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Application of the maximum cumulative ratio (MCR) as a screening tool for the evaluation of mixtures in residential indoor air

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HIGHLIGHTS

- The MCR proved useful to screen indoor air samples for cumulative health risks.
- Combined exposure caused concern for toxicity in a considerable number of samples.
- More harmonization of chemicals monitored in indoor air surveys is recommended.

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ABSTRACT

The maximum cumulative ratio (MCR) method allows the categorisation of mixtures according to whether the mixture is of concern for toxicity and if so whether this is driven by one substance or multiple substances. The aim of the present study was to explore, by application of the MCR approach, whether health risks due to indoor air pollution are dominated by one substance or are due to concurrent exposure to various substances. Analysis was undertaken on monitoring data of four European indoor studies (giving five datasets), involving 1800 records of indoor air or personal exposure.

Application of the MCR methodology requires knowledge of the concentrations of chemicals in a mixture together with health-based reference values for those chemicals. For this evaluation, single substance health-based reference values (RVs) were selected through a structured review process.

The MCR analysis found high variability in the proportion of samples of concern for mixture toxicity. The fraction of samples in these groups of concern varied from 2% (Flemish schools) to 77% (EXPOLIS, Basel, indoor), the variation being due not only to the variation in indoor air contaminant levels across the studies but also to other factors such as differences in number and type of substances monitored, analytical performance, and choice of RVs. However, in 4 out of the 5 datasets, a considerable proportion of cases were found where a chemical-by-chemical approach failed to identify the need for the investigation of combined risk assessment.

Although the MCR methodology applied in the current study provides no consideration of commonality of endpoints, it provides a tool for discrimination between those mixtures requiring further combined risk assessment and those for which a single-substance assessment is sufficient.

1. Introduction

Humans are constantly exposed to multiple substances from multiple sources. However, regulatory programmes such as REACH (Registration, Evaluation, Authorisation and Restriction of Chemical substances) in the European Union and TSCA (Toxic Substances Control Act) in the United States evaluate risks on a substance-by-substance basis and do not require the consideration of cumulative risks (being defined as the risks caused by the combined adverse health effects due to exposure to multiple chemical stressors via all relevant routes; Meek et al., 2011; Sexton, 2012) when determining human health effects. It has been asserted that the determination of risk on a single chemical basis could underestimate the combined risks of mixtures (EC, 2009); however, considering cumulative risks is a challenge for policy makers (Sarigiannis and Hansen, 2012).

The indoor environment is one situation where the issue of simultaneous exposure to multiple substances is of high relevance. A wide

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range of gases, vapours and particles enters the building as a component of outdoor air via ventilation, and additional substances are emitted into indoor air from building materials, furnishings and consumer products, from combustion of fuel for cooking and heating, and from people, plants and pets (Crump et al., 2009; ECA, 2006).

Up to now the majority of indoor air risk assessments in the EU have focused on individual substance evaluation (e.g. Jantunen et al., 1998; JRC, 2005; Sarigiannis et al., 2011). In a recent application of statistical methods for the evaluation of mixture effects, including indoor and outdoor air studies, Billionnet et al. (2012) highlighted the necessity of a multi-substance approach.

Notwithstanding recent scientific developments and calls for a transition to a multi-substance paradigm at both the scientific and regulatory levels, there is currently a lack of practical tools for the evaluation of health effects associated with co-exposure to multiple substances, and in particular a lack of demonstration of the application of such tools in case studies on indoor air (Johns et al., 2012; SCHER, 2007). In this paper, the application of the maximum cumulative ratio (MCR) approach, which is a practical screening tool for the evaluation of mixtures, is demonstrated for the case of indoor air. The MCR approach is an extension of the hazard index (HI) which is commonly used as a screening tool for evaluating mixture toxicity (Meek et al., 2011; Sarigiannis and Hansen, 2012). In addition to HI, MCR quantifies the significance of cumulative toxicity compared to single component toxicity (Junghans et al., 2006) and is a tool for investigating the magnitude of the toxicity potentially missed if a cumulative risk assessment is not performed (Price and Han, 2011). As described in Price and Han (2011), the MCR can be calculated using the hazard quotients (HQs) for each substance present in a mixture and the hazard index (HI) of the mixture. The value of MCR for an individual exposed to a mixture of n substances in an environmental media is calculated by:

$$HQ_i = \frac{C_i}{RV_i}$$

$$HI = \sum_i HQ_i$$

$$MCR = \frac{HI}{\max HQ_i}$$

where C_i is the concentration of the ith substance in the media to which an individual is exposed and RV_i is the health based reference value of substance i (expressed as a concentration). HQ_i is the hazard index of the individual's exposure to the ith substance. The MCR of the individual's exposure to the mixture is the ratio of the HI of the mixture to the maximum of the hazard quotients of the individual components (max HQ_i).

The HI and MCR approaches are based on the hypothesis of dose addition, which is considered a conservative assumption for evaluating mixture effects of non-carcinogenic substances (Meek et al., 2011), especially when applied to whole mixtures without considering communalities in endpoints or mode of action, which is the case when combining RVs of various substances based on different endpoints in HI and MCR. The default assumption of dose addition is in line with the approach taken in screening steps of various mixtures risk assessment frameworks (WHO-ICPS framework in Meek et al., 2011; SCHER, SCENIHR, SCCS, 2012; US-EPA, 2007).

As noted by Könemann (1981) the MCR ratio is bounded by 1 and n (n = the number of analysed substances in the mixture). An MCR close to 1 means that one substance is responsible for nearly all the toxicity of the mixture. Exposures to a mixture of n substances with equal toxicities would have an MCR of n. Price et al. (2012a, 2012b) describe how the MCR and the HI can be used to classify mixture exposures into the following four groups according to the CEFIC-MIAT (Mixtures Industry Ad-Hoc Team) decision tree, each one requiring a different risk management strategy (Price et al., 2012a, 2012b; and Table 1):

- Group I: single substance concern
- Group II: low concern
- Group IIIA: concern for combined effect dominated by one substance
- Group IIIB: concern for combined effect by several substances.

The MCR methodology has been used to investigate the potential human health effects of environmental mixtures of plant protection products in surface waters, mixtures of substances in groundwater wells (Han and Price, 2011), mixtures of substances in surface waters and waste water treatment effluents (Price et al., 2012b) and cumulative exposures to multiple dioxin-like substances (Han and Price, 2012). However, the methodology has not until now been applied to mixtures of substances in indoor air.

Noting the wide variability of indoor sources, indoor spaces and personal behaviours, all of which potentially impact the composition of mixtures to which an individual is exposed, it was decided for this study to consider mixtures of substances at the individual level rather than using grouped data for populations or regions where averaging would hide the inherent variability of the individual exposures. We therefore reviewed seven national and multi-national European surveys of indoor air or personal exposures that sampled at least 50 locations or persons in each study area (Billionnet et al., 2011; Geiss et al., 2011; Jantunen et al., 1998; Raw et al., 2004; Schulz et al., 2012; Swaans et al., 2012; Stranger et al., 2009). Further details of these studies, including pollutants measured, sampling strategies used and number of participants are summarized by Crump et al. (2013). Raw data were accessible for four of these surveys either because the data is publicly available or because permission for its use in this study was granted by the data owners. These datasets were used for the MCR assessments.

This paper presents the results of the MCR assessments of mixtures in indoor air and in air sampled in the breathing zone (personal exposure). Specific attention is given to the impact of a) the number and identity of substances included in each of the surveys, and b) the criteria for selecting the toxicological reference values. The values of the MCR and HI are used to assign the mixtures into the four categories (MIAT groups I, II, IIIA, IIIB), to identify those mixtures for which full combined toxicity assessments are most needed, and provide information on the specific substances that drive the toxicity of the mixtures.

2. Material and methods

2.1. Datasets for indoor monitoring data from European countries

The indoor exposure monitoring database used for the MCR calculations was compiled from the datasets of four European indoor air studies containing results of indoor air or personal exposure (dosimeters) measurements at the individual level. The EXPOLIS study measured personal exposures and indoor air at home and work in 6 European cities (Athens, Basel, Helsinki, Milan, Oxford and Prague) during 1996–2000 (Jantunen et al., 1998). For the MCR calculations, only the residential indoor and personal exposure data were used. The *Flemish homes* study measured indoor air quality in 360 homes and the *Flemish schools* study involved 90 classrooms from 30 schools in Flanders during 2008–2011 (Stranger et al., 2009; Swaans et al., 2012), while the *French Indoor air quality survey* (OQAI) measured indoor air quality in 567 homes across France during 2003–2005 (Billionnet et al., 2011).

Table 2 summarises the main characteristics of these studies in terms of locations, population groups, substances measured and survey dates. Sampling strategy, analytical detection method and the list of measured substances varied across the studies. All the studies involved single event sampling of individual buildings/people and sampling was undertaken either throughout the year (EXPOLIS and Flemish homes), at times categorized as summer or winter (OQAI), or winter months only (Flemish schools).

All monitored volatile organic carbons — VOCs (including aldehydes, aromatic hydrocarbons, terpenes, acetates and chlorinated hydrocarbons)