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.

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
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 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 HQi).

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 complexities 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 Könnemann (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)
The HI and MCR calculation methodology addresses cumulative risks for endpoints that have a threshold effect (non-genotoxic effects), and accordingly we define a health based reference value (RV) as a threshold level below which chronic exposure to an individual substance is unlikely to provoke adverse non-cancer effects. There is no single information source available that provides RVs for all or even most of the substances in the indoor air monitoring database. RVs for chronic exposure were therefore retrieved from an array of data sources using a step-wise approach. Consulted sources were ranked by date (priority was given to evaluations issued within the last 5 years) and only used when the technical basis and the standard setting process were open and transparent. For the purposes of this study, primary sources were international, national and state agencies with established peer review procedures (WHO, ATSDR, USEPA IRIS, USEPA PPRTV and INDEX; for references to these sources: see Table 3); secondary sources were judged to have less intense peer review and/or transparency (Health Canada, RIVM, individual scientific publications), while the tertiary source was the ECA (2012) list referring the ‘lowest concentration of interest’ (LCI) values used for evaluation of emissions from building materials in place in Germany (AgBB) and France (AFSSET) (AgBB, 2012; AFSSET, 2009). AgBB and AFSSET/ANSES LCI values are, for some (data-poor) substances, derived from occupational exposure limits.

This process of ranking sources and selecting RVs is outlined in the flow scheme presented in Fig. 1. Chronic inhalation DNELs (derived no-effects levels) for the general public derived under the EU REACH legislation as published on the public database at ECHA’s website (http://echa.europa.eu) were not used as their derivation is neither transparently documented on ECHA’s website nor peer-reviewed; consequently, the consistency in derivation of DNELs across substances is questionable and therefore they are not used in the MCR assessments.

The ‘basic RV list’ contains all RVs which have been derived according to established, transparent procedures (from above mentioned primary and secondary sources), using data from animal or epidemiological studies. The ‘extended RV list’ contains additionally RVs from tertiary sources i.e. based on those LCI values with no clear derivation including the use of occupational exposure limits as the starting point, and from which extrapolation to the general public is poorly justified.

Two additional RV lists were compiled to investigate the sensitivity of the MCR to the choice of the RV. The ‘min RV list’ and the ‘max RV list’ contain respectively the lowest and the highest RV values that were considered in the selection procedure for the basic RV list (i.e. primary and secondary sources).

2.3. MCR calculation

The calculation of MCR values reflecting cumulative risk for non-cancer threshold effects was based on the approach described by Price and Han (2011), referred to in the introduction. MCR values were calculated for each record (individual indoor air or personal exposure sample) of the surveys extracted into a study database, using the basic and extended RV lists. The sensitivity of the MCR calculations with regard to choice of RV was tested by applying either the min RV or max RV list. MCR calculations of contrasting subsets of the entire database were compared to assess the impact of the different sets of monitored substances, regional differences, indoor versus personal measurements and homes versus schools.

3. Results

3.1. Chronic inhalation reference values for individual substances

The chronic reference values (RV) for the substances measured in the indoor air studies are listed in Table 3. From all considered substances, 30 have a basic RV value, another 14 are included in the extended RV list, and for 2 substances (tetrachloroethene and 1,1,2-trichloroethene) no RV was found. The ratio between the maximum and minimum RV for a single substance established by two or more toxicological agencies ranges from 1 to 300.

3.2. MCR calculation

Fig. 2 shows the scatter plots of MCR values versus HI for the EXPOLIS indoor (homes) and personal data (upper graph), Flemish homes and schools data (middle graph) and the OQAI data (lower graph), with MCR values calculated using the basic RV list. The values of MCR in the five datasets range from 1 to 5.8 and averaged 1.8. The maximum value of MCR of an individual exposed to a mixture is bounded by “n” the number of chemicals in a sample. In all of the samples MCR was found to be small relative to n, indicating that the toxicity of the mixtures was in general driven by only a few of the chemicals. Across the datasets, there is a statistically significant decline of MCR as HI values increase (Spearman correlation test, p-value < 0.0001). In general, the individuals with the largest values of HI occurred in group I (Fig. 2).

Substantial differences in group classification between the different data sets were found (Table 4): the large majority of the Flemish school...
<table>
<thead>
<tr>
<th>Substances</th>
<th>Date of survey</th>
<th>Country/city/region</th>
<th>numbers of samples</th>
<th>Type of measurement</th>
<th>Sampling device</th>
<th>Sampling duration</th>
<th>Analytical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPOLIS</td>
<td>1996–1998</td>
<td>Helsinki</td>
<td>201 working adults, aged 25–55 y; across all seasons</td>
<td>Personal (p) and, indoor residential (l)</td>
<td>VOCs: pumped Tenax TA tube, sampling volume: 2–3 l</td>
<td>VOCs p: 48 h VOCs i: 26 to 30 h NO2: 48 h</td>
<td>TD/GC/MS&amp;FID</td>
</tr>
<tr>
<td>31 substances (VOCs &amp; aldehydes, NO2b)</td>
<td></td>
<td></td>
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<tr>
<td>1997–1998</td>
<td>Athens</td>
<td>50 50 non-smoking adults (11 work at home), 25–55 y, approx. equal numbers in summer and winter</td>
<td>50 50 office workers, 25–55 y, approx. 6 persons/month sampled</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1997–1998</td>
<td>Milan</td>
<td>50 50 local government employees, 25–55 y, across all seasons</td>
<td>50 50 adults in a study cohort, 25–55 y; sampled across all seasons</td>
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<tr>
<td>1998–2000</td>
<td>Oxford</td>
<td>50 50 adults in a study cohort, 25–55 y; sampled across all seasons</td>
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<tr>
<td>1997–1998</td>
<td>Basel</td>
<td>50 50 adults, random selection from civil register, 25–55 y; across all seasons</td>
<td></td>
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<td></td>
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<tr>
<td>Flemish homes study</td>
<td>2008–2011</td>
<td>All 5 provinces in Flanders</td>
<td>72 homes in each province; sampling approx. equal numbers each month.</td>
<td>Indoor at home (living room)</td>
<td>VOCs: passive radial sampler aldehydes: passive radial sampler NO2: diffusive, Palmes tube</td>
<td>VOCs: 48 h NO2: 48 h</td>
<td>Solvent desorption and GC/FID</td>
</tr>
<tr>
<td>21 substances (VOCs, aldehydes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Flemish schools study</td>
<td>2008–2009</td>
<td>All 5 provinces in Flanders</td>
<td>30 schools; samples in 3 classrooms per school; sampling during winter.</td>
<td>Indoor (classroom)</td>
<td>VOCs: passive radial sampler aldehydes: passive radial sampler NO2: diffusive badge sampler</td>
<td>VOCs: 48 h NO2: 48 h</td>
<td>Solvent desorption and GC/Ms; aldehydes: solvent desorption and HPLC</td>
</tr>
<tr>
<td>10 substances (VOCs, aldehydes)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OQAI survey</td>
<td>2003–2005</td>
<td>Across France</td>
<td>567 dwellings (370 winter, others summer)</td>
<td>Indoor at home (main bedroom)</td>
<td>VOCs: passive radial sampler (Carbograph sorbent) Aldehydes: passive radial sampler (Florisil coated with DNPH)</td>
<td>7 days</td>
<td>TD/GC/FID&amp;MS</td>
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<tr>
<td>20 substances (VOCs and aldehydes)</td>
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<td></td>
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<td></td>
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</tr>
</tbody>
</table>

* Only in Helsinki for sub-population.

b Not in Milan or Athens.
The impact of using the extended RV list, thereby adding a number of substances to the MCR calculations with an RV value generally derived from occupational exposure limits, is small (results not shown).

There is an increase of about 4% in the number of mixtures in group IIIB (concern for combined effects by several substances) in the EXPOLIS indoor dataset and of about 2% in the EXPOLIS personal monitoring dataset. There is a less than 1% increase in group II(A + B) (concern for combined effects) for the OQAI and no increase for the Flemish (homes + schools) datasets.

The substances having the highest frequency of max HQ in the samples in the concern groups (I, II, and IIIB) are NO2 and trichloroethylene for the EXPOLIS and Flemish homes surveys. NO2 was not monitored in the OQAI survey, but was not monitored in the Flemish homes or schools surveys. For the Flemish schools, n-butyl acetate is the most relevant chemical component in the OQAI survey, but was not monitored in the Flemish homes or schools surveys.

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The substances having the highest frequency of max HQ in the samples in the concern groups (I, II, and IIIB) are NO2 and trichloroethylene for the EXPOLIS and Flemish homes surveys. NO2 was not measured in the Flemish schools or the OQAI surveys. Acrolein is a critical component in the OQAI survey, but was not monitored in the EXPOLIS or Flemish homes and schools surveys. For the Flemish schools, the xylenes have the highest frequency of max HQ in the few samples that fall into the concern for combined effects group (IIIB).
3.3. The EXPOLIS study (upper graph of Figs. 2 and 3)

The EXPOLIS data allow us to compare personal and indoor monitoring results, as well as regional differences between European cities.

No major differences in the classification of mixtures in the 4 groups were found between indoor and personal data at database level (Table 4). The largest difference was that 10% of the indoor data but only 1.3% of the personal monitoring data was categorised as low concern (group II). Personal measurements generally had a higher HI than the corresponding indoor air measurements: the average ratio of personal to indoor HI was 1.5 (min 0.15; median 1.2; max 19); the average personal to indoor MCR ratio in the EXPOLIS dataset was 1.04 (min 0.32; median 1.00; max 2.52). When using personal measurements instead of indoor measurements, 10% of the cases moved from a ‘low concern’ (group II) to a ‘concern’ classification (group I, IIIA or IIIB). When personal instead of indoor data were used for risk screening, more cases shifted from the combined effects concern groups (IIIA or IIIB) to the single substance concern group (I) (15%) than vice-versa (5%). Thus, use of indoor air rather than personal monitoring data could lead to diverging conclusions with regard to combined risk, with a potential for underestimating the risk.

Clear differences in mixtures classifications were found when comparing indoor air samples from different EXPOLIS cities (Fig. 3): for 3 cities (Athens, Prague and Milan), the majority of indoor air samples are situated in the single substance concern group (Athens: 84%, Prague: 65% and Milan: 73%). Most of the remaining indoor air samples for these cities are located in the group of concern for combined effects (groups IIIA & IIIB), while <1% of samples are located in the low concern group. In contrast, for the cities of Helsinki, Oxford and Basel, a minority of samples are situated in the single substance concern group (Helsinki: 9%; Oxford: 30% and Basel: 17%). The majority of samples are situated in the group of concern for combined effects due to multiple substances (group IIIB: Helsinki: 66%; Oxford: 60% and Basel: 60%) with only 20% (Helsinki), ~1% (Oxford) and 7% (Basel) of indoor air mixtures in the low concern group (group II).

3.4. The Flemish homes and schools surveys (middle graph of Fig. 2)

Table 4 shows that there is a larger fraction of indoor samples in the low concern group for the Flemish school data (group II: 98%; group I and IIIA: 0% and group IIIB: 2%) compared to the Flemish homes data (group II: 58%; group I: 8%; group IIIA: 9% and group IIIB: 25%). However, this difference is largely due to the differences in the number and type of substances on which the MCR calculations are based. Whereas 10 substances were monitored in the school campaign, 21 substances (including the 10 substances from the schools campaign) were monitored in the homes monitoring campaign (see Table S1 of supplementary information). Removing the 11 additional substances from the MCR calculations for the residential indoor air samples, and thus calculating the
NO2 which was critical in the EXPOLIS and Flemish surveys, was not a critical component in the OQAI study. However, as shown in Table 3, the published RVs are based on a common set of substances, the difference in classification between schools and homes becomes small.

3.5. The French OQAI study (lower graph of Fig. 2)

The OQAI data have a larger fraction of samples classified as single substance concern (group I) compared to the EXPOLIS and Flemish homes and schools data (Table 4).

In the OQAI survey acrolein, which was not monitored in the EXPOLIS and Flemish surveys, turns out to be the critical component. NO2 which was critical in the EXPOLIS and Flemish surveys, was not measured in OQAI.

Retaining only the 11 substances which were measured in both OQAI and EXPOLIS (excluding NO2 and acrolein, for example) provides a better comparison of the OQAI and EXPOLIS data, and, indeed, the resulting classifications become very similar (Table 5). In such a comparable analysis, trichloroethylene is then the critical substance both in the EXPOLIS and the OQAI data.

3.6. Impact of choice of RV on MCR–HI classification

The basic RV list is derived using a decision-tree process to arrive at a consistent set of RVs. However, as shown in Table 3, the published RVs for the same substance vary by a factor of between 1 and 300. When replacing the basic RV list by the min RV list, almost all samples are assigned to the single substance concern group (group I) (Fig. 4). For the Flemish homes and schools data, all samples shift to group I, which is mainly due to formaldehyde exceeding its min RV value. Formaldehyde is also the main reason for the shift of the OQAI samples towards group I. In EXPOLIS, trimethylbenzenes are responsible for a partial shift to group I, and about 40% of the samples remain in group IIIB (concern for combined effects by several substances). Using the max RV list, on the other hand, leads to about 80% (EXPOLIS) and more than 90% (Flemish homes and schools) of the samples being classified as “low concern” and thus requiring no further action. Since the min and max RV values for acrolein are almost equal, the number of samples in group I in the OQAI data is reduced by only 10%.

3.7. Impact of treating non-detects on MCR–HI classification

In all of the above described analyses, non-detects were assigned half the value of the LOD or LOQ (depending on which one was reported in the database). Sensitivity of the analytical method can significantly impact the MCR in cases where chemicals are found at levels around the LOD/LOQ and in the same range as the health-based reference values used. We explored the impact of analytical sensitivity by replacing the non-detects by zero. This resulted in a larger fraction of samples in the low concern group in the EXPOLIS data (shift from 10 to 36% for the indoor data and from 1 to 23% for the personal monitoring data). There was hardly any effect of this non-detect treatment on the classification for Flemish homes and schools and for the OQAI data.

4. Discussion

The results show that the pattern of combined risks observed in earlier studies of exposures to mixtures in water (Han and Price, 2011) also occurs for the indoor air data. Specifically, MCR is small relative to n, MCR declines as HI increases, the mixtures with the largest HI values fall into the group of single substance concern (group I), and HI does not increase with increasing number of substances detected in the samples (data not shown).

A high variability in the proportion of mixtures of concern for combined effects (groups IIIB and IIIB) was observed across the different surveys and analyses (including different approaches for selecting RVs). The fraction of samples in these groups of concern for combined effects varied from 1% (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 substances monitored, analytical performance, and choice of RVs.
None of the studies included all the substances on the priority list for monitoring proposed in the INDEX report (JRC, 2005). Only four substances were common across the EXPOLIS, OQAI and Flemish homes and schools surveys. The number and identity of the substances included in the surveys had a significant impact on sample classification. Using the whole list of substances of each survey resulted in apparently large differences with regard to concern for potential mixture effects in the EXPOLIS and OQAI surveys (Fig. 2). Limiting the MCR calculations for these surveys to their common substances (n = 11), and thereby excluding some of the substances driving the MCR, led to only marginal differences in classification between the surveys. A similar effect was seen when the Flemish datasets (homes and schools) were reduced to their common substances (n = 10), resulting in much more convergence in the classification.

Choice of the health-based reference value (RV) strongly influences the results of the MCR assessment — potentially even more than it would influence a substance-by-substance assessment. There is no database available that provides a consistent set of RVs for all substances in our study. Moreover, RVs derived by different institutions or organizations for the same chemical can differ by more than an order of magnitude, even when the same endpoint is considered. We followed a step-wise approach to select the most appropriate RV for each substance from the available databases (Fig. 1). Then, the impact of the choice of the RV was illustrated by selecting either the lowest or the highest RVs for all substances in the database. As there is no single list of toxicological reference values for all the substances of interest, it is likely that — from a precautionary viewpoint — a risk assessor would select the lowest values from the databases consulted.

For mixtures, however, this approach carries the risk of a focus on compounds with very low and very uncertain RVs extrapolated from in vivo or even in vitro data, without due regard for compounds with (higher) RVs based on solid human epidemiology. A step-wise approach is therefore advisable, as undertaken for the basic list in this study, resulting in the application of both low and high RVs. Nevertheless, there is definitely a need for a more extended authoritative database of toxicological reference values for (indoor) air substances than is currently available (e.g. the WHO (indoor) air quality guidelines). The AgBB and AFSET LCI values do not always meet the requirements as set out in the current study.

When applying the MCR to five indoor air data sets, consisting of individual indoor or personal non-occupational exposure data in EU countries, from 2% (Flemish schools) to 77% (Expolis, Basel, personal) of the data was classified in the groups of concern for combined effects (groups IIIA and IIIB of the MCR methodology). This represents a significant number of cases where a chemical-by-chemical approach would fail to distinguish the need for further investigation of such combined effects. The majority of the mixtures in groups IIIA and IIIB were not the ones with the largest HI-values. Those mixtures occurred in group I and would have been identified by a chemical-by-chemical approach as in group I the HQ of at least one compound exceeds 1. For group I and IIIA mixtures risk management could be focused on the substance corresponding to the HQmax.

By using the MCR as a screening tool, the task of performing combined risk assessments can be limited to those mixtures which are identified to be of concern for combined effects of several substances (group IIIB).

The MCR methodology (Price and Han, 2011) makes use of available chronic health-based guidance values, without consideration of commonality of endpoints or mode of action. Thus, the MCR screening tool
is based on the conservative assumption that all substances present in the mixture could provoke the same endpoint, via the same mode of action; in other words, the MCR tool is based on a dose addition assumption for all substances in the mixture.

The MCR screening tool identifies mixtures with a potential concern of mixture toxicity. For group IIIB mixtures, higher tier cumulative risk assessment would then be needed in order to evaluate whether the potential toxicity is caused by the overly conservative assumptions of the screening method, or whether the substances in the mixture really pose a mixture toxicity concern.

A first step in the higher tier combined risk assessment could involve refining hazard characterization by considering communalities in health endpoints or target organs (Meek et al., 2011), and thereby replacing the generic HI from the screening tool by endpoint or target organ specific HIs. In other words, for substances affecting dissimilar health endpoint or target organs, independent action (effect addition) can be assumed, and its HQs are no longer summed in the higher tier target organ or endpoint-specific HI. Besides application of the two additivity concepts (dose additivity for joint action and effect additivity for independent action), additional refinements could be made by considering whether interactions (antagonistic or synergistic) are in place; ATSDR proposed a modified hazard index approach, accounting for interactions by multiplying the HI with a factor reflecting both the uncertainty and strength of evidence that interactions take place (ATSDR, 2004). However, in most cases exposures at environmentally relevant levels are best represented by dose addition (Kortenkamp et al., 2009).

Other higher tier steps in refining the hazard assessment involve incorporating additional information on the potency of individual substances for the common effect (which is not always the critical effect the RV is based on), using the point of departure instead of the RV, incorporating more specific information on mode of action, and both kinetic and dynamic aspects (Meek et al., 2011).

5. Conclusions

This work demonstrates the usefulness of MCR as a screening tool for identifying indoor air mixtures requiring further assessment of combined exposure. For those identified mixtures, higher tier assessment could involve considering communalities in endpoints, target organs, mode of action affected by the various substances present in the mixtures. Ideally, classification of mixtures should be based on MCR calculations using datasets that contain all compounds with a potential significant contribution to the MCR. This highlights the need for a comprehensive, harmonized and common set of substances in pan-European IAQ monitoring surveys as further discussed by Crump et al. (2013).

Further challenges in unravelling the issue of mixture toxicity in indoor air are i) the generation of indoor air databases that are optimal for the assessment of mixture toxicity and include an appropriate target list of substances determined with a sufficiently low level of quantification, ii) identification of relationships between indoor sources and groups of substances with a substantial contribution to MCR, and iii) investigation of interactions between pollutants in indoor air, including chemical reactions occurring in the indoor air.

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Potential conflicts of interest

One of the authors, namely Paul Price, works for the Dow Chemical Company. The Dow Chemical Company produces a wide range of chemicals, some of which have been detected in indoor air. Since this paper addresses the pattern of exposures in observed monitoring data and is not focused on the safety of specific compounds the author declares no conflict of interest.

Disclaimer

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