Toxic Mixtures

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C6860 Modern Methods of Pollutant Analysis

TOXIC MIXTURES

- What are toxic mixtures.
- General principal or past approach to assess toxic mixture.
- Modern approach to assess toxic mixture.
- Methodology
- Knowledge gaps
- Conclusions

TOXIC MIXTURES

- **Products:**Substances that are mixtures themselves multi-constituent substances, MCS; materials of unknown or variable composition, complex reaction products or biological materials, UVCB, Products that contain more than one chemical.
- **Emission**:Chemicals jointly emitted from production sites, during transport processes, and consumption or recycling processes.
- **Imissions:**Several chemicals that might occur together in environmental media (water, soil, air), food items, biota and human tissues, as a result of emission from various sources, via multiple pathways.

Groups

- Metals zinc with other metals, such as copper, vanadium, nickel and iron
- Dioxins, polychlorinated biphenyls and other chlorinated hydrocarbons
- Long chained hydrocarbans with aromatic rings
- Pesticides, herbicides, fungicides
- Cosmatic products etc

General principles of mixture toxicology

- More than 50 years ago, three basic types of action for combinations of chemicals were defined (Bliss 1939, Loewe and Muischnek 1926, Plackett and Hewlett 1948, Plackett and Hewlett 1952):

1-Dose/concentration addition (similarly acting chemicals)
2- independently acting chemicals
3-Interactions

General principles of mixture toxicology

- **Dose/concentration addition (similarly acting chemicals):** the effects can be estimated directly from the sum of the doses/concentrations, scaled for relative toxicity
-

$$D_{mix} = \sum_{i=1}^{n} aD_i$$

General principles of mixture toxicology

- **Independently acting chemicals:** the effects can be estimated directly from the probability of responses to the individual components (response addition) or the sum of biological responses (effects addition).
- $pM = 1 – (1-p1) (1-p2) (1-p3)… (1-pn)$

General principles of mixture toxicology

- **Interactions**:Interaction describes the combined effect of two or more chemicals as stronger (synergistic, potentiating, supra-additive) or weaker (antagonistic, inhibitive, subadditive,infra-additive) than would be expected on the basis of dose/concentration addition or response addition. Interactions may therefore vary according to the relative dose levels, the route(s), timing and duration of exposure (including the biological
- persistence of the mixture components), and the biological target(s).

General principles of mixture toxicology

- **Toxicokinetic interactions**; these are a common cause of deviations from additivity. Examples are chemicals modifying the absorption of others e.g., skin penetration enhancing substances in cosmetics.
- **Metabolic interactions**: chemicals modifying the metabolism of other mixture components.
- **Toxicodynamic interactions**: interactions between the biological responses resulting from exposure to the individual chemicals, for example resulting from similar targets (e.g., ligand-receptor interaction)
- Kortenkamp *et al. (2009)*

General principles of mixture toxicology

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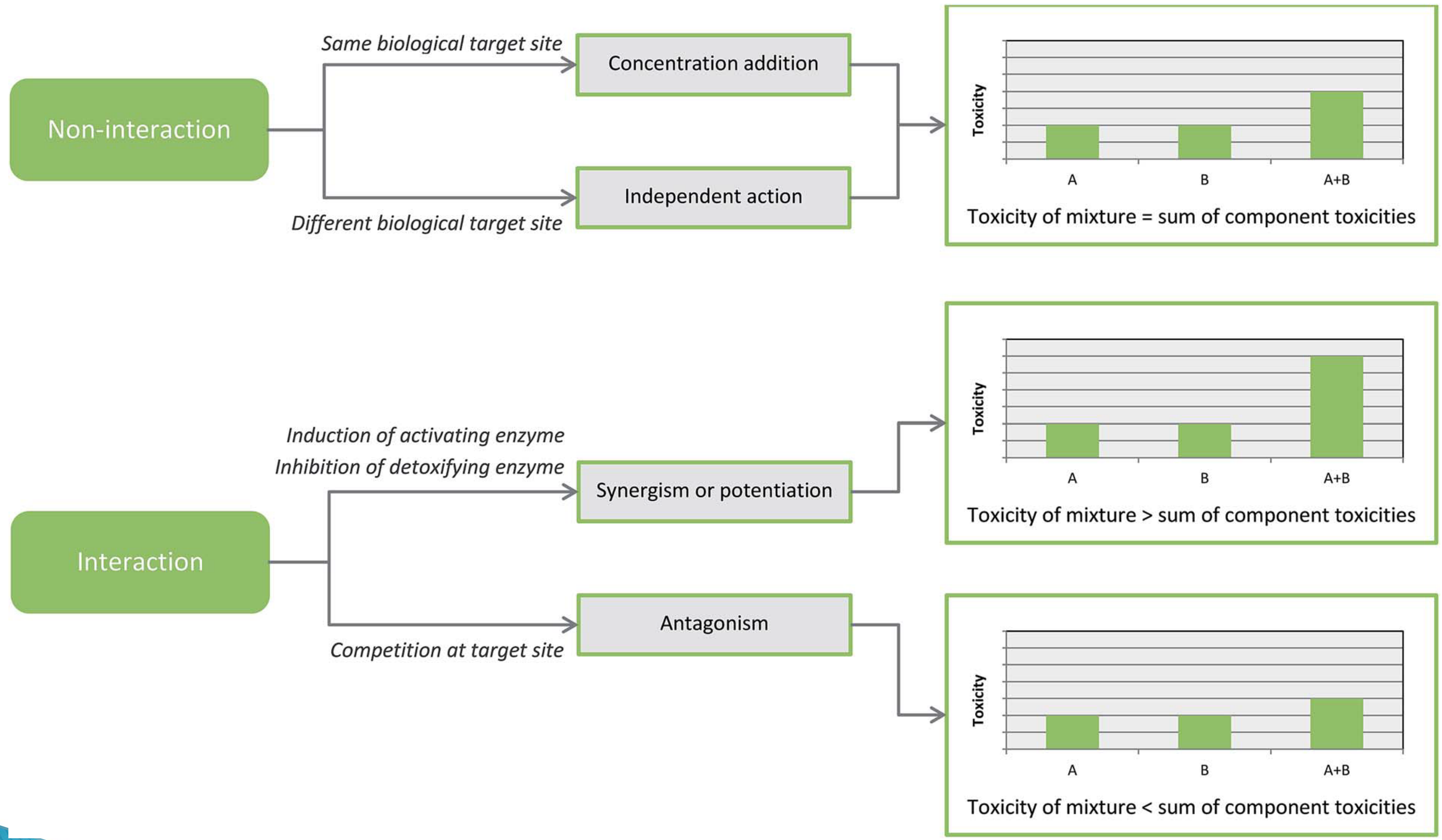

Fig. Schematic demonstrating the theoretical models of chemical mixture effects.

Modern approach for assessing toxic mixtures

- **Whole-mixture approaches**: An assessment may also be based on data generated with a mixture of reasonably similar composition or a “surrogate mixture.
- If a mixture cannot be assessed in its entirety, it may be possible to separate fractions (e.g., mixtures of petroleum hydrocarbons into aliphatic fractions of certain chain length ranges and aromatic fractions) and to assess the toxicities of the fractions e.g diesel exhaust (gaseous fractions and particulate matter fraction).
- **Limitation:** Testing whole mixtures does however not provide specific information on interactions or the toxicity of individual mixture components.

- **Advantage:** of accounting for any unidentified materials in the mixture and for any interactions among mixture components (Boobis et al. 2011).

Modern approach for assessing toxic mixtures

- **Component based approaches**: If the components of a mixture are known, a component-based approach is usually
- performed. Information on the mode of action should be used to assess the type of
- combined action (independent action, similar action) applicable.

Modern approach for assessing toxic mixtures

- **Grouping of mixture components based on structural similarities:** The chemicals in a mixture can be grouped into assessment groups or “blocks” on the basis of their chemical structure using tools such as the OECD (Q)SAR Application Toolbox (OECD 2009) and also according to ECHA and EFSA guidelines.

Modern approach for assessing toxic mixtures

- **Dose/concentration addition approaches:** Methods for dose/concentration addition approaches most frequently used are the hazard index (HI), the reference point index (RfPI, also known as point of departure index (PODI), the relative potency factor (RPF), or the toxic equivalency factor (TEF).

Modern approach for assessing toxic mixtures

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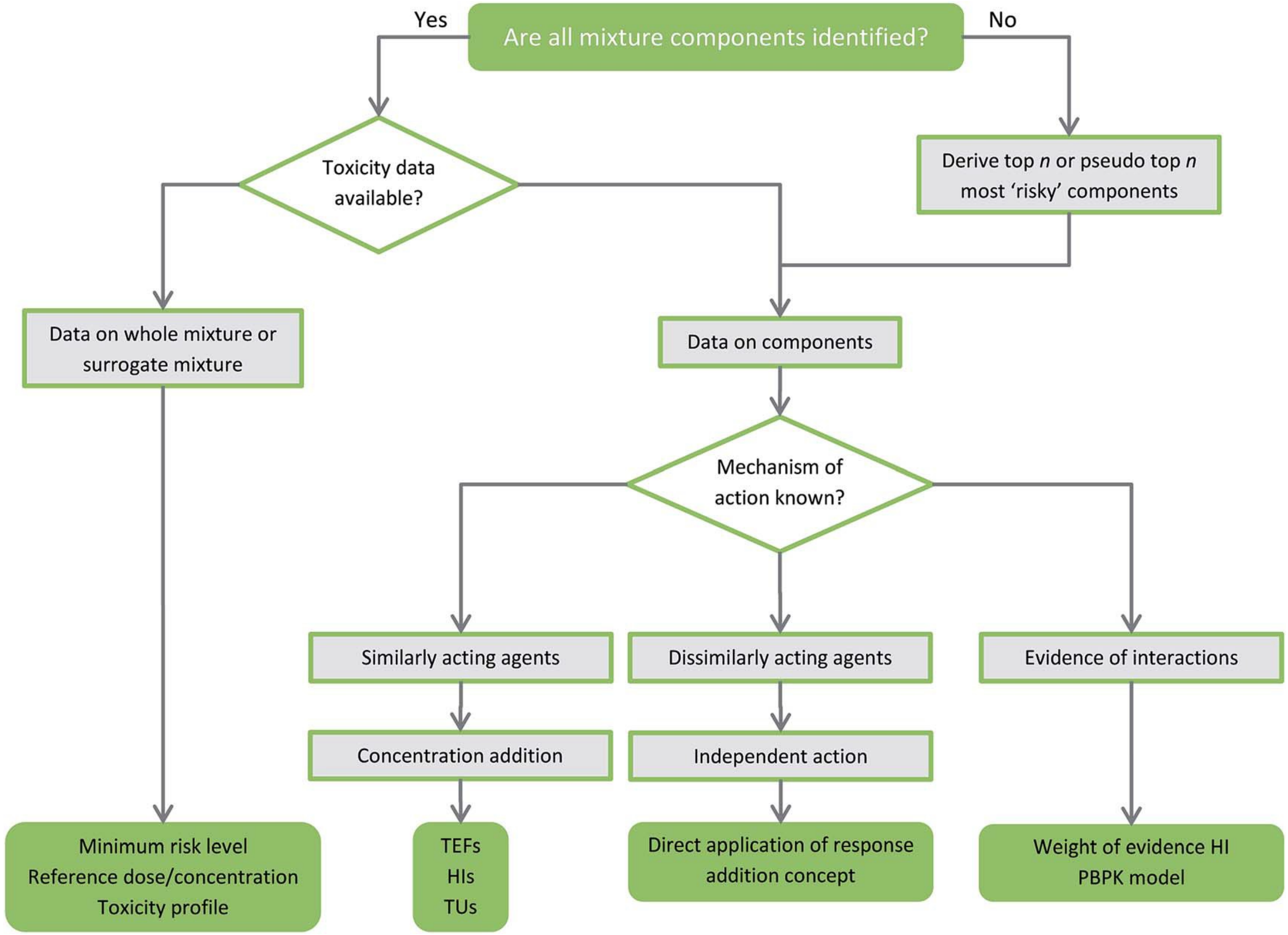

Fig. Flow chart of general guidance on the depth of toxicity data available for chemical mixtures and appropriate risk assessment methods.

Methodology

- According to WHO/IPCS 2009
- Iterative process (exposure and hazard)
- Several tiers of increasing data analysis for next step
- Decision based analysis of relevant information at early stage
- Early consideration of potential for exposure compared to TCC (Threshold of Toxicological Concern)
- Public health concern

Methodology

- Under **REACH** regulation, some complex substances of pesticide and biocidal formulations, and cosmetic products are considered for risk assessment.
- At **EU** level there is currently no generally accepted approach for the methodology to conduct a risk assessment for chemical mixtures and a case-by-case approach is followed depending on the mixture under review.
- Guidance for conducting cumulative risk assessments has been published by the Environmental Protection Agency of the USA **(USEPA 2002),** the UK Committee on
- Toxicity of Chemicals in Food, Consumer Products and the Environment **(COT 2002)**, the
- Norwegian Scientific Committee for Food Safety **(VKM 2008)**, and the German CVUA **(CVUA 2007).**

Knowledge gaps

- With regard to the assessment of chemical mixtures a major knowledge gap at the present time is the lack of knowledge on where, how often and to what extent humans and the environment are exposed to certain chemical mixtures and how exposure may change over time.
- There is a need to better understand human and environmental exposures, both through the use of monitoring and modeling (Tornero-Velez *et al. 2011).*
- For many chemicals, there is no good information on mode of action. Currently there is neither an agreed inventory of modes of action, nor a defined set of criteria on how to characterize or predict a mode of action for data-poor chemicals or how to group chemicals into assessment groups.
- Interactions of chemicals in mixtures are difficult to see, particularly for long-term effects.
- Research is needed to define criteria that predict potentiation or synergy.

Knowledge gaps

- In ecotoxicology, the problem is even more complex. A knowledge of all possible modes of action that may occur in the different types of organisms of a complex biological community is difficult (if not impossible) to be attained. On the other hand, it must be considered that ecologically relevant endpoints are generally broader and not so specific Toxicity and Assessment of Chemical Mixtures (e.g. toxicity on specific organs, etc.) as in human toxicology. A full review of the literature should be made to prepare a state-of-the-art on mixtures biodegradation modeling.

Conclusions

- Is there scientific evidence that when organisms are exposed to a number of different chemical substances, these substances may act jointly in a way (addition, antagonism, potentiation, synergies, etc.) that affects the overall level of toxicity?
- Yes, under certain conditions, chemicals will act jointly in a way that the overall level of toxicity is influenced.
- Although Several approaches for the assessment of the mixture effects of chemicals already exist such as dose addition and independent action. And have their advantages and disadvantages of the different approaches but still sufficient knowledge is required to assess chemical mixtures in a more detailed way.

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Thank You