chemsec
SIN LIST

Comprehensive methodology for substance inclusion on the SIN List

From 2008 until 2018

Content

Context and background

REACH AND SUBSTANCES OF VERY HIGH CONCERN

In 2007 the European Union's new framework policy on industrial chemicals, REACH,[1] entered into force. REACH stands for registration, evaluation, authorisation and restriction of chemicals. REACH aims to ensure that basic information on industrial chemicals used in the EU is provided and that the use of the most hazardous chemicals is limited or prohibited through either restriction or authorisation procedures. The success of REACH is dependent on a prompt, effective process for identifying the most hazardous chemicals on the European market and replacing them with safer alternatives.

REACH requires companies to register information about the chemicals they produce or import. The registration of existing substances has been divided into three different deadlines; in 2010, 2013 and 2018 depending on production volume and known hazardous properties.

The most hazardous substances in REACH can be designated as Substances of Very High Concern (SVHCs) and are subject to close scrutiny. At the heart of the authorisation process is a Candidate List of chemicals that meet the criteria for Substances of Very High Concern as defined in the legislation, such as those that may cause cancer or persist in our bodies and the environment for long periods of time. Placing of a substance on the Candidate List triggers specific obligations for companies to inform downstream users and consumers about the presence of this substance in products in the supply chain.

However, the mere fulfilment of the SVHC criteria does not mean a substance is automatically placed on the Candidate List. In order for a substance to be listed it needs to be nominated by either an EU member state or the European Chemicals Agency (ECHA) on behalf of the European Commission. These must prepare a dossier to justify the reasons for inclusion, such as the officially harmonised classification and/or scientific evidence to support the nomination and then all member states must unanimously decide that it is indeed an SVHC. From the Candidate List, substances are later selected for further scrutiny and eventually restricted or allowed only for specifically authorised purposes.

The EU is populating the Candidate List with SVHC substances, but the process has so far been quite slow and unpredictable. The EU Commission has set up a roadmap guiding the work towards a goal of having "all relevant" substances on the candidate list by 2020. The current official candidate list can be found on ECHA's official webpage.[2]

SVHCS ARE DIVIDED INTO SIX DIFFERENT CATEGORIES.

1. Carcinogenic [C]
2. Mutagenic [M]
3. Toxic to Reproduction [R]
4. Persistent, Bioaccumulative and Toxic [PBT]
5. Very Persistent and very Bio-accumulative [vPvB]
6. Equivalent level of concern, such as endocrine disruptors [57 (f)]

THE SIN LIST

The SIN (Substitute It Now!) List has been developed to highlight the need for swift implementation of the REACH system for identifying and phasing out high-concern chemicals. It has also proven valuable for companies as well as for financial investors as a preview of which substances are likely to be regulated within the EU in the near future. This paper will explain how the SIN List has emerged and the methodology that has been used for selecting and evaluating substances for the SIN List.

All substances on the SIN List do according to ChemSec fulfil the criteria for SVHCs as defined in the REACH regulation, and fall into at least one of the six categories above. The first SIN List, 1.0, was presented in September 2008, and the SIN List released in May 2011 brought into focus endocrine-disrupting chemicals (EDCs) as a group of SVHCs that need to be urgently addressed by the EU. The update in 2014 did also put EDCs into focus together with PBT/vPvB substances. In addition the SIN List was divided into 31 substance groups, based on structure. This grouping served as a basis for development of a tool, SINimilarity, to compare structures of substances outside of the SIN List with substances on the SIN List. For details on grouping and SINimilarity please consult the separate methodology document. In addition to these major updates there has been a number of "technical updates". The technical updates followed new classification of CMR substances or newly available registration information. We have also added substances from the Candidate List in those cases we have not allready had them on the SIN List. The latest version of the full update history can be found here:

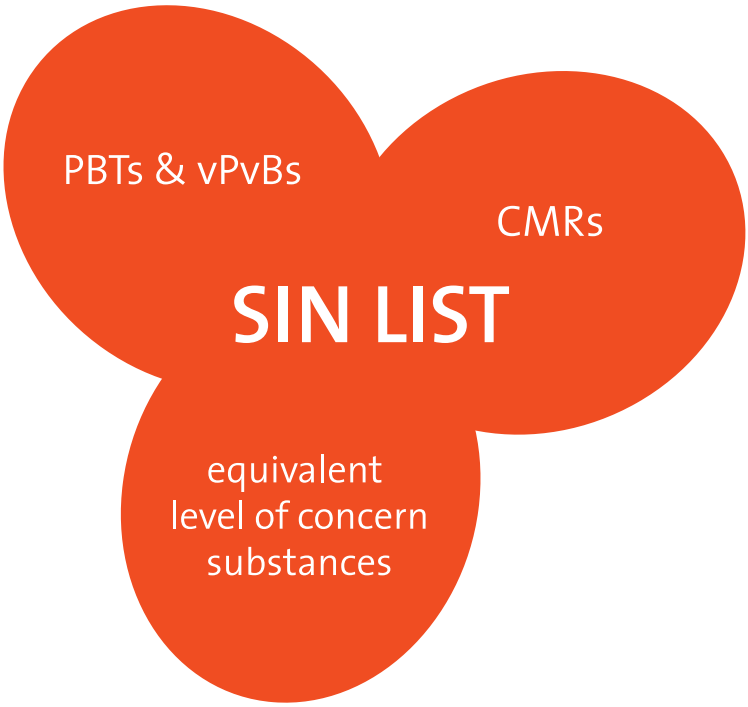
http://chemsec.org/business-tool/sin-list/sin-list-updates/

1. http://echa.europa.eu/web/guest/regulations/reach/legislation
2. http://echa.europa.eu/web/guest/regulations/reach/legislation

General principles used for the compilation of the SIN List

TARGETING SUBSTANCES SUBJECT TO REACH

All substances on the SIN List – CMRs, PBTs, vPvBs or equivalent level of concern substances – have been screened to identify substances covered by the authorisation provisions in REACH. Substances exempt or otherwise not regulated by REACH, such as pesticides, intermediates and unintentionally produced substances, have accordingly been removed.



BASED ON PUBLICLY AVAILABLE DATA

All information used for selection and assessment of substances for the SIN List is publicly available, as is described in more detail for the different categories of substances below.

For CMRs the official CLP (Classification, Labelling and Packaging) classification has been used. These substances have been agreed on a EU-wide basis to have properties corresponding to the SVHC criteria.

PBT and vPvB chemicals for the first version of the SIN List were added directly from the European PBT Working Group List which was developed by the former European Chemicals Bureau (ECB), which duties have since been taken over by ECHA.

Equivalent level of concern substances (REACH article 57(f)) added to the SIN List have undergone a more in-depth scientific evaluation and case-by-case assessment, based on publicly available peer-reviewed scientific studies. This has also been the case for evaluation of PBTs/vPvBs in 2014.

EXCLUSIVE RATHER THAN INCLUSIVE

It should be clearly stated that the absence of the substance on the SIN List does not indicate that this is a non-hazardous chemical. There are several reasons why a substance has not been added: it was never present in the "starting material" for an update (typically other priority lists, reports and review studies) or it was assessed but there was at the time not enough available data to include it on the SIN List. Therefore the SIN List should not be considered as a final list, but rather an important first step towards a more comprehensive list of SVHCs in need of regulation.

Substances officially classified as CMRs

CMRs are substances that are carcinogenic, mutagenic, or toxic to reproduction. In other words, they have inherent properties that can cause cancer, alter DNA or damage reproductive systems. These properties correspond to article 57 a-c of REACH.

To identify CMRs the EU Regulation on Classification, Labelling and Packaging (CLP, EC 1272/2008) was used as a source. The CLP regulation contains a register of all officially classified substances including CMR substances category 1A or 1B. These substances are recognised under REACH as by default meeting the criteria of SVHCs (according to article 57 a, b and c). From the above-mentioned register, pesticides having a standardised name assigned by the International Organisation for Standardization (ISO) have not been included in the SIN list if not registered with a full REACH registration dossier.

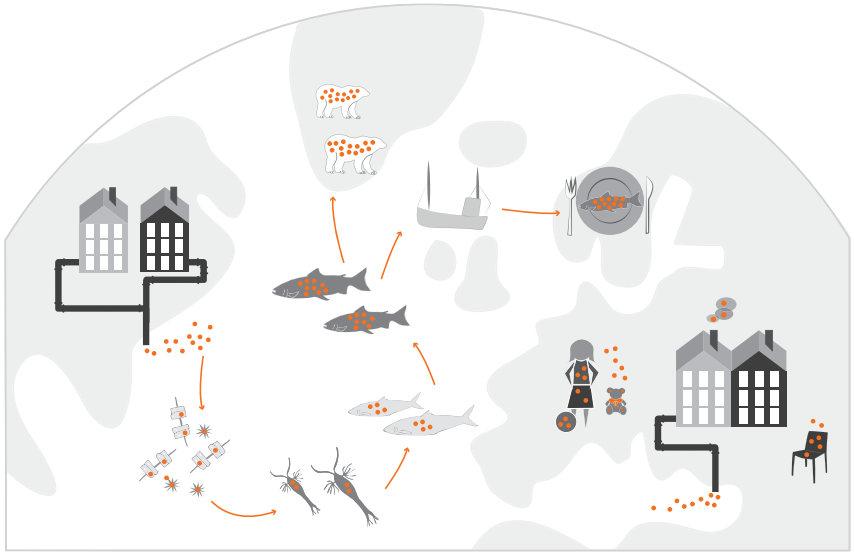
Entries in the above-mentioned register referring to mixtures where one of the substances is a CMR and is present in the mixture in concentrations above 0.1% have not been included in the SIN list either. Neither entries lacking CAS numbers and EC numbers since they do not identify a unique substance or a unique substance group.

For each SIN List update chemicals that have been newly classified as CMR 1a and 1b in the interim have been added.

Substances officially recognised as PBT/vPvB

These substances are Persistent, Bio-accumulative and Toxic (PBT) or very Persistent and very Bio-accumulative (vPvB). These properties correspond to article 57 d-e of REACH. They do not easily break down in nature. Instead they build up in the environment and in, for example, the fatty tissue of mammals, where they have the potential to cause serious and long-term irreversible effects. Due to their longevity, these chemicals have the potential to cause great harm even at low toxicity, since they can build up and multiply over time.

The PBT Working Group, an official assembly of representatives from EU member states as well as experts from the former European Chemicals Bureau (ECB), had by 2008 concluded that a number of substances fulfil the EU criteria as PBT or vPvB. These criteria were very similar, although not identical, to those in REACH. For the first version of the SIN List these substances were added to the SIN List, with the exception of substances outside the scope of REACH such as certain pesticides.



Persistent and bioaccumulative chemicals are used in a variety of products, including textiles, furniture, toys and building materials. Persistent chemicals do not easily degrade and can in many cases be transported also to remote parts of the world. Bioaccumulative chemicals that enter the food chain will magnify for each level, leaving top predators – such as whales, eagles, polar bears and ourselves – with the highest concentrations.

EVALUATION OF NEW PBTS FOR THE 2014 UPDATE

SCREENING PHASE

Initially ChemSec screened a number of sources for suspected PBTs, including scientific papers[3, 4], reports[5, 6], priority lists from authorities[7, 8, 9] and from organisations.[10]

From this gross, comprehensive list substances already on the SIN List were removed, resulting in more than 1,000 substances.

To narrow down the number of substances, ChemSec considered the use of the substances. Indicated consumer use was defined as substances being present on a selection of product-type related substances lists.[11] Proven consumer use was defined as substances that have been detected in consumer articles in a number of studies (120) performed by Danish EPA[12]. The presence of a chemical on any of these lists or studies was not considered as strict criteria, but only as guidance.

SCIENTIFIC EVALUATION

In total 81 substances were pre-evaluated and 25 substances evaluated in-depth by the scientific team of Professor Martin Scheringer and Dr Carla Aparecida, ETH Zürich. Chemicals were investigated for (i) fulfilment of the Annex-XIII criteria of REACH for PBT or vPvB substances, (ii) substantial structural similarity to chemicals already regulated under REACH as PBT or vPvB substances or under the Stockholm Convention on persistent organic pollutants, (iii) degradation in the environment or organisms into substances that fulfill (i) or (ii).

Data Sources

For literature search, the following databases were used:

- SciFinder[13]
- ISI Web of Science
- ChemSpider[14]
- ChemIDplus[15]
- Reaxys[16]
- FatePointers Search Module[17]
- OECD eChemPortal Substance Search[18]
- US EPA ECOTOX Database[19] h
- Categorization Results from the Canadian Domestic Substance List[20]
- Japanese Chemical Risk Information Platform[21]
- EURAS Bioconcentration Factor (BCF) Gold Standard Database[22]
- Experimental log BCF values used in a training set[23]

The chemical properties that indicate the persistence and bioaccumulation of a chemical are difficult to measure. They inclu-

3. *http://www.ncbi.nlm.nih.gov/pubmed/22982223*
4. *http://www.ncbi.nlm.nih.gov/pubmed/21168217*
5. *http://miljodirektoratet.no/old/klif/publikasjoner/2462/ta2462.pdf*
6. *http://norden.diva-portal.org/smash/record.jsf?pid=diva2:701876*
7. *www.rivm.nl/bibliotheek/rapporten/601356001.pdf*
8. *http://www2.mst.dk/udgiv/publications/2011/05/978-87-92708-95-3.pdf*
9. *http://echa.europa.eu/en/information-on-chemicals/evaluation/community-rolling-action-plan/corap-list-of-substances*
10. *http://saferchemicals.org/chemicals/*
11. *SPIN database http://90.184.2.100/DotNetNuke/*
    - *GADSL http://www.gadsl.org/*
    - *EFSA Food contact materials, plastic and non- plastic.*
      - *Plastic: https://webgate.ec.europa.eu/sanco_foods/main/?event=substances.search&substances.pagination=1*
      - *Non-plastic: http://www.efsa.europa.eu/fr/supporting/pub/139e.htm*
    - *Swerea Database on textile and EEE. http://extra.ivf.se/chemicall/login.asp?u=%2Fchemicall%2FDefault.asp%3F*
12. *http://www.mst.dk/Borger/Kemikalier/kortlaegn_af_kemikalier_i_forbrugerprodukter/*
13. *http://scifinder.cas.org*
14. *http://www.chemspider.com*
15. *http://chem.sis.nlm.nih.gov/chemidplus*
16. *http://www.reaxys.com*
17. *http://esc.syrres.com/fatepointer/search.asp*
18. *http://www.echemportal.org/echemportal/page.action?pageID=9*
19. *http://cfpub.epa.gov/ecotox/browse_index.cfm?sub=chemical*
20. *http://webnet.oecd.org/CCRWEB/Search.aspx*
21. *http://www.safe.nite.go.jp/english/sougou/view/ComprehensiveInfoDisplay_en.faces*
22. *http://ambit.sourceforge.net/euras*
23. *http://www.tandfonline.com/action/showPopup?id=T0002&doi=10.1080/10659360500474623.*

de long biodegradation half-lives, high or very high octanol-water partition coefficients (K_{ow}) and bioconcentration factors (BCF), and low or very low effect concentrations for chemicals that have low or very low water solubility. This has several important implications:

- measured data for these properties are not available for many chemicals and are generally scarce.
- measured data for these properties may be subject to substantial measurement errors and, generally, high uncertainty.[24, 25]
- estimation methods are important as a source of property data needed for PBT assessments.
- estimated property data can be considered to be at least equally reliable as measured data, i.e. estimated data should not be seen as of lower quality, but measured and estimated data should be given the same weight and importance[26]. This applies in particular to the K_{ow}, for which the existing estimation methods are based on extensive sets of measured K_{ow} values.

Estimation methods

– EPI Suite

The following modules of EPI Suite (version 4.11) were used to obtain half-lives in air, water and soil, log K_{OW}, log K_{AW}, BCF and ecotoxicity estimates:

- KOWWIN v1.68
- HENRYWIN v3.20
- AOPWIN v1.92
- BIOWIN v4.10 (Biowin3, ultimate survey model)
- BCFBAF v3.01 (regression-based method)
- ECOSAR v1.11

– Baseline Toxicity of Low Solubility Chemicals

For chemicals with low water solubility, ECOSAR can give incorrect estimates of baseline toxicity (narcosis) if estimates of LC50 are based on the K_{OW} and on the solubility of the solid chemical. In these cases ECOSAR often returns the result: NES ("No Effect at Solubility"). For these chemicals, the baseline toxicity was estimated using the LC50-K_{OW} relationship developed by McCarty et al.[27] which gives an estimate in the middle of the range of available LC50-K_{OW} relationships[28]

$$\log LC50 = -0.90 \log K_{OW} + 1.71$$

where the LC50 is in units of mmol/L, which can be converted to mg/L by multiplying by the molecular weight in g/mol.

– ChemAxon

ChemAxon was accessed via www.chemicalize.org to obtain estimates for log K_{OW} and pK_a. For substances that occur in the dissociated/ionic form in the environment, the log KD is additionally read from the pH – log K_D plot.

– COSMOtherm

COSMOconf (remake beta 1.0) was used to obtain the geometry and the energy and a set of conformers for each compound. The log K_{OW}, log K_{AW} and the half-life in air (OH radical reactions) was then estimated with COSMOtherm (C3.0 Release 13.01). The default OH radical concentration from EPI Suite, i.e. $1.5 \cdot 10^6$/cm^3 during a 12-h day (equalling $7.5 \cdot 10^5$/cm^3 overall), was used.

– OECD Tool

The OECD P_{OV} and LRTP Screening Tool (hereafter "OECD Tool"), version 2.2[29] was used to estimate the long-range transport potential (LRTP) of the substances under evaluation. The characteristic travel distance (CTD) metric was selected to assess the LRTP with a value of 5.097 km as a threshold. For input parameters with more than one reliable data point, the geometric means of all (non-log-transformed) data were used. For log-transformed data, i.e. partition coefficients, the arithmetic means were used.

The findings for each of the evaluated substances were summarised and forwarded to ChemSec.

EVALUATION AGAINST REACH CRITERIA

After having received the summaries ChemSec discussed and consulted with a number of experts from authorities, NGOs and research institutes and thereafter selected thirteen substances for this SIN list update. These thirteen substances were identified using a weight of evidence approach considering:

- Measured data
- Estimated data
- Read-across
- Degradation products
- Biomonitoring data

24. *Stieger, G., Scheringer, M., Ng, C.A., Hungerbühler, K., 2014. Assessing the persistence bioaccumulation potential and toxicity of brominated flame retardants: data availability and quality for 36 alternative brominated flame retardants. Chemosphere, online: http://dx.doi.org/10.1016/j.chemosphere.2014.01.083*
25. *Jonker, M.T.O., van der Heijden, S.A., 2007. Bioconcentration factor hydrophobicity cutoff: an artificial phenomenon reconstructed. Environ. Sci. Technol. 41, 7363-7369.*
26. *Strempel, S., Scheringer, M., Ng, C.A., Hungerbühler, K., 2012. Screening for PBT chemicals among the "existing" and "new" chemicals of the EU. Environ. Sci. Technol. 46, 5680-5687.*
27. *McCarty, L.S., Mackay, D., Smith, A.D., Ozburn, A.D., Dixon, D.G., (1992). "Residue-based interpretation of toxicity and bioconcentration QSARs from aquatic bioassays: neutral narcotic organics." Environmental Toxicology and Chemistry 11: 917–930.*
28. *Stieger, G., Scheringer, M., Ng, C. A. and Hungerbühler, K. (2014). "Assessing the persistence, bioaccumulation potential and toxicity of brominated flame retardants: Data availability and quality for 36 alternative flame retardants." Chemosphere in press.*
29. *Wegmann, F., L. Cavin, et al. (2009). "The OECD software tool for screening chemicals for persistence and long-range transport potential." Environmental Modelling & Software 24(2): 228–237.*

Substances fulfilling REACH criteria on equivalent level of concern

Finally the last group of SVHCs, is a category introduced as a safety net in REACH authorisation in order to include very hazardous substances of equivalent level of concern to the other categories where there is scientific evidence for probable serious effects (REACH article 57f). Substances with endocrine disrupting effects are mentioned as one example of a group of substances causing such equivalent level of concern. Identification is taking place on a case-by-case basis [30].

In short, identifying equivalent level of concern substances as SVHCs and adding them to the SIN List has been a three-stage process.

1. Selection and filtering of substances relevant for REACH
2. Literature research on selected substances
3. Evaluation against REACH criteria for SVHCs and justification for inclusion

For more details, see specific methodology for each update including 57(f) substances below.

METHODS FOR INCLUSION OF 57(F) SUBSTANCES IN SIN 1.0 2008

FIRST STEP – SCREENING PHASE

First, a rough list was compiled of substances from many different records and lists of recognised hazardous chemicals. Examples of such lists are the OSPAR[31] list of chemicals of possible concern & priority action, the EU Water Framework Directive, the Swedish Chemicals Agency's (KEMI) PRIO list, as well as lists by the US and Canadian Environmental Protection Agencies. Further, substances listed on collaborating companies' grey and black lists were included.

The resulting rough list contained altogether approximately 4,000 substances with different levels of concern. Throughout the compiling procedure, all risk phrases and classifications (official and unofficial) were kept attached to each substance to facilitate the subsequent screening process. To ensure positive identification of each substance, any duplicate entries, references to substance groups and other substances not having a CAS or EC number were removed. Then the Swedish Chemicals Agency (KemI) was asked to search its "Products Register"[32] for the occurrence of these 4,000 substances in chemical products and preparations available to consumers. KemI responded with a refined list of approximately 250 of the original 4,000 substances[33]. Information from the European Chemicals Bureau was then used to obtain information on high production volume chemicals. This refined the list further to roughly 150 substances.

From this point on, substances were manually selected and screened. Substances whose hazardous properties were only of a physical nature (corrosive, explosive, flammable etc.) were removed together with chemicals already officially classified as CMRs (category 1A & 1B) already covered above, pesticides and other substances that are exempted from REACH in total or from the authorisation procedure.

When selecting substances, priority was given to substances whose properties indicated them to be EDC, CMR (category 2), PBT or toxic to aquatic organisms which may cause long-term

30. *Substances – such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties, which do not fulfil the criteria of points (d) or (e) – for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59*
31. *OSPAR is the Convention for the Protection of the Marine Environment of the North-East Atlantic, adopted in 1992*
32. *http://kemi.se/start/produktregistret/*
33. *Granted, the chemical uses in the Swedish Product Register might not be representative of all uses in all of Europe. This is nevertheless a good basis for identifying hazardous chemicals to which consumers are exposed. The actual uses, in Europe and globally, presumably go beyond the Swedish Product Register, thus the potential number of chemicals eligible for inclusion may be far greater.*

adverse effects in the aquatic environment[34]. This gave a total of 35 substances.

Further high-profile substances often found in human bio-monitoring studies or else frequently mentioned in human health and environmental studies were selected for evaluation. The presence of man-made chemicals in nature or in human bodies often indicates persistence and possible bioaccumulation. This added another 15 substances.

Endocrine disrupting chemicals (EDCs) assessed to be of high or medium concern in the European Commission report on EDCs (COM (2001/262)[35] added another 10 substances to the list.[36] Making the final number of potential equivalent level of concern substances to be evaluated and assessed 60.

SECOND AND THIRD STEP – SCIENTIFIC LITERATURE REVIEW AND ASSESSMENT

In order to make a proper assessment toxicologists were assigned to conduct an exhaustive literature search for each of the 60 substances of potential equivalent level of concern filtered out in the first screening phase. They were also asked to conduct an in-depth assessment on each substance to determine whether these substances would qualify as Substances of Very High Concern under REACH. The toxicologists were instructed to use the official REACH guidance document on how to identify equivalent level of concern SVHCs and prepare an Annex XV dossier as stated in the "*Guidance for the preparation of an Annex XV dossier on the identification of substances of very high concern*"[37] from June 2007. This was then used as a basis for the SVHC assessment.

The background data used was primarily published scientific literature but also data from existing risk assessments and EU studies of these substances, when available. The assesment looked at the combined properties of these substances, meaning that all known properties and gathered data were considered. The dataset included CMR and endocrine disrupting properties as well as tendencies to persist in nature and/or bio-accumulate and whether the substances had been detected in humans and biota. This combination of different hazards, which individually might not have fulfilled the criteria for SVHC, when assessed together built up a strong case for an equivalent level of concern substance.

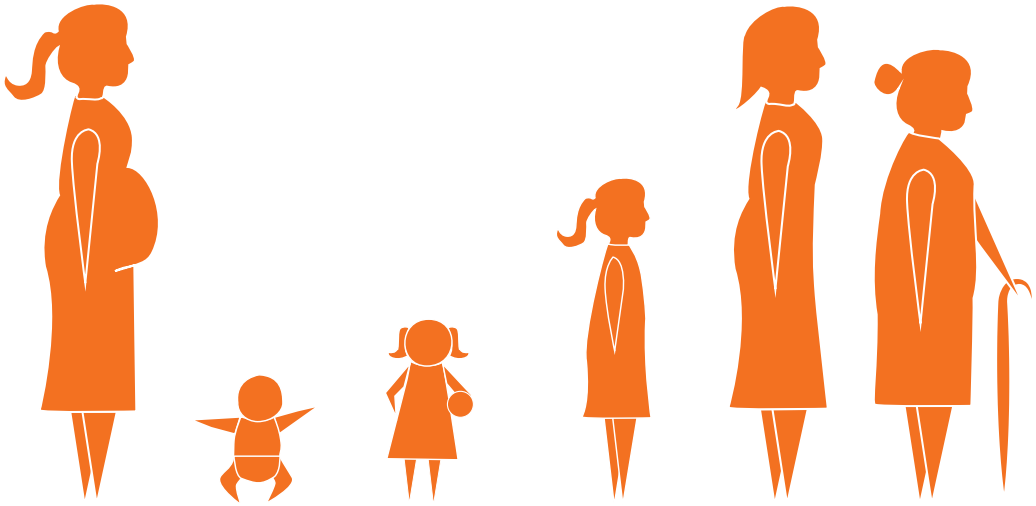
After the toxicologists' assessments, the background data and conclusions were subject to further scrutiny by external scientists. The final result was the decision by ChemSec to add 30 substances here the evidence was sufficient to demonstrate probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other SVHCs.

34. *These properties are based on the information from the original lists and the substances are therefore not necessarily officially classified within the EU according to these risk phrases.*
35. *http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm*
36. *The complete EDC list from this report contains numerous PCBs, DDTs, dioxins/furans, CMRs and pesticides, which were excluded since they were either not subject to REACH or already addressed as classified CMRs. Substances without a CAS number were also removed. One large group of chemicals, tin-organic substances, have both very similar properties and metabolites therefore only the most common tin-organic compounds were selected.*
37. *http://echa.europa.eu/documents/10162/13638/svhc_en.pdf*

METHODS FOR INCLUSION OF EDC SUBSTANCES ON SIN 2.0 IN 2011

During the development of the SIN List 1.0 endocrine disrupting properties were considered as one property, among many other end-points. Among the chemicals analysed for SIN List 1.0, 25 were designated SIN List chemicals partly due to the evidence of endocrine disrupting properties. However, in the development of SIN List in 2011 (2.0) only chemicals with endocrine-disrupting properties were considered and included in the assessment.

These substances are only partly covered by official classification within the EU (e.g. as reprotoxic substances) but they pose a threat to human health and the environment due to their negative impacts on the hormone system that can lead to a variety of harmful effects. Many of them are also available in consumer products (articles and preparations) indicating a wide dispersive use, and many of them are produced in high volumes.



FIRST STEP – SCREENING PHASE

The starting point was the European Commission's database of potential endocrine disruptors[38] developed under the "community strategy for endocrine disruptors". This database consists of 553 substances that have been evaluated with regard to their endocrine disrupting potential. Only substances belonging to the categories 1 or 2, for which there was evidence of EDC properties, were selected – leaving 319 substances.

Based on available information, substances were excluded from the evaluation list based on the same exclusion criteria as used for SIN List 1.0.

This was followed by an evaluation of possible uses for each substance. This evaluation was based on three sources. First, the assessments from the European Commission's database were used to identify uses as reported in the background documentation. Second, the Hazardous Substances Data Bank (HSDB)[39] was used to get further information on potential uses. And finally, for substances for which no uses had been identified, an internet search was carried out to check if there were any other probable uses that had not been addressed by the first two sources.

Substances having no known uses according to the above-mentioned sources were removed along with substances likely to be used only as intermediates or other uses not relevant to REACH such as pharmaceuticals and registered pesticides. To ensure consistency, these process and selection criteria were the same as those used for SIN List 1.0. The application of these filters left a total of 41 substances to be assessed more closely by toxicologists with an expertise in endocrine disruption.

38. EU COM EDC database: http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm

39. HSDB, US National Institutes of Health: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

SECOND STEP – SCIENTIFIC LITERATURE REVIEW

The literature research phase was intended to give a better understanding of the EDC properties associated with the selected substances by verifying the existing data from the European Commission EDC database as well as including the latest research on these substances.

The primary work of this phase was conducted by the members of the scientific staff of The Endocrine Disruption Exchange (TEDX)[40]. The process included a literature search, initial screening, abstract review, selection of studies, data entry and verification, and internal peer review.

Literature search: A comprehensive literature search was conducted in PubMed for each chemical. Search terms were selected based on TEDX experience in reading endocrine-related literature. The general approach was to be inclusive, using terms such as endocrine, hormone and receptor, as well as terms for the many organs involved in endocrine activity. For a few chemicals, very little information was found on PubMed, and additional searches were performed in Web of Science and ToxLine.

Initial screening and abstract review: The literature search generated a list of publications for each chemical. The initial screening of these lists involved scanning abstracts to remove studies that were not published in peer-reviewed journals, did not represent original primary research, or were clearly irrelevant. For example, studies of pest control, remediation, analytical methods and toxico-kinetics were removed at this level of screening. Review articles and other secondary research were used only to locate further primary research. Most studies of human environmental exposure were removed at this level primarily because they were based on retrospective self-reporting, failed to control for simultaneous exposure to other chemicals, and/or were unable to report any measure of exposure dose.

Selection of studies: Following the initial review of abstracts, the remaining studies were downloaded for review. The goal was to select the studies that provided the strongest evidence for endocrine effects. In addition to the oestrogenic, anti-androgenic and thyroid-based effects that tend to be the focus of regulatory attention, evidence of hormonally-based mechanisms of action in other organs, glands and systems and at other levels of effect (e.g. gene expression, signalling mechanisms) was included.

Every effort was made to select the most scientifically robust studies. Studies that did not use appropriate control conditions or for which there were inconsistencies in the text or tables were not selected. No studies in which null findings directly contradicted significant findings from another study were found. High dose studies measuring gross endpoints only (e.g. organ weights) in which the mortality rate was excessive were not selected. Exceptions were made for chemicals for which only high dose studies were available and there was evidence of an endocrine effect (not a toxic effect). Additionally, in some cases, effects were found only at the lowest doses studied. Such studies were evaluated carefully and were not rejected for this reason alone, as endocrine-related effects are known to exhibit non-monotonic dose responses.

Data entry and verification: Only statistically significant findings were reported, with the rare exception of particularly compelling results for which no statistical analyses were conducted (e.g., gene arrays or changes in morphology). With regard to dose, it was not always practical to present the full range of doses used, as some studies used complex experimental designs and others only reported relative binding affinity.

Internal peer review: The final analysis was conducted via a collaborative effort within the researcher team. The researchers reviewed the chemicals one by one, evaluating each study in the database. The test methods employed were discussed as well as the assays used, whether the effects were truly endocrine-related, and how the authors interpreted their results.

According to TEDX, it was not unusual that studies never mentioned endocrine disruption, despite findings that were clearly relevant to the endocrine system. On this point, TEDX relied on the principles of endocrinology that endocrine effects encompass not only direct effects on traditional endocrine glands, their hormones and receptors, but also entire signalling cascades. These cascades affect reproductive function and foetal development, as well as the nervous system, behaviour, immune system, liver, bone and many other organs and glands.

THIRD STEP – EVALUATION AGAINST REACH CRITERIA FOR SVHCS

The evaluation process aimed to determine whether there was sufficient evidence for including substances as Substances of Very High Concern was led by ChemSec with support from an external group of scientists and toxicologists.

The official REACH guidance document on how to identify equivalent level of concern SVHCs and prepare an Annex XV dossier as stated in the *"Guidance for the preparation of an Annex XV dossier on the identification of substances of very high concern"*[41] dating from June 2007 was used as basis for the SVHC assessment. The

40. The Endocrine Disruption Exchange (US): http://www.endocrinedisruption.com/

41. http://echa.europa.eu/documents/10162/13638/svhc_en.pdf

guidance, however, does not give clear criteria on how to do this beyond that it should be applied on a case-by-case basis. The guidance mentions a few mechanisms and factors to be considered, and acknowledges that substances displaying endocrine-active properties can result in changes in growth, development, reproduction or behaviour in the organism or in future generations.

The guidance document and the definitions developed for the European Commission database, as well as advice from external EDC experts, were used as the basis for our assessment. All eligible substances needed to have robust data, primarily from in vivo tests obtained through studies of documented endocrine disruption in actual and intact animals. Only the studies carefully selected by TEDX, as described above, were considered. This information was then complemented with research papers with in vitro data from experiments performed in test tubes and on individual cells, as supporting evidence. To establish a reliable and robust dataset, at least three studies were considered necessary with a minimum of two in-vivo studies, to qualify for in-depth evaluation.

Following this approach and the subsequent evaluation, 22 substances were identified as having strong enough evidence to be considered Substances of Very High Concern with regard to their endocrine disrupting properties, and were subsequently added to the SIN List 2.0.

SUBSTANCES IDENTIFIED AS SVHCS AND OFFICIALLY INCLUDED IN THE REACH CANDIDATE LIST ADDED TO THE SIN LIST 2.1 IN 2013

The SIN List identifies substances that are relevant for the REACH Candidate list. In addition the 2013 update of the SIN List (2.1) included substances that had already been proposed by EU member States and included on the official REACH Candidate List. The substances added to the SIN List 2.1 update shortly after they were included on the Candidate List include:

– CMR substances, including substances without a CAS number, reaction products and mixtures.
– vPvBs previously not identified as such by the EU PBT Working Group, but for which new data provided in the REACH Annex XV dossiers proved these fulfil vPvB criteria.
– Respiratory sensitisers as equivalent level of concern substances, as information in the REACH Annex XV dossiers supported the identification of these substances as SVHCs.

METHODS FOR INCLUSION OF EDC SUBSTANCES IN 2014

FIRST STEP – SCREENING PHASE

Initially ChemSec screened a number of sources for suspected EDCs, including scientific papers,[42, 43] reports,[44, 45] priority lists from authorities[46, 47, 48] and from organisations.[49, 50]

From this gross list substances already on the SIN List were removed, resulting in more than 1000 substances.

To narrow down the number of substances, ChemSec considered the use of the substances. Indicated consumer use was defined as substances being present on a selection of product-type related substances lists.[51] Proven consumer use was defined as substances that have been detected in consumer articles in a number of studies (120) performed by Danish EPA.[52] Presence of any of these lists or studies was not considered as strict criteria, but only as guidance. About one hundred substances were prioritized and during discussions and first screenings with the scientists, 25 substances were selected for full evaluation.

42. *http://www.ncbi.nlm.nih.gov/pubmed/22982223*
43. *http://www.ncbi.nlm.nih.gov/pubmed/21168217*
44. *http://miljodirektoratet.no/old/klif/publikasjoner/2462/ta2462.pdf*
45. *http://norden.diva-portal.org/smash/record.jsf?pid=diva2:701876*
46. *www.rivm.nl/bibliotheek/rapporten/601356001.pdf*
47. *http://www2.mst.dk/udgiv/publications/2011/05/978-87-92708-95-3.pdf*
48. *http://echa.europa.eu/en/information-on-chemicals/evaluation/community-rolling-action-plan/corap-list-of-substances*
49. *http://saferchemicals.org/chemicals/*
50. *http://endocrinedisruption.org/endocrine-disruption/tedx-list-of-potential-endocrine-disruptors/overview*
51. *SPIN database. http://90.184.2.100/DotNetNuke/*
GADSL. http://www.gadsl.org/. EFSA Food contact materials, plastic and non- plastic
Plastic:https://webgate.ec.europa.eu/sanco_foods/main/?event=substances.search&substances.pagination=1
Non-plastic: http://www.efsa.europa.eu/fr/supporting/pub/139e.htm
Swerea Database on textile and EEE. http://extra.ivf.se/chemicall/login.asp?u=%2Fchemicall%2FDefault.asp%3F
52. *http://www.mst.dk/Borger/Kemikalier/kortlaegn_af_kemikalier_i_forbrugerprodukter/*

SECOND STEP – SCIENTIFIC LITERATURE REVIEW

For the scientific evaluation The Endocrine Disrupting Exchange, TEDX, founded by Professor Theo Colborn and with Dr Carol Kwiatkowski as executive director was contracted. In discussions with the scientific team the number of substances subject to detailed evaluations were narrowed down to 25.

Chemical Search: Literature searches for each chemical were performed using common name, common synonyms, and CAS# in PubMed. If the PubMed results yielded less than 500 records then an additional search using common name, common synonyms, and CAS# in Web of Science was performed. These searches were then scanned for duplicate records and incorrect chemical identification and those records were removed at this step. The remaining records identified from the search process were then uploaded to an on-line systematic review software program (DistillerSR) for screening.

Screening of Literature: Two independent reviewers screened all articles for relevance by reviewing the abstract and title. All studies in which physiological effects were evaluated after chemical exposure were included. Excluded studies were categorized according to the reason for exclusion as follows: analytical method, bioaccumulation, biomonitoring, bioremediation, case study, ecotoxicology, environmental fate/ levels, metabolite, pest control, remediation, review, route of exposure, use/source, not relevant, other. Discrepancies between screeners, and other questions regarding relevance, were resolved by discussion. Articles in foreign languages (non-english) were excluded after screening. The remaining relevant studies were downloaded for full review.

Data Extraction: Studies obtained for full review were read and data were extracted and entered into an Access database, then cross checked for accuracy. Studies deemed irrelevant at this point were excluded and categorized on a case by case basis. Specific exclusions included studies of contact dermatitis, ototoxicity, color vision impairment, mortality studies in invertebrates and aquatic organisms, studies in subjects self-identified as having Multiple Chemical Sensitivity, and articles that were the incorrect study type (vis a vis the categories listed above). All articles were reviewed independently by two reviewers. Discrepancies in the recording of data or the exclusion of studies were discussed between the two reviewers. A third reviewer was consulted when necessary.

INDIVIDUAL STUDY QUALITY ASSESSMENT:

IN VIVO

All in vivo studies (e.g. experimental animal and epidemiological studies) were assessed for risk of bias (ROB) using the following questions developed by OHAT.[53] Two independent reviewers answered applicable questions and noted justifications for each answer.

Selection Bias

1. Was administered dose or exposure level adequately randomized?
2. Was allocation to study groups adequately concealed?
3. Were comparison groups appropriate?

Confounding Bias

4. Did the study design or analysis account for important confounding and modifying variables?

Performance Bias

5. Did researchers adjust or control for other exposures that are anticipated to bias results?
6. Were experimental conditions identical across study groups?
7. Were the research personnel and human subjects blinded to the study group during the study?
8. Did deviations from the study protocol impact results?

Attrition/ Exclusion Bias

9. Were outcome data incomplete due to attrition or exclusion from analysis?

Detection Bias

10. Were the outcome assessors blinded to study group or exposure level?
11. Were confounding variables assessed consistently across groups using valid and reliable measures?
12. Can one confident in the exposure characterization?
13. Can one confident in the outcome assessment?

Selective Reporting Bias

14. Were all measured outcomes reported?

Other

15. Were statistical methods appropriate?

Additional data

16. Can study results be applied to humans?
17. Was conflict of interest (COI) reported by the authors?
18. What were the reported funding sources?
19. Did the authors indicate that the study was performed in accordance with Good Laboratory Practice (GLP)?

IN VITRO STUDIES

Currently there is no validated method for assessing the quality of in vitro studies, however the following data was collected for each in vitro study.

›››

53. *National Toxicology Program, Office of Health Assessment and Translation. Draft OHAT Approach For Systematic Review And Evidence Integration For Literature-Based Health Assessments February 2013. Research Triangle Park, North Carolina: National Institute of Environmental Health Sciences (NIEHS); 2013 Feb 26a.*

›››

1. Were statistical methods appropriate?
2. Can study results be applied to humans?
3. Was conflict of interest (COI) reported by the authors?
4. What were the reported funding sources?
5. Did the authors indicate that the study was performed in accordance with Good Laboratory Practice (GLP)?

Overall Study Quality Determination: In order to determine overall study quality two key questions from the individual study quality assessment for in vivo animal studies and three key questions for human studies based on methods described in the OHAT Approach were used. Key questions are used to determine an initial study quality then the ratings for the remainder of the questions and translated this into an overall rating of high, moderate, or low quality were summed.

In vitro Evidence Assessment: Standardized protocols evaluating in vitro study quality are not available, therefore those studies could not be evaluated for RoB. Thus, a 'moderate' or 'strong' rating for an in vitro body of evidence (BoE) does not reflect the quality of studies themselves, but rather the degree to which they demonstrate a mechanism or biological plausibility. The strength of the BoE was assessed using aspects outlined by OHAT. The strength of the evidence was determined to be strong, moderate, or weak for a given endpoint based on the aspects listed below (see Appendix C for details). Endpoints with fewer than three studies could not be assessed for strength of evidence.

Summaries: The findings for each chemical were summarized and categorized by the model studied (i.e. human, animal, in vitro) and then by positive effect categories (e.g. estrogenicity, androgenicity). In vivo endpoints were summarized using the study quality for human and animal studies, then where applicable, in vitro findings with Evidence Assessments were used to support in vivo models.

THIRD STEP – EVALUATION AGAINST REACH CRITERIA FOR SVHCS

For the final decision on inclusion on the SIN List ChemSec based its evaluation on the summaries from TEDX as well as discussions with experts from authorities, NGOs and research institutes. Recent reports on identification and assessment of EDCs were also taken into account in the decision process.[54, 55, 56]

As suggested by the experts advisory group and in the document "Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances" from the European Commission Joint Research Centre[57] the following aspects were considered in the discussions on the available evidence:

– an endocrine mode of action
– probability for serious effects
– possible link between the two above

Remarks

Previously the different updates of the SIN List have been named by version numbers (1.0, 1.1, 2.0, 2.1). For the update in 2014 it was decided to abandon this and just talk about The SIN List to avoid confusion. Still, in this document, we mention the versions for simplicity when explaining earlier updates.

Even if the SIN List methodology aims to exclude non-REACH relevant substances, we are aware that not all uses of the substances included in the SIN List will always fall under REACH or authorisation procedures. Specific uses may still be exempted such as substances used as intermediates, in fuel, or as pesticides.

On the other hand, some of the substances removed in the screening phase may indeed classify as SVHC for specific uses covered by REACH, but we do not currently know which. Substances removed during the screening phase might potentially be considered as SVHC under REACH in the future.

54. *http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/endocrine_disrupters/jrc-report-scientific-issues-identification-endocrine-disrupting-substances/at_multi_download/file?name=LBNA25919ENN.pdf*
55. *http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/*
56. *http://ehp.niehs.nih.gov/120-a346/*
57. *http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/endocrine_disrupters/jrc-report-scientific-issues-identification-endocrine-disrupting-substances/at_multi_download/file?name=LBNA25919ENN.pdf*

ANNEX A GLOSSARY

Bio-accumulative	A property causing the substance to build up (accumulate) in the body. Such substances build up in fat tissue in the body and cannot be excreted by the body.
Candidate List	A list of substances within REACH meeting the criteria for Substances of Very High Concern, and proposed by either the European Commission or the EU member states. These substances are candidates for REACH authorisation.
Carcinogenic	A carcinogenic substance causes cancer.
CARACAL	Competent Authorities for REACH and Classification and Labelling in the EU member states.
CAS number (#)	Chemical Abstracts Services registration number. A unique number assigned to each substance submitted to CAS. Used worldwide to positively identify chemicals.
CMR	CMR is the abbreviation for Carcinogenic, Mutagenic and toxic to Reproduction; chemicals with inherent properties which can cause cancer, alter DNA or damage reproductive systems. Part of the REACH Substances of Very High Concern.
EC number (#)	European Commission registration number. The unique number under which a substance is registered in the European Union.
ECB	European Chemicals Bureau. ECB's mission has been to provide scientific and technical support to the conception, development, implementation and monitoring of EU policies on chemicals and consumer products. Its duties have now largely been taken over by ECHA.
ECHA	The European Chemicals Agency in Helsinki, Finland. The EU authority established to oversee and implement the REACH system.
Endocrine disruptor/EDC	A substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an organism or population.
Equivalent level of concern	The safety net of the REACH regulation for substances which do not automatically fall into the categories CMR, PBT or vPvB, but are of equivivalent level of concern in terms of the potential damage they may cause.
ESIS	European chemical Substances Information System. An IT system with information on chemicals related to Biocidal Products, PBTs vPvBs, Classification and Labelling, Export and Import of Dangerous Chemicals and HPV/LPV substances.
Hazard	Hazard refers to the intrinsic properties of a substance which are always present. See also "Risk"
HPV	High Production Volume chemical, manufactured/imported at more than 1000 tonnes/year
LPV	Low Production Volume chemical, manufactured/imported at more than 100 tonnes/year
MSCA	Member State Competent Authority. The authority in each EU member state which monitors REACH and other chemical issues.
Mutagenic	Causes irreparable mutations in the DNA that will be transferred on to the next generation.
PBT	Substances that are Persistent, Bioaccumulative and Toxic are substances that do not easily break down, instead they build up in nature and in e.g. the fatty tissue of mammals, with a potential to cause serious and long-term irreversible effects. Part of the REACH Substances of Very High Concern.
Persistent	A persistent substance will not break down or degrade in humans, animals or nature. This means that they will remain for a very long time once produced.
REACH	REACH is the Regulation for Registration, Evaluation, Authorisation and Restriction of Chemicals, the EU chemical regulation entered into force in 2007.
Risk	Risk is the combination of "Hazard", probability and exposure. See also "Hazard".
SIN List	The "Substitute It Now" List of Substances of Very High Concern identified by ChemSec in accordance with REACH criteria. A ChemSec project aiming to speed up the REACH implementation process and provide a substitution tool for companies.
Substance of Very High Concern	Substances of Very High Concern (SVHCs) are the most hazardous substances according to article 57 of REACH. These are substances that are Carcinogenic, Mutagenic and toxic to Reproduction (CMR), Persistent, Bioaccumulative and Toxic (PBT), very Persistent and very Bioaccumulative (vPvB) or substances of equivalent level of concern.
SVHC	See Substances of Very High Concern.
Toxic for Reproduction	A substance which is toxic to reproduction will impair the ability to produce offspring or cause irreversible harm to the offspring itself.
Very Bio-accumulative	A very bio-accumulative substance accumulates to an even higher degree in the body than "ordinary" bio-accumulative substances.
Very Persistent	A very persistent substance persists to an even higher degree in nature than "ordinary" persistent substances.
Working List	ECHA prioritises a number of substances from the Candidate List and works actively to put them through Authorisation.
vPvB	vPvBs are substances that are very Persistent and very Bioaccumulative but are not necessarily toxic as defined today. However they persist in the environment and accumulate in the food chain for such a long period of time that they are also considered to be Substances of Very High Concern according to REACH.

www.chemsec.org

ChemSec August 2018