Die Stellungnahme der Scientific Committees der Generaldirektion Gesundheit zur Bewertung von Kombinationswirkungen von Chemikalien.

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BACKGROUND

The EU Chemicals legislation, in common with the situation in other parts of the world, is based predominantly on assessments carried out on individual substances. However, in reality humans are exposed to a wide variety of chemicals throughout their lives as indeed are animals and plants. While current assessment methods incorporate safety factors to take account of a range of uncertainties,
the Commission is concerned to ensure that EU chemicals' legislation takes proper account of the latest scientific information on mixture toxicity.

In the light of the above considerations,
SCHER/SCCS/SCENIHR (and experts of relevant agencies: EFSA, EEA, EMEA, ECHA) have been asked to advise the Commission on 6 issues related to chemical mixture.

Structure of the Opinion

3.1 Problem formulation
3.2 Scope of the opinion
3.3 General Principles of Mixture Toxicology
3.4 Methodology
3.4.1 Effects assessment
3.4.1.1 Whole-mixture approaches
3.4.1.2 Component based approaches
3.4.2 Specific aspects relating to ecological effects assessments
3.4.3 Exposure assessment
3.4.3.1. Human
3.4.3.2. Environment

3.5 Uncertainty
3.6 Discussion
3.7 Conclusions and Recommendations

3.3 General Principles of Mixture Toxicology

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

- similar action (dose/concentration addition)
- dissimilar action (independent action)
- interactions

Dose/concentration addition (similar action, similar joint action): chemicals in a mixture act by the same mechanism/mode of action, and differ only in their potencies.

Independent action (response addition, effect addition): chemicals act independently from each other, usually through different modes of action that do not influence each other (simple dissimilar action).

Interactions: synergism and antagonism
describes the combined effect of two or more chemicals as stronger (synergistic, potentiating, supra-additive) or weaker (antagonistic, inhibitive, sub-additive, infra-additive) than expected from dose/concentration-addition or response-addition (changes of absorption, impaired inactivation, enzyme induction etc).

Ergebnis

Basierend auf den Prinzipien der Wirkung einzelner Chemikalien in Gemischen und nach Bewertung von Studien, aus denen eine Wirkung bei oder unterhalb der NOELs der einzelnen Substanzen abgeleitet wurde, wird gefolgert:

Ausser für Gemische aus Substanzen mit identischen Wirkungseigenschaften ergibt sich kein Hinweis auf adverse Wirkungen bei Konzentrationen der einzelnen Substanzen unterhalb oder im Bereich ihrer NOELs.

Allerdings bedeuten experimentell bestimmte NOELs oder NOECs nicht unbedingt die Konzentration ohne Wirkung. Dies trifft jedoch zu für TDIs, DNELs, PNECs oder anderen Werten, die unter Verwendung von Sicherheitsfaktoren abgeleitet worden sind.

3.4.1 Effect assessment

Whole mixture approaches

Advantage: accounts for any unidentified materials and for any interactions among mixture components.

Disadvantage: no specific information on interactions or toxicity of individual components.

Component based approaches

- Knowledge of modes or mechanisms of action of individual components, dose-response information, concentrations
- Information on groups of similar or identical modes of action (assessment groups).

Grouping of mixture components

If (eco)toxicological data are lacking on the individual components or the mixture, read across, TTC or (Q)SAR-based approaches could be used for grouping on the basis of chemical structure e.g. using the OECD (Q)SAR Application Toolbox (OECD, 2009). For each group or individual chemical a limit value needs to be derived. This value can be based on the limit value of a representative substance in a group.

Grouping by toxicological or biological responses/ effects

Grouping of chemicals having similar endpoints including dose descriptors for critical effects such as benchmark doses, LOAELs or NOAELs.

The advantage is that for many chemicals such information is available.

Dose/concentration addition approaches

Methods for dose/concentration addition approaches:

- the Hazard Index (HI),
- the Reference Point Index (RfPI) or Point of Departure Index (PODI),
- the Relative Potency Factor (RPF)
- the Toxic Equivalence Factor (TEF)
- The toxic unit concept preferentially used in environmental toxicology

Terms of reference and Conclusions

1. Is there scientific evidence that when organisms are exposed to a number of different chemical substances, that these substances may act jointly in a way (addition, antagonism, potentiation, synergies, etc.) that affects the overall level of toxicity?

•Chemicals with common modes of action produce combination effects that are larger than the effects of each mixture component . These effects can be described by dose/concentration addition.

•For chemicals with different (independent) modes of action no robust evidence is available that exposure to a mixture is of health concern if the individual chemicals are present at or below their zero-effect levels.

- The examples, in which independent action has been expected, dose (concentration) addition slightly overestimated the actual mixture toxicity. This suggests that the use of the dose/concentration concept for unknown toxic mechanisms is sufficiently protective.

- For ecological effects, exposure to mixtures of dissimilarly acting substances at low but potentially relevant concentrations should be considered relevant, even if all substances are below the individual PNECs.

- Interactions (including antagonism, potentiation, synergies) usually occur at medium or high dose levels (relative to the lowest effect levels). At low exposure levels they are either not occurring or toxicologically insignificant.

2) If different chemical substances to which man/environment are exposed can be expected to act jointly, which affects their impact/toxicity, do the current assessment methods take proper account of these joint actions?

•Different chemical substances may act jointly in a way which affects their toxicity for man and the environment. Current assessment methods for mixtures can take account of joint actions, such as dose/concentration addition or response / effect addition generally only under specific circumstances. With these methods, effects of chemical mixtures composed of either dissimilarly or similarly acting substances can be reasonably well predicted.

•Interactions, are generally more difficult to assess and require expert judgement on a case-by-case basis.

3) Several approaches for the assessment of the mixture effects of chemicals already exist such as dose addition and independent action. What are the advantages and disadvantages of the different approaches and is there any particular model that could be considered as sufficiently robust to be used as a default option?

- In cases of similar mode of actions a dose/concentration addition approach is appropriate.
- Its application to mixtures with unknown modes of action may result in an over-prediction of toxicity, whereas the independent action approach may underestimate toxicity. Therefore, a dose/concentration addition approach is preferable to ensure an adequate level of protection.
- A significant limitation of component-based approaches is that they are only applicable to mixtures of which the major components are known.

4) Given that it is unrealistic to assess every possible combination of chemical substances what is the most effective way to target resources on those combinations of chemicals that constitute the highest risk for man and the environment?

- Exposure to one or more components approaching the threshold levels for adverse effects means that the mixture should be given priority for assessment. A TTC like approach can be used to eliminate combinations that are of low or no concern.
- For the environment, attention should be paid to mixtures of chemicals, individual components of which approach the PNEC.
- In view of the difficulty to retrieve or generate an appropriate dataset for hazard characterisation and exposure estimates, a tiered approach may be considered.

5) Where are the major knowledge gaps with regard to the assessment of the toxicity of chemical mixtures?

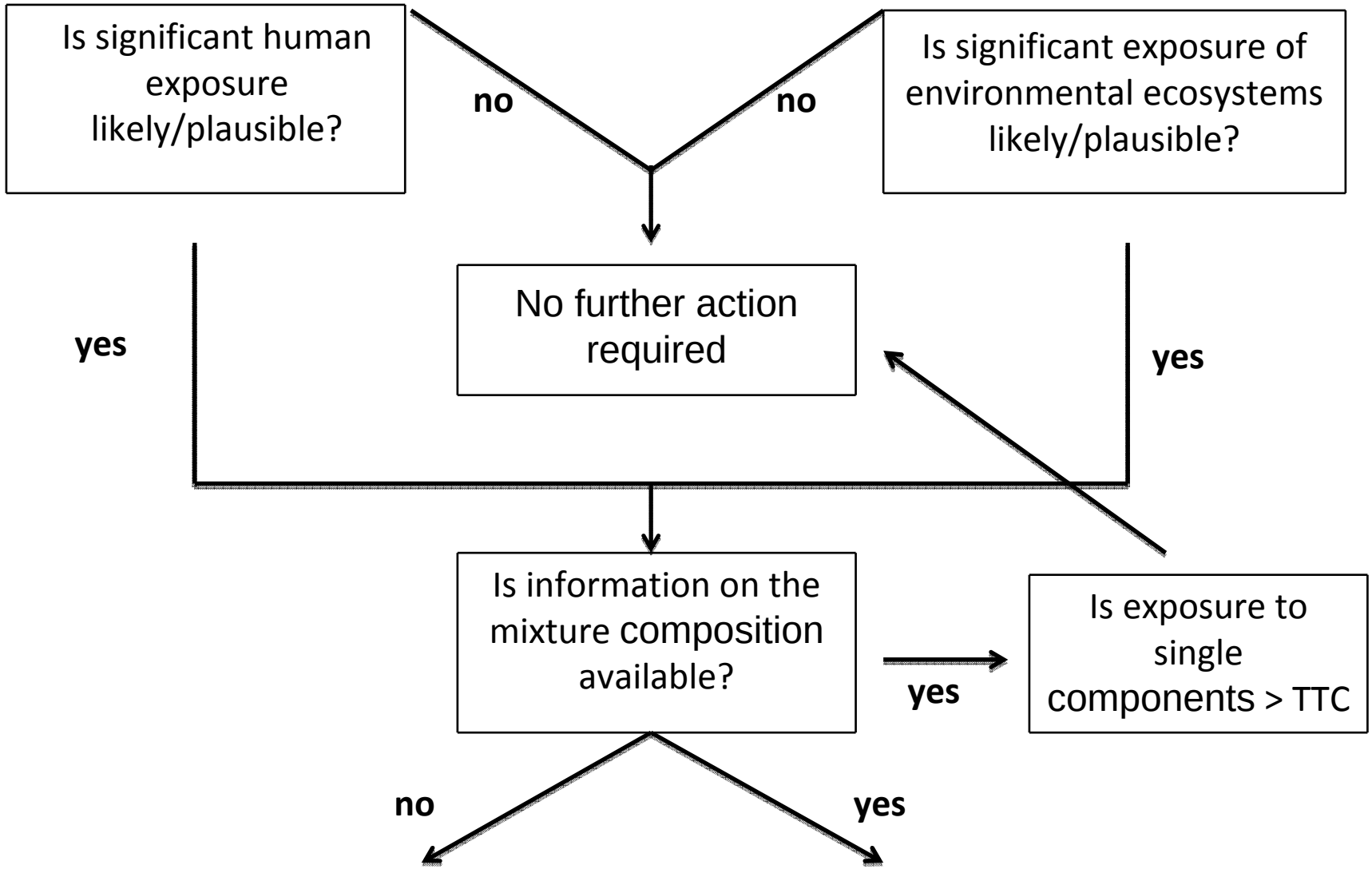
•A major knowledge gap is the limited number of chemicals for which there is good mode of action information.
•In ecotoxicology knowledge of all possible modes of actions in the different types of organisms of a complex biological community is difficult (or impossible) to be attained. On the other hand, ecologically relevant endpoints are generally broader and not so specific (*e.g.* toxicity on specific organs, *etc.*) as in human toxicology.

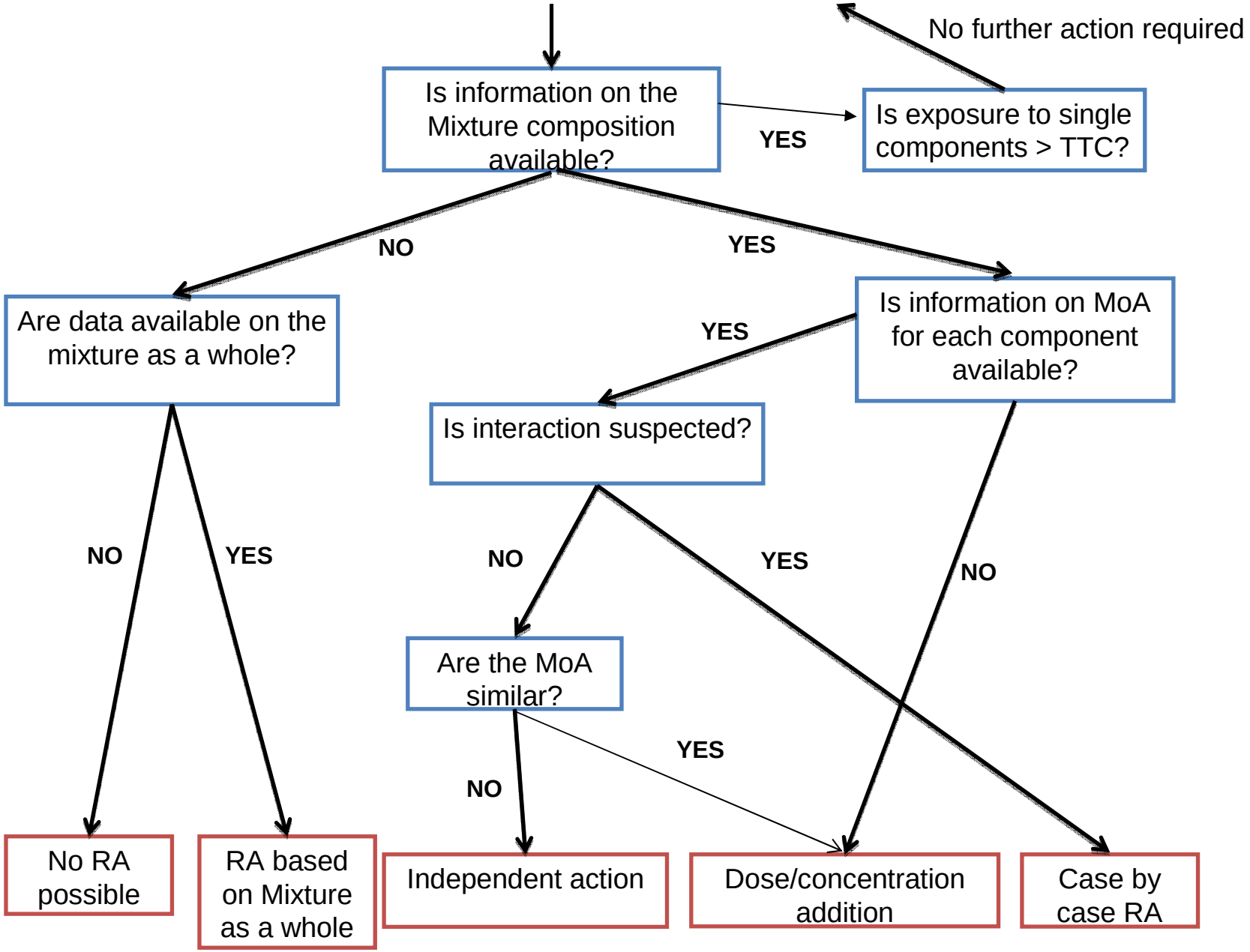
Other major knowledge gaps are:
•The general lack of robust and validated tools for the prediction of interactions.
•How exposure and/or effects change over time

6) Does current knowledge constitute a sufficiently solid foundation upon which to address the toxicity of chemical mixtures in a more systematic way in the context of EU legislations?

- In many cases, knowledge on concentration and effects of components is insufficient for a robust scientific analysis.
- If toxicologically significant interactions can be excluded, either a dose addition or independent action model should be applied.
- Grouping of chemicals into categories and assessment groups may cover insufficient information.
- In ecotoxicology the dose/concentration addition concept may be generally appropriate for predicting effects at the population level.

Decision tree for the risk assessment of mixtures




Is information on the Mixture composition available?
YES
Is exposure to single components > TTC?
No further action required
NO
YES
Are data available on the mixture as a whole?
Is information on MoA for each component available?
YES
Is interaction suspected?
NO
YES
NO
YES
NO
Are the MoA similar?
YES
NO
No RA possible
RA based on Mixture as a whole
Independent action
Dose/concentration addition
Case by case RA

Die Kommentierungsphase endete Anfang September 2011.
Sie hat keine wissenschaftlich fundierten Einwände ergeben.

Titel der Opinion:
Toxicity and Assesssment of Chemical Mixtures

http://ec.europa.eu/health/scientific_committees/environmental_risks/opinions/index_en.htm#id9

SCHER-Opinions: others

Stellungnahme von SCHER/SCCS/SCENIHR und Institutionen der EC: EFSA, EEA, EMEA, ECHA

The TTC concept describes
Levels of "no appreciable risk" (ug/person per day)

Structural alerts	microg/person and day
Alerts for genotoxicity	0.15
Any other compound without alerts for genotoxicity	1.5
Specific structural classes (e.g. organophosphates)	18
Cramer Class III	90
Cramer Class II Cramer Class I	540 1800

Structural classes see Toxtree 2008

Studies, which have been used to suggest joint effects of independently acting compounds:

Study with guppies (Hermens et al 1985): LD50 measured of mixtures, without determining the individual NOECs.

Studies with algae (reproduction) (Faust *et al.* 2003, Walter *et al.* 2002): The studies resulted in additive effects as predicted.

Study on human breast cells (Payne *et al.,* 2001): Although the individual concentration-response plots showed differences in shape and position, the combined effect could be predicted on the basis of dose-response.

Receptor-ligand interaction

Replacement of a physiological ligand, *i.e.* an oestrogen from the receptor by a competitor, i.e. a xenoestrogen, depends on its relative affinity to the receptor and its concentration. For example, replacement of the physiological ligand from the receptor by a compound of 1000-fold lower affinity requires a 1000-fold higher concentration than the endogenous compound.

Although this oversimplifies competitive interaction of compounds at a receptor, it demonstrates the need for information on the relative binding affinities of the compounds in question and their concentration in the organism.

Hazard Index (HI): the sum of the Hazard Quotients (HQ), *i.e.* the ratios between exposure and the Reference Value (RV) for each component to be evaluated.

Reference Point Index (RfPI): the sum of the exposures to each chemical expressed as a fraction of their respective RfPs (also known as Point of Departure) for the relevant effect (e.g., the dose that causes a 10% effect, or the NOAEL).

Relative potency factor methods/Toxic equivalency factor/ potency equivalency factor.

Toxic Units (TUs) concept: used in ecotoxicology, represents the ratio between the concentration of a component in a mixture and its toxicological acute (e.g. LC50) or chronic (e.g. long term NOEC) endpoint.