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Examining the feasibility of mixture risk assessment: A case study using a tiered approach with data of 67 pesticides from the Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

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ABSTRACT

The way in which mixture risk assessment (MRA) should be included in chemical risk assessment is a current topic of debate. We used data from 67 recent pesticide evaluations to build a case study using Hazard Index calculations to form risk estimates in a tiered MRA approach in line with a Framework proposed by WHO/IPCS. The case study is used to illustrate the approach and to add detail to the existing Framework, and includes many more chemicals than previous case studies.

A low-tier MRA identified risk as being greater than acceptable, but refining risk estimates in higher tiers was not possible due to data requirements not being readily met. Our analysis identifies data requirements, which typically expand dramatically in higher tiers, as being the likely cause for an MRA to fail in many realistic cases. This forms a major obstacle to routine implementation of MRA and shows the need for systematic generation and collection of toxicological data. In low tiers, hazard quotient inspection identifies chemicals that contribute most to the HI value and thus require attention if further refinement is needed. Implementing MRA requires consensus on issues such as scope setting, criteria for performing refinement, and decision criteria for actions.

1. Introduction

Mixture risk assessment (MRA) is the assessment of the cumulative risk to human health or the environment from multiple chemicals via multiple routes. Currently, chemicals are routinely assessed on a chemical-by-chemical basis, with the notable exception of the approach to dioxin-like chemicals, wherein selected PCBs, dioxins and furans are assessed collectively by application of a toxic equivalency quotient/factor (TEQ/TEF) approach (van den Berg et al., 1998). There is concern that the chemical-by-chemical approach may not be sufficiently protective if two or more chemicals have the same toxic effect (Boobis et al., 2008; Kortenkamp et al., 2009). It is incontrovertible that humans are exposed to more than one chemical at a time, for example to the multiple chemicals found in food, in air and drinking water, and in household and consumer products and cosmetics. Mixture toxicology is the branch of toxicology that deals with predicting and managing the exposure of humans or the environment to multiple chemicals and their associated toxicological effects. The existence of a mixture *per se* does not always indicate a risk to human or environmental health, but indicates the need to examine whether more accurate estimations of risk will be produced by considering all of the chemicals that are present.

Whilst there is a broad consensus on the basic science of mixture toxicology (Kortenkamp et al., 2009; DG Health and Consumer Protection, 2011), the path to regulatory implementation of these considerations, as an MRA, in chemical risk assessment is less clear. Options were outlined in an EFSA opinion (EFSA,

Abbreviations: ADI, acceptable daily intake; AL, acceptable level; CAG, cumulative assessment group; EL, exposure level; GAP, good agricultural practice; GEMS, Global Environment Monitoring System-Food contamination and assessment programme; HI, hazard index; HQ, hazard quotient; IEDI, international estimated daily intakes; JMPR, Joint FAO/WHO Meeting on Pesticide Residues; LOAEL, lowest observed adverse effect level; MCR, maximum cumulative ratio; MoE, Margin of Exposure; MRA, mixture risk assessment; MRL, maximum residue level; NOAEL, no observed adverse effect level; PBDE, polybrominated diphenyl ether; PoD, point of departure; PPDB, pesticide properties database; RfD, reference dose; SF, safety factor; SMILES, Simplified Molecular Input Line Entry Specification; SMTR, supervised trials median residue; TTC, Threshold of Toxicological Concern; WHO/IPCS, World Health Organization/International Programme on Chemical Safety.

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2008) and, currently, proposals for MRA approaches include a Framework developed by WHO/IPCS for "Risk assessment of combined exposure to multiple chemicals" (Meek et al., 2011), a decision tree of the European Commission Scientific Committees (DG Health and Consumer Protection, 2011) and an approach examining the contribution of individual mixture components to the joint effect, termed maximum cumulative ratio (Price et al., 2014). Of these, the WHO/IPCS Framework is the most widely used. It has the stated aim of aiding "risk assessors in identifying priorities for risk management for a wide range of applications where co-exposures to multiple chemicals are expected." The Framework is described as hierarchical, phased and tiered with "integrated and iterative consideration of exposure and hazard at all phases, with each tier being more refined". A 'more refined' tier is described as being less cautious, more certain, more labour intensive and more data intensive than the preceding tier. The underlying philosophy is to invest more resources in the analysis only if assessments based on less data intensive assumptions indicate that levels deemed to be acceptable are exceeded. The tiers detailed in the WHO/IPCS Framework are not fixed; their use will depend on data availability, and tiers can be added or removed as necessary. Use of either predictive or probabilistic methodologies is placed in various tiers and uncertainty is considered at each tier.

Two areas in which the WHO/IPCS Framework does not provide much detail are 1) criteria for ceasing refinement and applying risk management measures, and 2) criteria for the grouping of chemicals within an MRA. A decision about ceasing refinement is needed at the end of each tier when the risk has not been shown to be acceptable. It is not clear whether the implementation of risk management that would be mandated if the highest tier was exceeded should also be mandated in low tiers when progression is not achievable due to data gaps or difficulties with data availability. Grouping of chemicals for MRA is proposed in the second tier of the WHO/IPCS Framework but no details are provided on what the need or prerequisites for grouping are. Outstanding questions include, for example, would grouping on the basis of chemical structure be acceptable? Should the grouping approach have particular demands in terms of retaining conservatism or would the Framework allow this property to be lost? EFSA has begun the process of identifying cumulative assessment groups (CAGs), commencing with the definition of CAGs covering phenomenological effects of pesticides on thyroid and nervous system (EFSA, 2013), although the full set of CAGs may need to be available before they can meaningfully be introduced into MRA. We have explored options in both these areas within this case study.

The guiding approach that is used in most MRA approaches is the Hazard Index (HI), in which firstly, hazard quotients (HQs) are calculated for each chemical in the exposure scenario by dividing their exposure level by an 'acceptable' level, such as an acceptable daily intake (ADI) or reference dose (RfD); secondly, the HQs are summed to give the HI (Teuschler and Hertzberg, 1995). Conventionally, a HI of greater than one indicates that the total exposure exceeds the level considered to be 'acceptable', where the definition of acceptable depends on the denominators used in the HQ calculation. The Margin of Exposure (MoE) approach is conceptually similar to the HI, but usually operates with 'points of departure' (PoD) values such as benchmark doses or no-observed adverse effect levels (NOAELs) to which safety or uncertainty factors have not been applied. Whereas the critical value for an HI is *greater than* or equal to 1, the critical value for an MoE is *less than* or equal to one hundred.

Two prior case studies have presented examples of MRA for triazole pesticides and for polybrominated diphenyl ethers (PBDEs) (EFSA, 2009; Meek et al., 2011). The triazole case study used the hazard index (HI) approach to explore a tiered strategy in detail, but artificially restricted their analysis to seven or eleven pesticides for endpoints of cranio-facial malformation and hepatotoxicity, respectively, for reasons of data availability (EFSA, 2009). The study calculated low tier HI values that were mostly below one: 0.1 (total Dutch population) and 0.24 (children sub-population). However, when HI values were calculated for individual food commodities, as part of an evaluation of the use of HI in maximum residue level (MRL) setting, exposure to bitertanol via apples had a HI of 1.19, which reduced to 0.17 in the next tier.

The PBDE case study dealt with a complex situation comprising seven components, each of which was itself a mixture of PBDE congeners. A Tier 1 assessment produced MoEs of 300 (based on upper-bound of a deterministic exposure estimate) or approximately 30 (based on biomonitoring) and, despite 30 being below the critical value of 100 for MoEs, the authors considered that the in-depth evaluation of human health risks from PBDE mixtures was a 'low priority' (Meek et al., 2011). Further refinement in higher tiers and the need for risk management was not explored. Both studies showed the need for further case studies to explore the possible outcomes for scenarios that are different to those reported so far; and in this paper we provide a scenario involving many more chemicals (67) than have been previously considered.

Here, we present a case study based on a dataset compiled from evaluations of 67 pesticides by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) between 2006 and 2010. We use this case study to explore the options for refinement within the hazard portion of a tiered MRA approach following the conceptual approach of the WHO/IPCS Framework (Meek et al., 2011). Our aim was to use a relatively large, regulatory data set to explore how refinement options affect the outcome of MRA where differing amounts of data are available. We have utilized the international estimated daily intake (IEDI) values calculated for 67 pesticides in annual JMPR reports from 2006 to 2010 and use this dataset to work through the tiers of the proposed Framework. The case study does not represent an actual MRA for pesticides, rather it is used to understand and explore the tiered approach and to explore the consequences of differing data requirements and assumptions for MRA.

2. Materials and methods

The guiding approach used in this case study is the Hazard Index (HI), which is calculated using the formula:

$$HI = \sum_{i=1}^{n} \frac{EL_i}{AL_i}$$

where *EL* is the exposure level, *AL* is the acceptable level, and *n* is the number of chemicals in the mixture. A hazard quotient (HQ) is calculated for each chemical, by dividing *EL* by *AL*, and the HQs are summed to give the HI. Various measures for exposure levels and acceptable levels may be applied; the only constraint is that both must be expressed in the same unit. Input values for AL can be, for example, Acceptable Daily Intake (ADI) values or Reference Doses (RfD) for specific endpoints. Where mean values are given, the ordinary arithmetic mean was used.

The dataset used in this case study was compiled from exposure and risk data provided for 67 pesticides that were evaluated in the five annual Joint FAO/WHO Meeting on Pesticide Residues (JMPR) reports from 2006 to 2010 (JMPR, 2010; JMPR, 2009; JMPR, 2008; JMPR, 2007; JMPR, 2006). 76 evaluations were included, with 9 pesticides being evaluated twice. JMPR reports establish acceptable daily intakes (ADIs) and also report international estimated daily intakes (IEDIs) which are calculated on a weight per person basis