

Annex V

Guidance for drafters of risk profiles on consideration of toxicological interactions when evaluating chemicals proposed for listing

Qualitative literature-based approach to assessing mixture toxicity under Annex E

I. Introduction

1. Mixtures in the environment are usually composed of multiple components from a range of sources with different chemical structures and modes of action. However, environmental risks of chemicals are still often assessed substance by substance, neglecting mixture effects, that is, the effects arising from the presence of multiple chemicals in mixtures. This may result in the underestimation of risk, as exposure to multi-component chemical mixtures occurs more often than exposure to individual chemicals in isolation. Empirical evidence relating to human toxicology and ecotoxicology have repeatedly demonstrated toxicological interactions and strongly supports the need to take such interactions into consideration during the estimation of acceptable human and environmental exposures.
2. This document aims to describe a practical approach to how the Persistent Organic Pollutants Review Committee could consider toxicological interactions. The approach is adapted to the working procedures of the Committee and is based on the state-of-the art knowledge on mixture toxicity.
3. The basic scheme for assessing the combined effects of different contaminants starts when scientific data are available indicating that the presence of other chemicals in the same organism may add to the hazard posed by a given chemical being reviewed for persistent organic pollutant characteristics.

II. Information to consider when assessing toxicological interactions

4. Information required for the assessment of toxicological interaction consists of standard information on the chemical under review, as specified in Annexes D and E, and additional information on toxicological interactions that may include, but is not limited to:
 - (a) The chemical identity of each component of the mixture;
 - (b) Monitoring data that provide information on the number and types of chemicals and their levels in environmental mixtures, biota and humans;
 - (c) Field data showing or indicating adverse effects in biota or humans exposed to complex environmental mixtures;
 - (d) Toxicological and ecotoxicological effects, such as harmful effects, modes of action, endpoints for the species that is the most sensitive to exposure to the mixture being studied, or the populations that are the most vulnerable to exposure to the mixture, as well as mechanisms of effects;
 - (e) The fate and behaviour of each component of the mixture under given environmental conditions, such long-range environmental transport, environmental mobility, environmental partition coefficients, including the partition coefficients n-octanol-water and n-octanol-air, sorption properties, bioavailability and bioaccessibility, abiotic and biotic transformations and transformation products.

III. Methodologies for the consideration of toxicological interactions

5. Additivity is the most probable toxicological interaction for mixtures of chemicals. Additivity analysis can be used when contaminants do not influence the potency of other present contaminants, or, in other words, synergistic or antagonistic effects do not occur.
6. Two types of additivity exist: dose (concentration) additivity and response additivity (independent action).
7. Mixture toxicity of substances that act through a common mode of action is best predicted by dose (concentration) addition. For these contaminants, the doses can be summed up, if necessary, after accounting for differences in potency.

8. Mixture toxicity of substances that act through different modes of action is best predicted by response addition (independent action).
9. As mixture toxicities higher than predicted by dose (concentration) addition are rare findings, dose (concentration) addition is proposed as a pragmatic default approach for describing the joint action of chemical mixtures, irrespective of the modes and mechanisms of the mixture components.
10. Synergistic effects occur when exposure to several contaminants results in a more than linear increase in the overall effect. This is well known, for example, for endocrine disruptors. Antagonistic effects occur when exposure to several contaminants results in a less than linear decrease in the overall effect.
11. Prediction and quantification of synergy and antagonism is difficult and therefore seldom done. In practice, non-interactive combined effects are assumed.
12. Ultimately the choice of method will depend on whether the mode of action of the chemicals is known.

IV. Basic scheme for taking into account toxicological interactions of contaminants when drafting risk profiles according to Annex E to the Convention

14. The basic scheme for taking into account the combined effects of different contaminants starts when human or biota data indicate that the presence of other chemicals may add to the hazard posed by the chemical being reviewed for persistent organic pollutant characteristics.

Step 1. Collection of relevant information

15. First the relevant information specified in section II of this guidance is collected. As with any other information to be considered by the Committee, it should be collected from already available literature such as peer-reviewed scientific publications, government reports and publications from other relevant sources.

Step 2. Choice of approach

16. In general, the approach will be defined by the information collected in step 1.
17. If the available data give no indication of synergistic or antagonistic effects, then the default assessment is to consider additivity for toxic interaction. The following concept is proposed as an approach to deciding on additivity:
 - (a) When there is documented evidence for additivity and no evidence against additivity, then additivity should be assumed;
 - (b) When there is no evidence for additivity and no evidence against additivity, then additivity should be assumed;
 - (c) When there is documented evidence against additivity and no evidence for additivity, then additivity should not be assumed;
 - (d) When there is documented evidence both for additivity and against additivity, then the evidence should be weighed and a decision made on the basis of the circumstances specific to the chemical under review.

18. As mixture toxicities that are higher than those predicted by dose (concentration) addition are rare, dose (concentration) addition is proposed as a pragmatic default approach for describing the joint action of chemical mixtures, irrespective of the modes and mechanisms of the mixture components. If detailed knowledge on the mode of action suggesting response addition (independent action) exists, then this approach should be employed.

Step 3. Integrating relevant information into the risk profile

19. For each relevant biota the toxic interaction of the proposed persistent organic pollutant with other chemicals present is to be assessed using the assessment approach that has been selected in accordance with step 2 above and the results are to be integrated into the risk profile.

Step 4. Applying information on toxicological interactions in decision making

20. Information on toxicological interaction must also be taken into account when deciding whether the criteria of Annex E are met.