Experiences and approaches by the European Food Safety Authority (EFSA)

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Food represents a complex mixture of chemicals. Usually substances are investigated as single entities and not in combination and this have raised the legitimate question whether other substances in food could exhibit combined or interactive adverse effects with the substance under investigation. There are three basic concepts of joint action or interaction of combination of chemicals.

Dose-additivity: All the chemicals in a mixture act in the same way, by the same mechanism and may only differ in their potencies. A group TDI should be allocated if exposure to several members of a structurally related series of chemicals is likely to occur frequently and if several members of the series have been demonstrated to have a common target organ(s), cellular target(s) and the same mode of action. Toxicological equivalence factors (TEF) can be introduced where there are adequate data and the potencies span 3-5 fold or more. It should be noted that with the exception of a few groups of chemicals, such as organophosphorous and carbamate pesticides or dioxins and dioxin-like compounds, precise mechanistic information on their toxic effects are scarce. Application of the dose addition model should not be applied to mixtures of chemicals that act by mechanism for which the additivity assumption is invalid.

Effect additivity: Allows for the addition of responses regardless of whether a common mechanism of action is known, e.g. US EPA approach to cancer assessment assumes effect additivity in decisions by summing excess individual cancer risk for separate chemicals which have different mechanisms of action. There is currently less convincing evidence for effect additivity across different classes of chemicals but there is a need for further consideration including the type of information required to define when the approach is valid.

Interactions: Responses deviate from additivity (synergism, antagonism). Interactions are generally only seen at exposure levels above the effect levels for the individual chemical (e.g. pharmacotherapy). There is presently hardly no evidence that such interactions would occur for man-made chemicals in food because risk characterisation based on NOAEL’s and uncertainty factors aims to ensure that the intake of each individual chemical would be without significant effects.
The European Food Safety Authority (EFSA)

Experiences and approaches for the assessment of chemical mixtures in food

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EFSA’ s Mission

- Provision of scientific advice and scientific and technical support in all fields which have a direct or indirect impact on food and feed safety
- Provision of independent information on all matters within these fields
- Risk communication
- Networking and collaboration
Scientific Activities (work themes)

- Providing scientific opinions, guidance and advice in response to questions;
- Assessing the risk of regulated substances and development of proposals for risk-related factors;
- Monitoring of specific risk factors and diseases;
- Development, promotion and application of new and harmonized scientific approaches and methodologies for hazard and risk assessment of food and feed.
Plant protection products

Legislative Framework: Regulation (EC) NO 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin
- (Art 10) EFSA shall assess the applications and the evaluation reports and give a reasoned opinion on the risks to the consumer associated with the setting, modification or deletion of an MRL
- (6) Important to carry out further work to develop a methodology to take into account cumulative and synergistic effects

Mixture Terminology

- Simple similar action (dose addition): same way, same mechanism, differs only in the potency
- Simple independent action (response or effect addition): mode of action and possible nature and site of action differ but chemicals do not modulate the effect of other constituents of the mixture
- Interaction (synergism or antagonism): combined effect resulting in a stronger or weaker effect than expected
Dose Additivity

- Allows for simple addition of doses for individual chemicals within a mixture regardless of whether the doses are themselves below threshold of actions.

Dose additivity – Group TDI

Group TDI should be allocated if:

- Exposure to several members of structurally related series of chemicals is likely to occur frequently.
- Several members of series have common target organ(s), cellular target(s) and the same mode of action.
- Toxicological equivalence factors (TEF) can be introduced where there are adequate data and the potencies span 3-5 fold or more.
Dose-additivity TEF approach

Toxic Equivalency Factors (TEF) approach relies on
- dose addition with no interactions between the components of the mixture.
- All chemicals exert the toxicological effect by the same mechanism of action and only differ in their potency.

Criteria for including a compound in the TEF scheme for dioxin-like compounds:
- Show a structural relationship to the PCDD/F
- Bind to the Ah receptor
- Elicit Ah receptor-mediated biochemical and toxic responses
- Be persistent and accumulate in the food chain

van den Berg at al. 1998
**Dose-additivity TEF approach**

Polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) and dioxin-like PCBs.

Total TEQ = \( \sum_{n1} (PCDD_i \times TEF_i) + \sum_{n2} (PCDF_i \times TEF_i) + \sum_{n3} (DL-PCB_i \times TEF_i) \)

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**TEF approach – Mixtures of PAH**

Several attempts to derive TEF for Polycyclic aromatic hydrocarbons (PAH) but:
- Lack of adequate data from oral carcinogenicity studies on PAH
- Binding to Ah receptor was not the only effect that determined the carcinogenic potency of PAHs
- Tumours in other tissues than those affected by critical compound (benzo[a]pyrene)

EC-Scientific Committee on Food, 2002
TEF approach – Mixtures of PAH

- Application of TEF approach for the assessment of PAH carcinogenicity after oral administration led to underestimation of potency of mixture PAH composition in coal tar
- Analytical data $\times$ TEF = carcinogenic potency of 1.5 $\times$ BAP content
- Oral administration of mixture = 5 $\times$ BAP content

EC-Scientific Committee on Food, 2002

Surrogate approach for mixture of PAH

Uses a single component as the measure of concentration in relation to the response of the whole mixture

For PAHs benzo[a]pyrene is used as a marker of exposure and of effects of the mixture

EC-Scientific Committee on Food, 2002
**Surrogate approach for mixture of PAH**

- Profiles (ratio relative to BAP) of measured carcinogenic PAH in food -> marker of occurrence
- Variation of profile in food compared to mixture used in carcinogenicity study (factor 2)
- Carcinogenic potencies of coal tar mixtures compared to potency predicted by BAP content (up to 5 times)
- Conservative assessment: carcinogenic potency of total PAHs in food is 10 times higher than of BAP content alone

*EC-Scientific Committee on Food, 2002*

**AFC Statement on the possibility of allocating a group-TDI for certain phthalates***

*expressed on 20 September 2005*

- Three phthalates (DBP, DEHP and BBP) appear to act on the same target organ (the testis)
- Their profile of effects at the hormonal and cellular level are however not identical and their individual modes of action have not yet been demonstrated
- DIDP and DINP primarily affect the liver rather than the testis; but even in this case, the end-points indicate that different mechanisms are involved.

“...Consequently, a group-TDI cannot be allocated for BBP, DBP, DEHP, DINP and DIDP...”

Effect additivity

Allows for the addition of responses regardless of whether a common mechanism of action is known. Currently less convincing evidence in support of effect additivity approach across different classes of contaminants with different MOA even when dealing with similar toxicological endpoints.

EFSA Dioxin Colloquium June 2004

Effect additivity


Review of toxicity data of approved additives in the EU showed that the possibility of effect additivity between food additives is a hypothetical rather than a practical safety concern.
**Effect additivity**

Need for further consideration of response additivity including the type of information required to define when the approach is valid

Examples of criteria

- No evidence of interaction
- Same type of response
- Same organs
- Available evidence indicates general MOA (inducers Vs promotors)

**Interactions**

Response deviate from additivity (synergism, antagonism), i.e. combined effect resulting in a stronger or weaker effect than expected
Interactions

- Interactions are generally only seen at exposure levels above the effect levels for the individual chemical.
- Presently virtually no evidence that such interactions would occur for man-made chemicals in food because risk characterisation based on NOAEL’s and uncertainty factors aims to ensure that the intake of each individual chemical would be without significant effect.

Conclusion on the assessment of dietary intake of low- dose chemical mixtures

- Dose-additivity: group ADIs for compounds with common target organ (cellular target), same MOA, co-occurrence
- Effect-additivity: Currently less convincing evidence in support of effect additivity across different classes of chemicals, but more research needed
- Interactions: only seen at exposure levels above the effect levels for the individual chemicals. Possibility of interactions between low-dose chemical exposure is rather a hypothetical rather than a practical safety concern.
THANK YOU FOR YOUR ATTENTION