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Submission by the Society of Environmental Toxicology and Chemistry on science-based guidance and a framework for the evaluation of persistent, bioaccumulative and toxic substances and persistent organic pollutants

Note by the secretariat

The secretariat has the honour to circulate, for the information of participants, a submission by the Society of Environmental Toxicology and Chemistry on science-based guidance and a framework for the evaluation of persistent, bioaccumulative and toxic substances and persistent organic pollutants. The submission, contained in the annex to the present note, has been reproduced as received without formal editing.

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Annex



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Science Based Guidance and Framework for the Evaluation and Identification of PBTs and POPs:

Summary of a SETAC Pellston Workshop

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Summary of the SETAC Pellston Workshop on Science Based Guidance and Framework for the Evaluation and Identification of PBTs and POPs, 28 January to 1 February, 2008, Pensacola, Florida, USA

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Preface

"Science Based Guidance and Framework for the Evaluation and Identification of PBTs and POPs" summarizes the outcome of a workshop and consensus-building process. The workshop was conceived by a small group of people in the public and private sectors who met informally as a steering committee for more than a year to discuss the need for improving the scientific foundation for the criteria and process for the evaluation of persistent, bioaccumulative and toxic substances (PBTs) and persistent organic pollutants (POPs). The workshop builds on the outcome of a previous Pellston workshop, held in 1998, which focused on the evaluation of persistence and long-range transport of organic chemicals in the environment, and is linked to other recent Pellston workshops, among them the "Tissue Residue Approach for Toxicity Assessment" workshop held in 2007.

The urgency and impact of the workshop are well established. The current regulations define PBT/POPs in terms of fairly strict criteria that were based on the state of the science in the late 1970s and early 1980s. Since then, an evolution in the state of the science has produced new

insights into persistence, bioaccumulation and toxicity of chemical substances and an array of new methods to identify PBT chemicals. The development of regulatory criteria has not kept up with the rapid development in environmental chemistry and toxicology, and, as a result, scientists often find themselves in the situation where guidance on PBT/POP criteria is limited and sometimes out-of-date.

With this background the workshop brought together experts from academia, industry and government to reach consensus on where we stand today and what we can accomplish with the current scientific understanding, as well as what should be done in the future as we address this issue. From the dialog will come a final Proceedings, of which this is the summary.

If this Workshop helps bring together those who devote their energies to the science, regulation and management of chemicals to work together more effectively towards a common goal of deciding how we must manage chemicals on our planet, it will have been a success.

Introduction

Several national regulations and regional or global conventions aim to identify and prioritize hazardous substances, including the Canadian Environmental Protection Act (CEPA), European Union (EU) Existing Chemicals and Registration Evaluation Authorization of Chemicals (REACH) Programs, United States Toxic Substances Control Act (TSCA) and Toxics Release Inventory (TRI) under the Emergency Planning and Community Right to Know Act (EPCRA), United Nations Economic Commission for Europe (UNECE) Convention on Long-Range Transboundary Air Pollution (LRTAP), and the United Nations Environment Program (UNEP) Stockholm Convention on POPs. The criteria for evaluating Persistence (P), Bioaccumulation (B), and Toxicity (T) characteristics of substances under the various regulations are not harmonized, but show large similarities.

Regulations focusing on PBT/POPs are generally supplementary to existing regulations covering 'other' chemicals. Their aim is to identify substances that may cause unexpected problems, such as those that persist and bioaccumulate and ultimately may lead to adverse effects in organisms, particularly in remote areas where the substances are not directly emitted or used.

The current regulations define candidate PBT/POPs in terms of fairly strict criteria that were based on the state of the science in the late 1970s and early 1980s. Since then, an evolution has taken place in the area of environmental and analytical chemistry, computational chemistry, information technology and environmental toxicology that has produced new insights into the persistence, bioaccumulation and toxicity of chemical substances and an array of new methods to identify PBT chemicals. The development of regulatory criteria has not kept up with the rapid development in environmental chemistry and toxicology. As a result, industry, regulators and academics find themselves in a situation where guidance on PBT/POP criteria is sometimes available, but it is often too limited and sometimes out-of-date. This has caused some major challenges. One key challenge is the interpretation of substance information in the form in which it is usually provided against the criteria as they are formulated. Very often these do not match. Another challenge is the identification of PBTs and POPs at an early stage, sometimes when there is still limited information available. Equally challenging is that the process of identification should be highly accurate - false negatives may cause environmental problems when impacts are discovered at a late stage, whereas false positives may cause significant business and societal consequences and may unduly deny society beneficial products. Overall it is of key importance that current legislations are applied in an effective way, taking advantage of the currently available state of the science.

Workshop Purpose and Goals

To foster the advancement of a sound scientific foundation for identifying and evaluating PBTs and POPs, an international workshop, sponsored by the Society of Environmental Toxicology and Chemistry (SETAC), was held 28-31 January, 2008, to discuss scientific issues related to persistence, long-range transport, bioaccumulation, and environmental toxicity relative to

identifying the potential for significant adverse effects. The workshop had broad, tripartite involvement from academia, government, and industry.

The specific objectives of the workshop were to discuss, reach consensus, and develop guidance on how to evaluate substances that may fulfill PBT and/or POP criteria using scientific information such as experimental data, monitoring data, computer models, etc. PBT/POP criteria are intended here in the broadest sense, including the various criteria defined in different regulations around the world, as well as recommendations for new criteria. The workshop participants addressed the information required to provide a weight-of-evidence for substance evaluation under the various regulations. After thorough discussions of each of the criteria and an evaluation of several case studies, the participants derived a framework with detailed guidance and recommendations on how to interpret substance specific scientific information relative to the various PBT/POP criteria.

Ultimately, the goal of the workshop is to provide timely input into national and international assessments of PBTs and POPs. Among the key work products is a state of the science review. In addition to the final report, the results of the workshop are presently being communicated broadly by SETAC using all appropriate means to the scientific community and to policy makers.

Participation and Format

The workshop followed the format of previous SETAC Pellston Workshops, and was limited to about 50 participants with broad international perspective and recognized expertise in environmental chemistry, toxicology, multimedia modeling, and risk assessment (see Participants List). To address the objectives, the workshop was organized into 9 individual sessions. A general plenary was held on the first day, where invited, authoritative discussion papers were presented to stimulate dialog. Based on expertise, each participant was assigned to a small workgroup, although interactions among the workshops were encouraged. A major goal of each workgroup was to develop a summary of their deliberations, including discussions of the state of the science pertinent to that workgroup; a critical analysis of available approaches; and methods to integrate these approaches into a framework for assessing PBTs and POPs. Key points from the discussions are summarized below. The complete workshop proceedings document is in preparation and will be available by early 2009.

Evaluating Environmental Persistence

The persistence of organic compounds is governed by the rates at which they are removed by chemical and biological processes such as biodegradation, hydrolysis, atmospheric oxidation, and photolysis. This work group focused on evaluating persistence of organic compounds in environmental media (air, water, soil, sediment) in terms of their single-medium degradation half-lives. The findings built upon the results of a previous Pellston workshop, as well as recent guidance developed for other chemicals assessment programs. The primary aim was to provide guidance to authors and reviewers of chemical dossiers in the government and private sectors. A second objective was to provide a summary of the current state of the science with respect to fate assessment for POPs.

Environmental persistence is influenced by many factors. Chemical structure ultimately determines which transformation processes may be significant for a given compound and which are not likely to be important. The structure also determines inherent properties, such as water solubility, which influence degradation rates. Characteristics of the receiving environment(s) are also important, including hydroxyl radical concentrations in air, as well as temperature, salinity, pH, oxygen concentration, redox status, test chemical concentration and nutrient status, which directly or indirectly impact rates of transformation in the other media. Transformation processes can significantly reduce the potential for exposure and significant adverse effects. In contrast, physical processes such as dilution and advection do not impact persistence because they do not reduce the environmental burden of the chemical.

After careful consideration of international and national POPs and PBT regulatory frameworks, guidance has been developed that identifies the information that a risk profile should contain in

order to conclude whether a chemical is persistent. Specific attention is given to addressing uncertainty and conflicting data, as part of a 'weight-of-evidence' assessment.

In general, fate testing should be conducted under relevant environmental conditions with respect to temperature, pH, substance concentration, etc. In weight-of-evidence assessments, preference should be given to valid test data over non-test data, such as information derived using quantitative structure activity relationships (QSARs). Further, it is important to understand the mechanism(s) by which loss of the parent material or intermediate degradation products occurs.

Higher tier biodegradation studies, often termed simulation studies, can be difficult to interpret. Although the tests were originally designed to generate kinetic information (e.g., first-order rate constants) on the biodegradation of a chemical, which can be converted into the corresponding half-life for comparison with criteria, the different mechanisms involved in removal of the parent compound may complicate the analysis of the results. For example, when the fate of certain chemicals is examined in soils or aquatic sediments, the results often yield dissipation times that combine removal due to biodegradation, sorption, and bound residue formation.

Critical issues for studies using soil or sediment are whether residues in soil or sediment are extractable using exhaustive extraction methods, and whether those that are not, i.e., the non-extractable residues, are covalently bonded to the matrix. The challenge thus lies in interpreting the output of such studies in terms of a chemical's behavior in the real world. A number of studies suggest that residues that cannot be extracted by aggressive techniques (e.g., Soxhlet extraction, supercritical fluid extraction, etc.) are unlikely to be bioavailable to soil organisms. It was concluded that where non-extractable residues can be shown to be covalently bonded to the soil matrix, rates of dissipation (including bound residue formation) can be included with degradation for comparison to the half-life criteria.

It is generally acceptable to take the sum of process-specific first-order rate constants for a given compartment (i.e. the sum of the rate constants for biodegradation, hydrolysis etc.). This cumulative rate constant can be used to derive a compartmental degradation half-life for comparison to persistence criteria or as input to models, as appropriate. However, rate constants for primary and ultimate degradation should not be combined.

In general, it is not sound scientific practice to use the Arrhenius equation (Q_{10} rule) to quantitatively correct biodegradation data to a common environmental temperature (e.g. 10 °C). This is because microbial populations generally are adapted to prevailing environmental conditions, and the transformations that they perform cannot be scaled directly with temperature as is the case for abiotic reactions.

No single half-life value can adequately describe degradation in the environment or any environmental compartment. Typically, where multiple degradation studies have been conducted, there is a range of observed half-lives. In such cases it is not appropriate to use the slowest or most conservative half-life.

Multimedia Partitioning, Overall Persistence and Long-Range Transport Potential

An important feature of chemicals released to the environment is that they can re-distribute between media. For example, a substance may be released to either air, water, or soil, and then subsequently move between these phases. It is important to assess the ability of a compound to undergo '*multi-media partitioning*', because this will affect its ability to be transported in air or water over long distances, its susceptibility to degradation in a particular compartment, the potential to transfer into living systems, and its *overall persistence* (P_{ov}) in the environment.

The distribution of a compound between environmental media is controlled by its physical and chemical properties, and by certain features of the environment (e.g., compartment volumes, and properties such as temperature, pH, and organic matter content). Evaluative models have been developed which make predictions about chemical distribution in a defined multi-media

environment. Such models are important tools in behavior profiling. Key physical-chemical property data required for such profiling are the solubility in water, vapor pressure, and information on its partitioning between media, including the Henry's law constant, and the n-octanol-water (Kow) and n-octanol-air (Koa) partition coefficients. Different experimental or estimation methods used to derive these properties may give different results. Chemical property data reported in the literature are often inconsistent and incomplete. Since the quality of the data determines the reliability of any PBT/POP assessment, care should be taken when such data are compiled. Partitioning properties should be checked for internal consistency and outliers should be identified and removed from the dataset.

The environmental behavior profile is further developed by combining assessments of the multimedia distribution of the chemical with information on its degradation kinetics in the different media. Environmental half-lives can be determined by various experimental methods; when measured half-lives are unavailable, a number of predictive methods (QSARs) can be employed. Uncertainty ranges for measured or estimated half-lives should be considered.

In current legislation, persistence is often assessed against criteria for single-media half-lives, typically for the relevant environmental compartment(s), i.e., those in which the compound resides. However, such approaches can overlook important features of chemicals that undergo re-distribution in a multi-media environment. For example, if a chemical released to water or soil is persistent in air and can readily undergo surface-to-air exchange, it could potentially be transported in air and reach remote environments. Similarly, persistent and water soluble compounds may travel great distances in rivers and oceans. Chemicals should therefore be assessed with respect to their overall environmental persistence (Pov) in an evaluative multi-media 'regional' or 'global' environment.

Several multi-media models have been developed which can evaluate the Pov of chemicals. The Organization for Economic Cooperation and Development (OECD) has supported the development and inter-comparison of such approaches, which led to the adoption of the OECD Pov and long range transport potential (LRTP) Screening Tool. The OECD Tool allows comparison of the test chemical against a series of reference chemicals, with well defined properties and well known environmental behavior. Hence, it is possible to define a Pov value which ensures that there is no net accumulation of a chemical in the environment. Such evaluations enable the 'management' of chemicals in a consistent way, irrespective of the particular combination of half-lives. For example, if 100 units of chemical with a Pov half-life of 90 days are released into a multi-media environment, the levels will decline to ~6 units within a year, while a chemical with a Pov half-life of 200 days will systematically accumulate. Because Pov depends on the environmental conditions, it may be inappropriate to define a specific Pov cut-off value. Rather, Pov should be used as part of the weight-of-evidence compiled to screen and evaluate chemicals.

Atmospheric transport is usually the primary mode for conveying persistent substances to remote regions. For this reason, the UNEP and UNECE Conventions define a criterion for half-life in air of >2 days. The original intent of this value was to highlight those chemicals that are sufficiently persistent to be able to travel through the atmosphere to 'remote regions'. Two days is a convenient metric that might apply to substances emitted in parts of temperate world which may travel with some efficiency to reach the Arctic. With the 2 day criterion, typically <3% of the chemical will be transported a distance of 1000 km or more. The OECD Tool permits an assessment of the long range transport potential for a candidate substance which can be compared and ranked against other well studied compounds.

Regulatory approaches often acknowledge the usefulness of monitoring data, often from remote locations, in highlighting potentially problematic chemicals. Their occurrence in remote regions is often taken as evidence of their persistence and long-range transport potential. However, detection of a chemical in a remote area is not evidence, *per se*, of these properties. Detection in remote environments needs to be assessed in the context of amounts and patterns of usage and

emission and the sensitivity of the analytical methods, to develop a robust, scientifically sound risk profile.

***In Vitro* and *In Silico* Approaches for Bioaccumulation Assessment**

Predictive tools are critical components of an overall strategy for assessing the potential of chemicals to bioaccumulate within the environment. The prioritization and assessment of chemicals is increasingly moving into the realm of data inadequacy. Consequently, there is and will continue to be, a reliance on predictive tools to complete regulatory requirements in a timely, humane, and cost effective manner.

The toxicokinetic processes of absorption, distribution, metabolism, and elimination (ADME) determine the extent to which chemicals bioaccumulate in living organisms (Figure 1). Mechanistic models of bioaccumulation explicitly consider these ADME processes but there is a lack of data needed to specify critical model input parameters, particularly for compounds that are extensively metabolized, exhibit restricted diffusion across biological membranes, or do not partition simply to tissue lipid.

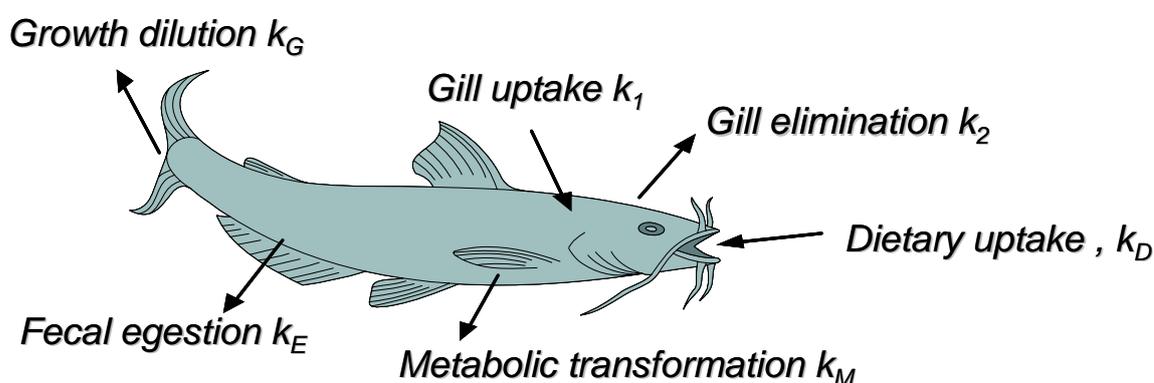


Figure 1. Conceptual diagram of ADME processes and the related kinetic rate constants for fish.

A variety of *in vitro* systems are available for estimating ADME properties, and the workshop explored the applicability of these assays for estimating input parameters for bioaccumulation models. Several *in vitro* assays have been developed by the pharmaceutical industry to predict the membrane permeation of drug candidates. Well-known examples include the Caco2 cell line and the parallel artificial membrane permeability assay (PAMPA). Both assays depend on the ability to measure chemical concentrations in water. As such, they are poorly suited for use with hydrophobic materials. An adaptation of the PAMPA assay that employs silicon disks for both dosing and sampling holds promise for use with high log K_{OW} compounds.

The *in vivo* rate of xenobiotic metabolism (k_M) can be estimated using *in vitro* systems derived from liver tissue (e.g., isolated hepatocytes, microsomes, and S9 fraction), in combination with a physiologically-based prediction model. These procedures explicitly consider chemical distribution within the animal, which can be represented as an apparent volume of distribution at steady state (V_{SS}). Using this approach, k_M may be viewed as a quotient that integrates information about metabolic clearance (CL) and chemical distribution: $k_M = CL / V_{SS}$. Limited studies have shown that incorporation of *in vitro* metabolism data into models of chemical bioconcentration substantially improves the accuracy of steady-state bioconcentration factor (BCF) predictions.

Efforts are also being made to predict metabolic rate constants from an *in silico* analysis of chemical structure. Current models use metabolic maps based on well-studied pathways in rodents to predict likely metabolic products in fish. These reactions operate against the “base-line” extent of accumulation predicted from simple partitioning considerations, and the probability of a specific reaction can be estimated by modeling to measured steady-state chemical concentrations.

A critical issue in bioaccumulation assessment is the question of whether there are molecular size cut-offs for ADME processes. There is a gradual effect of size on membrane permeation but this effect is driven by the kinetics of permeation and is not partitioning-based. Several size cut-offs have been estimated from model-based evaluations of chemical uptake and accumulation in fish. These operationally-defined cut-offs depend on the structure of the model used for their estimation and the conditions under which the data were collected (e.g., fish size and water temperature). As such, they are highly context-specific. Similar considerations apply to the estimation of metabolism rate cut-offs for bioaccumulation.

The workgroup developed guidance for the use of bioaccumulation prediction methods within the context of a weight-of-evidence approach. Important to this usage is the “domain of applicability” of results generated from *in silico* modeling efforts and *in vitro* assays. An approach is described which provides the basis for evaluating predictions from multiple models. The reviewed *in vitro* approaches are promising tools for identification and prioritization of chemicals in bioaccumulation assessment. Their application in regulatory assessment schemes is relatively new, however, and will require continued research to elucidate potential advantages and limitations.

Evaluation of Bioaccumulation using Whole Organism Lab and Field Studies

The objective of this working group was to prepare guidance on the collection and evaluation of bioaccumulation data from whole organisms in lab and field studies. Although applicable for national and regional chemical management programs, the guidance is specifically framed to support the development of the screening information required under Annex D of the Stockholm Convention on POPs, and the risk profiles drafted in accordance with Annex E.

A primary concern for chemicals is to identify whether they biomagnify to concentrations sufficient to pose health concerns to humans or wildlife. Historically, markers of *in vivo* exposure (e.g., egg shell thinning, bill deformities) have retrospectively led to the identification of POPs. Today, multiple bioaccumulation metrics from lab and field studies are available to understand and predict the bioaccumulation potential of a possible POP.

A variety of laboratory procedures have been described for exposing aquatic species (e.g., fish, invertebrates), and, on occasion, other species (e.g., mammals, birds) to a chemical and measuring the resulting tissue residues. Exposures to the test compound can be accomplished via multiple routes, e.g., aqueous, dietary, or through soil/sediment. A number of standard guidelines are available for measuring bioconcentration, bioaccumulation, and other metrics such as biomagnification factor and biota-sediment accumulation factor (BMF, BSAF) in the laboratory (e.g., OECD, U.S. EPA, ASTM). Results of laboratory bioaccumulation studies should be critically evaluated, and only high quality data should be used in the screening analysis and resulting risk profile. Further, care should be taken when evaluating the results of laboratory studies conducted using ¹⁴C-labeled test chemicals, as the results are often based on total radioactivity, which can often include metabolites present in the test organism. The degree of metric variability between species is discussed, in addition to the general variability that may be observed even within a given species, particularly for fish BCF and BMF determination. Field monitoring data for free or caged organisms and associated bioaccumulation metrics (e.g., trophic magnification factor (TMF), bioaccumulation factor (BAF)), non-standard tests, and data from tests conducted for other purposes (e.g., toxicity feeding study of birds with measured tissue residues, critical body burdens) are also described and discussed. The advantages and disadvantages of the various lab and field tests are described, so that the relative merits of the metrics are transparent and can be applied in a weight-of-evidence case. Also, the various bioaccumulation metrics and methods used to normalize data (e.g., concentrations based on wet weight, lipid weight, or dry weight) are evaluated. Guidance is provided on how to interpret data uncertainty, and how to evaluate data reliability to select the most credible data to support decisions in screening and risk profiles.

Benchmarking of proposed POP candidates is also described, as comparisons of test compounds against chemical class analogues that may or may not be listed as POPs may prove useful. This

step may prove advantageous in identifying trends in chemical structure and class, understand factors that might compromise test results (e.g., highly volatile substances), and evaluate data consistency.

Based on the bioaccumulation information shared in eight draft risk profiles for candidate POPs, the workgroup developed recommendations for the types of information that are critical, or at least beneficial, to significantly aid transparency and certainty in decision making. Recommendations are related to clearly stating the bioaccumulation metric and units, data quality, identity of location and species (or sample types), isomers or congeners of greatest concern, references to primary and recent literature, comparison to established POPs, and linkage of the bioaccumulation and/or exposure metric to a significant adverse effect and long range transport.

Revisiting Bioaccumulation Criteria

Currently, Bioaccumulative (B) substances are defined in terms of criteria, expressed in the form of the BAF, BCF, or Kow. In view of the absence of a recognized definition, we have defined a B substance as one which biomagnifies in the food-web, i.e. increases in normalized concentration (or fugacity) with increasing trophic position. Chemicals that biomagnify, bioaccumulate to a greater degree than chemicals that do not biomagnify. Biomagnifying substances have therefore a greater potential to reach high concentrations in upper-trophic level organisms (including humans) and cause adverse effects within the food-web.

The workgroup concluded that the most relevant B criterion is the TMF (also referred to as a Food-Web Magnification Factor) and that the most conclusive evidence to demonstrate that a chemical substance biomagnifies is a TMF > 1. TMF is derived from a correlation between appropriately normalized chemical concentration in biota and trophic position. It is crucial for the characterization of TMF that both aquatic and terrestrial food-webs are considered. This is because chemicals can exhibit fundamentally different TMFs in aquatic and terrestrial food-webs due to differences in the bioaccumulation mechanisms between water and air breathing organisms.

In the absence of data on the TMF, the BMF, either derived in the laboratory or based on field data, is a reliable indicator. The BMF is expressed as a ratio of normalized chemical concentrations in a specific organism and that in the organism's diet or prey at steady-state. A BMF > 1 indicates the capability of the chemical to biomagnify. For the differences noted above, BMFs in both air and water breathing organisms must be considered. For laboratory based BMF measurements, we recommend the use of rainbow trout and rats (or mice) because of the long-term experience with these commonly used test species and because of access to data previously collected for these animals.

The workgroup concluded that the BCF is not a good surrogate for BMF or TMF in terrestrial food-webs, and that in many cases, the BCF is not even a reliable indicator of biomagnification for aquatic food-chains. This is because the BCF quantifies chemical bioaccumulation from water but not the diet. This conclusion is supported by analysis of draft risk profiles, which identified 5 substances to be bioaccumulative in the environment although the BCF criteria were not met. Despite these difficulties, the workgroup concluded that the BCF can be a useful indicator of biomagnification if the route of exposure (water) does not affect the biotransformation rate of the chemical in the organism, and if bioavailability issues are not significant experimental artifacts.

Because empirical data regarding the TMF and BMF are available for only a small fraction of chemicals in commerce, it is important to propose surrogate criteria to identify potentially biomagnifying substances. For non-ionizable, non-polar organics, chemicals with a log Kow < 4 do normally not biomagnify in aquatic food-webs, and there is no evidence that these substances exhibit BCFs > 5000. For the evaluation of chemical biomagnification potential in terrestrial food-webs involving air-breathing organisms, we expect chemicals with a log Koa < 5 will not biomagnify in terrestrial food-webs. These substances may not require BMF tests. For substances whose Kow and Koa exceed these criteria, there is the potential for including *in vivo*

biotransformation rate constants (k_M). This is because chemicals that are rapidly degraded in organisms cannot bioaccumulate or biomagnify to a high degree. Modeling studies have suggested that chemicals with biotransformation rate constants on the order of 0.1 d^{-1} cannot biomagnify in food-webs, although further work is needed. Screening assessments can also benefit from the use of food-web bioaccumulation models to calculate BMFs and TMF. Such models have benefits over using chemical property data alone, since they can be parameterized to make use of available biotransformation rate data.

The workgroup recognized several research needs to support and improve B assessments. They include (i) technical guidance for the determination of TMF, (ii) development of a standard protocol for BMF tests in rat and fish, (iii) guidance on the use of field studies for the development of BMF in mammalian/bird and submerged aquatic species, (iv) investigation of the potential application of currently available rat and fish dietary data, and (v) investigation of the possibility of deriving a single biotransformation half-life criterion for identify non-biomagnifying chemicals. We further recommend that additional information is gathered on the relationships between the BCF, BMF and TMF.

To ensure that B assessments are carried out based on the current state of the science, it is essential that dietary magnification and an assessment of both water and air breathing organisms are included. A framework for B assessment is presented in Figure 2.

Stage	Description	Evaluation	Outcome
Step 1	Food-web assessment	What food-webs should be considered?	Aquatic Terrestrial
Step 2	TMF-assessment	Is TMF > 1?	B status Confirmed
Step 3	BMF-assessment	Is BMF > 1?	B status Probable
Step 4	BCF/BAF-assessment	Is BCF or BAF > 5,000?	B status Possible
Step 5	Phys-Chem, ADME, Food-Web Model Assessment	Log Kow > 4, log Koa > 5 BMF > 1, TMF > 1	B status Potential

Figure 2. Framework for bioaccumulation assessment

Use of Measurement Data in Evaluating Exposure of Human and Wildlife to POPs/PBTs

The Stockholm Convention on Persistent Organic Pollutants (POPs) recognized that POPs resist degradation, undergo long-range transport (LRT) and accumulation in remote terrestrial and aquatic ecosystems. The convention also acknowledged that indigenous communities, particularly in the Arctic, were at risk because of the biomagnification of POPs and contamination of their traditional foods. This recognition was largely based on environmental monitoring data, and demonstrates the need to have adequate guidance on data collection and use. Indeed the Stockholm convention (Annex E) requires monitoring data for “exposure in local areas and, in particular, as a result of long-range environmental transport”.

Figure 3 depicts a variation of the exposure/effect continuum. The first part of the continuum, the “exposure” portion depicts the “environmental chemical” originating from a “source,” moving into the environment where it may undergo various “fate and transport” steps; humans coming into “contact” with the environmental media and a portion of the chemical entering the body by one or more exposure routes (ingestion, inhalation, and dermal).

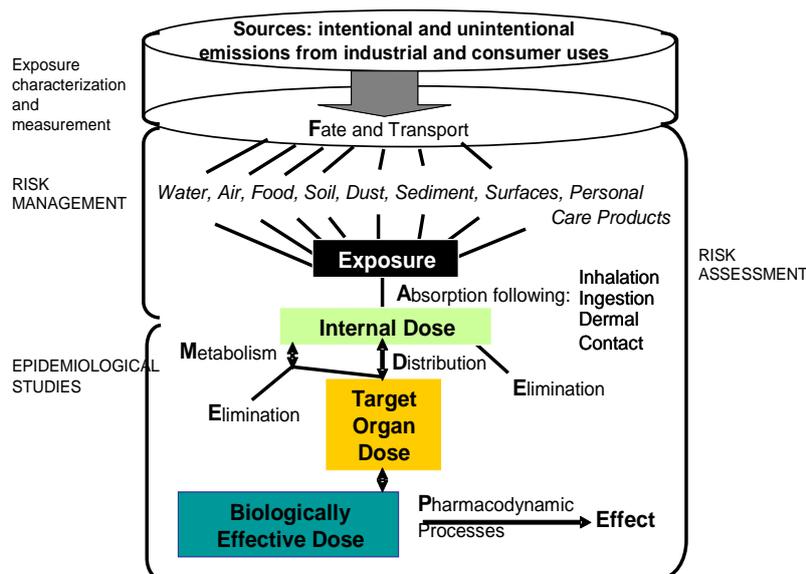


Figure 3. Exposure-effect continuum for humans and top predator wildlife for PBT chemicals

For the so-called legacy POPs, including those on the list of the Stockholm Convention, the primary route of human exposure is, and has been, dietary ingestion. However, for some of the new candidate POPs such as polybrominated diphenyl ethers and perfluorooctane sulfonate, the exposure routes while still including dietary ingestion, may also include non-dietary ingestion of household dust as well as potentially inhalation of that dust.

To develop robust data sets on the extent of exposure of wildlife species to POPs requires careful consideration of many factors because of the potentially wide range of possible species and habitats. Based on more than 30 years of extensive measurements of the legacy POPs in biota there is lot of information available and the need to monitor compliance with the Stockholm Convention has stimulated recent comprehensive reviews of the issues and publication of a UNEP guidance document. However, there is relatively little guidance on the most appropriate environmental measurement approaches particularly for new candidate POPs, and on how to create a weight-of-evidence based on such data.

As we move beyond the “dirty dozen” there are technical challenges associated with developing robust datasets of new candidate POPs. Many candidates are, or were until recently high production volume chemicals, used in a wide variety of industrial and consumer products. Background contamination during lab analysis or field collection (that could yield false positives), and lack of certified analytical methods and standards, are measurement challenges which need to be recognized in risk and exposure assessments. In addition to quality assurance issues, development of robust datasets also requires appropriate study designs, incorporating consideration of statistical power, geographical (local, regional and remote sites) and temporal scope, and key environmental media/tissues, to develop the weight-of-evidence for exposure. Studies which combine measurements of new candidates with benchmark chemicals such as PCBs are particularly useful for comparative assessment.

The recommended matrix for human monitoring for assessing exposure to POPs, is blood or its components, such as serum or plasma. The primary reason is that exposure to most all POPs can be assessed by analyzing blood, and even though analyzing breast milk has the advantage of directly assessing exposure to the nursing infant, this information can be ascertained by analyzing the blood of the mother, both post-partum and during pregnancy. Of course, analyzing milk or serum does not in general give us knowledge as to the pathway and specifically the route of exposure; these analyses integrate exposure and absorption through all routes.

In developing guidance for global environmental monitoring of legacy POPs, the UNEP Guidance for a Global Monitoring Programme recommends focusing on air, human milk or blood, as well as widely measured biota such as mussels, marine mammals, bird eggs, and fishes as most appropriate types of samples because of past extensive studies and assuming that species close in taxonomy and trophic levels to existing well established programs, seem most appropriate also for new candidate POPs.

The working group recommends that for assessing exposure in humans and top predators, the use of direct measurements of the compound of concern from a significantly and uniquely exposed population (indigenous populations, remote populations), as well as data demonstrating biomagnification and time trends if possible. These data must be from the appropriate sample matrix type, must be collected and analyzed using accepted methodologies, be reviewed for quality assurance, and be interpreted correctly in order to be used to assess exposure.

Modeling Exposure to Persistent Chemicals in Hazard and Risk Assessment

Fate and exposure models are used routinely in regulatory applications to inform decision making and have been useful in improving the understanding of POPs and PBT chemical fate, hazards and potential risks. There are many opportunities to improve the risk profile evaluation of significant adverse effects in either the UNEP Stockholm or UNECE LRTAP Conventions by using fate and exposure models. Therefore, the goal here is to motivate the use of models in preparing the risk profile in the POP assessment procedure and to provide strategies and guidance for their application.

The goal of an exposure assessment for POPs and PBTs is to establish the link between chemical emissions to the environment and exposure in the target organisms of concern. To accomplish this goal, several models are generally needed. First, an environmental fate model is required to describe the fate and presence of the chemical in the various environmental compartments as a result of emissions. Secondly, bioaccumulation models are needed to predict the resulting exposures in target organisms of various food webs arising from the concentrations in the physical media. These models can either be separate or linked within a modeling package. Further, in the context of preparing a risk profile for a candidate POP, an additional goal is to predict chemical exposures in remote regions that result from long-range transport. Currently there is no standardized consensus model for use in the risk profile context. Therefore, to choose the appropriate model, the risk profile developer must evaluate how appropriate an existing model is for a specific setting, and whether the assumptions and input data are relevant under the conditions of the application.

There are a variety of ways that fate and exposure models can be used to improve and inform the development of a risk profile. Model-based exposure predictions can be compared to existing monitoring data to establish whether the monitoring data and the exposure predictions are reasonable, representative, and consistent. Confidence in the predictions of many existing models is possible because of their fundamental physical and chemical mechanistic underpinnings and the extensive work already done to compare model predictions and empirical observations. Sensitivity analysis of the model can be performed to identify the key processes and most important model parameters which impact the exposure, thereby allowing, when desired, focused research or measurement to improve the risk profile. In the absence of quantitative emission information, benchmarking can be performed where the ratio of exposure and emissions of candidate chemicals is compared to the same ratio for known POPs. Such approaches enable the possibility of combining the relative magnitude of this ratio with the relative emissions and relative hazard to arrive at a measure of relative risk. Models can also be used in the risk management context for predicting future time trends, including how quickly exposure levels in remote areas would respond to reductions in emissions.

As an illustration of the application of models to predict human exposures in support of the risk profiling process, the workgroup considered a variety of candidate POPs that have been nominated for consideration under the Stockholm Convention. Models were initially used to benchmark the candidates against a series of acknowledged POPs and non-POPs. Additional simulations were performed for one of the candidates to compare predicted data to concentrations measured in the environment. Based on sensitivity and uncertainty analysis of the findings, it was clear that accurate estimation of emission rates is a prerequisite to obtaining useful estimates of exposures and risks. Further, the biotransformation half-lives were shown to be the most sensitive parameter and most influential for determining the predicted human body burden.

The working group recommends that a model benchmarking tool for human and wildlife exposure in remote regions be developed. This tool would be analogous to the benchmarking tool for persistence and LRT developed for the initial stage of the POP review process. Such a tool would allow a non-expert to do a model-based exposure assessment with confidence, and would contribute to lowering the barriers to exploiting the potential of models. Furthermore, the working group suggests the development of a second model benchmarking tool for the recovery time of remote environments following the cessation of chemical emissions. Such a tool would provide transparent, readily comprehensible information on an important motive underlying the concern about POPs, namely the reversibility of potential risks.

Use of (Eco)Toxicity Data as Screening Criteria for the Identification and Classification of PBT / POP Compounds

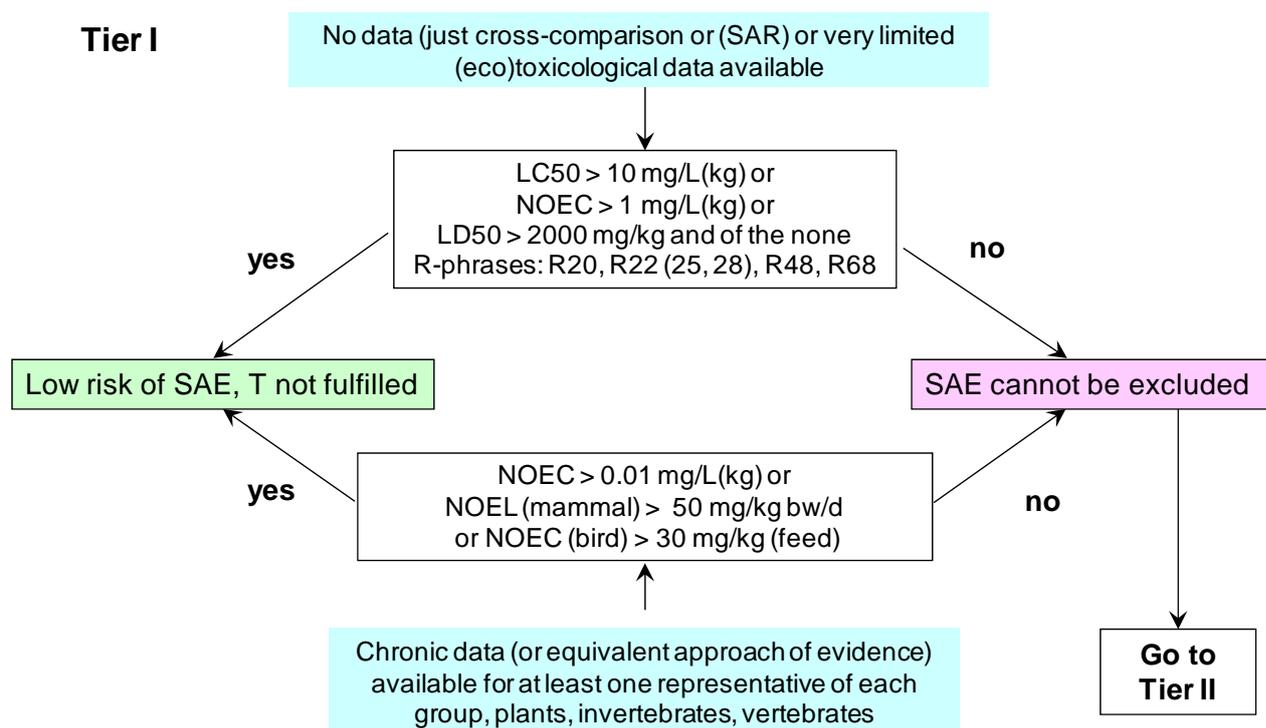
Characterization of significant adverse ecotoxicological effects of POPs and PBTs presents particular challenges. In the various international conventions, guidance on the definition and criteria for evaluating toxicity are not detailed and, in some cases, unclear. This paper focuses on several key issues in relation to the selection of assessment endpoints, the use of appropriate effect measures, and methods to address uncertainty in the face of limited data.

The protection goal of POP/PBT regulations is to prevent the occurrence of significant adverse effects on humans and the environment. For humans, the protection goal is aimed at the individual, and the standards of acceptable risk are well defined, particularly for substances that may cause serious effects, such as cancer or reproductive dysfunction. In contrast, significant adverse effects endpoints for most environmental species are mostly at the level of the population, although community level effects and overall ecological function and sustainability must also be considered. Additional protection may be appropriate for some rare and endangered species for other than strict ecological reasons.

In principle, there is a large array of standardized guideline studies available to assess the toxicity of POPs and PBTs. However, only a limited number of substances have sufficiently robust datasets for characterizing adverse effects on the diversity of environmental species. The best database for characterizing toxicity of organic chemicals can be found for pesticides, for which a large number of acute and chronic tests are available for a number of taxa, including mammals. For many industrial chemicals, the database is more limited, and indirect methods for characterizing toxicity, such as the use of QSARs or extrapolation within modes of action are necessary. Further, the question of differential sensitivity has been raised, particularly for organisms found in polar regions. While there are few data to address such differential sensitivities, there is no reason to suggest that, if differences exist, they are sufficiently large that data from temperate organisms cannot be used in the assessment of adverse toxicological effects for arctic species. However, it should be considered that recovery from disturbances may take longer time in polar regions than under temperate or tropical conditions.

Because POPs are persistent and bioaccumulative, the assessment of toxicity should generally not be based on concentrations in environmental matrices but rather on body or tissue residues in an organism that are causally linked to adverse responses. The exception is where clear correlations exist between matrix concentration and adverse effects.

Figure 4. Diagrammatic representation of the Tier-I decision tree.



Because such information is not generally obtained when using existing guideline protocols, toxicity testing methods may need to be modified or substantiated by toxicokinetic information to ensure that substances with PBT-like properties are adequately characterized. These data can be more easily matched to environmental monitoring measurements of body/tissue residues for the purposes of assessing whether adverse effects are occurring in the environment. In the face of persistence and accumulation in the food chain, and considering the extent and suitability of data available, a suitable policy on the use of uncertainty factors may need to be applied when making judgments about toxicity.

When toxicological data are limited, a variety of approaches can be taken in the assessment of a chemical, including the use of structure activity relationships and consideration of the mode of toxic action. Various Structure-Activity Relationships (SAR) and QSARs have been developed and tested for a variety of chemical classes. Further, understanding the mode of action of a chemical enables a reasonable extrapolation of potential sensitivity and effect responses across taxonomically diverse groups of organisms. When such information is used to supplement experimental data, a weight-of-evidence approach can inform decisions in a rigorous and scientifically defensible manner. In this context, weight-of-evidence is defined as the use of all available data in conjunction with expert knowledge to reach a conclusion. In the case of PBTs, this would include incorporating information on tissue residues and critical body burdens with documentation of historical effects and traditional toxicological studies. Given the data limitations for toxicity or measured environmental effects for most PBTs, a well-documented weight-of-evidence approach is preferred for characterizing the ecotoxicity of these substances.

A series of draft risk profile reports for candidate POPs were reviewed to assess whether the information presented for various endpoints of concern supported the conclusion that the substances met the criterion of causing significant adverse effects. From the analysis, it was apparent that the profiles lacked consistency in the type of endpoint considered, and there was no clear evidence that a consistent, generally accepted decision-making process was followed. Use of an evaluative scheme (Figure 4) based on a tiered approach is recommended to ensure that all

of the same endpoints are considered in each assessment, and that the amount and type of data used from these endpoints is uniform. It is anticipated that use of such approaches will lead to consistent, well formulated and informed decisions as to whether the substance in question may cause significant adverse effects at environmentally relevant concentrations.

Framework for Identification and Assessment of PBTs and POPs

Several national regulatory programs and regional or global agreements address the assessment and ultimate control of PBT and POP substances. Reviews of substances generally involve an initial priority-setting phase, followed by a more in-depth assessment phase of the properties of prioritized substances and their potential for adverse effects. The ultimate basis for decisions as to whether a substance is a PBT or POP, and whether risk management decisions are required, will depend on the goal and mandate of the initiative. For example, under the Stockholm Convention, decisions are made about potential POPs on the basis of “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”. The existing frameworks for evaluation of POPs and PBTs provide adequate flexibility to introduce additional, new and emerging, scientific evidence into the processes.

In assessing any of the properties associated with potential PBTs or POPs (P, B, T, LRT, SAE), a range of approaches, including use of empirically-derived and model-derived information, can be considered and applied as appropriate. In so doing, both quantitative and qualitative lines of evidence can be used, but the reporting of results should recognize and communicate uncertainties associated with both of these. Although this workshop concentrated on scientific issues, it is important to note that public and other stakeholder views, plus legislation in force in different national jurisdictions, will also influence the way in which POPs and PBTs are evaluated, as will the particular requirements of those commissioning the evaluation. For example, there is a fundamental difference in the methods used to rank and prioritize chemicals for PBT/POP properties when compared to detailed PBT/POP assessment of chemicals that have already been prioritized. In the former case, well defined prioritization criteria are used at first to filter out substances that are likely neither PBTs nor POPs, or to identify substances with potential for being PBTs or POPs (e.g., Canadian DSL Categorization, US New Chemicals PBT modeling, and EU PBT work group). In this first, priority-setting phase, rapid and efficient approaches should be used, and will generally be developed to minimize the probability of false negative results. Substances that are identified as priorities or as potential PBTs or POPs by this process need to be assessed in more detail in a second, assessment phase by collating empirical and other robust data. The use of more specific models, consideration of data for analogous chemicals and weight-of-evidence approaches, as discussed in this workshop summary, are recommended in this assessment phase.

The basic framework for PBT or POP assessment is shown in Figure 5, and can be enhanced as new scientific approaches and information arise. The main question that should be asked of any new approach or information is: will it help in appropriately identifying potential PBTs or POPs for further assessment, or is it designed to help evaluate a small number of chemicals accurately and precisely? The answer to this question will determine whether the information or approach is of use primarily in the priority-setting phase or the assessment phase of the framework.

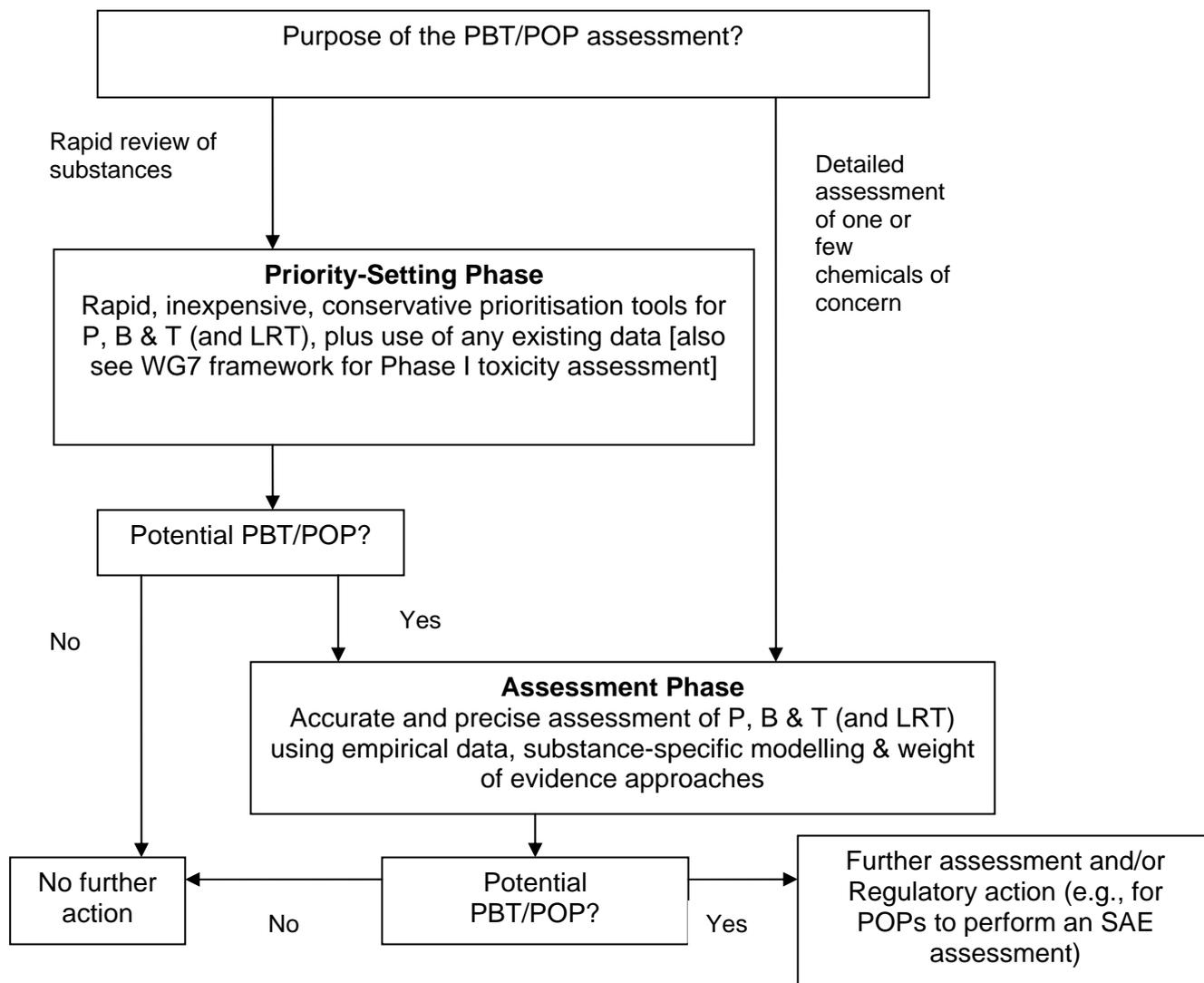


Figure 5. Framework for PBT/POP evaluation

Many of the approaches and methods discussed at this workshop are most appropriate for application in the assessment phase of this framework. However, there was some discussion of appropriate, rapid prioritization for P, B, T and LRT through use of QSARs and software programs such as the OECD Toolbox or the OECD Long Range Transport Tool. It should be noted that Annex D of the Stockholm Convention on POPs discusses “screening criteria”, which partly overlap with the approaches proposed for the priority-setting phase of this framework. However, the Stockholm Convention screening criteria also provides for consideration of empirical data from experimental and monitoring studies, which generally might better apply in the assessment phase of the proposed framework.

The following conclusions from the workshop are relevant to the use of rapid tools in the priority-setting phase of the proposed framework:

General

- In general, reliable data from empirical studies should carry more weight in an assessment than should results from predictive tools or estimates. However, empirical data are unavailable for many substances, so reliance on modeling is usually inevitable during priority setting.
- The advantages and disadvantages of predictive approaches (e.g., QSARs) need to be understood by users, including the domain of applicability (boundary conditions), so that application in assessment regimes is informed.

Persistence

- Uncertainty ranges for estimates of chemical half-life based on QSARs and degradation studies may vary by a factor of 5 to 10.
- In current legislation, persistence is often assessed against criteria for single media half-lives for the most relevant environmental compartment(s). However, some structure-activity approaches can overlook important features of chemicals that undergo redistribution in a multi-media environment. Chemicals should therefore also be assessed with respect to their overall environmental persistence (PoV) in an evaluative multi-media “regional” or “global” environment. Tools such as the OECD PoV and LRTP Screening Tool are available for performing this type of evaluation.
- For volatile and semi-volatile compounds, atmospheric transport is usually the primary mode for conveying persistent substances to remote areas. The UNEP and UNECE criterion of a half-life in air of >2 days is an appropriate threshold for prioritizing these compounds.

Bioaccumulation

- Non-ionizable, non-polar organic chemicals with a log Kow <4 do not normally biomagnify in aquatic food webs via enrichment in fat tissues, and there is no evidence that these substances exhibit BCFs >5000. In terrestrial food webs with air-breathing organisms, chemicals with a log Koa <5 are not expected to biomagnify.
- If molecules of a substance are larger than 1.5 nm they are not likely to exceed a BCF of 5000. However, this observation is context-specific - no size threshold can be defined for BMF, for which additional uptake routes are possible.

Toxicity

When toxicological data are limited, a variety of approaches can be taken in the assessment of a chemical, including the use of structure activity relationships and consideration of the mode of toxic action. Various (Q)SARs have been developed and tested for a variety of chemical and organism classes. Furthermore, understanding the mode of action of a chemical enables a reasonable extrapolation of potential sensitivity and effect responses across taxonomically diverse groups of organisms.

The following conclusions from the workshop are relevant to the use of more detailed tools and empirical approaches in the assessment phase of the proposed framework:

Persistence

- Fate testing should be conducted under relevant environmental conditions with respect to temperature, pH, substance concentrations, etc.; it is important to understand the mechanism(s) by which degradation or distribution of the parent material or intermediate degradation products occurs.
- Higher tier biodegradation (simulation) studies can be difficult to interpret because of the different mechanisms involved in removal and distribution of the parent compound. One critical issue for sediments and soils is whether residues are bound in a way that might reduce their bioavailability. Another critical issue for water/sediment simulation studies is the unrealistic ratio between water and sediment in the test vessels compared to natural water bodies.
- No single half-life value can adequately describe degradation in the environment or any environmental compartment. Typically, where multiple degradation studies have been conducted, there is a range of observed half-lives, all of which might be considered when assessing degradation in the relevant compartment. In such cases it is not appropriate to use the slowest or most conservative half-life. Instead, care should be taken when such data are compiled: partitioning properties should be checked for internal consistency and outliers should be identified and not taken into consideration.
- Detection of a chemical in a remote area is not evidence, *per se*, of persistence and long range transport potential. Detection in remote environments needs to be assessed in the

context of amounts and patterns of usage and emission and the sensitivity of the analytical methods.

Bioaccumulation

- Bioaccumulation models and studies can be improved substantially by incorporating information on ADME. Methods for estimating these properties from *in vitro* studies are developing rapidly. The mechanistic nature of more recent *in silico* models makes them more transparent and interpretable, and affords the opportunity to incorporate *in vitro* derived ADME information.
- According to recent findings, the most relevant B criterion is the TMF, and the most conclusive evidence to demonstrate that a chemical substance biomagnifies is a TMF >1. TMF is derived from a correlation between appropriately normalized chemical concentration in biota and trophic position. It is crucial for the characterization of TMF that both aquatic and terrestrial food-webs are considered. This is because chemicals can exhibit fundamentally different TMFs in aquatic and terrestrial food-webs due to differences in the bioaccumulation mechanisms between water- and air-breathing organisms. However, a high BCF is also a strong indicator for a high bioaccumulation potential of a chemical, including secondary poisoning effects in food webs.

Exposure and Effects

- The recommended matrix for human monitoring for assessing exposure to POPs is blood, or its components such as serum or plasma, because exposure to most POPs can be assessed by analyzing blood. Human breast milk may also be used in some jurisdictions.
- Diet-based or tissue-based approaches are direct, accurate and site-specific methods for assessing the risks of top predator secondary poisoning by PBTs and POPs. The diet-based method uses estimates of the ingestion of POPs by predators from their diet. The advantage of this is that the only requirements for exposure assessment are samples of the predator's diet, realistic estimates of dietary composition, ingestion rates, and measured concentrations in the prey items. The even more direct tissue-based approach uses measurements of PBT/POP concentrations in the tissues of receptor species (top predators) to determine 'internal' exposure directly, and compares this exposure concentration to tissue-based effect concentrations ('toxicity threshold values') to determine risk. The advantage of this is that uncertain estimates of PBT/POP transfer to top predators from lower trophic levels are not required. In practice, availability of dose-response and internal exposure-response relationships is limited for PBT/POPs in top predators, so dose-response relationships for surrogate species must often be used. Ideally, these surrogate species data are supported by field biomarker data on PBT/POP exposure and biological responses in the receptor species of interest.
- In developing guidance for global environmental monitoring of legacy POPs, UNEP Guidance for a Global Monitoring Programme recommends focusing on air, human milk or blood, as well as widely measured biota (mussels, marine mammals, bird eggs, and fishes) as the most appropriate types of samples because of past extensive studies. This is also the most appropriate approach for new candidate POPs.
- The overall recommendation for assessing exposure in humans and top predators is to use or obtain direct measurements of the compound of concern from a significantly and uniquely exposed population (indigenous populations, or remote populations), as well as data demonstrating biomagnification and time trends, if possible.

Exposure and Long Range Transport

- A consensus modeling tool should be developed for benchmarking a PBT/POPs exposure-to-emissions metric. This model or modeling system should 1) have the ability to couple models describing environmental fate, bioaccumulation and LRT potential, 2) incorporate the ability to include metabolic loss and transformation of the chemical at all trophic levels, 3) allow for incorporation of new partitioning mechanisms such as those observed for ionizable chemicals, and 4) include the ability to model non-steady state conditions to allow time trend concerns to

be scientifically addressed in a risk profile. Such model development should build on the consensus approach used in developing and gaining acceptance for the current LRT models.

Risk characterization, as defined in existing risk assessment frameworks and paradigms as an integration of exposure and effects assessments, is a useful model in assessing PBTs and evaluating the potential for significant adverse effects resulting from long-range transport in POPs assessments. While risk profiles or assessments of PBTs or POPs may not necessarily be full quantitative risk assessments, inclusion of information on risks and uncertainties is desirable at the assessment phase, notably in helping producers, importers, and users of chemicals, or regulatory authorities (such as the Stockholm Convention POP Review Committee, the Conference of the Parties, or national authorities) to set priorities and make decisions. Lack of full scientific certainty about currently available approaches and tools (such as models) should not prevent their use in providing an integrated risk characterization which considers the weight of multiple lines of evidence and associated uncertainties.

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