Chemicals of Global Concern

A strategy and criteria for their identification

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This report was commissioned by the Swedish Chemicals Agency. It was written by Professor Thomas Backhaus, University of Gothenburg, Sweden, Professor Martin Scheringer, ETH Zürich, Switzerland and Masaryk University, Brno, Czech Republic, Dr Åsa Arrhenius, University of Gothenburg, Sweden and Dr Sandy Ubl-Kägi, ETH Zürich, Switzerland. Project leader and contact person at the Swedish Chemicals Agency was Dr Gunilla Ericson.

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Glossary

ATDSR	US Agency for Toxic Substances and Disease Registry
Chemical	A chemical substance that is characterized by a chemical structure, or a defined or undefined mixture thereof, used as a defined entity for commercial purposes. In the context of this report, only synthetic or mined chemicals are considered, but not naturally occurring chemicals at the concentrations at which they are part of the natural environment and food items. Used synonymously with “substance”.
CCISS	Chinese Chemical Inventory Search System
CMR	A chemical that is carcinogenic or mutagenic or toxic to reproduction.
ECHA	The European Chemicals Agency
EC10	The concentration that is estimated to cause a 10% effect relative to an untreated control, specific for a given biological assay, endpoint and exposure duration.
EDC	A substance with endocrine disrupting properties (endocrine disrupting chemical).
EFSA	The European Food Safety Authority.
NOEC	No Observed Effect Concentration, the highest concentration that was tested in a given biological assay that did not cause a statistically significant effect, specific for a given biological assay, endpoint and exposure duration.
PBT	A chemical that is persistent and bioaccumulative and toxic.
PMT	A chemical that is persistent and mobile in the water phase and toxic.
SAICM	The Strategic Approach to International Chemicals Management of the United Nations Environment Programme.
Substance	Used synonymously with “chemical”.
TSCA	The Toxic Substances Control Act of the US
UBA	Umweltbundesamt, the German Environment Agency
vPvB	A chemical that is very persistent and very bioaccumulative.
vPvM	A chemical that is very persistent and very mobile in the water phase.

Summary

This report provides suggestions for criteria to identify chemicals or group of chemicals of global concern in the context of the Strategic Approach to Chemical Management (SAICM). The criteria were developed for assessing the involuntary exposure of the general public and the environment to commercial chemicals, i.e. those substances that are deliberately synthetized or mined, including the degradation- and by-products that are generated along a chemical's lifecycle.

A hazardous chemical should be recognized as causing global concern if there is a disconnect between the emission/exposure event and the (eco)toxicological impact. This can be caused by either a *chemical persistence*, which enables a chemical to travel extensive spatial distances before causing an impact on human health or the environment), or a *persistence of the (eco)toxicological action*, which can cause a sizeable delay before the (eco)toxicological impact of a chemical becomes visible and/or before such an impact ceases to exist, even if the exposure has ended earlier. Even modern national and regional chemical management systems might be inadequate under these conditions.

We therefore suggest to identify chemicals with PBT (persistent, bioaccumulative and toxic), vPvB (very persistent and very bioaccumulative), PMT (persistent, mobile in the waterphase and toxic), vPvM (very persistent and very mobile in the waterphase), endocrine-disrupting properties and neurotoxicants as chemicals of global concern, especially if they are used in the context of products that are either lead to an exposure of the environment (e.g. pesticides, detergents, etc.) or the general public (e.g. in personal care products, textiles, packaging materials, etc). In order to facilitate international consensus and to avoid re-inventing the wheel, we suggest to employ the criteria used by the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and REACH, as far as possible.

Applying these criteria requires a substantial amount of high quality toxicological and ecotoxicological data, which are not available for most chemicals. Such a data-driven strategy might therefore focus predominantly on already well-known chemicals and runs the risk of overlooking potentially problematic data-poor chemicals, even if produced and used in substantial quantities. It is therefore important to also consider the systematic screening of existing inventories of commercially relevant chemicals.

Sammanfattning

Rapporten ger förslag på kriterier för att identifiera kemikalier eller en grupp kemikalier som är globalt oroväckande i samband med den globala kemikaliestrategin SAICM (Strategic Approach to International Chemicals Management). Kriterierna utvecklades för att bedöma den ofrivilliga exponeringen av människan och miljön för kommersiella kemikalier, dvs de ämnen som medvetet syntetiseras eller utvinns ur malm, inklusive nedbrytnings- och biprodukter som genereras under en kemikalies livscykel.

En farlig kemikalie bör anses vara globalt oroväckande om det inte finns en direkt koppling mellan utsläpp/exponering och den (eko)toxikologiska effekten. Detta kan bero på kemisk persistens som gör att en kemikalie kan förflyttas över större avstånd innan den påverkar människors hälsa eller miljön, eller en persistens av den (eko)toxikologiska verkan, vilket kan orsaka en betydande försening innan en negativ effekt av en kemikalie märks och/eller innan en sådan effekt upphör, även om exponeringen har upphört tidigare. Moderna nationella och regionala kemikaliehanteringssystem kan vara otillräckliga under dessa förhållanden.

Vi föreslår därför att identifiera kemikalier med PBT (persistenta, bioackumulerande och toxiska), vPvB (väldigt persistenta och väldigt bioackumulerande), PMT (persistenta, mobila i vattenfas och toxiska), vPvM (väldigt persistenta och väldigt mobila i vattenfas) och endokrinstörande egenskaper samt nervgifter som globalt oroväckande kemikalier. Särskilt oroväckande om de används i produkter som antingen leder till en exponering av miljön (t.ex. bekämpningsmedel, tvättmedel etc.) eller allmänheten (t.ex. i produkter för personlig vård, textilier, förpackningsmaterial osv.). För att underlätta internationell konsensus och för att undvika att uppfinna hjulet på nytt föreslår vi att vi använder kriterierna som används i FN:s globalt harmoniserade system för klassificering och märkning av kemikalier (GHS) och REACH så långt som möjligt.

Tillämpningen av dessa kriterier kräver en betydande mängd toxikologisk och ekotoxikologisk information av hög kvalitet som inte är tillgänglig för merparten kemikalier. En strategi som bygger på god informationstillgång kommer därmed främst fokusera på redan välkända kemikalier och riskera att förbise potentiellt problematiska kemikalier som saknar en betydande mängd information, även om de produceras och används i stor utsträckning. Det är därför viktigt att även systematiskt screena befintliga registreringar av kommersiellt relevanta kemikalier för att inte missa problematiska kemikalier.

Terms of Reference

The following text provides suggestions for criteria to identify chemicals or group of chemicals of global concern in the context of the Strategic Approach to Chemical Management (SAICM). The work was funded by the Swedish Chemicals Agency. However, the text is the sole responsibility of the authors.

The set of criteria was developed for assessing the involuntary exposure of the general public and the environment to commercial chemicals, i.e. those substances that are deliberately synthetized or mined, including the degradation- and by-products that are generated along a chemical's lifecycle.

The voluntary exposure to tobacco products, alcohol, other drugs and to the various types of pharmaceuticals was excluded from the assessment (however, incidental exposure to pharmaceuticals via the environment is included). Also chemicals that are the natural components of various food commodities, such as sugar and saturated fatty acids, are excluded from the analysis. The text also does not consider issues related to occupational health and intentional poisoning.

The particular focus of this report shall not, by any means, be taken to conclude that any of the excluded materials, chemicals or exposure scenarios are not relevant for human health and/or the environment. It is just beyond the scope of this particular report to cover them all.

Furthermore, the report focuses exclusively on toxicological and ecotoxicological impacts, but not on other types of harm, e.g. eutrophication potential, risk for physical injury (due to flammable and explosive properties for example) and the global warming potential of a chemical.

Finally, it should be emphasized that no recommendations on the type of regulatory action that could follow the identification of a chemical as a chemical of global concern are given. For the exposure situations considered, appropriate action can include, but is not limited to, improved labeling, improved waste treatment, a complete or partial ban, taxation and/or the substitution with less problematic alternatives. The most appropriate measure will be highly context-specific, dependent on whether the concerns relate to environmental or human exposure, which species and (eco)toxicological endpoints are particularly sensitive, under which conditions exposures takes place, the socio-economic benefits of using a given chemical and the particular protection goals at hand.

1 Introduction

Roughly 160 million chemicals are listed in the CAS registry (CAS, 2020a) and more than 394 000 substances are listed by CAS as being regulated in key markets across the globe (CAS, 2020b), because they are used in commerce, found in the environment or recognized as potentially having an impact on human health and/or the environment in any of the 195 countries on the globe. This figure corresponds to the recently published estimate of slightly more than 350 000 chemicals listed in national and regional chemical inventories (Wang, 2020). The United Nations Environment Programme together with the International Council of Chemical Associations estimated that around 40 000 to 60 000 industrial chemicals are actually used commercially somewhere on the globe (Alpizar et al., 2019).

In view of this complexity, it is a common task in chemical safety assessment to first identify chemicals of particular concern and then focus on regulatory action on those substances. Relevant grouping and prioritization efforts implemented in regulatory strategies include for example the roadmap for the identification of SVHCs (Substances of Very High Concern) under REACH (EU Commission, 2013), the identification of priority pollutants under the European Water Framework Directive using the COMMPS Procedure (Fraunhofer Institut für Umweltchemie und Ökotoxikologie, 1999), the prioritization of chemicals for risk evaluation under the chemical prioritization process rule of the Toxic Substances Control Act (TSCA, see US EPA 2017), Canada's systematic approach to the categorization and prioritization of domestic substances (Canada, 2020a, 2020b), and the Dynamic Selection and Prioritisation Mechanism for Hazardous Substances (DYNAMEC, OSPAR 2020). Prioritization strategies are also published and discussed in the open scientific literature, see e.g. Arnot et al. (2012), Bu et al. (2013) and Muir et al. (2019).

In a perfect world, grouping and prioritization efforts would be based on complete, validated, up-to-date and transparent information on the exposures, hazards and risks of the chemicals commercially used. In the real world, however, such information on many, if not most, chemicals is incredibly scarce. Additionally, exposure patterns are continuously changing, reflecting changes in production, use and disposal patterns. It has therefore repeatedly been discussed whether and to what extent effective chemical management can be implemented, or at least started, using incomplete information, e.g. hazard information only, or exposure information only.

The Stockholm Convention on persistent organic pollutants (POPs) starts to address chemicals that are of global concern based on their hazard characteristics. POPs are of global concern because they circulate in the environment for long times and on a global scale, which means that their impacts cannot be managed and handled by individual countries, but have to be understood as truly global concerns. The key property that makes POPs a global concern is their high persistence (or: slow degradation) in the environment. This is because high persistence gives these chemicals sufficient time to undergo long-range transport, to bioaccumulate in the food chain, and to finally exert toxic effects in humans and wildlife all over the world. Overall, the purpose of the POP criteria under the Stockholm Convention (reproduced in Annex 1) is to provide guidance in the process of identifying, nominating and evaluating chemicals with a potential for global contamination.

However, we argue that also other hazard characteristics might give rise to an equivalent level of concern. And the SAICM process, which is briefly introduced in the following, has an adequately broad scope to also cover chemicals that raise concerns that go beyond the Stockholm Convention.

1.1 The Strategic Approach to International Chemicals Management (SAICM) and the post-2020 process

The Strategic Approach to International Chemicals Management (SAICM) was adopted on the 6th February 2006 by the First International Conference on Chemicals Management (ICCM1) in Dubai. SAICM supports the achievement of the goal agreed at the 2002 Johannesburg World Summit on Sustainable Development to "ensure that, by the year 2020, chemicals will be produced and used in ways that minimize significant adverse impacts on the environment and human health".

However, 2020 is here now and, despite substantial progress in many areas, the aforementioned goal has not been fully reached, which is discussed in the detail in the recent second Global Chemicals Outlook (Alpizar et al., 2019). The fourth session of the International Conference on Chemicals Management (ICCM4), therefore initiated an intersessional process to prepare recommendations for the sound management of chemicals and waste beyond 2020, the so-called post-2020 process. In particular, it is expected that a process will be established to identify, prioritize and address chemical-related issues of concern that warrant global action.

This includes developing a strategy to address (groups of) chemicals and chemical uses that pose an unreasonable or otherwise unmanageable risk to human health or the environment, and to establish criteria for their identification. In a footnote to paragraph 14(d) of SAICM's Overarching Policy Strategy it is suggested that the following groups of chemicals could be prioritized for assessment and related studies: "persistent, bioaccumulative and toxic substances (PBTs); very persistent and very bioaccumulative substances; chemicals that are carcinogens or mutagens or that adversely affect, inter alia, the reproductive, endocrine, immune, or nervous systems; persistent organic pollutants (POPs), mercury and other chemicals of global concern; chemicals produced or used in high volumes; those subject to wide dispersive uses; and other chemicals of concern at the national level.".

Additionally, Annex B of SAICM's compilation of recommendations for consideration at the fifth session of the International Conference on Chemicals Management (SAICM, 2020), which documents the outcome of the IP3 thematic group C on mechanisms to support implementation, lists the following provisional criteria (without further specification): Toxicity, bioaccumulation, toxicity for reproduction, mutagenicity, exposure data gaps, vulnerable populations, ecosystems ecotoxicity, persistence, carcinogenicity, endocrine disruption, other toxicities.

The following text contributes to the aforementioned processes by suggesting specific criteria for the identification of chemicals of global concern.

2 Criteria for identifying chemicals of global concern

2.1.1 Definition

"Chemicals of global concern" need to be defined in relation to their (eco)toxicological properties and their use patterns. Furthermore, chemicals of "global concern" need to be – explicitly or implicitly – contrasted with chemicals of "local or regional concern". An appropriate definition can approach the issue from two different perspectives:

Firstly, a hazardous chemical can be recognized as causing global concern because its use causes concerns in several countries or regions. However, such concerns can, at least in principle, be managed similar to issues that are of only local or regional concern (and the distinction between "just a few" and "several" countries or regions will always be arbitrary to some extent). We therefore argue that national or regional legislation is an adequate approach for risk management even if a given chemical is used in several countries or regions. This is not to negate that many countries are struggling with establishing and enforcing adequate chemical management systems, and that it is therefore important to improve international harmonization and build capacities. But global action and perspectives should be used as a supplement to national regulatory systems, and not as a surrogate for inadequate national or regional risk management.

However, the situation is fundamentally different for chemicals and use scenarios for which the emission or exposure event is disconnected from the impact event, i.e. the toxicological impact on human health and/or the ecotoxicological impact on populations of organisms in the environment or on whole ecosystems.

Such a disconnect can be caused either by a chemical persistence, which enables a chemical to travel extensive spatial distances before causing an impact on human health or the environment). The disconnect might also be caused by a persistence of the (eco)toxicological action, which can cause a sizeable delay before the (eco)toxicological impact of a chemical becomes visible and/or before such an impact ceases to exist (even if the exposure has ended earlier).

Managing such chemicals is notoriously difficult, and even modern national and regional chemical management systems might be inadequate. This is because the actor that is responsible for an emission or exposure event and the exposed humans or ecosystems might be located in different jurisdictions. Additionally, organisms, including humans, might cross the border of local, national and regional jurisdictions after the exposure took place, but before the (eco)toxicological consequences of an exposure manifest themselves.

In the context of this report, chemicals of global concern are therefore defined follows:

1. substances that cause non-reversible toxicological or ecotoxicological impacts on general public health or the environment;
2. substances that cause health impacts even if the exposure event took place in previous generations;
3. substances that cause (eco)toxicological impacts far away from the emission source; and
4. substances that might cause (eco)toxicological impacts even a long time after emissions have ceased.

Chemicals that fulfill the screening criteria of the Stockholm Convention that were internationally adopted in 2001 (Annex D) are considered a priori to be chemicals of global concern. More stringent PBT criteria have since then been adopted regionally, .e.g. under REACH (ECHA, 2017).

Hazardous chemicals are also frequently found in internationally traded goods and articles. As long as such chemicals and products are im- and exported in the "classical" way by internationally trading companies, a country or region has, in principle, the means to control the stream of goods and articles entering its jurisdiction. Additionally, the Rotterdam and Basel Conventions provide international frameworks for the international movement of hazardous chemicals.

However, international trade is increasingly driven by millions of individual consumers buying directly from international retailers located in different jurisdictions, which renders the monitoring and control of the associated chemical flows basically impossible. From this perspective, consumer-driven international trade can be regarded as another situation in which the actual release of a hazardous chemical from the control of a given company (i.e. its incorporation into a consumer product) is disconnected from the exposure event (i.e. the use and disposal of said product by a consumer who might be living on the other side of the planet).

2.1.2 Some remarks on the context and scope of the developed criteria

In a perfect world, chemical assessment and management is based on the detailed and validated knowledge of a chemical's toxicological and ecotoxicological properties – which is then compared to an equally detailed and validated knowledge of the exposure of the various human (sub)populations and the myriad of environmental organisms, resulting from the different uses along the chemical's lifecycle.

In the real world, however, chemical assessment and management is challenged with substantial knowledge gaps. It is therefore usually based on a tiered approach that uses a combination of hazard and exposure-based assessments, developed to make optimum use of the limited data at hand and balancing different and often conflicting societal demands.

Especially exposure data are extremely scarce for many, if not most, chemicals used in commerce. Additionally, exposure patterns constantly change, in reaction to market developments and the resulting shifts in chemical production and use. We therefore consider hazard-based criteria, although being a cruder instrument than full-fledged risk-based approaches, more suitable for defining criteria for substances of concern. However, it should be obvious that level of concern is also dependent on the amount of a chemical emitted into the environment or into the vicinity of human populations.

Criteria for the identification of a certain group of chemicals from a bigger pool usually come in the form of "bright lines" that serve as guideposts and decision criteria. Initially discussed mainly in the context of exposure considerations (Presidential/Congressional Commission on Risk Assessment and Management, 1997), bright lines are also often used for establishing hazard-based criteria.

Such bright lines enable comparatively straightforward yes/no decisions based on the results of a given test (e.g. "Half-life in water exceeding 2 months, yes or no?" which is then used to answer the question "persistent, yes or no?"). However, it should be emphasized that the underlying natural phenomena are continuous in nature (i.e. a compound can obviously have any half-life).

The decision on where to put the decision line between “criterion fulfilled” and “criterion not fulfilled” is therefore not a scientific one. Instead, such a decision is taken from a pragmatic and practical perspective while also considering socio-economic consequences and various stakeholder perspectives. Unfortunately, this often leads to substantial controversy, especially related to the question on whether a given numerical value is sufficiently protective or not.

In order to facilitate international consensus-finding, the current report therefore uses, as far as possible, existing international criteria. This relates especially to the criteria put forward in international conventions (in particular the Stockholm Convention) and the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Additionally, we used elements from the European REACH Regulation (on the Registration, Evaluation, Authorisation and Restriction of Chemicals), a system already developed and established across national jurisdictions.

Different countries, regions and stakeholders might have different data available and/or assess a given set of (eco)toxicological data differently. This might result in diverging or even conflicting classifications of one and the same chemical. Appropriate institutional arrangements and conflict-resolving mechanisms are therefore needed in order to implement an international approach for the identification of chemicals of global concerns.

Chemicals never occur as single, isolated entities in the environment or in human surroundings and also consumer products usually contain a complex mélange of different substances. Exposure therefore is always to complex chemical mixtures. The assessment of mixtures adds yet another layer of complexity on the assessment of individual substances. For a recent overview of the global scientific state of the art and policy recommendations for Europe, see Swedish government official report (SOU 2019:45).

In line with the strategy to use internationally established instruments as far as possible, we suggest following the GHS strategy for the classification and labelling of chemical mixtures (see GHS chapter 1.3). The basic idea of the GHS classification of mixtures is to use endpoint-specific cut-off values and concentration limits of the mixture ingredients, unless data on the actual mixture of concern are available (which are then assessed as if the mixture in question were a single substance).

2.2 Suggested criteria for substances of global concern

The following (combinations of) hazard criteria, which are defined on the level of individual chemicals, indicate reason for global concern, as they might cause the aforementioned spatial or temporal disconnect between emission, exposure and (eco)toxicological impact (see summary in Table 1). The criteria are presented in no particular order.

Table 1: Summary of suggested hazard criteria for substances of global concern

Category	Assessment criteria
PBT	**Persistence:** – half-life in marine water > 60 days *or* – half-life in fresh or estuarine water > 40 days *or* – half-life in marine sediment >180 days *or* – half-life in soil or other sediments >120 days *and* **Bioaccumulation:** – bioconcentration factor > 2000 *and* **Toxicity:** – long-term NOEC or EC10 for aquatic organisms < 10 µg/L.
vPvB	**Persistence:** – half-life in water > 60 days *or* – half-life in soil or sediments >180 days *and* **Bioaccumulation:** – bioconcentration factor > 5000
CMR	**Carcinogenicity** – GHS (Category 1A or Category 1B) *or* **Mutagenicity** – GHS (Category 1A or Category 1B) *or* **Reproductive toxicity** – GHS (Category 1A or Category 1B)
Endocrine Disruption	– Adverse effect in non-target organism, including humans *and* – Endocrine mode of action *and* – Alters the function of the endocrine system *and* – Adverse effect is a consequence of the endocrine mode of action
Respiratory or skin sensitizer	**Skin sensitizer** – GHS (Category 1A) *or* **Respiratory sensitizer** – GHS (Category 1A)
Neurotoxi-cant	– Target organ is the nervous system, including the peripheral nervous system *and* – Specific organ toxicity, single exposure, according to GHS (Category 1 or Category 2) or specific organ toxicity, repeated exposure, according to GHS (Category 1 or Category 2)

2.3 PBT and vPvB substances

Chemicals that are persistent, bioaccumulative and toxic (PBT chemicals) were recognized as a particular concern in the 1990s. Environment Canada and the US EPA identified sets of PBT chemicals under the Great Lakes Binational Toxic Strategy in 1997. Also in the European Union (EU) and in Japan, the concerns about PBT chemicals were identified at the same time. In the EU, the Technical Guidance Document on Risk Assessment of 2003 (ECHA 2003, p. 162–163) expresses these concerns as follows:

"These additional concerns […], which may not be adequately addressed by the traditional risk assessment methodologies, can be summarised as:

(a) the concern that hazardous substances may accumulate in parts of the marine environment and (i) that the effects of such accumulation are unpredictable in the long-term; (ii) that such accumulation would be practically difficult to reverse;
(b) the concern that remote areas of the oceans should remain untouched by hazardous substances resulting from human activity, and that the intrinsic value of pristine environments should be protected.

These concerns particularly occur with substances that can be shown both to persist for long periods and bioaccumulate in biota, and can give rise to toxic effects after a greater time and at a greater distance than chemicals without these properties. […] For PBT substances a `safe' concentration in the environment cannot be established with sufficient reliability."

Under the main European chemicals regulation, REACH, PBT chemicals were given a specific status because the regulation uses PBT properties as one of the decision criteria to identify a chemical as a Substance of Very High Concern (SVHC). The current Guidance Document on PBT Assessment under REACH expresses the concerns about PBT chemicals in the same way as the earlier Technical Guidance Document of 2003 (ECHA 2017, p. 11–12).

Overall, the concerns about PBT chemicals are similar to those about persistent organic pollutants (POPs) under the Stockholm Convention. Again, the conceptual focus is on the problem that the methods for chemical risk assessment are not suitable for PBT chemicals because these chemicals build up higher and higher levels in more and more regions of the world. Consequently, a large number of species and ecosystems, potentially all over the world, might be exposed, and a "safe" concentration cannot be estimated with sufficient certainty.

The B and T properties of a chemical are not independent, but sometimes correlated. This is because there is one mode of toxic action, baseline toxicity, that is caused by the same process as bioaccumulation, namely the enrichment of chemicals in lipid tissue. Cell membranes consist of phospholipids, and chemicals that accumulate in storage lipids in the body also partition into cell membranes, by which the structure and function of the membranes are disturbed, which causes a toxic effect. This implies that chemicals with a high bioaccumulation potential into lipid tissue often also have a high baseline toxicity (Maeder et al., 2004).

In contrast to the Stockholm Convention, REACH also established a class of chemicals with "very persistent and very bioaccumulative properties, so-called vPvB chemicals, that are not explicitly assessed for their toxicity. However, it is assumed that the vPvB properties "may,

based on experience from the past with such substances, lead to toxic effects and have an impact in a manner which is difficult to predict and prove by testing, regardless of whether there are specific effects already known or not" (ECHA, 2017). That is, although not explicitly mentioned, also vPvB substances are identified as being of concern because of their expected ecotoxicological impacts, which might, at least partly, be driven by the aforementioned mechanism of baseline toxicity.

Substances fulfilling the REACH PBT or vPvB criteria are identified as Substances of Very High Concern (SVHC), and are only allowed on the European market after careful consideration, in-depth risk assessment and an authorization requirement.

The Stockholm Convention and REACH use different numerical criteria (Table 2). Translated into the nomenclature of REACH, POPs would be labeled as "vPvBT substances with long-range transport potential". In addition to chemicals fulfilling the POP criteria under the Stockholm Convention that were developed in the late 1990s, we suggest to also identify compounds that fulfill the extended PBT criteria (i.e. including toxicity to terrestrial organisms) or the vPvB criteria according to REACH (see Table 2) as fulfilling the hazard criteria of substances of global concern. For a detailed discussion of the PBT criteria used under different legislations and of the corresponding data needs and methods, see Abelkop et al. (2015).

Table 2: Comparison of the criteria for persistence, bioaccumulation, toxicity and long-range transport for PBT, vPvB chemicals under REACH and POPs under the Stockholm Convention Further details given in ECHA (2017), Stockholm Convention (2001).

	REACH	**Stockholm Convention**
Persistent	– half-life in marine water > 60 days *or* – half-life in fresh or estuarine water > 40 days *or* – half-life in marine sediment > 180 days *or* – half-life in soil or other sediments > 120 days	– half-life in water > 60 days *or* – half-life in soil or sediment > 180 days *or* – other evidence
very Persistent	– half-life in water > 60 days *or* – half-life in soil or sediment > 180 days	*no equivalent categorization*
Bioaccumulative	– bioconcentration factor in aquatic species > 2000	– bioconcentration factor in aquatic species > 5000 or – high bioaccumulation in other species or – biomonitoring data *or* – log Kow > 5 (in the absence of data)
very Bioaccumulative	– bioconcentration factor in aquatic species > 5000	*no equivalent categorization*
Long-Range Transport	*no equivalent categorization*	– measured levels of the chemical in remote locations; *or* – monitoring data showing long-range environmental transport; *or* – environmental fate properties and/or model results; *or* – half-life in air > 2 days
Toxicity (Human Health)	– carcinogen (category 1A or 1B, Reg 1272/2008) *or* – germ cell mutagenicity (category 1A or 1B, Reg 1272/2008) *or* – toxic for reproduction (category 1A, 1B or 2, Reg 1272/2008) *or* – specific target organ toxicity (STOT RE category 1 or 2, Reg 1272/2008)	– evidence of adverse effects that justifies consideration *or* – toxicity data that indicate the potential for damage
Toxicity (Environment)	– NOEC or EC10 in marine or freshwater organisms < 0.01 mg/L	– evidence of adverse effects that justifies consideration *or* – toxicity data that indiciate the potential for damage

2.4 PMT and vPvM substances

PMT chemicals are substances that are assessed as being persistent and mobile in the aquatic phase and toxic. Correspondingly, vPvM chemicals are very persistent chemicals that are assessed to be very mobile in aquatic systems, defined as “pristine and sometimes remote freshwater ecosystems, surface water reservoirs, river water that undergoes bank filtration, groundwater aquifers or other aquatic environments that could potentially be used as a drinking water source” (UBA, 2017). PMT and vPvM chemicals are considered to pose a high risk to any of those aquatic systems (Arp et al., 2019, Neumann et al., 2019).

A chemical shall be classified as a PMT substance in the context of this report if it fulfills all three criteria for persistence, mobility and toxicity. It shall be classified as a vPvM substance if it fulfills both the criteria for very persistent and very mobile (vPvM). The classification makes direct use of the persistence criteria and the criteria for aquatic toxicity under REACH (Annex XIII), which facilitates the re-use of existing classifications.

Similar to the criteria used to identify PBT chemicals, the P criterion is considered to be fulfilled if the half -life in marine water exceeds 60 days or the half-life in fresh or estuarine water exceeds 40 days or the half-life in marine sediment exceeds 180 days or the half-life in soil or other sediments exceeds 120 days .

The vP criterion is considered to be fulfilled if reliable empirical data on biodegradation according to REACH Annex XIII (EU Commission, 2019) demonstrate a half-life in surface water exceeding 60 days or a half-life in sediments or soil that exceeds 180 days.

The M criterion is considered to be fulfilled if the organic carbon-water coefficient is less than 10 000 (i.e., log KOC < 4.0) over a pH range of 4-9.

The T criterion is considered to be fulfilled if empirical data on chronic aquatic toxicity yield a NOEC or EC10 smaller than 0.01 mg/L or if the substance can be classified according to GHS as having a specific organ target organ toxicity after single exposure (Category 1 or Category 2, see Annex IV) or if the substance can be classified according to GHS as having a specific target organ toxicity after repeated exposure (Category 1 or Category 2) or if the Derived No Effect Level (DNEL) for the general population is less than 9 µg/(kg*day).

The specification of the criterion for chronic aquatic toxicity stems directly from the REACH Annex XVIII criteria, while, in deviation from the original PMT criteria suggested by UBA (UBA, 2017), the criteria for specific target organ toxicity are taken from GHS, in order to re-use existing international classifications as much as possible. The DNEL criterion is based on the threshold of toxicological concern (TTC) for compounds that exhibit “moderate or low biological activity” (see Annex 3).

It should also be pointed out here that the original PMT criteria as suggested by UBA (2017, see also Berger et al. (2018)) include CMR criteria as part of the T classification. In the current approach, those criteria are separated out (see Table 1), so that also non-persistent CMR-chemicals might be identified as chemicals of global concern.

Further details on the PMT/vPvM strategy are given in a series of reports by the German Environment Agency UBA (UBA, 2017, Arp et al., 2019, Neumann et al., 2019).

2.5 CMR substances

CMR substances are chemicals that are carcinogenic, mutagenic or toxic to reproduction (CMR). They are of specific concern due to the long term and often non-reversible effects that they may exert on human health, often after only low-dose exposures.

A chemical shall be classified as a CMR substance and hence as a chemical of global concern in the context of this report if it fulfills the GHS criteria of carcinogenicity (Category 1A or Category 1B) or germ cell mutagenicity (Category 1A or Category 11B) or reproductive toxicity (Category 1A or Category 1B). The GHS definitions of the various CMR classes are reproduced in Annex 4.

2.6 Endocrine disrupting chemicals

The WHO defines endocrine-disrupting substances (EDC chemicals) as follows "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations". Exposure to EDCs has been linked to various impacts on human health, including "alterations in sperm quality and fertility, abnormalities in sex organs, endometriosis, early puberty, altered nervous system function, immune function, certain cancers, respiratory problems, metabolic issues, diabetes, obesity, cardiovascular problems, growth, neurological and learning disabilities, and more" (Endocrine Society, 2020). Exposure to EDCs might have particularly severe impacts on pregnant women, unborn babies and children, with life-long consequences. EDC chemicals also cause a plethora of long-lasting ecotoxicological impacts, see e.g. the discussion and literature provided by Godfray et al., (2019).

In the context of this report, a chemical shall be identified as an EDC chemical, and, consequently, as a chemical of global concern, if it (a) causes an adverse effect in a non-target organism, including humans, (b) has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system and (c) its adverse effect is a consequence of the endocrine mode of action. Details can be found e.g. in the recent guidance document published by ECHA and EFSA (2018). However, it should be noted that the guidance document only specifies criteria in the context of the European regulation for biocides and pesticides. The urgently needed consistent cross-sectorial European regulation and assessment strategy for EDC chemicals is still missing. Also on an international level, the debate on how to identify and assess endocrine disrupters is still ongoing. That is, in contrast to the internationally agreed criteria on POPs, PBTs or CMR substances, the assessment of endocrine disrupters is still in its infancy.

2.7 Respiratory or skin sensitizing substances

Respiratory and skin sensitizing substances are chemicals that cause a hypersensitivity in the airways (asthma) and an allergic response after skin contact, respectively. Similar to CMR substances, such chemicals might cause long term and often non-reversible effects, sometimes already after a single exposure event. Sensitizing substances are therefore often identified as causing a level of concern that is equivalent to CMR substances, e.g. under REACH. The European Chemicals Agency ECHA states that "The assessment is based on the consideration that in certain cases it can be demonstrated that the impacts caused by substances with sensitising properties, on the health of the affected individuals and on the society as a whole, are comparable to those elicited by carcinogens, mutagens and/or reproductive toxicants (CMRs). In such cases it might be justified to conclude, on a case by case basis, that such a sensitiser is of equivalent level of concern in accordance with REACH Article 57(f)." (ECHA, 2012).

A chemical shall be classified as a respiratory or skin sensitizing substance and hence as a chemical of global concern in the context of this report, if it fulfills the GHS criteria of a skin

sensitizing substance (Category 1A) or respiratory sensitizer (Category 1A). The GHS definitions of the various sensitizer classes are reproduced in Annex 4.

2.8 Neurotoxicants

Neurotoxicants are capable of causing adverse effects in the central and peripheral nervous system including organs of perception (eyes, ears). As a result, they might cause short-term adverse impacts on exposed humans (including narcosis, nausea, dizziness and vertigo) and/or long-lasting effects including movement coordination problems, impaired memory and behavior as well as severe developmental disorders. Exposure to neurotoxicants has also been associated with neurodegenerative diseases like Alzheimer's disease. Especially the developing child seems particularly vulnerable and even low-dose transient exposures can cause life-long impairments. Lead, a well-known developmental neurotoxicant has already been defined as an "emerging policy issue" under SAICM.

There are currently no specific labeling requirements for neurotoxic chemicals under GHS. Such chemicals are classified under the categories "specific target organ toxicity", single or repeated exposure (see Annex 4). In the context of this report, a chemical shall therefore be classified as a neurotoxicant, and hence as a chemical of global concern, if it is classifiable under GHS for specific organ toxicity, single exposure (Category 1 or Category 2) or specific organ toxicity, repeated exposure (Category 1 or Category 2) and if the target organ can be identified as the nervous system, including the peripheral nervous system, according to data generated e.g. by the testing strategy outlined by the OECD (2004a).

3 Exposure considerations

The aforementioned hazard characteristics indicate only the potential of a chemical of being of global concern. Whether such a concern might actually be realized depends on whether and to what extent an exposure of humans or the environment takes place. Although there are no strict scientific criteria at which point an exposure becomes "relevant", or even "globally relevant", especially two factors warrant consideration during such an evaluation.

First and foremost, the exposure potential is related to global production and use volumes. Unfortunately, an international inventory of the amounts of chemicals used in commerce does not exist. The United Nations Environment Programme together with the International Council of Chemical Associations estimated that 40 000 to 60 000 industrial chemicals are commercially used around the globe (UN Environment, 2019). 6 000 of those chemicals account for more than 99% of the total production volume. Any of those substances might be identified as being of actual global concern if it fulfills any of the previously mentioned hazard characteristics.

Secondly, the exposure potential is related to the use pattern of a given substance. Those that are used in close contact to humans and/or in the open environment are particularly relevant. This includes especially chemicals used in the following articles and products: agricultural and non-agricultural pesticides, detergents, pharmaceuticals, other down-the-drain products (e.g. personal care products, cleaning agents), impregnation agents, paints, textiles, packaging materials and the various building materials including furniture. Chemicals used in either of these product types should be considered chemicals of global concern if they fulfill any of the previously discussed hazard characteristics.

4 The need to systematically screen for chemicals of global concern

Applying the criteria that are outlined in the previous chapter requires a substantial amount of high-quality toxicological and/or ecotoxicological data, which are not at hand for the vast majority of commercially relevant chemicals. One might therefore quickly end up in a situation of "searching for the lost key under the lamppost", i.e. focusing on data-rich chemicals and well understood (eco)toxicological effect types. The phenomenon that data-rich chemicals are continuously investigated, assessed and debated in ever greater detail, while data-poor chemicals are largely ignored is also called the Matthew principle and is well demonstrated in the area of chemical assessment (Grandjean et al., 2011, Daughton, 2014, Sobek et al., 2016).

In other words, basing the identification of chemicals of global concern on the aforementioned criteria provides a solid foundation for reaching a consensual decision to nominate a chemical as being of global concern. At the same time, however, this strategy risks to overlook potentially problematic chemicals, even if produced in substantial quantities, simply because they are poorly studied. In order to overcome this limitation, it is therefore important to also consider the systematic screening of existing inventories of commercially relevant chemicals, such as the list of chemicals registered under REACH (ECHA, 2020), the chemicals listed in the TSCA Inventory (US EPA, 2020), the Chinese Inventory of Existing Chemical Substances (CCISS, 2020), the Japanese Existing and New Chemical Substances Inventory (ENCS, see NITE, 2020) or the Canadian Domestic Substances List (DSL, see Canada, 2020c), amongst others. Such an approach should also make use of existing local and regional priority list, such as ATDSR's substance priority list (ATDSR, 2020), the REACH candidate list of Substances of Very High Concern, (ECHA, 2020), the List of Priority Chemicals from the Chinese Ministry of Environmental Protection (MEP, 2020), the EU list of priority pollutants under the Water Framework Directive, the list of priority substances from the Norwegian Environment Agency (2020), the priority list of the Philippian Department of Environment and Natural Resources (2020) and others.

The Canadian IRAP process (identification of risk assessment priorities) is a particular example of a systematic approach for the continuous assessment, categorization and prioritization of a huge chemical inventory (Canada, 2020a, 2020b). Within this process, Environment and Climate Change Canada and Health Canada completed the categorization of the roughly 23 000 chemicals on Canada's Domestic Substances List (DSL). Approximately 4,300 substances were then identified as priorities for screening assessments.

Figure 1 provides an overview of such a screening strategy. The basic idea is that the screened chemicals are grouped into "chemicals of global concern" or "low priority chemicals" if the underlying data allow such a distinction. Data-poor chemicals are prioritized for further evaluation, in particular if they already occur on national or regional priority lists and/or frequently occur in chemical-analytical monitoring campaigns. A subsequent two-tiered assessment strategy can then start with a simple screening step in order to filter out suspected chemicals of global concern using various in silico tools and screening criteria (Annex 2, Annex 3). Compounds that are suspected chemicals of global concern can then be subject to empirical testing.

It should be emphasized that the decision to group substances as "chemicals of low priority" is taken in light of the evidence at hand at the time of the substance evaluation. Given that the decision is based on the absence of certain substance characteristics (i.e. of not being PBT,

vPvB, PMT, etc), compounds initially designated as low priority might need to be revisited in case the numerical cut-off values change in light of new evidence, or if completely new criteria are introduced into the process.

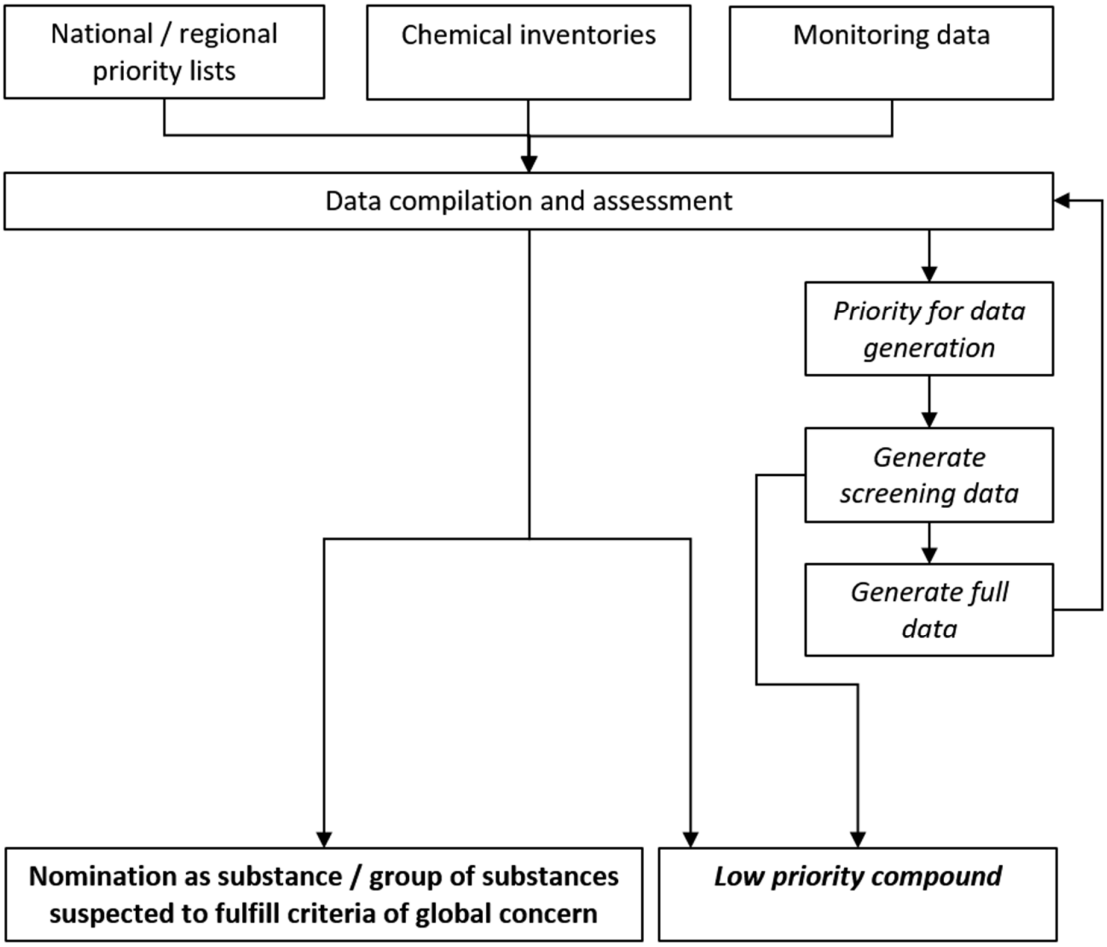

Figure 1. The suggested approach for the systematic screening for chemicals of global concern.

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Annex 1: POP criteria according to Annex D of the Stockholm Convention

The screening criteria for persistent organic pollutants (POPs) are defined in Annex D of the Stockholm Convention (in terms of persistence (P), long-range transport potential (LRTP), bioaccumulation (B), and toxicity (T) as follows:

Persistence:

i. Evidence that the half-life of the chemical in water is greater than two months, or that its half-life in soil is greater than six months, or that its half-life in sediment is greater than six months; or
ii. Evidence that the chemical is otherwise sufficiently persistent to justify its consideration within the scope of this Convention;

Bio-accumulation:

i. Evidence that the bio-concentration factor or bio-accumulation factor in aquatic species for the chemical is greater than 5,000 or, in the absence of such data, that the log Kow is greater than 5;
ii. Evidence that a chemical presents other reasons for concern, such as high bio-accumulation in other species, high toxicity or ecotoxicity; or
iii. Monitoring data in biota indicating that the bio-accumulation potential of the chemical is sufficient to justify its consideration within the scope of this Convention;

Potential for long-range environmental transport:

i. Measured levels of the chemical in locations distant from the sources of its release that are of potential concern;
ii. Monitoring data showing that long-range environmental transport of the chemical, with the potential for transfer to a receiving environment, may have occurred via air, water or migratory species; or
iii. Environmental fate properties and/or model results that demonstrate that the chemical has a potential for long-range environmental transport through air, water or migratory species, with the potential for transfer to a receiving environment in locations distant from the sources of its release. For a chemical that migrates significantly through the air, its half-life in air should be greater than two days; and

Adverse effects:

i. Evidence of adverse effects to human health or to the environment that justifies consideration of the chemical within the scope of this Convention; or
ii. Toxicity or ecotoxicity data that indicate the potential for damage to human health or to the environment.

Annex 2: in-silico estimation methods and tools for relevant chemical properties

Chemical property data needed and corresponding estimation methods

The physicochemical properties that are needed for the assessment of candidate chemicals include:

- the degradation half-lives in different environmental media (soil, water, sediment, air) for the assessment of the chemical's persistence (P);
- the octanol-water partition coefficient, Kow, and the bioconcentration factor, BCF, and also some other partition coefficients such as the coefficient for protein binding for the assessment of the chemical's bioaccumulation potential (B).

In addition, for the assessment of the chemical's toxicity (T), the LC50 or EC50 for effects in aquatic organisms needs to be estimated. If possible and if there are no measured data available, also the carcinogenicity, mutagenicity and toxicity for reproduction should be estimated.

Available methods: A good starting point is provided by the methods included in the EPI (Estimation Programs Interface) Suite that is available free of charge from the US EPA (US EPA 2012; US EPA 2017a).

Specifically, the most relevant methods in the context of the assessment of P, B and T properties are:

- BIOWIN3 for the half-lives of aerobic biodegradation in soil and water (Boethling et al. 1994)
- HYDROWIN for the half-life of hydrolysis (Wolfe and Jeffers 2003)
- AOPWIN for the half-life of degradation by OH radicals and light in air (Atkinson et al. 1988)
- KOWWIN for the octanol-water partition coefficient, Kow (Meylan and Howard 1995)
- KOCWIN for the organic-carbon-water partition coefficient, Koc (Sabljic et al. 1995)
- BCFBAF for the bioconcentration factor and the bioaccumulation factor (Arnot and Gobas 2003, Arnot and Gobas 2006, Arnot et al. 2009)
- ECOSAR for aquatic ecotoxicity (Moore et al. 2003).

Each of these methods is described in detail in the scientific literature, see the references provided in the list above. A comprehensive overview of property estimation methods in the context of chemicals assessment is provided by Schüürmann et al. (2007) for physicochemical properties and by Worth et al. (2007) for (eco)toxicological properties..

Of course, all of these methods have limitations, see below, and additional and more sophisticated estimation methods may be used in addition, for example COSMOtherm for physicochemical properties (http://www.cosmologic.de/products/cosmotherm.html). However, many of the more sophisticated methods are not freely available.

In general, used models should be evaluated following the OECD principles for the validation of quantitative structure-activity relationships (OECD 2004).

Specifically, BCFBAF tends to underestimate the bioconcentration factor of highly hydrophobic chemicals because in the measured BCF data for this type of chemicals there are

artifacts that incorrectly indicate that for chemicals with (very) high Kow the BCF does not further increase with increasing Kow, but may level off or even decrease (Jonker & van der Heijden 2007). The BCFBAF tool in EPI Suite was trained on these data and reflects the leveling off and decreasing trend of the BCF for high Kow values. However, these effects have been identified as artifacts (Larisch & Goss 2018) and it is important to critically evaluate the output of the BCFBAF tool in light of these newer findings and, if necessary, use other methods. There are also methods for determining the bioaccumulation of highly hydrophobic chemicals (Goss et al., 2018, Larisch & Goss 2018); as this area is currently a focus of ongoing research, more new methods can be expected to be developed.

Highly hydrophobic chemicals are a group of substances where estimation methods are particularly important because these chemicals are very difficult to test experimentally. Because of their low solubility in water, these substances strongly sorb to all kinds of surfaces (walls of testing vessels, suspended matter, skin of animals) and their concentration in water is difficult to control. In addition, the kinetics of their uptake by aquatic organisms is very slow and, therefore, many established tests for bioconcentration and aquatic toxicity are too short for these substances. Currently, measurement methods are being developed, but are not yet commonly applied for the B and T testing of these substances. (The OECD Testing Guideline for bioaccumulation (TG 305) was revised in 2012 and now also covers dietary exposure, but not many results have been reported from tests according to the new version of the guideline.)

Another group of chemicals that are difficult to test is the poly- and perfluorinated alkyl substances (PFASs). These substances bind to proteins in the blood and the liver and there are new methods for estimating the strength of the protein binding of these substances (Cheng & Ng 2018) as well as their toxicity (Cheng & Ng 2019).

For acids and bases, the pH-dependent distribution coefficient, Dow, is derived from the Kow and used instead as input to estimation methods based on the Kow.

Using estimation methods in the identification of chemicals of global concern

The estimation methods for the P, B and T properties of candidate chemicals can be used at two levels or tiers (ECHA 2017). The first is the generation of raw output from the estimation methods and comparison of this output to screening criteria, for example a Kow threshold for bioconcentration or a threshold of BIOWIN3 output for persistence. BIOWIN3 output has the form of values between 0 (very persistent, half-life on the order of years) and 5 (degradable, half-life on the order of hours). Under REACH, a screening criterion for persistence is a BIOWIN3 output below 2.2, which corresponds to a degradation half-life around one month.

The second tier is the conversion of estimated data into estimates of the bioconcentration factor and degradation half-lives and comparison of these estimates to criteria defined in terms of BCF and half-lives. Strempel et al. (2012) provide an example of such an assessment; using BIOWIN3, BCFBAF, and ECOSAR, they compared estimated P, B and T properties with the REACH PBT criteria for more than 90’000 substances and identified a set of approximately 2900 potential PBT substances on this basis. Strempel et al. (2012) also provide an extensive discussion of the uncertainties associated with the estimation methods and of the potential for false positives and false negatives in the identification of potential PBT substances.

Estimation methods and measured data in combination

Both measured and estimated chemical property data needed for the assessment of P, B and T are fraught with uncertainties. Depending on the type of chemical and the property investigated, the uncertainties may be even higher for measured data than for estimated data because the measurements are difficult to perform or are not physically or biologically meaningful (toxicity tests with concentrations above the chemical's solubility). In many contexts, it is establish practice to assign higher reliability to measured data than to estimated data. We think this practice is not well supported by empirical findings and recommend that the same weight be given to measured and estimated data. Stieger et al. (2014) present various examples of grossly incorrect experimental data on the Kow and aquatic toxicity of several brominated flame retardants.

Annex 3: The threshold of toxicological concern (TTC) and the threshold of ecotoxicological concern (ecoTTC)

The threshold of toxicological concern (TTC) is a *de minimis* concentration below which exposure is assumed to be unlikely of concern for human health (EFSA and WHO, 2016). Correspondingly, the threshold of ecotoxicological concern (ecoTTC) is a concentration below which an exposure is unlikely to cause toxic impacts on environmental organisms.

The (eco)TTC approach is distribution-based and derives chemical-class specific concentration limit values from the cumulative distributions of experimental No Observed Effect Levels (NOELs) on relevant toxicological endpoints (EFSA and WHO, 2016). Central to applying this approach when estimating impacts on human health is the Cramer decision scheme which classifies chemicals into one of 3 broad groups (the Cramer Classes), based on the presence of potentially toxic functional groups. The decision tree was originally developed in the 1970s (Cramer et al., 1976) using a very limited set of chemicals. However, EFSA and WHO recently concluded that the scheme is, even in the light of modern toxicological knowledge, sufficiently protective (EFSA and WHO, 2016).

The TTC/ecoTTC approach therefore only requires that the chemical structure of the substance in question is known and that the exposure is estimated. As such, it is especially suitable for a first prioritization of data-poor chemicals, so that more resource-intensive assessments can focus on relevant chemicals and exposure scenarios.

Environmental impacts or impacts on human health cannot be ruled out for chemicals that occur at concentrations exceeding the corresponding TTC/ecoTTC values. Within a full chemical risk assessment (see Figure 3), the TTC approach is therefore used as a first screening criterion to separate low-priority chemicals from chemicals of potential concern for which a full hazard evaluation might be needed. In the approach outlined above, the hazard information provided from the GHS is used to focus on chemicals that are likely to cause concern, should they occur at concentrations exceeding the TTC/ecoTTC.

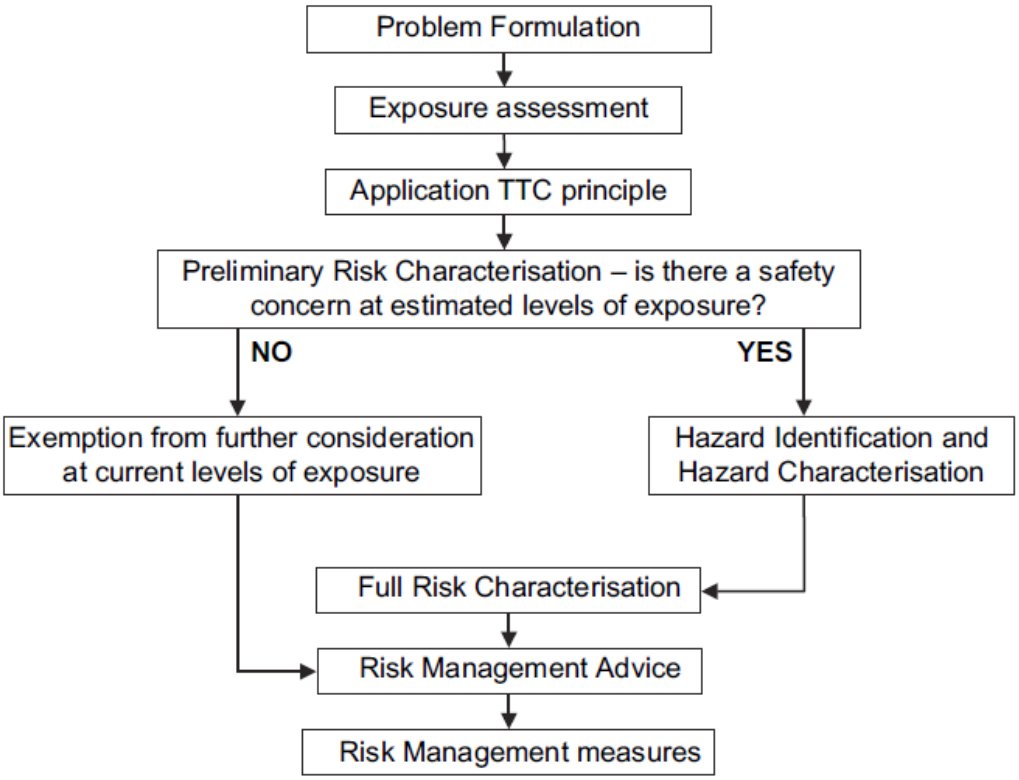

Figure 3: The role of the (eco)TTC approach in the context of chemical risk assessment (reproducted from Kroes et al., 2005)

EFSA recently agreed on the following TTC values (EFSA Scientific Committee, 2019):

- Chemicals falling into Cramer Class I: 30 µg/kg bodyweight per day
- Chemicals falling into Cramer Class II: 9 µg/kg bodyweight per day
- Chemicals falling into Cramer Class III: 1.5 µg/kg bodyweight per day
- For substances that have the potential to be DNA-reactive mutagens and/or carcinogens: 0.0025 µg/kg body weight per day.
- For organophosphates or carbamates: 0.3 µg/kg body weight per day

For an overview of TTC values for other groups of chemicals and specific endpoints, see Hennes (2012).

In comparison, the setting of the corresponding ecological thresholds of ecoTTC is only it its infancy. In particular, optimizing the grouping of ecotoxicological data according to modes of action is still an area of active research. However, novel large curated publicly available databases with ecotoxicological data, such as EnviroTox, are likely to lead to improved ecoTTC values in the near future (Connors et al., 2019). First estimates of ecoTTCs are already published for the following groups of chemicals:

- Inert and organic chemicals in the waterphase: 0.1 µg/L (de Wolf, 2005).
- Cationic surfactants in the waterphase: 0.008 µg/L (Gutsell et al., 2015)
- Anionic surfactants in the waterphase: 0.23 µg/L (Gutsell et al., 2015)

- Estrogen agonists: 0.0003 – 0.0092 µg/L, depending on ecotoxicological endpoint used (Gross et al., 2010)

To our knowledge, no ecoTTC values have been estimated for terrestrial ecosystems, sediments and marine ecosystems. It should also be pointed out that the underlying data collections usually show a substantial scarcity of data for tropical and subtropical species.

Certain classes of chemicals are specifically excluded from the application of the TTC approach (EFSA and WHO, 2016, EFSA Scientific Committee, 2019). This includes certain carcinogens (aflatoxins, azoxy and N-nitroso compounds and benzidines), steroids, nanomaterials, radioactive substances, inorganic chemicals including metals, organometals and organosilicons. Substances with a potential to bioaccumulate are also excluded. It should also be pointed out that the (eco)TTC approach is based on the implicit assumption of strictly monotonous concentration-response curves, which has be challenged especially for endocrine-disrupting chemicals (see e.g. Myers et al., 2009, Vandenberg et al., 2012).

Annex 4: GHS Criteria for Carcinogenicity, Mutagenicity, Reproductive Toxicity, Target Organ Toxicity and Sensitization

Reproduced from GHS, 8th edition (UN, 2019)

CATEGORY 1:	**Known or presumed human carcinogens**
	The placing of a substance in Category 1 is done on the basis of epidemiological and/or animal data. An individual substance may be further distinguished:
Category 1A:	**Known to have carcinogenic potential for humans; the placing of a substance is largely based on human evidence.**
Category 1B:	**Presumed to have carcinogenic potential for humans; the placing of a substance is largely based on animal evidence.**
	Based on strength of evidence together with additional considerations, such evidence may be derived from human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
	Classification: Category 1 (A and B) Carcinogen
CATEGORY 2:	**Suspected human carcinogens**
	The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.
	Classification: Category 2 Carcinogen

CATEGORY 1:	**Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans**
Category 1A:	**Substances known to induce heritable mutations in germ cells of humans**
	Positive evidence from human epidemiological studies.
Category 1B:	**Substances which should be regarded as if they induce heritable mutations in the germ cells of humans**
	(a) Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or
	(b) Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxic tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or
	(c) Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
CATEGORY 2:	**Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans**
	Positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from:
	(a) Somatic cell mutagenicity tests *in vivo*, in mammals; or
	(b) Other in vivo somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays.
	NOTE: *Substances which are positive in in vitro mammalian mutagenicity assays, and which also show structure activity relationship to known germ cell mutagens, should be considered for classification as Category 2 mutagens.*

CATEGORY 1:	**Known or presumed human reproductive toxicant** This category includes substances which are known to have produced an adverse effect on sexual function and fertility or on development in humans or for which there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. For regulatory purposes, a substance can be further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).
CATEGORY 1A:	**Known human reproductive toxicant** The placing of the substance in this category is largely based on evidence from humans.
CATEGORY 1B:	**Presumed human reproductive toxicant** The placing of the substance in this category is largely based on evidence from experimental animals. Data from animal studies should provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.
CATEGORY 2:	**Suspected human reproductive toxicant** This category includes substances for which there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects, and where the evidence is not sufficiently convincing to place the substance in Category 1. For instance, deficiencies in the study may make the quality of evidence less convincing, and in view of this Category 2 could be the more appropriate classification.

CATEGORY 1:	**Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following single exposure** Placing a substance in Category 1 is done on the basis of: (a) reliable and good quality evidence from human cases or epidemiological studies; or (b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) to be used as part of weight-of-evidence evaluation.
CATEGORY 2:	**Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure** Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) in order to help in classification. In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.1.9).
CATEGORY 3:	**Transient target organ effects** There are target organ effects for which a substance/mixture may not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category only includes narcotic effects and respiratory tract irritation. Substances/mixtures may be classified specifically for these effects as discussed in 3.8.2.2.

NOTE: *For these categories the specific target organ/system that has been primarily affected by the classified substance may be identified, or the substance may be identified as a general toxicant. Attempts should be made to determine the primary target organ/system of toxicity and classify for that purpose, e.g. hepatotoxicants, neurotoxicants. One should carefully evaluate the data and, where possible, not include secondary effects, e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems.*

CATEGORY 1:	**Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure** Placing a substance in Category 1 is done on the basis of: (a) reliable and good quality evidence from human cases or epidemiological studies; or, (b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) to be used as part of weight-of-evidence evaluation.
CATEGORY 2:	**Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure** Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).
NOTE: *For both categories the specific target organ/system that has been primarily affected by the classified substance may be identified, or the substance may be identified as a general toxicant. Attempts should be made to determine the primary target organ/system of toxicity and classify for that purpose, e.g. hepatotoxicants, neurotoxicants. One should carefully evaluate the data and, where possible, not include secondary effects, e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems.*	

CATEGORY 1:	**Respiratory sensitizer**
	A substance is classified as a respiratory sensitizer: (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or (b) if there are positive results from an appropriate animal test[1].
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitization rate in humans based on animal or other tests[1]. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitization rate in humans based on animal or other tests[1]. Severity of reaction may also be considered.

CATEGORY 1:	**Skin sensitizer**
	A substance is classified as a skin sensitizer: (a) if there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons, or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitization in humans. Severity of reaction may also be considered.

Figure 3.8.1: Hazard categories for specific target organ toxicity following single exposure

CATEGORY 1: **Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following single exposure**

Placing a substance in Category 1 is done on the basis of:

(a) reliable and good quality evidence from human cases or epidemiological studies; or

(b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) to be used as part of weight-of-evidence evaluation.

CATEGORY 2: **Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure**

Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) in order to help in classification.

In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.1.9).

CATEGORY 3: **Transient target organ effects**

There are target organ effects for which a substance/mixture may not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category only includes narcotic effects and respiratory tract irritation. Substances/mixtures may be classified specifically for these effects as discussed in 3.8.2.2.

NOTE: *For these categories the specific target organ/system that has been primarily affected by the classified substance may be identified, or the substance may be identified as a general toxicant. Attempts should be made to determine the primary target organ/system of toxicity and classify for that purpose, e.g. hepatotoxicants, neurotoxicants. One should carefully evaluate the data and, where possible, not include secondary effects, e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems.*

Figure 3.9.1: Hazard categories for specific target organ toxicity following repeated exposure

CATEGORY 1: **Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure**

Placing a substance in Category 1 is done on the basis of:

(a) reliable and good quality evidence from human cases or epidemiological studies; or,

(b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) to be used as part of weight-of-evidence evaluation.

CATEGORY 2: **Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure**

Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification.

In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).

NOTE: *For both categories the specific target organ/system that has been primarily affected by the classified substance may be identified, or the substance may be identified as a general toxicant. Attempts should be made to determine the primary target organ/system of toxicity and classify for that purpose, e.g. hepatotoxicants, neurotoxicants. One should carefully evaluate the data and, where possible, not include secondary effects, e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems.*

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