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Should the scope of human mixture risk assessment span legislative/regulatory silos for chemicals?

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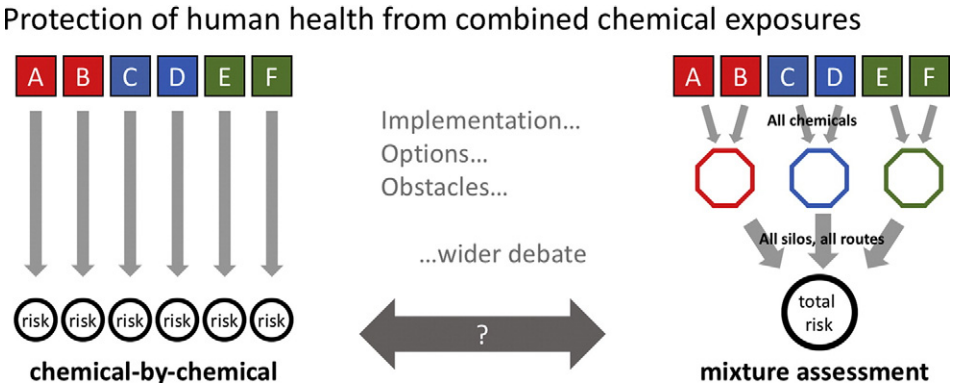
HIGHLIGHTS

- Humans are exposed to multiple chemicals covered by different EU regulations.
- Mixture effects that have been shown experimentally are not currently regulated.
- Combined human health risk from multiple chemicals/routes is not routinely assessed.
- Presented examples show the need for MRA to bridge regulatory 'silos'.
- A wider debate of options and obstacles in MRA implementation is desirable.

GRAPHICAL ABSTRACT



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ABSTRACT

Current chemicals regulation operates almost exclusively on a chemical-by-chemical basis, however there is concern that this approach may not be sufficiently protective if two or more chemicals have the same toxic effect. Humans are indisputably exposed to more than one chemical at a time, for example to the multiple chemicals found in food, air and drinking water, and in household and consumer products, and in cosmetics. Assessment of cumulative risk to human health and/or the environment from multiple chemicals and routes can be done in a mixture risk assessment (MRA). Whilst there is a broad consensus on the basic science of mixture toxicology, the path to regulatory implementation of MRA within chemical risk assessment is less clear.

In this discussion piece we pose an open question: should the scope of human MRA cross legislative remits or 'silos'? We define silos as, for instance, legislation that defines risk assessment practice for a subset of chemicals, usually on the basis of substance/product, media or process orientation. Currently any form of legal mandate for human MRA in the EU is limited to only a few pieces of legislation. We describe two lines of evidence, illustrated with selected examples, that are particularly pertinent to this question: 1) evidence that mixture effects have been shown for chemicals regulated in different silos and 2) evidence that humans are co-exposed to chemicals from different silos. We substantiate the position that, because there is no reason why chemicals allocated to specific regulatory silos would have non-overlapping risk profiles, then there is also no reason to expect that

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MRA limited only to chemicals within one silo can fully capture the risk that may be present to human consumers. Finally, we discuss possible options for implementation of MRA and we hope to prompt wider discussion of this issue.

1. Introduction and background

The current approach to chemical regulation routinely depends on assessment on a chemical-by-chemical basis, however there is concern that this approach may not be sufficiently protective if two or more chemicals have the same toxic effect on humans (Boobis et al., 2008; Kortenkamp et al., 2009). Under EU law, the only notable exception to the chemical-by-chemical paradigm is the Toxic Equivalency Quotient/Factor (TEQ/TEF) approach (van den Berg et al., 1998) in which dioxin-like chemicals, including selected polychlorinated biphenyls, dioxins and furans, are assessed collectively in regulations concerning maximum limits in food items (Regulation EC No 1881/2006 on setting maximum levels for certain contaminants in food). Nonetheless, this approach, as conceived, is limited to the risk assessment of a particular set of compounds (halogenated aromatic hydrocarbons) with a particular property (toxicological similarity to dioxin as manifested by AhR activation).

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. The unintentional exposure of humans to multiple chemicals through multiple routes constitutes the 'mixture' situation that is the focus of our interest in this discussion pieces; and our discussion does not apply directly to commercial products that contain multiple, defined ingredients, sometimes called 'intentional' mixtures. Although the existence of a mixture per se does not always indicate a risk to human or environmental health, experimental evidence of mixture effects with chemicals combined at low, ineffective levels (Kortenkamp, 2014) highlights that this should become the topic of assessments that examine whether more accurate estimations of risk will be produced by considering all of the chemicals that are present.

Mixture risk assessment (MRA) is the assessment of the cumulative risk to human health or the environment from multiple chemicals via multiple routes. 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. In the United States, guidelines on the Health Risk Assessment of Chemical Mixtures have existed for some time (EPA, 1986; 2000). In Europe, options were outlined in an opinion of the European Food Safety Authority (EFSA, 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). The German Federal Institute for Risk Assessment (BfR) have drafted a concept for how to take account of cumulative aspects in the context of the regulation of plant protection products and biocides (Stein et al., 2014).

In this discussion piece we pose an open question: should the scope of human mixture risk assessment (MRA) cross legislative remits? We have defined legislative remits, or regulatory 'silos', as the scope of single pieces of legislation that define the collection of toxicology or monitoring data for a subset of regulated chemicals, for example pesticides, biocides, food contaminants, food contact materials, pollutants and pharmaceuticals (Table 1). In the European Union, silos may be based on substance- or product-oriented regulations (e.g. pesticides, food contaminants, pharmaceuticals), media-oriented (e.g. water, soil etc.) or process-oriented pieces of legislation (e.g. industrial emissions). Currently any form of legal mandate for MRA in human health is limited to only a few pieces of legislation, or silos (e.g. maximum residue limits for pesticides in food; registration, evaluation and authorisation of chemicals (Kortenkamp et al., 2009)), and so it is likely that the scope of an MRA will naturally be set within a silo unless the need for a wider scope is recognised.

If the aspiration is the protection of human health from risks of all chemicals by all routes and uses, then two lines of evidence are

Table 1
Examples of regulatory remits ('silos') in European Union law.

	Remit ('silo')	Legislation	Type
General chemicals control	Authorisation of chemicals (REACH)	Regulation (EC) No 1907/2006	Substance-oriented
	Classification, labelling, packaging (CLP)	Regulation (EC) No 1272/2008	Substance-oriented
Special uses of chemicals	Pesticides authorisation	Regulation (EC) 1107/2009	Substance-oriented
	Biocidal products	Regulation (EU) 528/2012	Substance-oriented
	Human medicines	Directive 2001/83/EC	Substance-oriented
	Herbal medicines	Directive 2004/24/EC	Substance-oriented
	Veterinary medicines	Direction 2001/82/EC	Substance-oriented
Emission control	Pollution prevention and control	Directive 2008/1/EC	Process-oriented
	Industrial emissions	Directive 2010/75/EU	Process-oriented
	Environmental impact assessment	Directive 85/337/EEC	Process-oriented
Quality of environmental media	Water framework	Directive 2000/60/EC	Media-oriented
	Drinking water	Directive 98/83/EC	Media-oriented
	Air quality	Directive 2008/50/EC	Media-oriented
Food law	Food additives authorisation	Directive 89/107/EEC	Substance-oriented
	Food contact materials	Regulation (EC) No 1935/2004	Substance-oriented
	Pesticide residues	Regulation (EC) No 396/2005	Substance-oriented
	Food contaminants	Regulation (EC) No 1881/2006	Substance-oriented
	Feed additives authorisation	Regulation (EC) No 1831/2003	Substance-oriented
	Feed additives assessment	Directive 2001/79/EC	Substance-oriented
Non-food consumer products	General product safety	Directive 2001/95/EC	Substance-oriented
	Cosmetics	Directive 76/768/EEC	Substance-oriented
Occupational health	Workplace health and safety	Directive 89/391/EEC	Process-oriented