (Fig 4). These calculations are affected by high uncertainties: All cancer cases were assumed to be fatal during the first year, resulting in a moderate overestimation of the disease burden. As several non-cancer health effects could not be considered, it is unclear whether the total EBD due to dioxins and related compounds is over- or underestimated.

The initial comparison of the results to results for the other eight environmental stressors of the study reveals substantial differences2: The highest EBD was estimated for particulate matter (PM 2.5) with approximately 8000 DALYs/year, followed by a middle field (100 – 1000 DALYs/year) with second-hand smoke, environmental noise, radon, PCDD/F and dl-PCB and lead. In the lowest group (less than 100 DALYs/year) are ozone, benzene and formaldehyde. This estimation is affected by various uncertainties. However, these results allow a rough evaluation of the health relevance of these nine stressors.

Constraints and research needs

The EBD/DALY approach combines concept data on exposure, dose response functions and health outcomes for quantifying and comparing the impact of different stressors on public health. Sound and complete data are a vital prerequisite for applying this approach to environmental health policy.

In terms of dioxins and dl-PCB EBD calculations are affected by substantial uncertainties due to data and methodological constraints. This is also true for other persistent organic chemicals causing endocrine effects. For improving the EBD analysis of dioxins and other persistent chemicals the following aspects should be considered:

Exposure: The oral intake of chemicals usually varies substantially with the population and is therefore often difficult to estimate. The body burden (measured by human bio-monitoring) promises to be a more appropriate exposure metric in EBD evaluation of persistent chemicals, as it reflects the absorbed dose and can be assumed to carry fewer uncertainties of daily intake estimates. This, however, also means that the internal exposure to dioxins and other persistent chemicals has to be regularly monitored on a population-representative basis. For contrasting national EBD estimates this monitoring has to be carried out in a comparable way. As demonstrated

by EBD calculations for lead (using blood levels measured in population surveys as exposure metric), this may substantially improve EBD estimates for dioxins and related compounds.
Health outcomes and dose-response functions: Using the internal exposure in EBD calculations also requires appropriate dose-response functions for connecting the body burden to health outcomes. Further epidemiological research is necessary to meet this need. Moreover, persistent chemicals cause various health effects that currently cannot be considered in EBD analyses as they are not operationalized as health outcome or specific disease. Further research is needed to sharpen the view on these endpoints and make them available for the EBD/DALY approach.
EBD modelling: Further methodological improvement of EBD methods is needed and should aim at taking long term and low dose exposures to persistent and endocrine disrupting chemicals into greater account.

Conclusions
The EBD/DALY approach is increasingly used in policy making. Currently, persistent organic pollutants may not be sufficiently represented in these analyses. Therefore, additional effort is needed to generate reliable and appropriate information on exposure, dose-response functions, and health outcomes with respect to these chemicals to improve the applicability of EBD/DALY or similar approaches on persistent organic pollutants with endocrine disrupting effects.

Acknowledgements
Thanks are due to all our partners in the EBoDE-project. The final report is available at http://www.thl.fi/thl-client/pdfs/b75f6999-e7c4-4550-a939-3bccb19e41c1 .

References
1. WHO (2006) WHO, Geneva, http://www.who.int/quantifying_ehimpacts/publications/preventingdisease/en/index.html
2. Hänninen O, Knol, A (eds) (2011) http://www.thl.fi/thl-client/pdfs/b75f6999-e7c4-4550-a939-3bccb19e41c1
3. Bilau M, Matthys C, Baeyens W, Bruckers L, De Backer G, Den Hond E, Keune H, Koppen G, Nelen V, Schoeters G, Van Larebeke N, Willems JL and De Henauw S (2008) *Chemosphere*, 70, 584-592
4. Kiviranta H (2005) [dissertation]. National Public Health Institute, Helsinki, http://www.ktl.fi/attachments/suomi/julkaisut/julkaisusarja_a/2005/2005a14.pdf
5. Umweltbundesamt (2011) http://www.umweltbundesamt.de/chemikalien/dioxine.htm
6. Fattore E, Fanelli R, Turrini A, di Domenico A (2006) *Mol Nutr Food Res.* Oct;50(10):915-21.
7. De Mul A, Bakker MI, Zeilmaker MJ, Traag WA, van Leeuwen SPJ, Hoogenboom RLAP, Boon PE, van Klaveren JD (2008) *Regulatory Toxicology and Pharmacology* 51, 278–287
8. Fréry N, Volatier J, Zeghnoun A, Falq G, Mouajjah S, Thébault A, Pascal M, Bérat B, Grange D, de Crouy-Chanel P, Sarter H, Heyman C, Guillois-Becel Y, Lucas N, Mathieu A, Noury U, Pouey J, Schmitt M, Salines G, (2006) *Epidemiology* 17(6), S298
9. US Environmental Protection Agency (2003) *National Academy Sciences (NAS) Review Draft* Part III Chapt. 5.2.1, http://www.epa.gov/ncea/pdfs/dioxin/nas-review/
10. EPA NAS – National Academy of Science (2006) http://www.ejnet.org/dioxin/nas2006.pdf
11. Prüss-Ustün A, Mathers C, Corvalán C, Woodward A (2003) WHO, Geneva, http://www.who.int/entity/quantifying_ehimpacts/publications/en/9241546204.pdf