

MANUAL FOR INVESTIGATION OF HPV CHEMICALS

CHAPTER 1: PROCEDURES, INCLUDING THE USE OF THE ELECTRONIC DISCUSSION GROUPS AND THE ON-LINE HPV DATABASE

ANNEX 3 : SYNERGIES BETWEEN THE CEPA 1999 PROGRAMME AND THE OECD HPV CHEMICALS PROGRAMME¹

SYNERGIES

1. While the activity on existing chemicals under CEPA 1999 and the activity within the OECD HPV Chemicals Programme share similar objectives and procedures, there are significant differences in terms of outputs and documentation. A detailed comparison of procedures and outcomes can be found in the Annex. Based on this comparison, it can be concluded that the output of the OECD HPV Chemicals Programme contributes to the CEPA 1999 programme at many stages, in particular in the processes of data collection, hazard characterisation, and recommendations, as outlined below.

Data Collection

2. After a company or consortium of companies agrees to “sponsor” a chemical or category of chemicals under the OECD HPV Chemicals Programme, the first step is to assemble the Screening Information Data Set (SIDS). The SIDS Dossier contains all the robust study summaries (RSS) necessary to perform an initial hazard assessment within the OECD HPV Chemicals Programme.

3. The SIDS Dossier can also serve as the basis for the categorisation and screening assessment under CEPA 1999. Indeed:

- The data requirements are covered to a large extent by the OECD SIDS test battery (see also section 3 and 4 of the Annex).
- Consistent guidance is applied when using the chemical category approach or (Q)SARs (see also section 6 of Annex 2).
- New information is generated using the OECD Test Guidelines.

4. On the contrary, RSS are not produced for all SIDS endpoints under CEPA 1999, but only for the most relevant endpoints for categorisation and screening assessment, i.e. degradation, bioaccumulation, aquatic toxicity, critical endpoint(s) for mammalian toxicity.

Hazard Characterisation

5. The format and content of screening assessments will vary, depending upon the priority of consideration of the substance based on potential for exposure and degree of hazard though broadly follows those of the SIAR. The most prominent differences are:

¹ This document was prepared by the OECD Secretariat based on the agreements reached in the OECD Existing Chemicals Programme up to February 2008

- The hazard assessment part of a CEPA 1999 screening assessment focuses only on the most critical effects (see also section 7 of the Annex).
- The CEPA 1999 screening assessment contains a quantitative exposure assessment and risk characterisation.

6. As a consequence, for substances where the SIDS Dossier and SIAR have been prepared for and agreed at a SIAM, the Canadian authorities can extract the relevant part of the SIAR for the preparation of the focussed hazard characterization in a screening assessment. To elaborate a SIAR based on a CEPA 1999 screening assessment, it would be necessary to add a number of details to the description of the study results, i.e. to assess in detail the less relevant endpoints of the SIDS.

Recommendations

7. The recommendation of the SIAR is comparable to the outcome of the CEPA 1999 categorisation with the exception that exposure is considered qualitatively from an environmental perspective for the former and based on persistence and bioaccumulation for the latter (see also section 3 and 7 of the Annex). The recommendations from the SIAR can therefore be used to confirm or review the categorisation results. It cannot be used *in lieu* of the recommendation from the CEPA screening assessment, which is based on a quantitative risk estimate.

8. Similarly, the results of the CEPA 1999 categorisation or alternatively the outcome of the screening assessment can help identify substances for which there is a need for an international assessment via the OECD Programme.

Conclusion

9. In conclusion, the SIDS Dossier and SIAR can be used as background documents for the focussed hazard characterization included in a CEPA 1999 screening assessment. The recommendation from the SIAR can be broadly compared with the results of the CEPA 1999 categorisation exercise. Conversely, the screening assessments from the CEPA 1999 programme cannot be directly used within the OECD programme, without significant revision of the current requirements concerning documentation on hazard characterization. Furthermore, the output of both categorization and screening provide considerable additional characterization of potential for exposure based on robust use profiling.

FURTHER INTEGRATION OF THE TWO PROGRAMMES

10. As demonstrated above and in the Annex, the products from the OECD HPV Chemicals Programme can be used to a large extent in the preparation of the focussed hazard components of the screening assessments under CEPA 1999. The reverse is not true. But whereas the OECD HPV Chemicals Programme will have assessed at best 1500 substances by the end of 2010, the Canadian Authorities have already categorised 23000 substances and are preparing to draft screening assessments for up to 2600 substances over the next few years, the extent of complexity of which will be tailored to priority based on potential for exposure and degree of hazard. It would therefore be worthwhile to investigate ways to better use the results from CEPA 1999 within the OECD programme.

11. Alternatively, it will be investigated whether Canada's contribution to the HPV Chemicals Programme can be increased through the development in parallel by Canadian authorities in collaboration with ICCA of SIDS Documents and CEPA 1999 screening assessments. This activity could focus on HPV chemicals which are also considered to be priorities under CEPA 1999. This would ensure that the hazard assessment part of the screening assessment is based on international agreements and would benefit

Canada by getting international recognition for their work (e.g. as a contribution to SAICM) and would allow Canada to fulfil its international commitments. In such a case, the following procedure could be envisaged:

- The Canadian authorities in collaboration with a consortium of companies or a consortium of companies alone, could develop the SIDS Dossier and the SIAR. The background information used for the CEPA 1999 categorisation would be used to elaborate the SIDS Documents.
- The corresponding quantitative exposure assessment for the CEPA 1999 screening assessment could be prepared by the Canadian Authorities in parallel. This would ensure that additional data requirements for the screening assessment are identified early in the process.
- The SIDS Documents can be submitted at any time to the OECD HPV Chemicals Programme by the Canadian authorities in collaboration with the industry consortium or directly by industry.
- After review of the SIDS Documents and endorsement of the conclusions and recommendations by the OECD member countries, the Canadian authorities in collaboration with the industry consortium or directly the industry consortium would prepare the final SIDS Documents for publication by UNEP Chemicals.
- The Canadian Authorities could then extract the relevant hazard assessment parts from the SIDS Documents for the CEPA 1999 screening assessment and finalise the risk characterisation.

12. Other procedures and mechanisms could also be envisaged. Depending on the possible evolution of the OECD HPV Chemicals Programme, further synergies might be identified.

ANNEX : TECHNICAL SIMILARITIES BETWEEN CANADA'S CEPA 1999 PROGRAMME AND THE OECD HPV CHEMICALS PROGRAMME

1. Introduction

The Canadian Environmental Protection Act, 1999 (CEPA 1999) required systematic consideration of approximately 22400 existing substances to set priorities for environment and human health assessment. This process, called categorization, was concluded in 2006 and 4300 substances were identified as requiring further work.

For many of the identified substances, a screening assessment will be conducted by Environment Canada and Health Canada. These screening assessments set the stage for either no further action, further in-depth assessment or risk management. They typically involve focused comparison of critical data on exposure and effect. These assessments involve an iterative approach where, in the first instance, upper bounding estimates of exposure are compared with lowest reported effect levels. The extent of assessment is limited to that necessary to determine that a substance is not a priority for risk management. For substances where margins of exposure are small or for which it is assumed that there is some probability of harm at all levels of exposure for critical effects, comparisons of exposure and effects are refined increasingly taking into account weight of evidence for hazard and mode of action, as necessary, to permit meaningful conclusion and provision of advice for next stages. Data which would permit more definitive conclusion are also identified.

2. Scope

The CEPA 1999 programme addresses all existing chemicals on the Canadian DSL, independent of the production or import volume and applies a rigorous priority setting scheme (categorisation) to identify those chemicals that need further assessment.

The OECD programme focuses on HPV chemicals. Furthermore the OECD Programme aims at obtaining OECD-wide agreed initial hazard assessments and making recommendations on the priority for further work, whereas the Canadian screening assessments aim at evaluating the risk of chemicals. While a Canadian screening assessment also contains a hazard assessment, the level of detail and the focus thereof is dependent on the exposure assessment. These screening assessments focus initially on conservative assessments of hazard or effect levels for critical endpoints and upper-bounding estimates of exposure.

In conclusion: the scope of the two programmes is different. Nevertheless, the assessments produced in both programmes contain a hazard assessment component.

3. Priority setting

Within the OECD HPV Chemicals Programme, the only priority setting is based on production/import volume. Any chemical being produced or imported in at least one member country at quantities exceeding 1000 tonnes/year is a candidate for an initial hazard assessment.

Under the CEPA 1999 programme, existing substances are categorized, using an elaborate risk-based priority setting scheme (categorisation), for both human health and environmental aspects. A summary of the categorisation procedure and criteria is outlined in Appendix I. In many aspects, the criteria are comparable to the criteria used in the OECD HPV Chemicals Programme to decide whether a substance should be considered for post-SIDS work by member countries (see section 7 below as well as Appendix III).

In conclusion: The priority setting schemes between the two programmes are significantly different. Nevertheless, both programmes use similar criteria for taking decisions regarding further work, although at different stages in the process. The recommendation from the SIAR is based on criteria similar to those used for the CEPA 1999 categorisation, though for environmental effects, this is based on qualitative consideration of exposure combined with persistence, bioaccumulation and aquatic toxicity in the OECD HPV Chemicals Programme versus persistence and bioaccumulation under CEPA.

4. Information requirements and responsibilities

While the information requirements in the OECD HPV Chemicals Programme are defined in the Screening Information Data Set [SIDS], there are no strictly defined information requirements for existing substances in the Canadian programme. The categorisation was performed with existing information. Data gaps were filled by using (Q)SARs and data from analogues, and in some cases, experimental studies to meet criteria that could not be obtained by (Q)SARs and analogues. For screening assessments, for substances which are considered priorities based on exposure, the Canadian authorities are requesting a dataset comparable to the SIDS. Therefore both programmes address the same endpoints.

In conclusion: the information requirements in both programmes are different. Nevertheless, both programmes address the same endpoints.

Regarding the differences in responsibilities, a large part of the work under the OECD Programme which results in draft SIDS Dossiers and SIARs is carried out in partnerships between consortia of industry companies and OECD Member Countries. Furthermore direct submissions by industry to the programme are possible. Within CEPA 1999, the assessment work is carried out by the government (Environment Canada & Health Canada). Draft assessments are posted for public comment and the chemical industry as well as other stakeholders may submit additional information for refining the assessment. Furthermore, OECD is a voluntary cooperative programme, whereas the Canadian screening assessments are carried out within a mandatory legislative programme.

In conclusion: the division of responsibilities between authorities and industry at the drafting stage is similar in the two programmes, though weighted to Government under CEPA versus industry in the OECD programme. Elaboration of SIDS Documents by industry on selected moderate CEPA priorities to the OECD programme would contribute to achieving additional balance in responsibilities.

5. OECD and CEPA 1999 Procedures

The current OECD programme, involves the following main steps, when input from the International Council of Chemical Associations [ICCA] initiative is used:

- Consortium of ICCA Member Companies is formed;
- ICCA Member Companies develop a SIDS Dossier and a SIAR;
- A sponsor country reviews the SIDS Dossier and the SIAR, or the consortium submits the SIDS Dossier and the SIAR directly to the SIDS Initial Assessment Meeting [SIAM];
- After possible modifications, the SIDS Dossier and the SIAR is submitted to the SIAM by the sponsor country;

- The SIAM discusses and agrees on the SIDS Dossier and SIAR, including the conclusions of the initial hazard assessment, recommendations on priority for further work and the rationale therefore.
- OECD governments endorse this.

The comparable steps for elaborating screening assessments under CEPA 1999 would be:

- Through categorization a chemical is identified as requiring further attention;
- Environment Canada and Health Canada draft the screening assessment for the environment and for human health, which is then reviewed via an internal and external peer-review process.
- The draft screening assessment, including the recommendation regarding further work, is released for public review for a period of 60 days;
- Based on the submitted comments, Environment Canada and Health Canada revise the screening assessment and publish it;

In conclusion: responsibilities under the OECD and CEPA 1999 processes are different, weighted to Government under CEPA versus industry in the OECD programme. Elaboration of SIDS Documents by industry on selected moderate CEPA priorities for the OECD programme would contribute to achieving additional balance in responsibilities, and meeting objectives both domestically and internationally.

6. Formation and use of Chemicals Categories

The principles for the formation and use of chemical categories within the CEPA 1999 programme are similar to those defined in the OECD *Manual for Investigation of HPV Chemicals*. No separate guidance document has been developed.

Conclusion: The principles for the formation and use of chemical categories are the same in the two programmes.

7. The OECD SIDS Dossier & SIAR and the CEPA 1999 screening assessment

The SIDS Dossier includes all the relevant background information for understanding the SIDS Initial Assessment Report and as such is intended to provide a common OECD information package for any national or regional work to be carried out on the substance. The CEPA 1999 screening assessment reports do not contain Dossiers with Robust Study Summaries of all the relevant studies. Instead, the screening assessment focuses for human health and the environment on the most relevant endpoint (key study results) and bases the assessment on those endpoints. A detailed description of the key study results is included in the main body of the screening assessment and robust study summaries are prepared for the critical studies. Although both programmes use the same concept of key study, robust study summaries (RSS) are developed in the CEPA 1999 screening assessments only for a very limited number of endpoints (usually one human health endpoint and one environment endpoint). It should be noted nevertheless, that for the categorisation exercise, Environment Canada published 2800 Robust Study Summaries for substances on the DSL on the endpoints persistence, bioaccumulation and inherent toxicity to non-humans. Unfortunately these RSS do not follow the OECD Harmonised Templates.

The SIAR is a SIDS Initial Assessment Report and as such is intended to provide an OECD-wide agreed initial hazard assessment and recommendation on the priority for further work, based on hazard conclusions and qualitative consideration of exposure. The latter is a common OECD starting point for decisions on national, regional or international work to be carried out on the substance.

The objective of a CEPA 1999 screening assessment is to consider in a preliminary fashion whether or not a substance is likely to pose a risk to human health or the environment. It is part of an overall strategy designed to focus action on those compounds that pose the greatest risks to the health or the environment. The focus of the screening assessment is limited principally to the information that is considered most critical in assessment of exposure to a substance and its related effects. It entails an initial look at this information only, thereby enabling a large number of existing substances to be evaluated more quickly and efficiently. If needed, some substances will undergo a more in-depth assessment of the risks, but only after a screening assessment has been conducted. Screening assessments are conducted to determine if a substance meets the criteria set out under section 64 of CEPA 1999 - that is, whether or not a substance "... is entering or may enter the environment in a quantity or concentration or under conditions that

- have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
- constitute or may constitute a danger to the environment on which life depends; or
- constitute or may constitute a danger in Canada to human life or health."

A screening assessment report is a brief (e.g., typically 4–8 pages) summary of the information on identity, production and uses, sources and levels of exposure and effects. The report also outlines the objective of the screening assessment, the approach to decision-making and conclusions and transparently delineates the databases that serve as the basis for determination of the critical effect levels and upper-bounding exposure estimates. An explicit summary is included in the text, and more detailed information that constitutes the basis for estimations of exposure and assessment of effects is presented in accompanying tables. A full reference list is included to ensure transparency of the identified database. Appendix II compares the formats of the screening assessment format and the SIAR. It follows that:

- the overall structure of both documents is similar;
- the screening assessment is less structured and contains less supporting details than the SIAR;
- the screening assessment focuses for each assessment type (Environment / Health) on the critical studies, i.e. those studies having resulted in effects that are likely to drive any risk assessment;
- the screening assessment contains a quantitative exposure assessment and risk characterisation.

In conclusion: The hazard assessment part of the screening assessment can be easily extracted from a SIAR, focusing on the critical studies and the conclusions. On the other hand, SIDS Documents can be written using the screening assessment, by adding a SIDS Dossier with Robust Study Summaries and for the SIAR, adding a number of details to the description of the study results for endpoints considered non-critical in a CEPA context.

7. Recommendations

The SIAR contains a recommendation regarding the priority for further work in national/regional/international programmes. Section 5 of Chapter 5 of the OECD Manual for Investigation of HPV Chemicals states that:

“The ‘Recommendation’ section of the SIAR proposes one of two possible statements regarding the need for further work on the chemical. The recommendation options, based on the conclusions and their context, are either that:

- the chemical is currently of low priority for further work ; or
- the chemical is a candidate for further work“ (in national/regional/international programmes)

The criteria for making recommendations can be found in Appendix III. These criteria are risk-based to some extent, as qualitative information on exposure is taken into account.

A CEPA 1999 screening assessments results in one of the following outcomes as prescribed in CEPA 1999 under Section 77(2):

- no further action is taken at this time in respect of the substance, if the screening assessment indicates that the substance does not pose a risk to the environment or human health;
- the substance is added to the CEPA Priority Substances List in order to assess more comprehensively the risks associated with the release of the substance, if the substance is not already on the List; or
- it is recommended that the substance be added to the List of Toxic Substances in Schedule 1 of CEPA, substances on Schedule 1 can be considered for regulatory or other controls.

These recommendations are based on a quantitative risk assessment.

In conclusion: in the CEPA 1999 programme, the decision whether a substance is a candidate for further work is based on the potential quantitative risk of a substance, whereas in the OECD programme the recommendation for further work is mainly based on the hazard assessment, taking qualitative exposure information into account. The recommendation from the SIAR could be used within the categorisation activity under CEPA, but not to derive the recommendation based on a screening assessment.

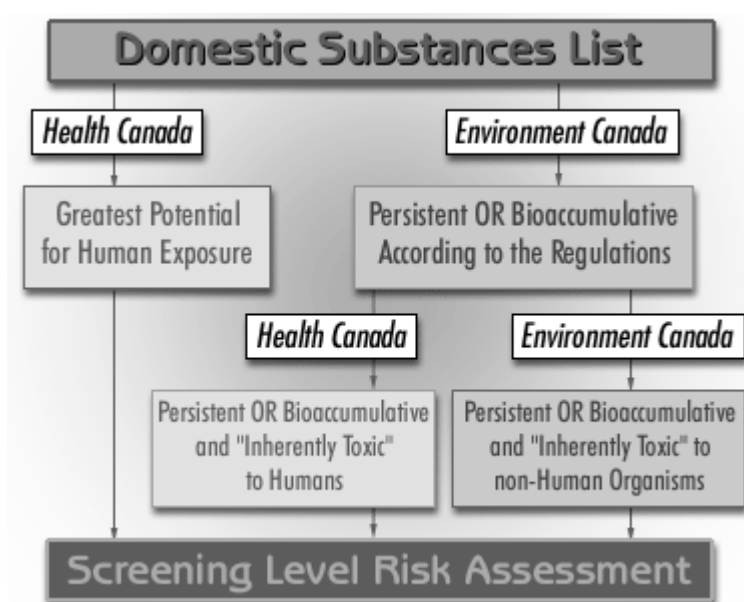
APPENDIX I : PROCESS AND CRITERIA FOR THE CEPA 1999 CATEGORISATION

The legislative requirement for the categorization exercise as outlined under CEPA 1999 was to identify those chemicals that are:

- **inherently toxic** to humans or to the environment and that might be:
persistent (take a very long time to break down), and/or
bioaccumulative (collect in living organisms and end up in the food chain)
- substances for which there was **greatest potential for exposure of humans**.

The following chart shows how Canada completed categorization.

INTEGRATED FRAMEWORK



The approach to consideration of the different criteria is summarized below.

Environmental Components

Persistence (P)

Persistence refers to the length of time a substance resides in the environment. The persistence of a substance is commonly measured by its half-life, i.e., the time required for the quantity of a substance to diminish or degrade to half of its original amount in a particular environmental medium. individual media (e.g., water, air, soil, sediment, groundwater, marine waters). The persistence of a substance in each of the relevant media (i.e., soil, water, or air) must be evaluated and compared against the categorization half-life criteria, as described in Table 1.

Table 1. Criteria for persistence

Persistence
<u>Medium Half-life</u> Air \geq 2 days Water \geq 182 days Sediment \geq 1 year Soil \geq 182 days

Substances that have the potential to be transported to remote areas of the globe are considered persistent, and the relevant evidence for long-range transport (LRT) will be taken into consideration in determining the persistence of substances.

Bioaccumulation (B)

Bioaccumulation is a general term describing a process by which substances are accumulated in organisms directly from exposure to water and through consumption of food containing the substances. The regulations express preference for bioaccumulation factors (BAFs) over bioconcentration factors (BCFs) or log octanol-water partition co-efficient (log K_{ow}). The bioaccumulation potential of a substance must be evaluated and compared against the categorization criteria described in Table 2.

Table 2. Criteria for bioaccumulation

Bioaccumulation
BAF \geq 5,000 or BCF \geq 5,000 or Log K _{ow} \geq 5

Bioaccumulation factor (BAF) refers to the ratio of the concentration of a substance in an organism to the concentration in water, based on uptake directly from the surrounding medium and food.

Bioconcentration factor (BCF) refers to the ratio of the concentration of a substance in an organism to the concentration in water, based only on uptake directly from the surrounding medium.

The octanol-water partition co-efficient refers to the ratio of distribution of a substance in octanol compared to that in water.

Inherent Toxicity (iT) to non-human organisms

The term inherent toxicity has been introduced and used under CEPA 1999 to distinguish this criterion from the term CEPA “toxic,” which is defined under section 64. Inherent toxicity refers to the hazard a substance presents to an organism. It is demonstrated by the concentration of a substance that

produces a toxic effect in an organism, tested under laboratory conditions or in other studies. Environment Canada prefers to use acute toxicity studies over chronic toxicity studies because more studies and QSAR models are available for acute endpoints. This makes it easier to directly compare the properties of a large number of substances.

The categorization for inherent toxicity to non-human organisms is based primarily on aquatic toxicity information and numerical criteria, as described in Table 3.

Table 3. Criteria for acute and chronic toxicity to aquatic species (algae, invertebrates, fish)

Exposure Duration	Criteria
Acute	LC ₅₀ (EC ₅₀) ≤ 1 mg/L
Chronic	NOEC ≤ 0.1 mg/L

LC₅₀ represents the concentration of a substance in water causing death on 50% of the experimental organisms in the water.

EC₅₀ represents the concentration of a substance in water inducing toxic effects on 50% of the experimental organisms.

NOEC, the non-observed-effect concentration, refers to the highest concentration of a substance at which there is no adverse effect observed in a toxicological study.

Human Health Components

In order to identify priorities for human health in a risk-based framework, potential for exposure and hazard for all substances on the DSL were considered. The potential for persistence or bioaccumulation to additionally contribute to exposure for certain subsets of substances — namely, those that are organic — was also taken into account, as illustrated in the diagram above.

Several tools were developed to iteratively identify priorities and these are described in the table below:

Tools for Health-Related Components of DSL Categorization

Exposure
<ul style="list-style-type: none"> • SimET (Relative ranking of all DSL substances based on submitters [S], quantity [Q] and expert ranked use [ERU])
Hazard (High or Low)
<ul style="list-style-type: none"> • SimHaz (Identification of high- or low-hazard compounds by various agencies based on weight of evidence) • ComHaz (Hierarchical approach for multiple endpoints and data sources [e.g., quantitative structure-activity relationships (QSARs)], including weight of evidence)

Greatest Potential for Human Exposure

Potential exposure of the general population to existing substances is considered from all routes (that is, inhalation, ingestion and contact on the skin) and sources (that is, ambient and indoor air, foodstuffs, breast milk for infants, soil and household and consumer products). The purview of CEPA 1999 is restricted to the general environment, and, as a result, occupational exposure is not considered.

A simple exposure tool (SimET) was developed which enabled the relative ranking of all entries on the DSL with respect to exposure potential based on the limited information that was submitted for each during the compilation of the DSL. This included the number of submitters, the quantity in commerce and use codes. The tool includes an index of potential human exposure in the general environment and through consumer products based on expert ranking of the use codes. Based on each of the three parameters (Table 4), substances were then grouped into three principal categories in relation to potential for exposure — namely, those with “greatest” (GPE), “intermediate” (IPE) and “lowest” (LPE) potential for exposure.

Table 4. Criteria for Greatest (GPE), Intermediate (IPE) and Lowest Potential for Exposure (LPE)

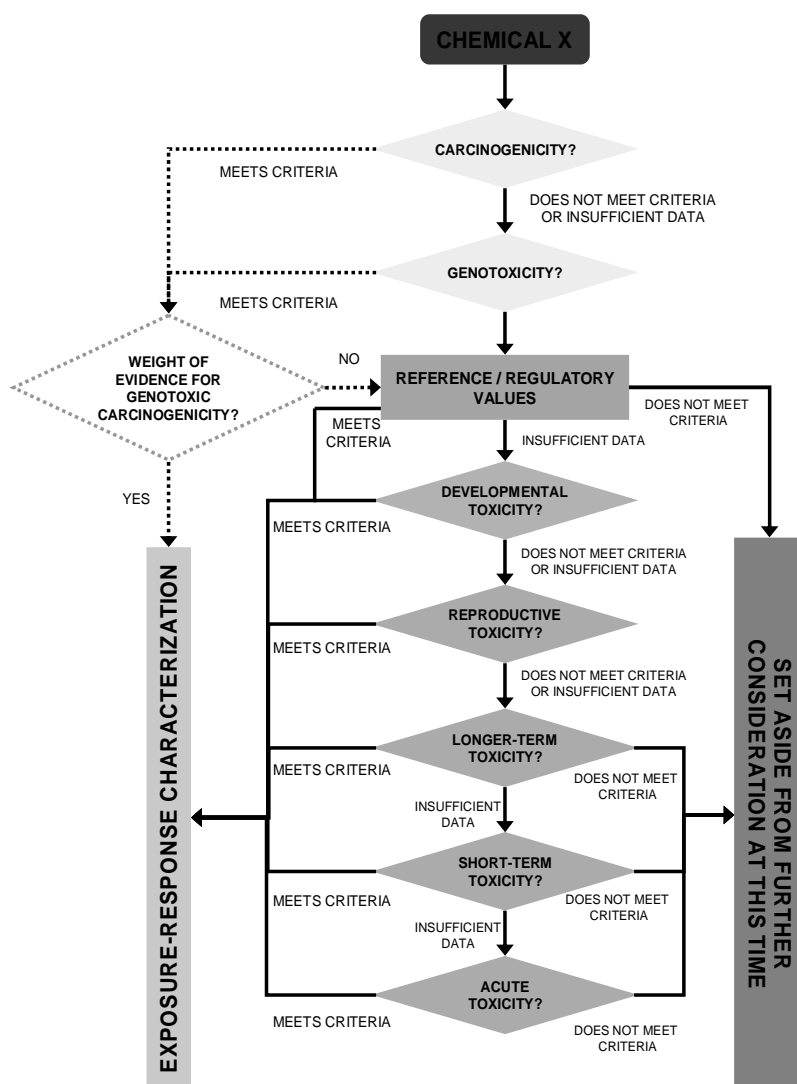
	Quantity (kg/year)	Number of submitters	Sum of the expert ranked use code indices
GPE	>100 000	Top 10%	Top 10%
IPE	>10 000	All	Top 30%
LPE	All	All	All

Inherent Toxicity to humans

A simple tool (SimHaz) was developed to identify those substances on the DSL, considered to present either high or low hazard to human health based on formalized weight of evidence criteria and/or peer review/consensus of experts. This tool has been developed through extensive compilation of hazard classifications of Health Canada and other agencies and consideration of their robustness based on availability of transparent documentation of both process and criteria.

Endpoints included in the high-hazard component of SimHaz are those that may be induced by modes of action for which there is a probability of harm at any level of exposure. These include carcinogenicity, mutagenicity, reproductive and developmental toxicity.

Additional low hazard substances were identified in categorization through the application of first stage considerations of a complex hazard tool. This involved hierarchical comparison of identified data, results of quantitative structure activity analyses against endpoint-specific criteria as illustrated in the following figure:



The qualitative and/or quantitative criteria for each of the endpoints included in the first stage of ComHaz are presented in Table 5.

Table 5. ComHaz Endpoint-Specific Qualitative and Quantitative Criteria

Endpoint	Type of criteria	Sources of information	Description of criteria
Carcinogenicity	Qualitative	Data or (Q)SAR	First hit, weight of evidence
Genotoxicity	Qualitative	Data or (Q)SAR	First hit, weight of evidence
Regulatory/reference values	Quantitative	Assessments from international/national agencies	Oral: ≤ 0.1 mg/kg bw per day Inhalation: ≤ 0.4 mg/m ³ Dermal: NA

Endpoint	Type of criteria	Sources of information	Description of criteria
Developmental toxicity	Quantitative	Data	Oral/dermal: LO(A)EL \leq 270 mg/kg bw per day NO(A)EL \leq 90 mg/kg bw per day Inhalation: LO(A)EC \leq 810 mg/m ³ NO(A)EC \leq 270 mg/m ³
	Qualitative	(Q)SAR	Sufficient positive evidence ^a
Reproductive toxicity	Quantitative	Data	Oral/dermal: LO(A)EL \leq 30 mg/kg bw per day NO(A)EL \leq 10 mg/kg bw per day Inhalation: LO(A)EC \leq 90 mg/m ³ NO(A)EC \leq 30 mg/m ³
Longer-term toxicity	Quantitative	Data or (Q)SAR (where appropriate)	Oral/dermal: LO(A)EL \leq 30 mg/kg bw per day NO(A)EL \leq 10 mg/kg bw per day Inhalation: LO(A)EC \leq 90 mg/m ³ NO(A)EC \leq 30 mg/m ³
Short-term toxicity	Quantitative	Data	Oral/dermal: LO(A)EL \leq 90 mg/kg bw per day NO(A)EL \leq 30 mg/kg bw per day Inhalation: LO(A)EC \leq 270 mg/m ³ NO(A)EC \leq 90 mg/m ³
Acute toxicity	Quantitative	Data or (Q)SAR (where appropriate)	Oral/dermal: LD ₅₀ \leq 500 mg/kg bw Inhalation: LC ₅₀ \leq 1500 mg/m ³ IP injection: ^b LD ₅₀ \leq 219 mg/kg bw IV injection: ^b LD ₅₀ \leq 154 mg/kg bw

^a Substances that satisfy the ComHaz criteria for developmental toxicity based on quantitative structure–activity relationship (QSAR) model predictions are prioritized for the generation of data on developmental toxicity.

^b These routes of administration (intraperitoneal [IP] and intravenous [IV]) are considered only in the absence of data on more relevant routes (i.e., oral, dermal or inhalation).

For each endpoint, the substance-specific sources of information are also considered hierarchically. Acceptable assessments of international or national agencies and secondary reviews are consulted initially, followed by original study accounts. If relevant data from these sources are not identified or are insufficient, predictions of quantitative structure–activity relationship (QSAR) models, information on chemical substructures of concern and analogues or surrogates are considered subsequently.

ComHaz is health protective, with the comprehensive approach and conservative nature of the proposed endpoint-specific criteria ensuring high confidence that substances not meeting the criteria in application of the first stage do not present a hazard to public health.

APPENDIX II: SCREENING ASSESSMENT AND SIAR FORMATS

Screening Assessment format	SIDS Initial Assessment Report Format
<p>GENERAL STRUCTURE Assessment Type (Environment/ Health)</p>	<p>GENERAL STRUCTURE 1. Assessment Type (Environment/Health) 1.1. Sub-Assess Type (Hum/Aqu/Ter/Other/Init Ass.) 1.1.1. <i>Effect</i> <u>Endpoint</u> 1. Studies in Animals 1.1 In vitro [Requested to use tables] 1.2 In vivo 1.2.X route of administration [Requested to use tables] 2. Studies in Humans 3. Conclusions:</p> <p>Note: The order of “route of administration” and “studies in animals/humans” not consistent for all end-points</p>
<p>Screening Assessment Report Identity, Properties, Uses and Sources of Release/Exposure</p>	<p>OECD SIDS Initial Assessment Report 1. Identification of the substance and physical and chemical properties 1.1. Identification of the Substance 1.2. Purity/Impurities/Additives 1.3. Physical-Chemical properties 1.4. Category Justification</p> <p>2. General Information on Exposure 2.1 Production volume and use pattern 2.2.1. Sources of Environmental Exposure 2.3. Human Exposure</p>

Screening Assessment format	SIDS Initial Assessment Report Format
Fate, Exposure and Effects	2.2 Environmental Exposure and Fate 2.2.2. Photodegradation 2.2.3. Stability in Water 2.2.5. Biodegradation 2.2.4. Transport Between Environmental Compartments 2.2.6. Bioaccumulation 4. Hazard to the Environment 4.1. Aquatic Effects 4.2. Terrestrial Effects 4.3. Other Environmental Effects 4.4. Initial Assessment for the Environment
Assessment of Risk (Environment)	
Exposure Assessment, Hazard Characterisation and Risk Evaluation (Human Health)	3. Human Health Hazards 3.1 Effects on Human Health 3.1.1 Toxicokinetics metabolism and distribution 3.1.2. Acute toxicity 3.1.3. Irritation 3.1.4. Sensitisation Respiratory system 3.1.5. Repeated dose toxicity 3.1.6. Mutagenicity 3.1.7. Carcinogenicity 3.1.8. Toxicity for reproduction Effects on fertility Developmental Toxicity 3.2 Initial Assessment for Human Health
Proposed Conclusion	5. Recommendations SIDS Initial Assessment Profile [SIAP]
Uncertainty	

**APPENDIX III: RECOMMENDATIONS IN THE OECD HPV CHEMICALS PROGRAMME
[EXTRACT FROM CHAPTER 5 OF THE MANUAL FOR INVESTIGATION OF HPV
CHEMICALS]**

[...]

The 'Recommendation' section of the SIAR proposes one of two possible statements regarding the need for further work on the chemical. The recommendation options, based on the conclusions and their context, are either that:

- the chemical is currently of low priority for further work; or
- the chemical is a candidate for further work.

[...]

The recommendation is usually based on two aspects of the substance: its hazard profile and its exposure potential. The criteria described in the Harmonized Integrated Hazard Classification System for Chemical Substances and Mixtures [GHS, see: <http://www.oecd.org/env/classify>] may be used as a general background reference for judging the hazard of a substance for the purpose of deriving consistent recommendations for substances assessed in the OECD HPV Chemicals Programme. It should be kept in mind that no classification is performed in the context of the OECD HPV Chemicals Programme. Guidance on how to derive recommendations can be proposed for different specific situations as outlined below.

Non-hazardous substances

For non-hazardous substances, the recommendation would normally be that the substance is of low priority for further work. However, depending on the exposure profile and information on the actual levels of exposure, a recommendation for further work may be warranted.

Hazardous substances with a low exposure potential

For hazardous substances, the identified environmental and human hazards need to be put into context using the available exposure information. If the exposure potential is low, e.g. for closed system intermediates, or because appropriate risk management measures are being applied, it can often be concluded that the chemical is of low priority for further work.

In the refocused SIDS programme, exposure information from the Sponsor country is sufficient to fulfil the SIDS elements. Therefore it can be difficult to decide on a recommendation due to the uncertainty of the exposure situation in other member countries. The uncertainty behind the recommendation can be highlighted. For example if based on the information available to the Sponsor country a hazardous substance is used solely as a chemical intermediate, the recommendation could be that the substance is currently of low priority for further work. The uncertainty behind the recommendation should be highlighted by stating that the recommendation is based on limited exposure information and that further work might be necessary in member countries with a different exposure situation or where no information is available. A prerequisite for basing the recommendation on anticipated low exposure is that the extent of the available exposure information is described in a very transparent manner in the SIAR as well as in the SIDS Profile.

Hazardous substances with a high exposure potential

A hazardous substance with a high exposure potential will normally be a candidate for further work (for exceptions, see “Other situations” below). For substances which are candidates for further work, the post-SIDS work expected should be clearly described and the reasons why such work is needed should be outlined. Examples of specific further work recommended could include additional exposure information gathering, in-depth risk assessment, exposure reduction measures or post-SIDS testing.

Some hazards are specifically relevant in the context of recommending that a substance is a candidate for further work. For hazards to human health, these would be hazards related to severe irreversible effects or with no or very low thresholds:

- acute toxicity (e.g. LD50 in rodents \leq 300 mg/kg)
- eye/skin corrosion
- sensitisation (skin, respiratory)
- mutagenicity
- carcinogenicity
- reproductive toxicity
- specific target-organ toxicity after single exposure and/or repeated exposure.

For hazards to the aquatic environment these would be hazards related to acute toxicity (e.g. L(E)C50 \leq 100 mg/l) in conjunction with a high bioaccumulation potential or lack of rapid degradation as well as severe acute toxicity (e.g. L(E)C50 \leq 1 mg/l) independent of biodegradation and bioaccumulation.

Some identified hazards are less relevant in the context of recommending that a substance is a candidate for further work. For hazards to human health, these would be hazards related to reversible, transient and non-lasting effects (e.g. dermal irritation: reversible effects in dermal tissue; eye irritation). The same would apply if the acute toxicity of the chemical is so low that it may become evident only at high exposure levels, which are not reached under normal conditions of manufacture or use (e.g. LD50 in rodents > 300 mg/kg). For hazards to the aquatic environment, these would be hazards related to acute toxicity which may become evident only at higher exposure levels (e.g. L(E)C50 > 1 mg/l), which are usually not reached under normal conditions of manufacture or use in conjunction with a low bioaccumulation potential and rapid degradation.

Substances for which only these “lesser hazards” (paragraph 8) have been identified, a recommendation for further work might not be warranted. A brief narrative should explain the rationale that supports the recommendation for low priority for further work, according to the reasons outlined above.

Independent of the recommendation-making process in the OECD HPV Chemicals Programme, there are exposure scenarios where hazards which are considered to be less relevant when recommending further work may be expressed e.g. use of aerosols in uncontrolled conditions, during sampling of enclosed systems. It is therefore indispensable that these “lesser hazards” are flagged so that they can be noted by chemical safety professionals and users.

Other situations

Internationally agreed classification criteria do not exist for some hazards, e.g. neurotoxicity, or immunotoxicity. There may therefore be cases when a recommendation for further work for human health is warranted, despite the fact that the substance does not pose a hazard according to the current classification criteria. In the same way, for the environment, the GHS only provides guidance on identifying hazards for the aquatic environment. Further work may also be recommended for substances which pose a hazard to the terrestrial or benthic environment or which have potential for adverse effects on the atmosphere such as ozone depletion or which have a potential for endocrine disruption. Also for substances which show severe chronic toxicity in long-term aquatic toxicity tests, further work could be recommended. Furthermore, there may be cases where further work would be recommended for very persistent and bioaccumulative substances for which available data do not show acute or chronic toxicity. In each of these cases, a scientific justification is to be given on a case-by-case basis.

There may be cases where high exposure suggests a need for post-SIDS testing in the absence of definite information regarding hazards. Further work could be recommended for example when the properties of a substance indicate a high potential for exposure to soil or sediment but there is no information available on its toxicity to soil or sediment dwelling organisms or if hazardous properties towards soil or sediment organisms can be estimated.

A recommendation of low priority for further work can also be appropriate for hazardous substances if it is thought that labelling or other types of regulatory controls or management options are in place in OECD member countries that adequately address the hazard concern.

For any of these more specific situations, an explicit rationale for deriving the recommendation should be provided.