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EXPLANATORY NOTE

ON HOW THE COMMENTS RECEIVED DURING THE PUBLIC CONSULTATION WERE TAKEN INTO ACCOUNT FOR THE FINAL OPINION ON TOXICITY AND ASSESSMENT OF CHEMICAL MIXTURES

This note sets out the rationale for the modifications made, after a public consultation, to the joint opinion of the three independent non-food Scientific Committees of the European Commission titled: "Toxicity and Assessment of Chemical Mixtures".

Introduction

In the Council conclusions from 22 December 2009, the Commission was invited, drawing on existing and future research and paying appropriate attention to the costs and benefits, to assess how and whether relevant existing Community legislation adequately addresses risks from exposure to multiple chemicals from different sources and pathways, and on this basis to consider appropriate modifications, guidelines and assessment methods, and report back to the Council by early 2012 at the latest.

In light of the above considerations, 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) received a request for a scientific opinion on the toxicity and the assessment of mixtures of chemicals. A call for information was also issued by DG SANCO between 7 July and 8 September 2010, in which interested parties were invited to submit scientific information (published articles, reports, etc.) that may help the Scientific Committees answer the questions listed in the mandate.

In line with its procedures for stakeholder dialogue, implemented in the Rules of Procedures of the new Scientific Committees set up by Commission Decision 2008/721/EC of 5 September 2008, the European Commission Health and Consumers Directorate General (DG SANCO) conducted a public consultation on the preliminary joint opinion of the Scientific Committees between 4 July and 9 September 2011.

Results/participation

By the deadline of 9 September 2011, DG SANCO received a total of 38 contributions. All contributions were reviewed by the Scientific Committees Working Group during two WG meetings: on Sept. 30th and Nov. 21st 2011. Appropriate modifications were introduced into the text of the opinion which was then discussed and adopted as the final joint opinion by the

Scientific Committees at their meetings as follows: the SCHER at its 15th plenary of 22 November 2011; the SCENIHR at its 16th plenary of 30 November 2011; and the SCCS at its 14th plenary of 13 December 2011.

Modifications to the opinion

The opinion has been modified to take into account those submitted comments which were assessed by the Scientific Committees to be pertinent and relevant for the subject matter and which were within the competences of the Scientific Committees and respected the clear separation between risk assessment and risk management that underpins the Scientific Advisory Structure of the European Commission. Comments on policy, risk management, legal clarification and the precautionary principle, were not considered as although pertinent to the subject matter they are outside the competences of the Scientific Committees.

Detailed explanations of the way the comments received were treated by the Scientific Committees are provided below. The numbering of paragraphs and lines correspond to the sections of the opinion approved by the three Scientific Committees at their respective plenary sessions.

Comments on question 1

A total of 38 comments were received for question 1. Text was *not* included for eight of these comments and the relevance of three others was unclear. The remaining 27 comments and responses have been summarised below. Five respondents agreed with no comments other than editorial suggestions. Fourteen of these comments led to the opinion being modified, the changes not being limited to the specific response to this question in section 3.7.

Comments that led to a modification of the text of the opinion:

The largest group of comments related to the section on Independent Action (page 11) where NO(A)ELs and NO(A)ECs were noted as not always representing zero-effect levels. The references to DNELs, PNECs etc. in the same part of the text were considered to be confusing. The references to DNELs, PNECs etc. have been removed.

A number of respondents suggested that definitions of certain terms would be useful and should be added to the text or glossary, and the Scientific Committees agreed that some comments arose from a lack of clarity in some terms. Changes have been made to the glossary and text as a result – in particular a definition of zero-effect level has been added, the definition of low dose has been expanded and a definition of effect addition added.

Some respondents felt that the opinion should provide more commentary on mode of action, in particular on “similar mode of action” and “dissimilar mode of action”. The description in the glossary for mode of action has been extended.

Two respondents questioned the relevance of the conclusions for metals. The Scientific Committees consider that the same principles apply to the evaluation of mixtures of metals, except for the essential elements, but as the opinion does not specifically address metals, the description of the scope of the opinion (Section 3.2, page 8, lines 36-9) has been revised to reflect this.

A number of editorial suggestions and corrections were provided and have been incorporated into the revised opinion.

Comments that did not lead to a modification of the text of the opinion:

Two respondents commented that the opinion appeared to come to different conclusions to those in the Kortenkamp *et al.* report. The Scientific Committees considered that the few studies on low-dose effects in that report were over-interpreted, and that the opinion adopted a weight of evidence approach to the whole of the evidence available. A further respondent suggested other studies are showing mixture effects below the zero-effect level of individual components; the Scientific Committees considered that these were included in the weight of evidence approach.

A number of respondents suggested that there was insufficient evidence to reach the conclusion in the answer to this question. The Scientific Committees emphasised the weight of evidence approach used, and felt that the expanded definition of low dose provided greater clarity.

One comment was considered to be beyond the remit of the opinion and the competences of the Scientific Committees, relating as it did to risk management and judicial matters.

The question of tumour initiators and promoters was raised by three respondents. The Scientific Committees considered that this was covered by the comments in the opinion on the specific evaluation of each situation, and concluded that no change to the opinion was required.

One respondent commented that consideration of metabolic interactions was not included in the opinion. The Scientific Committees felt that interactions were addressed in the opinion, and needed to be considered on a case-by-case basis.

Comments on question 2

A total of 38 comments were received for question 2. Text was *not* included for 13 of these comments (seven were in agreement with the Scientific Committees' position, four mostly agreed and two were uncertain). The remaining 25 comments and responses have been summarised below (five agreed, 16 mostly agreed, three mostly disagreed and one was uncertain). Only 14 of these comments lead to the opinion being modified, although the changes are not limited to the specific response to this question in section 3.7.

Comments that led to a modification of the text of the opinion:

The conservative approach used to derive human based guidance values (HBGVs) such as TDIs, DNELs or equivalent values, has been clarified in the relevant section on human health assessment in the discussion (section 3.6, page 32, lines 12-23 and 25-32). Given that a number of conservative assumptions are made, it is unlikely that exposure at the level of the HBGVs will result in significant risk. This is implicit in risk analysis policies of organisations such as the European Commission, where HBGVs derived from the application of a 100-fold uncertainty factor to the NOAEL are used in risk characterisation. The Committees consider

this rule in general terms unless specific data exists to deviate from it towards an increase or decrease. The HBGVs are therefore expected to represent a value at which no effects are produced; thus for threshold substances, the assumption is that this value is equal to or lower than the no-effect level. A sentence has also been added explaining that for mixtures, the probability of needing the full default uncertainty factors continues to decrease as the number of chemicals in the mixture increases.

The first paragraph in answer to question 2 has been rewritten and the word "no" added. The statement has been modified to address the lack of regulatory request and clearly states that at present, risk assessment on the combined effects of chemicals in a mixture is neither commonly carried out, nor required by most EU regulations (section 3.7, page 34, lines 28-9). The following text (page 34) has been deleted, "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".

Clarification related to the equal importance of combination effects for both acute and long-term effects has been provided in response to several comments expressing concern that the opinion gives the impression that combination effects are only applicable to acute effects (section 3.7, page 34, lines 29-33). Direct toxicity testing is performed with mixtures, for some purposes only. For example, direct toxicity testing is performed with certain formulations or waste water effluents and is generally limited to acute effects, whereas joint actions between chemicals on a long-term basis are equally important and far more difficult to estimate.

The paragraph on biodegradation has been reworded and it has been clarified that the biodegradation of each component of a mixture can be strongly influenced by the presence of other components (section 3.4.2. page 29, lines 26-34). The following sentence has also been deleted from page 28, "However, persistence of each component of a mixture can be heavily influenced by the other components".

The Scientific Committees agree with the comment that endocrine disruption is not always receptor mediated and have modified the text accordingly (section 3.3, page 14, lines 4-10).

Some references on the ecotoxicologicial risks of pesticide mixtures have been included in the revised version (Finizio *et al.* 2005; Junghans *et al.* 2006; Verro *et al.* 2009) (section 3.4.2, page 30, line14) in response to several comments.

The Scientific Committees agree that the evaluation of mixtures of metals involves some complex and extraordinary aspects. Therefore, the Committees have concluded that metals should be addressed separately. The scope of the opinion (section 3.2, page 8, lines 36-9) has been revised to reflect this.

<u>Comments that did not lead to a modification of the text of the opinion:</u>

The majority of the comments received on question 2 were largely in agreement with the Scientific Committees' position. A comment regarding regulatory policy, and whether or not current regulatory regimes do enough to compel risk assessors to address pertinent and potentially significant combinations of substances, has not lead to a modification of the opinion because this is not within the mandate of the Scientific Committees. Similarly, a question posed by a respondent concerning the absence of a legal mandate in the EU to

perform a comprehensive integrated assessment of cumulative effects over different routes of exposure and different products is not within the mandate of the opinion.

One respondent raised concerns that the current methodology does not adequately address chemical combination, particularly at low doses. It is felt that while expert judgement on a case-by-case basis is important, it is open to misinterpretation and the application of the precautionary principle is therefore essential to public safety. The precautionary principle, however, is related to risk management measures and is not within the mandate of the Scientific Committees. Furthermore, the opinion used a weight of evidence evaluation based on the existing knowledge and expert judgement is considered to be relevant.

The Scientific Committees are of the opinion that the current risk assessment methodology in use under EU regulations in most cases deals with individual chemicals and does not account for possible effects of mixtures. This is already clearly stated in the text, and therefore no changes were made.

No changes were made in response to a comment about how multi-constituent and UVCB substances are evaluated under REACH as this is already addressed in the opinion (section 3.4, page 19, lines 7-13). The text also clearly states that under the current EU pesticides and biocides regulation, plant protection and biocidal products are generally assessed for acute toxicity, skin and eye irritation, and skin sensitisation.

One of the respondents was of the opinion that for endocrine disruptors, critical windows of exposure are more important than potency and concentration of specific substances. However, the Scientific Committees are of the opinion that while the window of exposure is an additional critical parameter for the effect to be expressed, it does not overrule the role of concentration: if the dose is not above zero-effect levels even during the critical windows of exposure the chemical is not toxic.

Comments on question 3

A total of 38 comments were received for question 3. Text was *not* included for 11 of these comments (five were in agreement with Scientific Committees' position, five mostly agreed and one was uncertain). The remaining 27 comments and responses have been summarised below (two agreed, 23 mostly agreed, one mostly disagreed and one was uncertain). Only 11 of these comments lead to the opinion being modified, the changes not being limited to the specific response to this question in section 3.7.

<u>Comments that led to a modification of the text of the opinion:</u>

Many of the comments received on question 3 were in agreement with the Scientific Committees' position. However, clarification was sought by several of the respondents regarding the statement that a combination of PNECS may be misleading. The text has been replaced with an explanation that a combination of PEC/PNEC ratios is less scientifically correct than the sum of toxic units (TUs). However, the sum of PEC/PNECs has been proved slightly more conservative and more easily applicable (in some cases) and therefore, for pragmatic reasons, may be used as a first-tier conservative approach (section 3.4.1, page 23, lines 30-3 and section 3.7, page 35, lines 21-4).

The text (section 3.7, page 35, lines 9-11) has been reworded for clarity to read, “Therefore, also in the case of unknown modes of action, the dose/concentration addition approach is preferable to ensure an adequate level of protection”.

Further information has been added to the dose/concentration addition section (section 3.3, page 9, lines 50-2) explaining that there is evidence to show that dose/concentration addition can produce reliable estimates of combined effects, if the components share a strictly identical mechanism of action or belong to the group of baseline toxicants.

The following sentence (section 3.3, page 11) has been deleted, “A major problem encountered in applying the dose/concentration additive approach is that data are usually lacking that address issues of chronic toxicity of more than two chemicals in a mixture at concentrations representative of actual human exposure”, in response to a comment that it seems strange to identify this as a problem, since this is a general issue in using animals for testing of possible effects in humans.

Several of the respondents raised the point that substances which clearly deviate from the concentration addition (CA) concept should be considered and mentioned, and that from a regulatory perspective, metals need to be considered properly as there is currently no guidance available. The scope of the opinion (section 3.2, page 8, lines 36-9) has been re-worded to clarify that it does not address essential metals and nutrients for human health. The opinion also does not address metals for environmental CA because these assessments involve specific approaches such as essentiality, background concentrations and bioavailability.

The section on “Epidemiological studies in cumulative risk assessment” has been rewritten and moved from “Exposure assessment” to “Effect assessment” (section 3.4.1, page 24, lines 28-56 and page 25, lines 3-30).

Despite being in agreement that the dose/concentration addition approach is preferable to ensure an adequate level of protection in order to avoid an underestimation of toxicity, concerns were raised by one respondent that the current risk assessment methods, as practiced and legally mandated in the EU, may already be leading to a systematic under-evaluation of risks because joint effects are not being assessed. It was suggested in the comment that the implications of using NOELs and PNECS, and the accompanying assessment factors in current risk assessment practices should be thoroughly reviewed, and recommendations made to ensure that better safety margins are developed. Where relevant, PNECs (used in parallel to NOELs) has been replaced by NOECs in the text. Furthermore, the respondent feels that the focus should be on chemicals for which there are indications of effects on common endpoints, regardless of whether the mechanisms of action are similar or well elucidated.

<u>Comments that did not lead to a modification of the text of the opinion:</u>

Despite agreeing with the majority of the Scientific Committees’ answer to question 3, some of the respondents felt that the conclusion that dose/concentration addition should be adopted as the default should not be considered in isolation. Instead, they argued that it should be considered in combination with the response to question 4 where a number of criteria for ensuring mixtures risk assessments are targeted to potential mixtures of concern are recommended. Concern has been expressed in several comments that adopting dose/concentration as the default in a more generalised manner would be hugely

conservative. The Scientific Committees considered that the opinion adequately addresses those points.

Some of the respondents were of the opinion that applying dose/concentration addition to ensure an adequate level of protection in the case of unknown modes of action is overly conservative because in most cases, even limited information on the chemicals within a mixture should permit the prediction that common MOA is unlikely and therefore prevent application of the dose additivity default. In multiple cases, there is the possibility to exclude similar MOA without assessing it in detail.

No modification was made to the text of the opinion in response to the comment that combination assessment (CA) is much more feasible than independent assessment (IA) because IA requires high resolution data of the individual toxicants which is very resource demanding to obtain.

The routine inclusion of an extra assessment factor in risk assessment to cover mixture effects, particularly where chemicals act on an endpoint which is common to many chemicals was recommended by several of the respondents. However, the review of the literature undertaken by the Scientific Committees' Working Group does not support this comment.

No changes were made in response to the comment that the section on “Epidemiological studies in cumulative risk assessment” omits to mention the major contribution of epidemiology to the assessment of whole-mixtures which includes studies that have demonstrated unacceptable risk leading to regulatory controls, and also studies that have excluded material risks to human health from mixed exposures. The respondent was also of the opinion that the criteria that are proposed for inclusion of epidemiological evidence in cumulative risk assessment are inconsistent with those that are applied to animal toxicology.

Comments on question 4

A total of 38 comments were received for question 4. Text was *not* included for 12 of these comments (four agreed, five mostly agreed, two mostly disagreed and one was uncertain). The remaining 26 comments and responses have been summarised below (four agreed, 17 mostly agreed, one disagreed and four mostly disagreed). Only 15 of these comments lead to the opinion being modified, the changes not being limited to the specific response to this question in section 3.7.

<u>Comments that led to a modification of the text of the opinion:</u>

Many of the respondents were of the opinion that while the TTC approach is well established in human toxicology, there is currently insufficient evidence (either conceptual or empirical) on how such an approach relates to common ecotoxicological descriptors of low effects or thresholds (e.g. PNECs, EQs). A publication by de Wolf *et al.* (2005) on the mode of action and aquatic exposure thresholds of no concern has been referred to in several comments.

According to the decision tree further action is never required if the individual compounds are present below their individual TTCs, even if all compounds are similarly acting. In view of the lack of conceptual and empirical models/data, some of the respondents felt it was somewhat premature to use the TTC criterion as a broad and general indicator for “no further

action required". Furthermore, the decision tree proposed in the opinion was considered to be more suited to human health assessment rather than environmental assessment, and a retrospective approach may be more suitable for the later. Further clarification on the use of the TTC approach in assessing possible human health effects of mixtures has been provided by the Scientific Committees and its current limitations in ecotoxicology evaluations are now addressed. A box has been added to the decision tree diagram along with some explanatory footnotes (section 3.7, page 38).

A typing error has been corrected to read, "A TTC like approach can be used to eliminate combinations that are of no concern" (section 3.7, page 36, lines 4-5).

It has been noted in a few of the comments that PNEC and NOEL/NOEC are sometimes erroneously used in the same context and clarification has been sought. A NOEL or NOEC is derived from experimental studies. An assessment factor is applied to this to derive the RV, e.g. DNEL or PNEC. The first bullet point (section 3.7, page 35, lines 37-8) has been amended to read, "Human and/or environmental exposure at significant levels (e.g. approaching the HBGVs, DNELs or PNECs for several components)".

The possible importance of metabolic interactions has been addressed in the opinion and the following sentence added (section 3.4.1, page 21, lines 4-5), "When considering which chemicals to assess together, the possibility of metabolic interaction should also be addressed".

A sentence has been added summarising that re-analysis of the four studies cited by Kortenkamp *et al.* (2009) supports the conclusion that at relevant human exposures the compounds acting by independent action are very unlikely to produce a biologically relevant increase in response (section 3.3, page 13, lines 4-6).

The discussion on environmental risk assessment for mixtures has been revised and the text reworded to read, "A PEC for the whole mixture could be determined if the individual composition is known" (section 3.4.2, page 28, lines 48-9).

Some references (ecosystem exposure to mixtures) have been added to the opinion (Finizio *et al.* 2005; Junghans *et al.* 2006; Verro *et al.* 2009) (section 3.4.2, page 30, lines 9-14).

Some text has been added (section 3.7, page 36, lines 10-4) explaining that the TTC model may not be appropriate for biological communities, where a threshold of concern may be several orders of magnitude different for different taxonomic groups of organisms (from bacteria to vertebrates). Furthermore, in some cases, for very sensitive taxonomic groups, even very low concentrations which are difficult to assess or measure may be not negligible.

"Substances of concern" have been added to the criteria proposed for consideration (section 3.7, page 36, line 41).

<u>Comments that did not lead to a modification of the text of the opinion:</u>

Many of the comments received were largely in agreement with the opinion and did not lead to the text being modified. Although one individual mostly disagreed with the Scientific Committees' answer to question 4, no details were provided as to the basis for their view, and therefore no changes were made to the opinion. A further respondent was uncertain as to

whether there was agreement on the response to question 4, but no indication is provided as to why this is the case.

Concerns have been raised by several respondents that there is insufficient experimental evidence to demonstrate that the TTC approach is protective. It has been suggested in the comments that either: (i) an additional, sufficiently large assessment factor should be used in the risk assessment to take account of potential mixture effects; or (ii) exposures to substances with endocrine disrupting properties should be eliminated whenever possible. The Scientific Committees are of the opinion that the TTC approach is conservative for the chemical types to which it is applicable, and an additional uncertainty factor is not required. Elimination of exposure to certain types of chemicals, for example EDCs, is a risk management issue which would require policy decisions and is therefore not within the mandate of this opinion.

The review of the literature undertaken by the Scientific Committees' Working Group does not support the comment that it is unrealistic to obtain sufficient information on the billions of mixture situations and therefore an additional default of 10 or 100 should be used in RA. The strategy proposed by the Scientific Committees does not require evaluation of billions of mixture situations, but rather suggests focusing on those of potential concern according to the criteria provided.

The suggestion that the number of chemicals in the mixture should also be a selection criterion, even if none of the chemicals are near any individual risk threshold, did not lead to the opinion being modified because this approach would be covered, as proposed in the opinion.

The Scientific Committees do not support the claim that it is essential to also consider the human and/or environmental exposure at low levels of exposure as these are the unexpected health effects that can have the most profound effect.

The comment that screening criteria (such as persistence and bioaccumulation) for prioritization of substances for evaluation of mixture effects are entirely inappropriate for use of metal prioritization has not lead to the text of the opinion being modified because issues specific to metals are not addressed by the Scientific Committees.

Comments on question 5

A total of 38 comments were received for question 5. Text was *not* included for 13 of these comments (12 agreed or mostly agreed and one was uncertain). The remaining 25 comments and responses have been summarised below (four agreed, 17 mostly agreed, two mostly disagreed, none disagreed and one was uncertain). Only four of these comments lead to the opinion being modified.

<u>Comments that led to a modification of the text of the opinion:</u>

In response to a suggestion by one of the respondents, the following section of the text was deleted: "…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 characterise a mode of action for data-poor chemicals." It was replaced

by this text: "lack of knowledge on where, how often and to what extent humans and the environment are exposed to what 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." (page 36). In addition, the following articles were reviewed and added to the bibliography: Tornero-Velez *et al.* 2011; and Ankley *et al.* 2010. These were mentioned by several of the respondents.

In response to a comment shared by two of the respondents, the following text was added to page 36: " 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 characterise or predict a mode of action for data-poor chemicals or how to group chemicals into assessment groups."

In addition, the sentence "Interactions of chemicals in mixtures are difficult to foresee, particularly for long-term effects" was included and the following two were deleted: "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."

Finally, the following sentence was included "A full review of literature should be made to make a state-of-the-art on mixtures biodegradation modelling", while this section was deleted:

"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"

<u>Comments that did not lead to a modification of the text of the opinion:</u>

Many of the comments received were largely in agreement with the opinion and did not lead to the text being modified. In their contributions, many of the respondents repeated the main points listed in the opinion and/or reiterated some of their earlier points raised in their respective comments in response to the first four questions.

One respondent requested that the Committees answer the question: "Do these certainly existing knowledge gaps hamper the implementation of the already existing knowledge into regulatory action or not?" The Committees considered this a risk management issue which is not in their competence and is not part of the mandate for the opinion

Two of the respondents mostly disagreed with the Scientific Committees' answer to question 5. One of them simply dismissed the question and its answer ("it is the wrong answer to the wrong question") and indicated that "the data gap is WHICH default factor we should choose to protect citizens including the vulnerable". The Committees considered those pronouncements too general which could not be addressed in the context of the opinion.

The second mostly disagreeing respondent indicated that "... for ecotoxicity these issues about extrapolation to community effects have been partly addressed already in scientific literature: multi-substance potentially affected fractions and mesocosms… that the

differences between response addition and dose/concentration addition are generally small, if not negligible compared to other uncertainties in the risk assessment. Response addition and dose/concentration addition can describe the vast majority of combined effects". The Committee felt that these points were largely addressed in the opinion already.

Comments on question 6

A total of 38 comments were received for question 6. Text was *not* included for 12 of these comments (nine agreed or mostly agreed, two mostly disagreed and one was uncertain). The remaining 26 comments and responses have been summarised below (four agreed, 16 mostly agreed, five mostly disagreed, one disagreed and one was uncertain). Only seven of these comments lead to the opinion being modified.

Comments that led to a modification of the text of the opinion:

In response to the comments received, some modifications of the text were introduced:

The verb "will" was replaced by "may" in the following sentence (page 37): "In future, pathway-based toxicity evaluations (*e.g.* inflammation - oxidative stress -genotoxicity) based on *in silico* and *in vitro* methodology (will) *may* become more feasible, enabling these methods to identify common effects."

As suggested by several of the respondents, the missing "yes" arrow was added to the decision tree (TTC box).

The following text was added to the TTC box of the decision tree (page 38): "… and to the combined exposure of components with a similar MoA larger than TTC."

The following footnotes were added to the decision tree for clarification (as suggested by numerous respondents):

*"Significant" exposure is determined by the frequency, the duration, and the magnitude of exposure.

**For the environment, an exposure driven assessment without at least a preliminary risk characterisation, as well as the TTC model, is hardly acceptable. Therefore, it must be considered as significant any exposure produced by emissions capable to modify the natural background conditions.

***Evidence for interaction can be found at various steps of the decision tree (e.g. comparing product information with compound-based assessment).

Comments that did not lead to a modification of the text of the opinion:

Three of the respondents emphasized the need for concrete EU legislative actions:
"Awaiting further knowledge is ipso facto denying some of the implications of the knowledge and that scientific analysis that currently exists. Moreover, we believe that the current knowledge suffices to undertake measures to address the harm from chemicals mixtures, in a systematic way, based on EU legislation. We seriously oppose further waiting until more data is available on modes of action; or for conducting assessments of mixtures toxicity only where significant exposures are considered likely or plausible."

"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."
"Where knowledge lacks, it is essential to fill in the gaps. As noted in a previous question, while expert judgement on a case-by-case basis is crucial in evaluating any lab results, it is not adequate alone and is open for misinterpretation. As Zeliger's research found, little is known about how low doses of chemicals interact, thus such untested judgement on a case-by-case basis is left open to misinterpretation in the face of scientific uncertainty. In such a case, it is essential to public safety to apply the precautionary principal."

The Committees thought that those issues go beyond the risk assessment mandate of the opinion and into regulation (risk management) and thus outside their competences.

In general many respondents went on to explain their views on the issue which, in general, were not in disagreement with those expressed by the Committees.