CHEM Trust's response to the SCHER/ SCENIHR/ SCCS pre-consultation opinion on "Toxicity and Assessment of Chemical Mixtures"

CHEM Trust is very grateful for EU Environment Council's conclusions of December 2009 in which they requested the European Commission to investigate and report back to the Council by 2012 about the possible need for legislative modifications, guidelines and assessment methods in relation to how to address the risks from the many chemicals to which humans and wildlife are simultaneously and concurrently exposed.

To illuminate the way forward, the Commission has commissioned a 'State of the Art Report on Mixture Toxicity' from Kortenkamp et al (2009) and has also asked for advice from its non-food Scientific Committees, including the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).

CHEM Trust, however, has several major concerns about the preliminary opinion of these Scientific Committees, on which this consultation is based. We outline these objections below.

In its present form, CHEM Trust considers that the preliminary opinion from the Scientific Committees needs significant modification if it is to be a suitable basis on which to progress. We are particularly concerned that this opinion seems perhaps rather too much influenced by a 'business as usual' approach in that it appears to be trying to 'contain' the problem for the sake of expediency. In particular, we consider that the opinion is fatally flawed by its insistence that chemicals should be grouped according to their common mode of action, which flies in the face of the opinions of other experts, who consider that if cumulative risk assessment is to be undertaken in a quantitative manner, chemicals should be grouped and assessed together if they have common adverse health effects (NAS, 2008; US EPA 2009; Kortenkamp, Backhaus & Faust, 2009).

CHEM Trust considers that the toxic effect of exposure to multiple chemicals is an issue which needs to be urgently addressed. Indeed, we consider that because consideration of chemical mixtures has been neglected in EU legislation, it is likely that wildlife in certain areas and some people in the population at large are at risk.

With regard to the potential effects of endocrine disrupting chemicals, we are particularly concerned about the effects caused be the cumulative exposures of some pregnant women, as the unborn child is considered to be most at risk.

The questions posed by the European Commission to the Scientific Committees and their conclusions are outlined below. In each case, CHEM Trust's views follow.

QUESTION 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?

Conclusions of the Scientific Committees

Yes, under certain conditions, chemicals may act jointly in a way that the overall level of toxicity is influenced.

Chemicals with common modes of action may act jointly to produce combination effects that are larger than the effects of each mixture component applied singly. These effects can be described by dose/concentration addition.

For chemicals with different modes of action (independently acting), no robust evidence is available that exposure to a mixture of such substances is of health concern if the individual chemicals are present at or below their zero-effect levels. It is important to note that these zero-effect levels are not represented by the NOELs or NOECs. NOEL(C)s or PNECs are derived from experimental studies and may be associated with effect levels of up to 20%. Chemicals with different modes of action may however also affect the same endpoint, for instance, acute toxicity or carcinogenicity (effect addition).

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

In the examples in which independent action provided a more accurate prediction, dose (concentration) addition slightly overestimated the actual mixture toxicity, which suggests that the use of the dose/concentration concept for risk assessment of chemicals of unknown toxic mechanisms is sufficiently protective.

Interactions (including antagonism, potentiation, and 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.

CHEM Trust's and WWF COMMENTS

Mostly agree

As a general remark we would like to state that in our view the method of gathering comments is inappropriate. Rather than forcing a summarized approval/disapproval of many different aspects at the same time, the consultee should be allowed to give comments to each chapter!

We agree with parts of the committee's response given under this question, but disagree strongly with others.

We do not consider that there is enough evidence to support the committees' conclusion that there is no human health concern for exposures to mixtures of independently acting chemicals at low levels. The answer by the Scientific Committees leads the reader to presume that only chemicals with a common mode of action may act jointly to produce combination effects on human health described by dose addition. However, the study by Christiansen S et al., 2009, EHP supports the assertion that chemicals with different mechanisms of action may also lead to combination effects. This study was undertaken on rodents which are used to assess the human health risks. Thus, chemicals with different modes of action can add to the combined toxicity of the mixture, and as such, the focus should not just be on chemicals with common modes of action. It is also noteworthy that Christiansen and colleagues also reported synergistic effects in relation to male genital malformations when animals were exposed to chemicals with different mechanisms of action.

We disagree with the Committees' conclusion that there is sufficient evidence to conclude that at low exposure levels synergistic effects are either not occurring or are toxicologically insignificant.

The Committees' opinion states that "the use of the dose/concentration concept for risk assessment of chemicals of unknown toxic mechanisms is sufficiently protective", but they fail to mention that this concept is currently not really applied in the EU's single substance risk assessments (see also question 2).

In line with other scientific reports, we consider that it should be chemicals with common adverse outcomes which are grouped together for the purposes of joint risk assessment. Argumentation to support this can be found in NAS, 2008; US EPA 2009; Kortenkamp, Backhaus & Faust, 2009.

We moreover think the following statement by the committees is very remarkable:

"It is important to note that these zero-effect levels are not represented by the NOELs or NOECs. NOEL(C)s or PNECs are derived from experimental studies and may be associated with effect levels of up to 20%."

It is a striking confession that the current practice in risk assessment of predicting "safe thresholds" is in reality allowing effects of up to 20%, as usually NOELs (= no observed effect level) and PNECs (=predicted no effect concentration) are considered as levels where no effects occur and on which further 'safety factors' or 'assessment factors' are imposed, to give what current risk assessment considers to be an adequate margin of safety.

Furthermore, with regard to 'zero effect levels' we suggest that whether or not there is a threshold for effects is actually very difficult to assess. The power of the experiment is unlikely to be sufficient to detect changes at very low dose levels, including changes that might not, on their own, be considered adverse.

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

Conclusions of the Scientific Committees
Risk assessment on the combined effects of chemicals in a mixture is not commonly carried out at present. However, for some purposes, toxicity testing will be applied to mixtures.

As outlined in the answer to question 1, 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 applied under specific circumstances. With these methods acute effects of chemical mixtures composed of either dissimilarly or similarly acting substances can be reasonably well predicted. Interactions, however, are generally more difficult to assess and require expert judgement on a case-by-case basis. Specific conditions under which synergistic actions, i.e., the most relevant of interactions with regard to the toxicological risk, might be expected are outlined in the above opinion.

The methodology for the (eco-) toxicological assessment of chemical mixtures appears, generally suitable. It is, however, often not applied in practice. Assessments of aggregated and combined exposures across different industrial and use sectors, in particular, are rarely performed.

CHEM Trust's and WWF COMMENTS

Mostly agree.

We mostly agree with the Committees' conclusions, however, we feel that the answer from the Scientific Committees obfuscates the issue. It should be clearly stated that whilst suitable scientific measures are available in principle, the current risk assessment methods in use under EU regulation do not take proper account of these joint actions. This may lead to a systematic under-evaluation of risks. Whilst for some purposes, toxicity testing will be applied to a few specific mixtures, e.g. certain industrial discharges, this does not equate to ensuring that full account is taken of the totality of chemicals to which man and the environment are exposed. We agree, therefore, with the Committees' acknowledgement that assessments of aggregated and combined exposures across different industrial and use sectors are rarely performed.

In particular, no prospective assessment of the expected mixture toxicity of cumulative exposures from different sources, as well as different chemicals, is carried out in advance of market approvals of chemicals for different uses.

As another example, in relation to human health, even if there is the ability within the Pesticides Regulation to look at the joint toxicity of certain pesticides in some instances – the risk assessment for humans would currently not take into account the concurrent exposure that may occur to industrial chemicals in consumer products. Neither does it take into account the existing body burdens of many pollutants. In short, 'mixtures' assessment does not straddle the legislative 'silos' that currently exist, and does not look at exposure from even all chemicals with similar modes of action to which humans are exposed via the diet, via inhalation, or via the dermal route. As noted in the updated report on the implementation of the Community Strategy on EDCs "Where EU legislation allows the possibility of assessing cumulative effects, the scope of such assessments is generally rather narrow. In the case of plant protection products, for example, the possibility exists to assess the cumulative impacts of the residues of different active substances remaining in food and feed. In the proposed revision to the Biocidal Products Directive, it will be possible to assess the cumulative effect of the same active substance used in different products. However, current EU legislation does not provide for a comprehensive, integrated assessment of cumulative effects taking into account different routes of exposure and different product types".[1]

QUESTION 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?

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[1] EUROPEAN COMMISSION (2011) COMMISSION STAFF WORKING PAPER, 4th Report on the implementation of the "Community Strategy for Endocrine Disrupters" a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (1999) 706). Brussels, 10.8.2011. SEC(2011) 1001 final

Conclusions of the Scientific Committees
In view of the huge variety of human exposures to chemical mixtures, the default assumption in human risk assessment had been that they generally acted by dissimilar modes of action. In cases, however, where information is available to indicate a similar mode of action, a dose/concentration addition approach is appropriate. A dose/concentration addition approach, if applied to chemical mixture components with unknown modes of action, may result in an over-prediction of toxicity; using the independent action approach may however underestimate toxicity. Therefore, also in this case, the dose/concentration addition approach is preferable to ensure an adequate level of protection.

Different methods exist for the dose/concentration addition approach (see above methodology section for details). When using the RfP or RV, one should be aware that NOAELs/LOAELs are based on single experimental data points and the values depend on the dose-spacing used in the experiment. In contrast, BMDLs are based on all experimental points and by that provide more reliable information on the dose response.

In ecotoxicology, any approach must be referred to specific endpoints and to defined taxonomic groups of organisms. The reference values (PNECs) are derived using different sensitive organisms for any type of chemical. Therefore, a combination of PNECs may be misleading.

A significant limitation of component-based approaches is that they are only applicable to mixtures of which the major components are known.

CHEM Trust's and WWF's COMMENTS

Do you agree with this part of the response given?

Mostly agree.

Whilst we agree that a dose/concentration addition approach is likely to provide the 'best estimate' of likely effects in cases where all exposures and dose response curves are known, in reality these are largely unknown. Moreover, as noted, we do not consider it appropriate to limit any such group assessment to chemicals with a similar mode of action, rather we consider it should embrace all chemicals with common adverse outcomes. The rationale for such an approach is well detailed in the US National Academies' report of 2008. We do, however, agree that BMDLs (bench mark dose levels) provide more reliable information on the dose response, and are more suitable for use than NOAEL or LOAELs (no or lowest observed adverse effect level).

Our main issue is that it will be impossible to know the complete exposure profile to which humans and wildlife are exposed, and as there will be immense variation depending on location, lifestyle etc. Therefore we consider that it would be better to routinely include an extra assessment factor in risk assessment to cover mixture effects, particularly where chemicals act on an endpoint which is common to many chemicals.

Assessment factors have long been used in risk assessment for dealing with uncertainty and we consider that this would be more appropriate as a default methodology.

QUESTION 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?

Conclusions of the Scientific Committees

In view of the almost infinite number of possible combinations of chemicals to which humans and environmental species are exposed some form of initial filter to allow a focus on mixtures of potential concern is necessary. The following criteria are proposed for consideration:

- Human and/or environmental exposure at significant levels (e.g. approaching the NOEL/NOEC or PNEC for several components).
- Chemicals that are produced and/or marketed as multi-constituent substances or commercial mixtures with several components and/or active ingredients (i.e., as defined by EU legislation, e.g., REACH, CLP, pesticides and biocidal products legislation, food law, *etc.*).
- Potential serious adverse effects of one or more chemicals at the likely exposure levels.
- Likelihood of frequent or large scale exposure of the human population or the environment.
- Persistence of chemicals in the body and/or in the environment. High persistence/bioaccumulation would be a property of importance.
- Known information of potential interaction at levels of human and environmental exposure.
- Predictive information that chemicals act similarly such as (quantitative) structure activity relationships and structural alerts.
- Particular attention should be paid to mixtures for which one or more components are assumed to have no threshold for its effects such as genotoxic carcinogens; a MOE or a lifetime cancer risk approach could be applied.

Exposure to one or more components approaching the threshold levels for adverse effects would mean that the mixture should be given priority for assessment. A TTC like approach can be used to eliminate combinations that are of concern (for details on the applicability of a TTC approach for the assessment of chemical mixtures see Boobis *et al.*, 2011 and Price *et al.*, 2009).

For the environment, attention should be paid to mixtures of chemicals, individual components of which approach the PNEC.

In view of the difficulty and time needed to retrieve or generate an appropriate dataset for hazard characterisation and exposure estimates, a tiered approach, such as proposed by the WHO/IPCS (2009b) or EFSA (2008), may be considered. (For details on the tiered approach, see above text.) The identification of the data gaps after the application of the tiered approach should determine the extent of testing of chemical mixtures and study design.

CHEM Trust's and WWF COMMENTS

Mostly disagree.

We disagree that a vast amount of knowledge on hazard and exposure on the individual components needs to be available before one can start considering the potential for combined effects. In order to move towards a more protective approach in risk assessment the assumption should rather be that "mixture exposure" is the real-life exposure assumption – at least for all compounds in consumer use or likely to reach the environment.

We are very skeptical concerning the application of the TTC approach as its scientific validity is dependent on the reliability of the underlying data which are often insufficient, in particular for chronic toxicity. Moreover**,** this concept which determines the TTC threshold values that will be applied, and the use of this approach, which is based on a presumption of safety below threshold values, is likely to result in inaccurate assessments for many chemicals.

In our view one important consideration for the most effective way to target resources is to differentiate between the different contexts and purposes of mixture assessment. For example, if the aim is to evaluate a factory effluent as a part of a site evaluation this is completely different to the authorization of a chemical under REACH.

The priority should be more on prospective mixture toxicity assessments rather than testing existing environmental mixtures. This would mean taking into account combination effects when setting environmental quality standards or in all legislation dealing with market approvals or authorization schemes.

Given the limitations of current legislation it is clear that not all chemicals with potentially additive effects can be adequately regulated at the outset. In particular, it is known that many substances target androgen or estrogen action, or other hormone systems. Moreover, there are concerns that adverse trends in male reproductive health, breast cancer and some other adverse health effects in women may be linked to exposure to EDCs. Therefore, we maintain that the Commission should, as a priority, move forward on addressing cumulative exposures to EDCs.

We consider that the draft opinion of the Scientific Committees does not address the need for urgent action to prevent harm. It can take years to implement cumulative quantitative risk assessment under various scenarios and given that it is difficult to address all exposure routes, it would still remain limited in its approach.

Best practice for EDCs would be to substitute these chemicals with safer alternatives, whenever possible, rather than get bogged-down in a long, drawn-out quantitative mixtures assessment process. REACH provides a useful starting point for this, and should be used to deliver an approach coherent with that of the new Pesticides Regulation, where the goal is also to substitute pesticides with ED properties with safer alternatives, rather than undertaking a quantitative risk assessment.

In summary, given that legislation does not currently allow for the 'basket-full' of exposures from all sources to have their risks assessed together, there are 2 options for a necessary and pragmatic way forward: Either (i) to impose an additional, sufficiently large assessment factor in the risk assessment to take account of potential mixture effects or (ii) to try to eliminate exposures to such substances whenever possible. For chemicals with ED properties which might play a role in observed adverse health trends we consider that this latter option is best, particularly as legislative mechanisms do not currently exist to address all exposure routes.

Furthermore, the aim of elimination of exposure where possible, could potentially be achieved fairly soon for chemicals which come under REACH or the Pesticides Regulation, although in the former case this would require the review required under Art 138(7) to extend the scope of Art 60(3) to substances having endocrine disrupting properties so that they are blocked from the 'adequate control of the risk route' to authorization.

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

Conclusions of the Scientific Committees

With regard to the assessment of chemical mixtures (as defined in the mandate), a major knowledge gap at the present time is the rather limited number of chemicals for which there is good mode of action information. Currently there is neither an agreed inventory of mode of actions, nor a defined set of criteria how to characterize a mode of action for data-poor chemicals.

Much of the work on interactions relates to enzyme inducers and inhibitors, to promoters of carcinogenic effects. The dose/concentration approach requires information on the dose response shape for the chemicals to be considered. This information is rarely available in sufficient quality. Research is needed to define criteria that predict dose additivity.

In ecotoxicology, the problem is even more complex. A knowledge of all possible modes of actions 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 (*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 may change over time

CHEM Trust's and WWF's COMMENTS
Mostly agree

We mostly agree with the Scientific Committees. However, we consider that the most important "major knowledge gap" is the extent (identity and numbers of chemicals) and levels (dose) of chemical exposures in humans and wildlife. We nevertheless agree that a major knowledge gap is the limited number of chemicals for which the mode of action is known, although as the cumulative risk assessment should include all those chemicals with a common adverse outcome rather then common mechanisms of action, this should not be an insurmountable barrier to moving forward.

QUESTION 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?

Conclusions of the Scientific Committees

In many cases, knowledge is insufficient for a robust scientific analysis.

If toxicologically significant interactions can be excluded, the components of a mixture are identified and known mode of action information is available, either a dose addition or independent action model should be applied. This set of information, in human toxicology, is however rarely available and, in most cases, very cost- and labour-intensive to generate. Often, it may not be possible to obtain the required data due, e.g., to limitations in existing study designs and analytical methods.

In ecotoxicology, the mode of action should be known for all the relevant taxonomic groups of aquatic and terrestrial ecosystems. So, the availability of information is even more difficult; in addition, modes of actions considered dissimilar at the individual level may affect the same population relevant endpoint, and therefore, the dose/concentration addition model may be more appropriate for predicting effects at the population level.

However, in most cases, when applying a dose/concentration addition approach, it is necessary to rely on assumptions such as mode of action, shape and slope of dose response curves of the individual components. These assumptions may be generated by grouping of chemicals into categories and assessment groups. However, no generally agreed criteria for the grouping of substances exist, adding to the uncertainties associated with this approach. Choosing independent action approach may however underestimate combined effects of similarly acting chemicals. Hence, if no mode of action information is available, the dose/concentration addition method should be preferred over the independent action approach.

Prediction of possible interaction requires expert judgement and hence needs to be considered on a case-by-case basis.

In future, pathway-based toxicity evaluations (*e.g.* inflammation - oxidative stress - genotoxicity) based on *in silico* and *in vitro* methodology will become more feasible, enabling these methods to identify common effects. However, the report of a recent meeting of the US National Academic's Standing Committee on Use of Emerging Science for Environmental Health Decision concluded that "many challenges remain to be addressed before the findings from high-throughput screens and *in silico* models may be considered sufficiently robust and informative" (Rusin and Daston, 2010). The Working Group agrees with this conclusion.

In ecotoxicology, a relevant issue may be related to combined effects capable to affect reproduction, population dynamics and ecosystem's health. For some chemicals these effects may become evident even some time after exposure stopped.

Having reviewed the available evidence, the Committees recommend that a mixture-dependent approach is used for the assessment of chemical mixtures as outlined in the diagram on page 37 of the preliminary opinion.

In order to prioritize chemical mixtures for possible assessment it is first necessary to consider whether there is significant human or environmental exposure to the mixture or its components. Unless there are indications for a significant interaction, a dose/concentration addition model could be used if the components of the mixture exert their biological effects via an identical or similar mode/mechanism of action. If the mixture components act dissimilarly, the independent action model would be applied. It further appears justifiable that a dose/concentration addition approach should be used as default approach in cases where neither mode of action nor dose-response information is available to ensure adequate conservatism in the assessment.

CHEM Trust's and WWF's COMMENTS

Mostly disagree

We consider that current knowledge constitutes a sufficiently solid foundation to require the toxicity of chemical mixtures to be addressed in a more systematic way in the context of EU legislations. Laboratory studies have clearly shown the need to address mixtures and highlighted methodologies for estimating the toxicity of a mixture of known components of known toxicity. Under current EU risk assessment approaches, humans and wildlife have been left unprotected from the potential mixture effects.

We disagree with the committee's conclusion that mixture toxicity should only be considered if SIGNIFICANT exposure is likely.

In transposing current knowledge into the legislative arena it is clear that knowledge on the extent and levels of exposure will not be easily and or soon available, and neither will information on the mechanisms of action of most substances. Therefore, a pragmatic approach, based on the use of additional assessment factors and reduction of exposure where possible, will need to be pursued.

It should be noted that the use of assessment factors has long been used in risk assessment in order to take account of the uncertainty in relation to extrapolation of effects from rodents to humans and inter-species variation

Additional remarks:

References Feron and Groten (2002) and Meek et al (2011) are missing in reference list.

9th September 2011