Health Canada Santé Canada

INTEGRATED FRAMEWORK FOR THE HEALTH-RELATED COMPONENTS OF CATEGORIZATION OF THE DOMESTIC SUBSTANCES LIST UNDER CEPA 1999

Questions & Answers

Health Canada

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Canada

List of Acronyms

ADI	acceptable daily intake
B	bioaccumulation/bioaccumulative
CEPA 1999	*Canadian Environmental Protection Act, 1999*
ComET	complex exposure tool
ComHaz	complex hazard tool
DSL	Domestic Substances List
FAO	Food and Agriculture Organization of the United Nations
GPE	greatest potential for exposure
HH	high hazard
IPE	intermediate potential for exposure
ITeco	inherently toxic to non-human organisms
IThuman	inherently toxic to humans
IUCLID	International Uniform Chemical Information Database
LPE	lowest potential for exposure
P	persistence/persistent
PSL	Priority Substances List
PSL1	First Priority Substances List
PSL2	Second Priority Substances List
QSAR	quantitative structure–activity relationship
RfD	reference dose
SAR	structure–activity relationship
SimET	simple exposure tool
SimHaz	simple hazard tool
TC	tolerable concentration
TDI	tolerable daily intake
TOXNET	Toxicology Data Network
TSCATS	Toxic Substances Control Act Test Submission
UVCB	substance of unknown or variable composition, complex reaction products and biological material
WHO	World Health Organization

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Questions & Answers

What is an existing substance under CEPA 1999?

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of the Environment and of Health to identify and determine which existing substances already in the environment pose a risk to human health and/or the environment. Existing substances include those in an inventory known as the Domestic Substances List (DSL), published in 1994.

The DSL is a compilation of about 23 000 substances used, imported or manufactured in Canada for commercial purposes between January 1, 1984, and December 31, 1986, at a quantity of greater than 100 kg per year. It includes discrete organic compounds, inorganic substances, organometallic substances, polymers and unknown or variable composition complex reaction products or biological material (UVCBs).

Substances that are not listed on the DSL are considered to be new to Canada.[1] The DSL is periodically amended to add substances that have met the listing requirements under the New Substances Notification Regulations of CEPA 1999.

How are existing substances selected for consideration under CEPA 1999?

CEPA 1999 specifies a number of ways in which existing substances can be identified for risk assessment. These are:

- categorization of substances on the DSL (Section 73);
- review of decisions of other jurisdictions (Section 75); and
- requests for addition to the Priority Substances List (PSL) made directly to the Minister of the Environment (Section 76).

The requirement to which this proposal relates (namely, categorization of substances on the DSL) represents, therefore, only one of the ways in which substances for which there is a need

[1] Substances new to Canada after December 31, 1986, are assessed under the new substances provisions of CEPA 1999.

for assessment of risk with respect to human health and/or the environment can be brought to the attention of the Ministers/departments.

What is categorization?

CEPA 1999 requires the Ministers, within seven years from Royal Assent of the Act, to categorize all substances on the DSL to identify those that may present, to individuals in Canada, the greatest potential for exposure (GPE) or those that are persistent (P) and/or bioaccumulative (B) and inherently toxic to humans (IThuman) or to non-human organisms (ITeco). A final list of substances identified by categorization will be published by the legally mandated deadline of September 13, 2006, and each substance on the list will subsequently undergo a screening assessment to consider potential risk to human health and the environment.

What is the role of the Minister of Health in categorization under CEPA 1999?

There are two aspects of the requirement to categorize substances on the DSL relevant to human health. Under Paragraph 73(1)(a) of CEPA 1999, GPE substances on the DSL must be identified. The Minister of Health is also responsible for identifying a subset of substances on the DSL that are priorities for risk assessment based on designation as IThuman.

How does this proposal contribute to Health Canada's responsibility for categorization under CEPA 1999?

This proposal describes an integrated framework for the identification and prioritization of substances for subsequent screening assessment based upon the requirements under Section 73 of CEPA 1999 to categorize substances on the DSL for GPE and IThuman. It addresses all substances through the application of simple and complex tools to assess human exposure and to identify potential hazards to human health.

This is the second proposal related to Health Canada's responsibilities for categorization of the DSL under CEPA 1999 that has been issued for public comment. Based on comments and information received in response to this proposal, and taking into account additional stages of refinement that continue to be developed, a finalized integrated framework for categorization for both GPE and IThuman will be developed. This framework and associated prioritized substances will be integrated with the approach and priorities for assessment from an environmental perspective prior to the 2006 mandated deadline for DSL categorization.

How does this proposal relate to an earlier one on "greatest potential for exposure" released by Health Canada in the autumn of 2003?

This proposal describes an integrated framework for the identification and prioritization of substances for subsequent screening assessment based upon the requirements under CEPA 1999 to categorize substances on the DSL for *both* GPE *and* IThuman.

The earlier proposal on GPE described an approach to the *first stage* of identification of priorities for further work in relation to the requirement under CEPA 1999 to categorize substances on the DSL for GPE *only*. This earlier proposal represents essentially the simple exposure tool (SimET) referred to in this proposed integrated framework.

By what process have these proposals been developed?

The proposed approach to designation of priorities for further consideration in this proposal and the associated maximal list have been developed based on the legislative construct of CEPA 1999, program experience and external input.

Stages of external input included peer input, consultation and review of technical components of the proposed methodology. These stages are distinct from those for consultation with stakeholders and the public.

Peer input includes interface internationally to access forward-looking peer-reviewed methodology addressing critical areas from all sectors and meetings to solicit information and comment at an early stage on the complex, progressive technical components. As the technical components are additionally developed, they are considered in peer consultation and review meetings, which are open to the public. Panels for these meetings are selected by an independent third party who also considers declarations related to potential conflict of interest. There is provision at the meetings for the submission or presentation of information from interested or knowledgeable parties, and meetings are advertised.

In addition to the various peer input and consultation sessions, there is continuing internal quality control auditing of proposed decisions regarding prioritization of individual compounds for further consideration in screening. There have also been several analyses based principally on the outcomes for the Priority Substances assessments of the predictivity or robustness of the tools described in the proposal for the integrated framework.

Critical elements of consultation on the Health Canada components of categorization distinct from those associated with peer review of technical components include public comment on robust proposals and associated preliminary summaries posted on the Existing Substances

Division web site (http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/index_e.html). Feedback at information sessions with all stakeholders is also critical.

What aspects of human exposure does Health Canada consider under CEPA 1999?

Health Canada assesses potential exposure of the general population to existing substances from all routes (that is, inhalation, ingestion and contact on the skin) and all possible 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.

What potential effects on human health does Health Canada consider under CEPA 1999?

Health hazards considered include the ability of substances to induce cancer, damage genetic material, cause birth and developmental defects, disrupt reproduction, affect the immune system, cause significant and long-term changes in behaviour or cause damage to individual organs or tissues (such as the lungs or liver). These hazards are evaluated based on studies of toxicity in mammals following short-, medium- and/or long-term exposures and clinical and epidemiological investigations in humans.

How does Health Canada identify relevant information on existing substances for consideration in priority setting and assessment of individual existing substances?

Relevant data for consideration in both priority setting and assessment are identified based on extensive, documented searches of available public sources, commissioned research studies and information submitted by stakeholders and others.

Why are so many tools necessary to fulfil the Minister of Health's responsibilities related to categorization of the Domestic Substances List under CEPA 1999? What are the benefits of this additional workload?

The Minister is looking at potential for exposure and health hazards for all 23 000 substances within a very short time frame, as a basis to identify priorities for further consideration in screening. The approach needs to address all of the very diverse groups of substances on the DSL (e.g., organics, inorganics, polymers, UVCBs) in a pragmatic and systematic fashion and draws maximally on the limited amount of information available for many. It must be sufficiently discriminating to set true priorities while being fully protective of human health. This necessitates development and use of tools of increasing complexity.

The simple exposure and hazard tools are applied first to address each of the 23 000 DSL substances, thereby generating a preliminary ("draft") list of substances identified for further consideration in categorization — i.e., the maximal list. Use of the more discriminating complex exposure and hazard tools in the subsequent stages enables a refining of the list, with the identification of true health priorities for both testing and assessment. Importantly, development and application of these tools are based on conservative assumptions in the absence of data, always erring on the side of protecting human health.

There are many benefits of developing both simple and complex exposure and hazard tools:

- This ensures the identification of true health priorities for subsequent screening assessment and data generation.
- It also avoids the bias towards the selection of only data-rich compounds for screening assessment, identifying priorities for both data generation and assessment.
- It addresses all groups of DSL compounds in a consistent fashion.
- Substances *identified* on the basis of exposure or hazard may then be *prioritized* for subsequent assessment on the basis of potential *risk* to human health.
- Application of the more complex tools in DSL categorization can minimize the requirements for information submission in the screening assessment phase.
- These tools are a critical component of ensuring efficiency in the subsequent screening assessment phase — particularly when dealing with non-human health priorities.
- These tools draw maximally on work completed in other jurisdictions and, owing to their robustness, are very likely to influence priorities internationally.

What are each of the tools, their strengths and limitations and differences between them?

The simple exposure tool (SimET) enables 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 includes 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.

The complex exposure tool (ComET) generates quantitative upper-bound exposure estimates based upon use scenario, physical-chemical properties and bioavailability. Compared with SimET, this tool requires more information to permit greater discrimination.

The simple hazard tool (SimHaz) enables the identification of high- or low-hazard compounds by various agencies based on weight of evidence. Though efficient, since it builds on the work of other jurisdictions, it is biased to identification of compounds that have been well tested.

The complex hazard tool (ComHaz) identifies potentially hazardous compounds using a hierarchical approach for multiple endpoints and data sources and includes additional, more discriminating stages to address weight of evidence. Though this tool is health protective (comprehensive) in nature and identifies substances that are priorities for both testing and assessment, it is rather resource intensive.

As noted above, the principal difference between the simple and complex tools relates to the level of information required for application of each and the associated degree of discrimination in identifying true priorities from an exposure or hazard perspective.

How do each of the tools contribute in defining priorities?

SimET was applied to all 23 000 substances to identify and rank priorities with respect to potential exposure. Each substance on the DSL was grouped into one of three broad categories in relation to its potential for exposure, based on application of specified criteria for each of the three parameters in SimET (namely, quantity, number of submitters and expert ranked use). These three broad categories are greatest potential for exposure (GPE), intermediate potential for exposure (IPE) and lowest potential for exposure (LPE). All substances within the GPE group and a subset of substances within the IPE group are considered priorities for additional consideration through application of the complex exposure and hazard tools.

ComET permits development of refined estimates of exposure based on information additional to that submitted in the compilation of the DSL. It is being applied to all GPE substances and a selected subset of IPE substances in part to further refine the list of priorities for consideration, but principally to determine highest priorities for early assessment following the 2006 deadline for categorization. The tool draws maximally on generic (i.e., non-substance-specific), publicly available information and transparently delineates assumptions and uncertainties. It is health protective, with conservative choices being made in the absence of data.

SimHaz was applied to all 23 000 substances on the DSL to identify those that are high or low hazard based on the weight-of-evidence hazard determinations of other agencies. The tool has identified high- and low-hazard substances in each of the GPE, IPE and LPE categories. Since SimHaz draws maximally and efficiently on weight-of-evidence hazard determinations of other agencies, it contributes to ensuring consistency of the DSL mandate with priorities in other jurisdictions. In general, however, SimHaz is biased to identification of substances for which there are a large number of data available. It is less relevant to the identification of substances for which testing is required.

ComHaz is being applied to all GPE substances and selected subsets of IPE substances to further refine the list of priorities for consideration. ComHaz involves the hierarchical consideration of

various sources of information for a range of toxicity endpoints. The first stage involves prioritization based on a conservative "first hit" approach for data and endpoints based on specified criteria; the next stage involves consideration of weight of evidence to further prioritize substances already captured on the basis of cancer or genotoxicity endpoints; and the final stage considers dose–response for critical endpoints for comparison with quantitative output of ComET. ComHaz identifies priorities for both testing and assessment, being applicable to both data-rich and data-poor substances.

How have persistence and bioaccumulation been taken into account in development of the integrated framework and draft maximal list?

Experience with profiling of thousands of substances on the DSL to meet the CEPA 1999 mandate for categorization indicates that P and B rarely, in themselves, identify priorities for either exposure or hazard from a human health perspective. Rather, use patterns and reactivity are more relevant parameters for identifying substances that are exposure- or hazard-based priorities for human health. For some types of substances, however — namely, those that are organic (including organic UVCBs) — depending on the use pattern, potential for exposure may be greater for substances that are P or B. In the integrated framework, the complex tools are proposed to be applied not only to all GPE substances, but also to organic substances (including UVCBs) that are IPE and have been determined by Environment Canada to be P and/or B and not ITeco. Organic UVCBs that are IPE for which determinations of P and/or B have not been made by Environment Canada have been included in the maximal list for further consideration. In this manner, the proposed framework more appropriately weights the often limited contribution of P or B to influence potential for human exposure in the context of more influential determinants such as use pattern. It is also conservative in the absence of the relevant information on P or B, retaining for additional consideration substances for which this information is not available.

How has it been ensured that the approach (i.e., integrated framework) has identified highest priorities and is protective of human health?

To the extent possible, the tools ensure consistency with other jurisdictions in identifying priorities, and their content and application are sufficiently robust to assure high confidence in the identification of true priorities for both testing and assessment from a human health perspective. The scientific robustness of the tools and individual nominations to the maximal list have been optimized through extensive technical input, critical review and testing, both internally and externally.

Development of these tools has drawn upon considerable technical expertise within Health Canada, acquired in meeting previous time-limited precedent-setting mandates for assessment

under CEPA 1999. In addition, the tools reflect comments received in review during several peer input and consultation sessions on the proposed methodology and continuing internal quality control auditing of proposed decisions regarding prioritization of individual compounds for further consideration in screening.

There have also been several analyses based principally on the outcomes for the Priority Substances assessments that verify the predictivity or robustness of both the exposure and hazard tools described in the integrated framework. Also, in all cases where relevant information has not been identified, conservative choices were made, retaining the substances for additional consideration.

How is information on individual substances identified for consideration in the simple and complex exposure and hazard tools?

Relative ranking by SimET relies solely on information submitted in the compilation of the DSL. Quantitative upper-bound exposure estimates developed in ComET are based on a comprehensive search strategy of public sources to efficiently identify relevant data on use and physical-chemical properties. Information from commissioned research studies and that submitted voluntarily or through mandated surveys by stakeholders and others are also taken into consideration.

The high- and low-hazard substance lists included in SimHaz were selected from hazard classifications from Health Canada and other agencies, taking into account the robustness of the classifications (including the transparency of the process and classification criteria), critical evaluation of data (including assessments of weight of evidence) and expert peer review. The lists were identified through comprehensive literature searches, contact with various national and international regulatory agencies and multiple surveys of high- and low-hazard substance lists.

Application of ComHaz relies on output of a comprehensive search strategy to efficiently identify relevant toxicity data in the public domain. The search strategy involves the initial identification of acceptable assessments or reviews produced by national or international agencies using the Internet and online databases, supplemented by additional journal and database searches to identify data published after the national or international assessments. In the absence of such assessments — or, if necessary, to supplement them — a comprehensive literature search can be conducted, including consideration of databases such as the U.S. National Library of Medicine’s TOXNET, TSCATS and IUCLID. Information from commissioned research studies and that submitted voluntarily or through mandated surveys by stakeholders and others are also taken into consideration. When possible, more recent reviews and/or toxicological data are targeted preferentially to identify studies most likely to be of sound design.

What is the draft maximal list? What do the designations of high, moderate and low probability/likelihood on the maximal list mean? What does inclusion of a substance on the maximal list mean?

Based on application of the "tools" to date, a maximum of 1896 substances (i.e., the draft "maximal" list) have been identified that will be further considered in additional stages of prioritization for screening assessment (i.e., categorization). These substances have been identified on the basis of GPE in Canada and IThuman, taking into account potential for P or B.

Health Canada released this draft maximal list (see http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/categor/max-list/index_e.html) to focus the submission of solicited information[2] on the identity, use and/or toxicity of any substance prioritized for further consideration. The release of this draft maximal list provides sufficient time and opportunity for interested parties to submit data to justify reducing the number of substances on the final list to be considered by Health Canada for screening assessment under CEPA 1999.

The terms high, moderate and low refer simply to the likelihood of a substance being considered for subsequent screening assessment after September 2006. Inclusion on the list merely refers to one of these likelihoods. The priority for assessing substances that are categorized "in" is being considered currently, both by group and within groups of identified substances.

How was the draft maximal list developed?

The draft maximal list was developed by applying the simple exposure and hazard tools to all substances on the DSL and considering P or B for some substances in the IPE group where such properties may inform the consideration of exposure potential. The initial conservative stage of ComHaz has also been applied to all GPE substances to which it is applicable and a specified subset of the IPE substances, where P or B might meaningfully additionally contribute to human exposure (namely, organic substances and organic UVCBs that are also P and/or B). This constituted the basis for identification of some of the substances on the maximal list considered to be low priorities for post-2006 consideration (i.e., some of the substances included in the "low likelihood" group).

[2] See the companion document entitled "Invitation to Provide Information on Substances Being Considered in Priority Setting for Health-Related Components of the Categorization of the Domestic Substances List under CEPA 1999" (http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/categor/max-list/invitation/index_e.html).

What will happen to the draft maximal list between now and the deadline for categorization of September 13, 2006? Which of the subsets are additionally being considered through application of tools, and which tools are being applied?

All substances within the "high likelihood" group most likely will continue to be considered as priorities for consideration in screening beyond 2006, since they have been identified as presenting high hazard. However, for a subset of these — namely, those that present lowest potential for exposure — information on any risk mitigation measures that may be in place is being requested to take this into consideration as a basis for setting priorities for assessment beyond 2006. This exercise represents an important pilot in accessing, in the issue identification stage of assessment, relevant information to additionally refine priorities post-2006.

The subset of principal focus for receipt of information to additionally refine priorities is the "moderate likelihood" group, since currently these substances represent those that are additionally being considered solely on the basis of exposure — i.e., they are GPE substances. Alternatively, they are IPE and P or B, but not ITeco. Additional consideration of these substances to identify those that are potentially non-hazardous is, therefore, being prioritized at this time. In particular, calls have been made to industry for information on polymers and UVCBs in this context.[3]

To the extent possible prior to the 2006 deadline, Health Canada will apply iterative additional stages of ComHaz to selected subsets of the substances in the moderate likelihood group of the maximal list, which may result in their eventually being considered as either high or low priority for screening assessment post–September 2006. Substances prioritized in this context will be those for which relevant information indicating potential low hazard has been submitted by stakeholders.

Substances in the moderate likelihood group that are potentially P and/or B and not ITeco will remain on the list unless determinations are made by Environment Canada that they do not meet the P and B criteria.

The inclusions in the "low likelihood" group are being reexamined to ensure that they do not constitute priorities for further work.

What does exclusion of a substance from the maximal list (i.e., setting aside from further consideration in categorization) mean?

[3] See the companion document entitled "Invitation to Provide Information on Substances Being Considered in Priority Setting for Health-Related Components of the Categorization of the Domestic Substances List under CEPA 1999" (http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/categor/max-list/invitation/index_e.html).

Exclusion of a substance from the maximal list means that the substance will not be considered for subsequent screening assessment arising from the DSL categorization activity. Essentially, the substance does not constitute a priority for assessment at this time, based on criteria established for priority setting within the context of the DSL exercise. It does not mean that the substance is considered safe, nor does it mean that the substance will never be considered once current priorities have been addressed or if additional information becomes available that indicates that it should be prioritized.

What information would be helpful in additionally defining priorities, and how and by what date is it to be submitted?

See response also to the question on what will happen to the maximal list between now and the categorization deadline and the companion document entitled "Invitation to Provide Information on Substances Being Considered in Priority Setting for Health-Related Components of the Categorization of the Domestic Substances List under CEPA 1999" (http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/categor/max-list/invitation/index_e.html).

Submission of information by September 2005 has been requested. The earlier this information is submitted, the more likely it is that it will be taken into consideration prior to the 2006 deadline. Submitted information that could not be considered prior to finalization of the maximal list will be taken into account in priority setting for screening of substances that remain on the list.

Why has it been suggested that information on risk management options or practices be considered for 301 substances identified in categorization?

These substances have been identified internationally as being of high hazard for human health. Most are genotoxic carcinogens for which Health Canada considered there to be some probability of harm at any level of exposure. While hazardous, the substances in this group are also LPE substances. If it can be shown that they are already being well controlled or managed — that is, they do not pose a risk to human health — they may not constitute priorities for full screening assessment. Alternatively, potential risk management options could be proposed that obviate the need for additional risk assessment. In this manner, risk assessment resources could be focused on other substances where potentially more widespread exposure requires additional consideration as a basis for potential appropriate control measures.

Why are 388 substances being identified as priorities for consideration of persistence and bioaccumulation?

Consistent with the approach to be conservative in the absence of information, 388 substances for which preliminary P and B determinations were not available were included on the maximal list. If these substances are determined to be neither P nor B, they will be removed from the maximal list and not considered as priorities for screening assessment. If they are determined to be P and/or B and ITeco, they will be removed from the maximal list and included within the list of substances categorized "in" by Environment Canada on the basis of their priority for assessment of risk to the environment.

How do these priorities (i.e., the draft maximal list) relate to those being identified by Environment Canada on the basis of persistence, bioaccumulation and designation as "inherently toxic" to non-human organisms?

There is limited overlap (approximately 10%, currently) between the Health Canada maximal list and the Environment Canada substances identified on the basis of preliminary decisions as being likely to be categorized "in" on the basis of P and/or B and ITeco. The proportion of overlap will continue to change as Health Canada and Environment Canada refine their preliminary determinations prior to the 2006 deadline for categorization. Subsequent to the categorization phase, as a basis for its contribution to the screening assessments on these substances, Health Canada will consider the output of the simple tools and/or apply the complex tools to determine whether or not the Environment Canada–nominated substances are considered to represent priorities from a human health perspective, for which full focused screening assessments of health risk are required.

What will happen post-2006 for substances that continue to be added to the DSL for which information available prior to the deadline of September 13, 2006, precludes their meaningful consideration?

It is envisaged that there will be an annual updating cycle to determine the priority for assessment of substances added to the DSL but not considered in categorization. Substances not included on the maximal list but added subsequently based on revised determinations of P, B or ITeco will be considered in the first year post-categorization. The limited number of substances in this category (i.e., those added to the DSL or identified as priorities by Environment Canada following development of the maximal list) are being tracked, currently, to ensure follow-up post-2006 to determine their priority for screening through application of the simple and/or complex tools.

What happens if new information becomes available after September 2006? Can decisions on categorization be changed?

For substances remaining on the list in 2006, new information will be considered in setting priorities for assessment and within the screening assessments. New information for substances not on the list in 2006 can be considered in the annual updates to the list of priorities for assessment mentioned above.

How have substances added to the DSL as a result of scheduling of the *Food and Drugs Act* been considered in the development of the draft maximal list?

Substances added to the DSL as a result of scheduling of the *Food and Drugs Act* do not have the necessary information to apply SimET. Some have been included in the maximal list on the basis of being designated "high hazard" through application of SimHaz. These substances are also being considered by Environment Canada in relation to P, B and ITeco.

How were high- and low-hazard substance lists in the simple hazard tool selected?

The high- and low-hazard substance lists included in SimHaz were selected from an extensive compilation of classifications of Health Canada and other agencies. Criteria for inclusion were robustness of content and process (including transparency of classification criteria), inclusion of critical evaluation of data (including assessment of weight of evidence) and extent of expert peer review. Classification systems that were not included often did not involve primary evaluation of relevant data; were not restricted to hazard, but included consideration of potential exposure; or lacked documentation to support transparency and robustness of weight-of-evidence considerations, criteria and/or processes for development. "Grandfathered" lists with little or no transparency on supporting assessments were not included.

What happens to the results of categorization if the lists that Health Canada used as the basis for the simple hazard tool are updated?

The lists used as the basis for SimHaz were current as of July 2004. The impact of updating these lists is being tracked and will be considered in the post-2006 annual updates mentioned above.

How were endpoints in the complex hazard tool selected?

The endpoints in ComHaz encompass those considered most relevant to the general population. They were selected on this basis, taking into account the likelihood of relevant information being available.

How are reproductive toxicity (including endocrine disruption), immunotoxicity and neurotoxicity taken into account in priority setting through the application of either the simple hazard tool or the complex hazard tool?

Substances can be prioritized by SimHaz based on reproductive toxicity if they have been classified as known to impair fertility, regarded as if they impair fertility in humans or cause concern for human fertility. Reproductive toxicity is also an endpoint in the ComHaz hierarchy, and the results of epidemiological or laboratory animal studies on reproductive toxicity, including effects such as endocrine disruption, can be assessed against the quantitative ComHaz criteria for this endpoint.

Immunotoxic and neurotoxic effects observed in developmental, long-term and short-term toxicity studies are considered when determining whether a substance meets the ComHaz criteria for these endpoints.

How are data versus predictive methods weighted in priority setting for hazard?

(See also response to question on how data gaps are addressed.)

For both the exposure and hazard tools, high-quality empirical data are weighted over predictive methods, owing to the generally greater confidence therein. For ComET, data gaps for physical-chemical properties (i.e., those for which empirical data are not identified based on extensive searching of public sources) are addressed by provision of information by industry or other stakeholders and/or the use of predictive tools or read-across data. For use patterns and release estimates, standard conservative scenarios are used in the absence of data.

When determining whether a substance meets specific criteria for an endpoint in ComHaz, acceptable assessments of international or national agencies and secondary reviews are consulted first, followed by original study accounts, predictions of quantitative structure–activity relationship (QSAR) and structure–activity relationship (SAR) models, information on chemical substructures of concern and analogue or surrogate approaches. This hierarchical approach ensures consultation initially of sources of information for which confidence is greatest (namely, data vs. predictive methods).

Data are also preferentially weighted over predictive methods in the ComHaz second-stage approach for assessing preliminary weight of evidence for genotoxic carcinogenicity. In general, empirical data are considered initially, followed by QSAR or SAR models, followed by analogues and/or surrogates. However, if only limited empirical data with low associated confidence are available on a substance, (Q)SAR model predictions may be given proportionally greater weighting in the overall weight-of-evidence determination. Scientific professional judgment is applied in determining what degree of weighting should be given to empirical data

compared with model predictions in weight-of-evidence decisions, taking into account confidence in any one line of evidence. Every attempt is made to transparently document the basis for the degree of confidence in data and/or predictions.

What are the predictive tools used in the complex hazard tool? How has reliability of output been ensured?

The predictive models considered for use in prioritization of DSL substances in ComHaz were critically evaluated on the basis of several criteria, including robust applicability to a wide range of diverse chemical structures, the capability to generate quantitative or qualitative predictions for endpoints relevant to initial prioritization, the ease of use and interpretation of results, computer requirements, availability, level of technical support and potential to be able to "validate" predictions against assessment criteria developed within the Health Canada Existing Substances program.

Application of predictive models is restricted principally to endpoints where confidence in output is highest — namely, cancer and genotoxicity. Decisions on other endpoints are not made solely on the basis of predictive tools.

QSAR models considered to be relevant to endpoints in ComHaz include TOPKAT (Accelrys Inc.) and CASETOX (Multicase Inc.). These models are based on statistical relationships between structure and activity or inactivity derived from databases of known toxicologically active and inactive compounds. Output of these models is interpreted in the context of relevant information on concordance, sensitivity and specificity for substances similar to those being considered in DSL categorization.

Also taken into account is the output of an expert system for SAR, namely DEREK (LHASA Ltd.). This system incorporates expert scientific knowledge about structural features that are known to be associated with toxicity. In view of the nature of its basis, underlying positive predictions are weighted, while negative predictions based on this tool are not weighted.

Comparison with chemical substructures of concern and/or analogues constitutes another source of relevant information, though these are considered only if they contribute additionally to the output of the (Q)SAR models described above. Data on toxicity of analogues are taken into consideration based on their identification through various approaches, including the (Q)SAR models mentioned above, expert-based visual grouping of the entire DSL by structure by Health Canada and cross-reference to "similar" analogues in an internal Health Canada database. The potential of more analytical tools such as Leadscope to identify analogues based on factors other than structure is also being investigated.

The (Q)SAR models have built-in features for determining the reliability of predictions, such as checks on the structural coverage of test substances, whether predictions are within optimal statistical parameters, the accuracy of predictions for similar substances of known toxicity and references to published information on the rationales for the toxicity of specific structural features. To the extent possible, judgments of output of predictive models take into account weight-of-evidence considerations, including consistency, biological plausibility, etc.

In addition, expert opinion was solicited in a peer consultation convened during the development of the weight-of-evidence component for consideration of data/(Q)SAR and analogues/surrogates in assessment of cancer/genotoxicity. There is also continuing internal quality control auditing of ComHaz output, including that from predictive models.

The predictivity or robustness of both the exposure and hazard tools described in the integrated framework has also been verified through several analyses based principally on the outcomes for the Priority Substances assessments. Also, in all cases where relevant empirical data have not been identified or there is high uncertainty in predicted hazard, conservative choices were made, retaining the substances for additional consideration.

What is the basis for the quantitative criteria for hazard in the complex hazard tool?

The quantitative criteria for each endpoint in ComHaz were developed following review of existing classification and ranking systems developed by various international and national agencies, other relevant literature on specific toxicological endpoints, consultation with Canadian and international experts in toxicology and health risk assessment and extensive testing to ensure consistency and coherence across endpoints.

What are the sources of the regulatory/reference values used in the complex hazard tool?

Tolerable daily intakes (TDIs), tolerable concentrations (TCs), acceptable daily intakes (ADIs), reference doses (RfDs) and other values from agencies such as the International Programme on Chemical Safety of the World Health Organization (WHO), the U.S. Environmental Protection Agency, the Joint FAO/WHO Expert Committee on Food Additives, Health Canada and the European Union are taken into consideration in determining whether the information on a substance meets the criteria for regulatory/reference values in ComHaz. The criteria used to determine whether regulatory/reference values are applicable to ComHaz are similar to the criteria followed for selecting the national/international assessments included in SimHaz. Factors taken into consideration include the transparency of the rationale behind the regulatory/reference values, comprehensiveness of literature review and the peer review processes followed. In some cases, professional judgment must be applied to consider selected regulatory/reference values on a case-by-case basis, as some agencies may provide comprehensive rationales for certain values,

but are not so transparent for others. In general, regulatory/reference values established for short-term exposures are not considered for ComHaz because of the difficulty in establishing cut-off criteria and lack of standardized methodology in their development. Reference values established for occupational exposures are also not considered relevant to ComHaz.

What is a "sentinel product" in the complex exposure tool? How is exposure through multiple products taken into account?

A sentinel product is a specific type of consumer product with a defined composition and use that yields the highest exposure of an individual for one of its component substances compared with other consumer products containing that substance.

The exposure to multiple products can be accounted for by appropriate summation of the exposures from individual sentinel products.

How are impacts of exposures to multiple chemicals being taken into account in priority setting and assessment?

All substances on the DSL have been visually grouped by structure to identify similar subsets. To the extent possible, then, substances are grouped for consideration by the complex tools.

However, categorization is an initial prioritization phase intended to identify the substances on the DSL of highest priority for further assessment. As a result, it does not include comprehensive consideration of potential combined effects from multiple chemical exposures. If data are available that would indicate patterns of use consistent with multiple chemical exposures and the potential for additive, synergistic or antagonistic toxic effects, these data would be considered for substances prioritized for more detailed screening and PSL assessments.

How are potentially sensitive subgroups (e.g., children, women of child-bearing age) accounted for in the proposed integrated framework?

Variations in potential exposure and hazard for different subgroups of the population are taken into account by both the simple and complex exposure and hazard tools.

For SimET, the extent of this consideration is limited to potential variations by age group accounted for in the expert ranked use codes. The use codes provide an indication of whether or not consumer exposure is expected, where variations in use pattern among age groups are likely to be greatest. For ComET and all health assessments for existing substances under CEPA 1999,

quantitative estimates of exposure are developed for six different age groups of the population, including infants and children.

SimHaz identifies substances as priorities for further consideration on the basis of several health endpoints, including those relevant to children and women of child-bearing age. These include the potential for developmental toxicity (i.e., toxic effects on the developing embryo, fetus or infant) or reproductive effects (i.e., toxic effects on reproductive systems of women and men) based on the results of studies in laboratory animals or human populations. SimHaz identifies substances based on classifications of "known to cause developmental toxicity or impair fertility," "regarded as if they cause developmental toxicity or impair fertility in humans" or "cause concern for humans owing to possible developmental toxic effects or effects on fertility."

The endpoints included in ComHaz and all health assessments for existing substances under CEPA 1999 address an inclusive range of effects with potential health impacts for the Canadian public, including potentially sensitive subgroups. For instance, the developmental toxicity endpoint in ComHaz includes available studies of toxic effects on the developing embryo, fetus and infant, and the reproductive toxicity endpoint includes a consideration of studies of toxic effects of substances on reproductive systems of women and men.

How will the order of screening assessments for substances remaining as priorities following the categorization deadline be determined? What are the expected timelines for completion of screening assessments on various priorities?

Substances prioritized for screening health assessments based on DSL categorization will be prioritized both by group and within each group. For example, those that are designated GPE and high hazard (HH) are the highest priorities for early completion of screening assessments. Within each of the prioritized groups (e.g., GPE/HH, IPE/HH, LPE/HH, GPE/IPE, P or B but not ITeco), each of the substances is ranked in order of its potential for exposure. Additional information on potential exposure and dose–response for critical endpoints in the highest-priority groups is currently being collected to additionally refine the order of health-based priorities for screening assessment.

The robust complex exposure and hazard tools and the several models of screening assessment that vary depending upon the priority of the substance and complexity of the issues addressed ensure efficient screening beyond 2006. Projections of time frames for completion of assessments within each of the prioritized groups are currently being developed, based on increasing experience in application of the complex tools.

Has assessment work been completed on the approximately 1200 substances from the health draft maximal list now considered as either high or moderate health priorities for further action?

No, these substances have been prioritized for further action on the basis of potential risk (exposure and effect), hazard and exposure considerations. This health-related categorization, while risk based and believed to identify true health-based priorities, is *not synonymous* with human health risk assessments conducted under CEPA 1999. For example, the substances in the high health priorities for action group have *not yet been critically assessed* in regards to any potential risks to human health. Rather, they have been *prioritized for further action* (i.e., assessment) on the basis of the risk-based considerations of exposure and hazard. Assessment enables additional quantification of risk from more fully characterized sources.

What are the next steps for the approximately 700 substances from the health draft maximal list that are now considered to not require further work for human health at this time?

This group of substances includes those that have been assessed and/or managed under the 1988 *Canadian Environmental Protection Act* or CEPA 1999 (that is, listed on PSL1 or PSL2 or Schedule 1 or 3 of the Act); low-hazard compounds (determined by application of low-hazard components of SimHaz and ComHaz) and low-concern polymers; and "deprioritized" substances reflecting changes to their designation as PBITeco. Health Canada will track these substances for any new information that might warrant subsequent action (e.g., assessment).

How are data gaps addressed in priority setting for categorization?

(See also response to question on reliability of predictive hazard tools.)

SimET relies solely on the information submitted for all substances in the compilation of the DSL. For ComET, data gaps for physical-chemical properties (i.e., those for which empirical data are not identified based on extensive searching of public sources) are addressed by provision of information by industry or other stakeholders and/or the use of predictive tools or read-across data. For use patterns and release estimates, standard conservative scenarios are used in the absence of data. If gaps cannot be satisfactorily filled based on standard scenarios or predictive tools, the substances will be retained as priorities for additional consideration and move forward to screening assessments, at which time data can be requested or generated.

For ComHaz, in the absence of empirical toxicological data, predictive tools (including QSAR models; a SAR expert system and/or consideration of chemical structures of concern; and data on toxicity of analogues or surrogates) are taken into consideration, based on confidence in their

output and weight-of-evidence considerations (such as consistency and biological plausibility). If gaps cannot be satisfactorily addressed based on consistent and confident output of predictive tools, the substances will be retained as priorities for additional consideration and move forward to screening assessments, at which time data can be requested or generated.

The application of the exposure and hazard tools is instrumental in identifying critical areas of data generation to address subsequent stages of prioritization and/or assessment

Is there a minimum data set for making categorization decisions? Are substances set aside if no relevant information is identified? Are data (e.g., environmental monitoring and biomonitoring data) being generated to support categorization efforts?

For the most part, as delineated under CEPA 1999, categorization is based on available data. The methodology (i.e., simple and complex tools) developed to meet the mandate ensures optimum utilization of existing data. The tools also identify priorities for data generation in screening. The minimum data set appropriate for screening assessment is considered to be that outlined in the Organisation for Economic Co-operation and Development's High Production Volume Chemicals Programme Screening Information Data Set.