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Technical work: approach to the evaluation of chemicals in accordance with Annex E to the Stockholm Convention

Discussion paper on the approach to the evaluation of chemicals in accordance with Annex E to the Stockholm Convention

Note by the Secretariat

As indicated in the note by the Secretariat on the approach to the evaluation of chemicals in accordance with Annex E to the Stockholm Convention,[1] the annex to the present note sets out the discussion paper on the approach. The discussion paper has not been formally edited.

* UNEP/POPS/POPRC.9/1.

[1] UNEP/POPS/POPRC.9/9.

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Annex

Discussion paper on the approach to the evaluation of chemicals in accordance with Annex E to the Convention and open issues

Working group on the application of the Annex E criteria

July 2013

1. Background of the evaluation of chemicals in accordance with Annex E

1. According to paragraph 7 (a) of Article 8 of the Stockholm Convention on Persistent Organic Pollutants (POPs), the POPs Review Committee prepares a risk profile for a chemical proposed for listing under the Convention to provide basis for deciding whether the "chemical is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and/or environmental effects, such that global action is warranted".

2. The information requirements for a risk profile have been identified in Annex E to the Convention. The first paragraph of Annex E, quoted below, which is substantially the same as that in paragraph (7) (a) of Article 8, has raised some discussions in the development of risk profiles and in the meetings of the Committee:

> "The purpose of the review is to evaluate whether the chemical is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and/or environmental effects, such that global action is warranted."

3. At its first meeting, the Committee developed and agreed on an outline of a risk profile.[1] The Committee also agreed that the length of a risk profile should be 20 pages and that there should be no annexes to the document.

4. The chapters on "synthesis of information" and "concluding statement" of a risk profile, as risk profiles have been formatted by the POPRC to date, contain critical parts of the summary rationale. Those chapters explain the Committee's conclusion as to whether a chemical under review is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and/or environmental effects, such that global action is warranted. Most of the risk profiles adopted so far by the Committee had comprehensive summary rationales which drew on the critical data elements contained in the body of the report and linked them into an overall weight-of-evidence evaluation to support the conclusion related to paragraph 7 of Article 8 and Annex E.

5. The present discussion paper on common practices and open issues in the evaluation of chemicals in accordance with Annex E comprises two chapters:

(a) Chapter 2: Examples of practices used and decisions made in the evaluation of chemicals by the Committee in accordance with Annex E to the Stockholm Convention. This chapter provides examples of the Committee's experience in preparing the risk profiles for the 11 POPs subsequently added to the Convention following the Committee's recommendations.[2]

(b) Chapter 3: Views on open issues in the evaluation of chemicals in accordance with Annex E to the Stockholm Convention. This chapter provides views of members and observers of the Committee on issues with no examples of decisions being made by the Committee.

2. Examples of practices used and decisions made in the evaluation of chemicals by the Committee in accordance with Annex E to the Stockholm Convention

2.1 Scope of a risk profile

6. The development of risk profiles by the Committee involved consideration of sources (production data, uses, releases); an assessment of hazards including consideration of toxicological interactions; data on environmental fate (physical and chemical properties, persistence and coupling to environmental transport, degradation and transformation to other chemicals, bio-concentration and bio-magnification factors based on measured values, except when monitoring data are judged to meet this need); monitoring and exposure data, in particular, as a result of long-range environmental transport and including information regarding bioavailability; national, international evaluations and peer-reviewed scientific studies; and the status of the chemical under international conventions.

7. Those components are analysed together using weight-of-evidence approach to answer the question in paragraph 7 of Article 8 and Annex E, "whether the chemical is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and environmental effects, such that global action is warranted".

[1] UNEP/POPS/POPRC.1/10, annex IV.

[2] The intersessional working group has revised the text contained in document UNEP/POPS/POPRC.8/INF/10.

2.1.1 Relationship between the evaluation in accordance with Annex E and the screening phase in accordance with Annex D

8. The following screening criteria are set out in subparagraphs (b) to (e) of paragraph 1 of Annex D:

"(b) Persistence;

(c) Bio-accumulation;

(d) Potential for long-range environmental transport; and

(e) Adverse effects".

9. In accordance with paragraph 3 of Article 8 of the Convention, the Committee examines the proposal and applies the Annex D screening criteria in a flexible and transparent way, taking all information provided into account in an integrative and balanced manner. The examination addresses all the screening criteria in Annex D, concludes for each criterion whether it has been fulfilled, and draws an overall conclusion on whether the screening criteria in Annex D have been fulfilled, according to paragraph 4 of Article 8.

10. As provided in the first paragraph of Annex E, the risk profile "further elaborates on, and evaluates, the information referred to in Annex D".

11. The following information requirements set out in paragraphs 2 and 3 of Annex D do not constitute screening criteria:

(a) The proposing Party shall provide a statement of the reasons for concern including, where possible, a comparison of toxicity or ecotoxicity data with detected or predicted levels of a chemical resulting or anticipated from its long-range environmental transport, and a short statement indicating the need for global control.

(b) The proposing Party shall, to the extent possible and taking into account its capabilities, provide additional information to support the review of the proposal referred to in paragraph 6 of Article 8. In developing such a proposal, a Party may draw on technical expertise from any source.

12. The above mentioned information is to be reviewed and further elaborated on in a risk profile in accordance with Annex E. In other words, the screening of the proposed chemical against the criteria in Annex D, in accordance with paragraph 3 of Article 8, does not address the question of potential risks of the proposed chemical as a result of its long-range environmental transport, but the risk profile should address that question.

13. It should be noted that the fact that the criteria in Annex D are fulfilled is not in itself an argument that the evaluation in accordance with Annex E has been completed. According to paragraph 6 of Article 8, the Committee shall further review the proposal, taking into account any relevant additional information received, and shall prepare a draft risk profile in accordance with Annex E.

2.1.2 Risk profile phase – Annex E

14. Under the provisions of the Stockholm Convention, a chemical which has been proposed for addition to Annexes A, B and/or C to the Convention and has passed the screening criteria set forth under Annex D, moves forward to the review under Annex E, in accordance with paragraph 4 (a) of Article 8. In this stage, the Committee prepares a risk profile based on the information specified in Annex E. Information relevant to the development of the risk profile is collected from all possible sources including literature, parties and observers. An intersessional working group prepares a draft risk profile based on the information received. The Committee considers the draft risk profile at its meeting and decides "whether the chemical is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and environmental effects, such that global action is warranted".

2.2 Common approaches to preparing risk profiles by the Committee

15. A risk profile builds on the work undertaken through the evaluation of the Annex D criteria provided in the original proposal, elaborating further the specific types of information specified in subparagraphs (a) to (g) of Annex E . It contains an analysis of "sources", "environmental fate", "monitoring data", "exposure", "hazard assessment for endpoints of concern, including consideration of toxicological interactions involving multiple chemicals", "national and international risk evaluations, assessments or profiles and labelling information and hazard classifications, as available" and "status of the chemical under international conventions" to make the case why the Committee considers that global action is warranted (Article 8, paragraph 7 (a)) or the proposal should not proceed (Article 8, paragraph 7 (b)).

16. Article 1 of the Convention calls attention to the potential consideration of a precautionary approach with the following statement:

> "Mindful of the precautionary approach as set forth in Principle 15 of the Rio Declaration on Environment and Development, the objective of this Convention is to protect human health and the environment from persistent organic pollutants."

17. Article 1 of the Convention has been incorporated in practice in paragraph 7 (a) of Article 8 and thus in Annex E, which is to decide:

> "That the chemical is likely as a result of its long-range environmental transport to lead to significant adverse human health and/or environmental effects such that global action is warranted, the proposal shall proceed. Lack of full scientific certainty shall not prevent the proposal from proceeding. The Committee shall, through the Secretariat, invite information from all Parties and observers relating to the considerations specified in Annex F. It shall then prepare a risk management evaluation that includes an analysis of possible control measures for the chemical in accordance with that Annex".

18. The Convention deals with persistent chemicals that are dispersed throughout the globe putting a special emphasis on prediction of fate and effects compared to rapidly degrading chemicals with only local impact.

19. Socio-economic considerations are not included in the risk profile because they do not contribute to the scientific analysis defining whether a chemical is a POP. However, socio-economic information is essential for the development of the risk management evaluation in accordance with Annex F to the Convention.

2.2.1 Use of local data and data from remote areas in the Committee's decision-making

20. The data that are measured in biota or abiotic compartments from areas close to the source of release are included in the risk profile as specified in subparagraph (e) of Annex E. This information can be considered as one line of evidence in the assessment of the fate and potential for uptake and effects in biota. As included in the same subparagraph, information on exposure resulting from long-range environmental transport (often referred to as exposure in remote areas) and information on bioavailability and metabolism within the biota is critical for the decision-making.

2.2.2 Comparison of exposure levels and effects data

21. The risk profile further elaborates and evaluates the information referred to in Annex D, including the information specified in paragraph 2 of Annex D, "where possible, comparison of toxicity or ecotoxicity data with detected or predicted levels of a chemical resulting or anticipated from its long-range environmental transport". The preparation of a *risk profile* in accordance with Annex E and its decision-making on the risk profile does not involve a quotient based *risk assessment*,[3] but it should, as provided in Annex E, "as far as possible" include a "hazard assessment for the endpoint or endpoint of concern, including a consideration of toxicological interactions involving multiple chemicals".

22. While a comparison of exposure and effect levels is not a specific requirement of the Convention, it has been carried out in the past, where possible, to more clearly illustrate the need for global action. The exposure levels and effects data for remote regions have been compared in chapter 2.4 on "hazard assessment for endpoints of concern" of the risk profiles adopted so far by the Committee.[4]

23. In the risk profile of hexabromocyclododecane,[5] the Committee evaluated concentrations in species against relevant adverse effect data near point sources and source regions, in remote areas and also for human health.[6] While the concentrations near point sources are not decisive for Annex E conclusion, the available studies for remote areas suggested potential for endocrine effects in fish, as well as risk for reproductive and developmental effects in wild birds.

24. In the risk profile on pentabromodiphenyl ether,[7] comparison using risk quotient data was made available to the Committee. In the risk profile on pentachlorobenzene,[8] analyses on lethal and critical body

[3] The definition of risk assessment according to IPCS Risk Assessment Terminology, WHO 2004. (http://www.inchem.org/documents/harmproj/harmproj/harmproj1.pdf) is as follows: "Risk assessment: A process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. The risk assessment process includes four steps: hazard identification, hazard characterization (related term: Dose–response assessment), exposure assessment, and risk characterization. It is the first component in a risk analysis process."

[4] For example, chapter 2.4.6 of the risk profile on hexabromocyclododecane (UNEP/POPS/POPRC.6/13/Add.2).

[5] UNEP/POPS/POPRC.6/13/Add.2.

[6] UNEP/POPS/POPRC.6/INF/25.

[7] UNEP/POPS/POPRC.2/17/Add.1.

[8] UNEP/POPS/POPRC.3/20/Add.3.

burden was submitted by industry, and peer reviewed critical whole body residue information was also made available to the Committee. Nevertheless, the Committee concluded that the exposure assessment was uncertain, stating in that risk profile that "expressing the toxicological effects as internal dose or, wherever possible, as critical body burdens, improves the effect assessment but only reduces partially its uncertainty".

25. At its second meeting, the Committee stated in the risk profile of perfluorooctane sulfonates[9] that the ad hoc working group on perfluorooctane sulfonates "had also concluded that all the elements of Annex E had been addressed; that the data used were recent, of high quality and reflected current monitoring in remote regions; and that current concentrations in birds and mammals were in the same range as laboratory-derived effect levels."

26. In the past, when the Committee compared exposure and effects data, attention was paid to restrictions and limitations as further described in chapter 3 of the present paper. When making comparisons, the Committee took note of the uncertainties in exposure (risk profile on pentachlorobenzene),[10] facts that environmental levels had been in the rise during the last decades and that the effects may depend on the timing of the exposure (risk profile on hexabromocyclododecane).[11]

27. While there was no data on hexabromocyclododecane in polar bears and seals in the remote areas, it was noted that there may be effects on Arctic mammals that become evident due to normal emaciation in the winter time. The environmental levels that are below effect levels cannot be interpreted to mean there is no risk of concern. However, when the exposure levels have been in the same range as or greater than the adverse effect levels, the Committee has considered this as one line of evidence that global action is warranted, in accordance with paragraph 7 (a) of Article 8 of the Convention.

2.2.3 Comparison of the data of a candidate chemical with the data of a listed POP (benchmarking)

28. One of the ways of evaluating the characteristics and effects of a substance for which not enough information exists is to compare it with better known chemicals of similar characteristics. This approach (known as "benchmark approach") was proposed by Scheringer (1997) and Beyer et. al., (2000).

29. In Annex E, benchmarking involves comparing the properties or the concentrations of a candidate chemical in biota from remote areas with those of an already listed POP. It is important to note, however, that the initial 12 POPs could not be screened against the Annex D criteria and were not subject to the Annex E evaluation. Using them for benchmarking would require assessing their properties according to Annex D and Annex E evaluations.

30. For example, as additional information in the risk profile on endosulfan,[12] a benchmark approach was used comparing endosulfan with lindane, a POP listed in 2009 based on the review process provided in Article 8. This approach in the risk profile showed that lindane, a listed POP, and endosulfan are found in comparable concentrations in biota from remote areas and that endosulfan has similar or higher toxicity than that of lindane. This information strengthened the decision-making on endosulfan.

31. Another example is the risk profile on hexabromobiphenyl[13] whose vapour pressure was compared with that of listed POPs.

32. If the concentrations of a candidate chemical and a listed POP in biota from remote areas are comparable, and the toxicity of the candidate chemical is comparable or higher than the toxicity of the listed POP, it has been considered to help support deciding that the chemical is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and/or environmental effects such that global action is warranted.

33. If benchmarking shows concentrations that are not comparable or the candidate is less toxic, it is not possible to conclude that the candidate chemical is of no concern without information on potential exposure (e.g. current and future releases, bioaccumulation over time).

2.2.4 Use of environmental modelling for chemicals withdrawn from the global market

34. For chemicals that have been long withdrawn from the global market, such as chlordecone and hexabromobiphenyl, the environmental concentrations and concentration in biota may be very low. Also, data on environmental concentrations may be limited. If analytical techniques for detection in various media are still in development, concentrations may have not yet been determined. In such cases, a comparison of

[9] UNEP/POPS/POPRC.2/17.

[10] UNEP/POPS/POPRC.3/20/Add.7.

[11] UNEP/POPS/POPRC.6/13/Add.2.

[12] UNEP/POPS/POPRC.5/10/Add.2.

[13] UNEP/POPS/POPRC.2/17/Add.3.

exposure data with effects data is not conclusive and therefore the potential for long-range environmental transport has been assessed using model calculations. Listing those chemicals under the Convention would prevent the reintroduction of the chemicals on the global market.

35. The Committee has used information from environmental modelling in the risk profile on chlordecone[14] when there were no measured environmental concentrations or concentrations in biota in remote areas as chlordecone had been long withdrawn from the global market. The assessment of the potential for long-range transport of chlordecone (Table 2.2 of the risk profile on chlordecone) was based on physical properties due to lack of concentration data in remote areas. Persistence, vapor pressure and the Henry's Law Constant were considered to be the most relevant properties.

36. Modelling was also used in other risk profiles to strengthen the evaluation on long-range transport potential such as for hexabromobiphenyl,[15] pentachlorobenzene[16] and endosulfan.[17]

2.2.5 Evaluation of time trends of releases or concentrations in the environment in remote areas

37. An example of the time trends of exposure levels in remote areas used by the Committee in the risk profile is pentabromodiphenyl ether,[18] in which it was noted that "With the chemical's volatility contributing to its long-range transport, however, levels of exposure to pentabromodiphenyl ether continued to rise in North America and remote Arctic regions".

38. Evidence or likelihood of an increase in concentrations in the environment over time is an additional argument for the Committee to consider that global action is warranted.

3. Views on open issues in the evaluation of chemicals in accordance with Annex E to the Stockholm Convention

39. This chapter collects views of the members and observers of the Committee on issues in which there are no established practices or common views in the Committee. The purpose of the chapter is to facilitate future discussions on the evaluation of chemicals in accordance with Annex E in various open issues, where experts may currently disagree.

3.1 Comparison of exposure levels and effect data

40. The Convention calls the proposing party to submit, "where possible, a comparison of toxicity or ecotoxicity data with detected or predicted levels of a chemical resulting or anticipated from its long-range environmental transport"[19] in the Annex D phase. This has been further elaborated in the Annex E evaluation by the Committee, where possible, as described in chapter 2 of the present paper.

41. While the comparison is not considered mandatory for the evaluation, it can be used to strengthen the case. This may involve a comparison of measured concentrations in the tissues and organs of a few selected species with a predicted no effect concentration (PNEC), no observable effect concentrations (NOEC), or no observable adverse effect level (NOAEL) derived from experiments with laboratory animals. Comparisons can also include measured concentrations or levels that showed adverse effects for the same selected species.

42. Laboratory tests, both in vitro and in vivo, may provide relevant and valid information/knowledge on the hazard posed by a certain chemical not only for the model organisms themselves but also for wild organisms and humans. Comparisons of exposure levels and effect data are done on a case by case basis and the conclusions are drawn using a weight-of-evidence approach taking into account all available data and data gaps. When a hazard assessment is conducted for higher-order animals (e.g. mammals), there may be cases where effects (e.g. in humans) are not predicted by animal studies[20] or others where effects observed with laboratory animals (e.g. rodent) are not applicable to humans due to differences in mode of action or metabolism, but these are limited and many are well-known.

Issue I

43. When comparing concentration data in biota with toxicological and or ecotoxicological data or known effects data on humans, the Committee should take into account the uncertainties of the exposure and effects

[14] UNEP/POPS/POPRC.3/20/Add.10.

[15] UNEP/POPS/POPRC.2/17/Add.3.

[16] UNEP/POPS/POPRC.3/20/Add.7.

[17] UNEP/POPS/POPRC.5/10/Add.2.

[18] UNEP/POPS/POPRC.2/17, paragraph 47.

[19] Paragraph 2 of Annex D to the Stockholm Convention.

[20] http://ec.europa.eu/consumers/sectors/cosmetics/files/pdf/animal_testing/final_report_at_en.pdf#lCR556.

data, especially when reading across from one species to another and when evaluating risks for higher-order animals living under complex and diverse environmental conditions, including exposure to multiple chemicals. These uncertainties may include the following:

(a) Wild organisms may have a different biology and physiology from the model organisms typically used in laboratory tests, e.g. Arctic animals typically have a high level of body fat and accumulate more POPs than organisms living in the temperate and tropic regions. This may render them more susceptible to POPs;

(b) Organisms could be exposed to several chemicals and not only one single chemical;

(c) Wild organisms, including animals in the Arctic, also experience other forms of stress such as temperature variation, starvation episodes, and reproductive phases. that may affect their sensitivity to the chemical in question;

(d) Environmental conditions may have an impact on exposure and toxicity;

(e) Wild organisms and humans may be exposed over their entire life time, including during sensitive developmental stages, in contrast to laboratory animals. Effects can become apparent after a long period of time or over generations;

(f) Exposure status may not be fully defined (e.g. whether it is in equilibrium, decreasing or still increasing, whether the exposure data represents the most exposed compartments). POPs tend to accumulate in sediment, and sediment organisms are generally not covered in monitoring programmes;

(g) The environmental levels may be measured in tissues while the effect levels found in tests represent administered doses or levels in the test water in aquatic tests.

44. Often, comparison is not possible because for many endpoints/effects typical for POPs, there are no standard laboratory tests or they are not part of existing test guidelines (e.g. endocrine sensitive endpoints).

Issue 2

45. The Convention does foresee that when a POP is listed in Annex A for elimination, its production and use are to be prohibited, and eventually its concentrations in the environment and in biota will decrease to a very low level. However, it does not foresee that the POP could be removed from the Annex to the Convention when the concentrations in the environment and in biota decrease to below a certain level. This is not the mandate of the Committee.

46. The term “a low level” is not used by the Convention, but should be considered as a level where POPs do not have significant adverse effects on ecosystem and human health (limited to cases where reliable data are available on toxicity studies). Due to the inherent properties of POPs, the individual chemicals may still contribute to the overall toxic interactions with other relevant chemicals even at low levels.

47. It has also been considered by the Committee that a POP has been listed under the Convention despite the low or not known environmental concentrations (e.g. hexabromobiphenyl and chlordecone) to avoid market re-introduction of the POPs that have intrinsic POPs properties.

3.2 Significant adverse effects and their likelihood

Issue 1

48. Annex D to the Convention defines adverse human health and/or environmental effects. However, the word “significant” in the Annex E evaluation (“that the chemical is likely as a result of its long-range environmental transport to lead to significant adverse human health and/or environmental effects such that global action is warranted.”) has not been defined. The Committee needs to consider the significant level of adverse human health and/or environmental effects such that global action is warranted for each chemical case by case.

49. The Committee has agreed in the past that significant adverse health and/or environmental effects used in the risk profiles for decision-making are hazard endpoints which lead to serious or irreversible effects and/or hazard endpoints that have either none or very low “no adverse effect level” such as endocrine disruptors, carcinogens or mutagens and substances with epigenetic potential.

50. The following open issues warrant further discussion and clarification:

(a) Whether safe threshold levels can be derived for endocrine-disrupting effects;

(b) What constitutes an endocrine disruptor and whether the potential to induce endocrine disrupting effects would automatically mean a chemical is an endocrine disruptor;

(c) While experimental data may show potential for endocrine disrupting effects in a risk profile, it is still necessary to consider whether observed endpoints are adverse effects or not. According to some experts[21] even when a chemical is considered to pose adverse effects as endocrine disruptors, it is not clear that the chemical causes adverse effects when NOAEL or NOAEC is sufficiently high compared to concentrations in the environment and biota in remote areas. Other experts[22] note that timing of exposure is critical and that endocrine disrupters can be active at low concentrations and act via dose-response curves that are non-monotonic.

51. There are diverging views in defining effect as "significant adverse effects" when minor effects have been observed and measured, especially for cases involving effects on human health. According to some experts, effects judged initially as minor may in fact disrupt other important processes such as development and/or have significant population effects. Since the establishment of reliable NOAELs is dependent on the identification of adverse effects, deliberations among experts are necessary to determine whether effects are adverse or not.

52. When evaluating significance of the adverse effects without NOAEL, it may be possible to calculate the likelihood of the effect and consider whether it is acceptable for the evaluation, but views on such acceptable likelihood vary from one expert to another. Therefore, it is difficult to agree upon the criteria or indications by the Committee, and this uncertainty may need to be communicated to the Conference of the Parties. Meanwhile, if reliable assessments are conducted by relevant institutions such as national governments or international independent bodies, such as the International Agency for Research of Cancer (IARC) of the existence and accuracy of evidence of carcinogenicity or other serious adverse effects, it is considered adequate to describe assessment results as well as reasons and justifications for such assessment on the risk profile, without further validation of those results.

Issue 2

53. How should chemicals with adverse effects where the NOAELs are higher than the environmental concentrations or concentrations in biota in remote areas be evaluated?

54. For chemicals that meet the Annex D criteria on persistence, bioaccumulation and toxicity, it is difficult to prove that the current and future environmental levels would be so low that would be no adverse effects. The likelihood that an adverse effect may become apparent after a certain period of time is high. According to the experience with POPs with similar characteristics, the time required to reverse such unwanted effects is more than decades and also very costly.

55. In addition to the general uncertainties related to defining NOAEL (see issue 1 of chapter 3.1 above), there are other questions related to levels in biota and environment to be addressed, for example:

(a) Are the concentrations in remote areas or biota already in steady state? Time series data are seldom available for new POP candidates and numbers of samples vary depending on chemicals (e.g. limited data available on short-chained chlorinated paraffins);

(b) Is the surface water the most relevant environmental compartment? POPs tend to accumulate in sediment and biota rather than in surface water and may not be immediately bioavailable in sediments, but emerge over time;

(c) Do the species compared in the assessment have the highest ability to accumulate? The ability to accumulate chemicals varies considerably among species and is affected by many environmental conditions;

(d) Are the effects already visible? Effects can become apparent after a long period of time;

(e) Are the effects related to the chemical under review? Effects could be additive or synergistic with other chemicals including POPs;

(f) Are the laboratory test data relevant to the species in the environment? Laboratory animals are usually considered to be less sensitive to chemicals than wild environmental species and humans. Generally assessment factors and/or species sensitivity distributions (SSDs) are used to account for differences and extrapolate from laboratory animal results to environmental species and humans. The term "laboratory-derived effect levels" should be defined better, incorporating this notion.

56. If emission and exposure continue in the future, and concentrations in the environment and biota in remote areas are likely to exceed NOAEL or NOAEC, global action may be warranted in accordance with paragraph 7 (a) of Article 8 and Annex E to the Convention. Taking also into account the precautionary

[21] International Council of Chemical Associations ICCA, comments in March and May 2013.

[22] UNEP – WHO State of the Science of Endocrine Disrupting Chemicals (2013).

approach mentioned in Article 1, the Committee has so far considered that when concentrations in the remote areas or biota are below NOAELs (e.g. risk profile of endosulfan),[23] global action may still be warranted. However, the Committee may also defer decision-making and collect further information or set the proposal aside with reasonable rationales, in accordance with paragraph 7 (b) of Article 8.

3.3 Use of environmental modelling for predicting fate and exposure to chemicals

57. When there are no measured environmental or biota concentrations or concentration in biota data from remote areas for chemicals that have been withdrawn from the global market, the Committee has used environmental modelling methods to estimate the environmental exposure in line with paragraph 1 d (iii) of Annex D (e.g. risk profiles on hexabromobiphenyl[24] and chlordecone[25]). The same concept has been proposed for predicting the exposure to chemicals more recently introduced to the global market for which the releases into the environment are still low.

58. The use of environmental modelling of exposure to chemicals with POPs properties in remote areas in decision-making for Annex E has not been fully agreed by the Committee yet. Support has been expressed for use of modelling data for more recently introduced chemicals as well, provided that the uncertainties related to data quality are sufficiently addressed. For environmental behaviour parameters used in environmental modelling methods, it is preferable to employ realistic and reliable data on persistence and bioaccumulation. If those data are not available, estimated concentration levels in remote areas may possibly be over/under estimated, and considerations on such possibility should be included in a risk profile. Moreover, the reasons and justifications for choosing the environmental modelling method and the parameters should be documented for transparency.

59. It has also been questioned how much weight could be given to such data in the overall evaluation. When using environmental modelling methods, it is preferable to validate estimated concentrations by comparing them with measured data in remote areas. This is not always possible. If estimated concentrations have not been validated, they should be regarded as reference information, and therefore should not be used for comparison of exposure levels and effect data.

60. The Committee has not selected any specific models for the assessment, but they should be considered on a case-by-case basis.

3.4 Evaluation of time trends of releases or concentrations in the environment in remote areas (including consideration of climate change impacts)

61. Time trends are not required for the evaluation in accordance with Annex E but have been used as additional evidence. Neither the lack of clear time trend nor lowering environmental concentrations prevented a proposal from proceeding from the Annex E phase to the Annex F phase.

62. Climate change is an element in the Committee's overall judgement of data (see guidance on how to assess the possible impact of climate change on the work of the Persistent Organic Pollutants Review Committee)[26]. For example, climate change may alter POPs use-patterns, affect their primary and secondary emissions and/or releases and influence the bioaccumulation and degradation of POPs. In addition, depending on the chemical, conclusions may differ.

63. In cases where information provided in accordance with Annex E suggests the chemical is likely as a result of its long-range environmental transport to lead to significant adverse human health and/or environmental effects such that global action is warranted but no time trend for either releases or environmental concentrations in the remote areas can be observed, it should not prevent global action, as per paragraph 7 (a) of Article 8 and Annex E. A single measurement data can prove that candidate POPs have been transported over long distances, assuming the sources of releases were remote from where measured. It may be possible to use the data in validating results from environmental modelling methods.

64. In the cases where monitoring trends show reducing concentrations in remote areas and remote concentrations are below NOAEL, the global action such as elimination/restriction of use of the chemical may still be warranted due to the same rationale mentioned in chapter 3.2 of the present paper. It is important to identify the reasons behind the time trends situation (e.g. regional bans, changes in environmental processes, food-web structure, and animal behaviour). The Committee can also set the proposal aside with reasonable rationales, taking into account Article 1 of the Convention.

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[23] UNEP/POPS/POPRC.5/10/Add.2.

[24] UNEP/POPS/POPRC.2/17/Add.3.

[25] UNEP/POPS/POPRC.3/20/Add.10.

[26] UNEP/POPS/POPRC.9/INF/15.

65. Anticipated future releases can be estimated based on environmental modelling methods. The Committee should treat such data as supplementary and take into account the uncertainties related to use of models. Predicted or evidence of secondary releases or mobilisation due to climate change should be considered when accompanied by scientifically sound rationales, as well as use and production data.

66. Future concentrations in the environment and in biota can be estimated based on environmental modelling methods. The Committee should treat such data as supplementary and take into account the uncertainties related to use of models as well as the uncertainties related to the data on potential effects of climate change, including secondary releases from contaminated sites, waste sites and other environmental sinks and releases coming from the breakdown of parent compounds.

3.5 Endocrine disrupting chemicals

67. Many known POPs have effects on the reproductive system, and some are recognized as endocrine disrupters and associated with obesity and type-2 diabetes. For endocrine disruptors, the issue of combination effects described below is relevant.

68. Criteria for endocrine disruptors, as well as how to address and assess their effects, are intensively discussed in scientific and regulatory circles and could also affect future discussions on risk assessment of a single POP and grouping in the context of the Stockholm Convention. A recent UNEP-WHO report[27] suggested that "there is no threshold for endocrine disrupting effects due to the presence of active hormone pathways, and endocrine disrupting chemicals are likely to have effects at low doses". There are still knowledge gaps, e.g. on determining types of endocrine related effects. For many endocrine disrupting effects, agreed and validated test methods do not exist, and humans and wildlife are exposed to many endocrine disrupting chemicals simultaneously. The report also notes risk of severely underestimating the disease risk from mixtures of endocrine disrupting chemicals while focusing on single substances.

69. Endocrine disrupting effects of proposed chemicals in the Annex E evaluation has been discussed with some of the POPs in the past (e.g. risk profile on hexabromocyclododecane).[28]

3.6 Combination effects/toxicological interactions

70. The Committee has discussed the possible toxic interactions or combination effects of persistent and bio-accumulative chemicals. To account these effects better in the Annex E phase, the Committee has prepared and agreed to use the "Guidance for drafters of risk profiles on consideration of toxicological interactions when evaluating chemicals proposed for listing". [29] The guidance and takes note of the different approaches and guides the drafter on how to include this information into the Annex E risk profile.

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[27] State of the science of endocrine disrupting chemicals 2012 / edited by Åke Bergman, Jerrold J. Heindel, Susan Jobling, Karen A. Kidd and R. Thomas Zoeller.
http://apps.who.int/iris/bitstream/10665/78102/1/WHO_HSE_PHE_IHE_2013.1_eng.pdf.

[28] UNEP/POPS/POPRC.6/13/Add.2.

[29] UNEP/POPS/POPRC.8/16, Annex V.