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An exposure-based framework for grouping pollutants for a cumulative risk assessment approach: Case study of indoor semi-volatile organic compounds ☆

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ABSTRACT

Humans are exposed to a large number of contaminants, many of which may have similar health effects. This paper presents a framework for identifying pollutants to be included in a cumulative risk assessment approach. To account for the possibility of simultaneous exposure to chemicals with common toxic modes of action, the first step of the traditional risk assessment process, i.e. hazard identification, is structured in three sub-steps: (1a) Identification of pollutants people are exposed to, (1b) identification of effects and mechanisms of action of these pollutants, (1c) grouping of pollutants according to similarity of their mechanism of action and health effects. Based on this exposure-based grouping we can derive "multi-pollutant" toxicity reference values, in the "dose–response assessment" step. The approach proposed in this work is original in that it is based on real exposures instead of a limited number of pollutants from a unique chemical family, as traditionally performed. This framework is illustrated by the case study of semi-volatile organic compounds in French dwellings, providing insights into practical considerations regarding the accuracy of the available toxicological information. This case study illustrates the value of the exposure-based approach as opposed to the traditional cumulative framework, in which chemicals with similar health effects were not always included in the same chemical class.

1. Introduction

Human beings use many chemicals in various circumstances, such as: manufacturing and use of products and articles, industrial processing, agriculture, etc. These chemicals and their by-products are likely to be found in the environment and are the source of diffuse and multiple contaminations of the different compartments: pesticides in soils, water, diet or air, persistent organic pollutants in the food chain, urban air pollution, volatile and semi-volatile organic compounds in indoor and outdoor environments, etc. As a consequence, human beings are exposed through oral, respiratory or dermal routes to a large variety of chemicals present in food, air, water and dust, generally at low doses. The presence of such pollutants and their metabolites in human biological fluids has confirmed this hypothesis. For example, the National Health and Nutrition Examination Survey – designed to assess the health and nutritional status of adults and children in the United States – included biomonitoring surveys that showed the presence of detectable levels of a large variety of chemicals and their metabolites in blood or urine of human people, such as metals, phthalates or pesticides' metabolites (NHANES, 2013).

Regulations related to the chemicals entering in European market, both for domestic and professional uses, are based on risk assessment and management (European Union, 2009, 2006). However, the laws on the use of chemicals (cosmetics, biocides, pesticides, medicines, food additives and more) do not allow a comprehensive and global risk analysis. Standard toxicological tools, in particular studies on laboratory mammals, are not suitable for studying the effects induced by complex and low-dose chemical mixtures. Little knowledge is routinely generated on the hazards of these chemical mixtures. The real impact of dietary and environmental contamination is not known and therefore not fully taken into account in public health decisions. The implementation of cumulative risk assessment strategies for complex mixtures is therefore of high concern as stated by Sarigiannis and Hansen (2012).

A variety of cumulative risk assessment (CRA) methodologies have already been suggested to improve risk management decision-making.

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For example, toxic equivalent factors have been defined for dioxins, furans, dioxin-like polychlorinated biphenyls (PCB-dl) and polycyclic aromatic hydrocarbons (PAHs), on the basis of their ability to bind the Aryl hydrocarbon receptor (Safe, 1990; Van den Berg et al., 2006, 1998). Similarly, the U.S. Environmental Protection Agency suggested using an approach based on relative potency factors (RPF) for organophosphate and carbamate pesticides on the basis of their ability to inhibit the acetylcholinesterase enzyme (US EPA, 2006, 2002). More recently, these approaches were extended to other molecules, such as pyrethroid pesticides (Wolansky et al., 2005) and phthalates (Hannas et al., 2011). However, these approaches generally take into account only one chemical family. Taking into account pollutants from different chemical families would undoubtedly better reflect actual environmental human exposures. This issue was first addressed by Kortenkamp and Faust (2010) who proposed a CRA based on the anti-androgenic abilities of 15 substances including pesticides (fungicides, insecticides), as well as phthalates, brominated compounds and parabens. The hazard index method was then chosen to afford more flexibility in dealing with various data quality issues by using varying uncertainty factors. However, the use of different critical doses (no observed adverse effect level versus lowest observed adverse effect level for example) led to difficulties in the interpretation of results. In addition, this pioneering study was based on the mechanism of toxicity of substances that people are not typically exposed to. It seems therefore necessary to pursue the improvement of the CRA methodology.

The objective of this work is to propose an additional step in the CRA approach, based on grouping pollutants people are actually exposed to. Only the threshold method will be developed (for non-carcinogenic or non-genotoxic compounds). We illustrate this exposure-based CRA framework with a case study based on exposure to semi volatile organic compounds (SVOCs) in French indoor environments.

2. A brief review of cumulative risk assessment methods

The risk assessment process was initially defined by the NRC in 1983 (National Research Council U.S. Committee on the Institutional Means for Assessment of Risks to Public 1983). In the traditional approach, four steps are used and described as follows: (1) Hazard identification, to determine whether a chemical is linked to one or more specific health effects, (2) dose–response assessment, to identify the relation between the magnitude of exposure and the likelihood or occurrence of health effects in a population. In its simplest form, this step is the choice of a toxicity reference value (a reference dose for example) according to an exposure route and duration, (3) exposure assessment, to determine the extent and the magnitude of human exposure, and (4) risk characterization, to describe the nature and magnitude of human health risk, including uncertainties. This last step is the combination of the previous ones. It generally compares the estimated human exposure with the selected toxicity reference value. It results in a hazard quotient (exposure/toxicity reference value) if the threshold assumption is used, or an excess risk (exposure $\times$ toxicity reference value) in the case of a non-threshold assumption.

A dose-additivity assumption has been used for forty years (Sprague 1970) in the cumulative risk assessment process, where a threshold hypothesis is used. The simplest approach is to sum the hazard quotient obtained for each chemical (US EPA, 2000, 1986) to obtain a hazard index. The main limitation is the lack of comparability of the ratio obtained for each pollutant when, for example, the reference doses are not defined based on the same critical effect. This method could be used to identify the chemical of most concern in the mixture but cannot predict the effect of the mixture. This method takes into account the most sensitive critical effect induced by each pollutant. The risk could be considered as negligible when the hazard index is less than one. If not, a more in-depth approach should be used. An improvement of this approach was proposed using the point of departure index which directly compares the exposure to a critical dose, or "point of departure", in which the same effect is selected for all substances, even if the point of departures are different: no observed adverse effect level, lowest observed adverse effect level or benchmark dose). The point of departure index is then compared to human exposure, leading to a margin of exposure that is interpreted keeping in mind the uncertainties of the toxicological data used to derive the point of departure. Another approach is directly derived and extrapolated from the toxic equivalent factor for dioxins, furans, PCB-dl and PAHs, based on their affinity to the arylhydrocarbon receptor. The RPF approach first described by US EPA (2002) is based on the assumptions of a similar mechanism/mode of action and parallel dose–response curves. The toxic potency of each chemical is normalized relative to the best-known compound. These RPFs can be constructed by comparing the toxicity indicators (benchmark doses based on the same mechanism for example, or an effective dose corresponding to a percentage of response or affinity). They are then used to weight the exposure of the different compounds, then added together to determine a hazard quotient based on the toxicity reference value of the index compound. This approach requires more accurate mechanistic information and can therefore be applied only to the most widely studied pollutants. Several reviews with a more in depth description of these approaches are available (Fournier et al., 2014; Kortenkamp and Faust, 2010; Sarigiannis and Hansen, 2012). These CRA methodologies have been used in various contexts. For example, Wolansky et al. (2005) derived relative potency factors for 11 pyrethroids after an acute exposure in rats, based on the prolongation of the open state of sodium channels. Similarly, US EPA (2006, 2002) proposed a CRA approach for 30 organophosphate pesticides based on brain cholinesterase inhibition in rats after exposure of 21 days or longer via oral, dermal or respiratory routes. RPFs were determined according to their respective benchmark dose. In 2011 the same approach was suggested to assess the risk related to exposure to a mixture of phthalates during pregnancy, based on a decrease in testosterone production and alteration of gene expression by fetal testes (Hannas et al., 2011). Jensen et al. (2013) published a cumulative risk assessment for 4 anti-androgenic fungicides belonging to different chemical classes (triazoles, imidazoles, dicarboximides). They used the RPF approach based on benchmark dose calculation to assess two effects (increased gestation period in pregnant females and increased nipple retention in male offspring) (Jensen et al., 2013).

In the case of situations where toxicological data are complete, with a deeper understanding of mechanisms and modes of action, it is possible to refine CRA by using toxicokinetic interactions and internal doses at the target site of action (Haddad et al., 2001). Taking into account the toxicokinetic interactions was also developed by Sarigiannis et al. They used a physiologically-based pharmacokinetic model to assess the internal dose of benzene following a co-exposure to four volatile organic compounds (benzene, toluene, ethylbenzene and xylene). These authors showed that benzene cancer risk estimate calculated from the combined exposure was lower than risk from benzene exposure alone. This was due to a metabolic competition (Sarigiannis and Gotti, 2008).

If these methods should be developed in the future, as it was suggested by the authors (Sarigiannis et al., 2009), these situations where mechanistic data are understood are unfortunately still too rare and it is not possible to develop this type of approach in all cases.