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

Health Canada

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List of Acronyms and Abbreviations

ACVM	Agricultural Compounds and Veterinary Medicines Group
ADI	acceptable daily intake
B	bioaccumulation/bioaccumulative
BOD	biochemical oxygen demand
bw	body weight
CDER	Center for Drug Evaluation and Research
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
ComET	Complex Exposure Tool
ComHaz	Complex Hazard Tool
DNA	deoxyribonucleic acid
DSL	Domestic Substances List
EAFUS	"Everything" Added to Food in the United States
EC	European Commission
EEC	European Economic Community
ERT	exposure–response tool
ERU	expert ranked use
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration (United States)
FEMA	Flavor and Extract Manufacturers Association
FISH	fluorescence *in situ* hybridization
GPE	greatest potential for exposure
GRAS	generally regarded as safe
HC	Health Canada
IP	intraperitoneal
IPE	intermediate potential for exposure
ITeco	inherently toxic to non-human organisms
IThuman	inherently toxic to humans
IV	intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LO(A)EC	lowest-observed-(adverse-)effect-concentration
LO(A)EL	lowest-observed-(adverse-)effect-level
LPE	lowest potential for exposure
MW	molecular weight
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NO(A)EC	no-observed-(adverse-)effect-concentration
NO(A)EL	no-observed-(adverse-)effect-level
NSNR	New Substances Notification Regulations
NTP	National Toxicology Program (United States)
NZFSA	New Zealand Food Safety Authority

OECD	Organisation for Economic Co-operation and Development
OTC	over the counter
P	persistence/persistent
PBITeco	persistent and/or bioaccumulative and inherently toxic to non-human organisms
PBIThuman	persistent and/or bioaccumulative and inherently toxic to humans
PMRA	Pest Management Regulatory Agency
PSL	Priority Substances List
PSL1	First Priority Substances List
PSL2	Second Priority Substances List
Q	annual quantity of use reported on the Domestic Substances List
QSAR	quantitative structure–activity relationship
RfC	reference concentration
RfD	reference dose
S	number of submitters
SAR	structure–activity relationship
SIAR	SIDS initial assessment report
SIDS	screening information data set
SimET	Simple Exposure Tool
SimHaz	Simple Hazard Tool
SP	sentinel product
TDC	tolerable daily concentration
TDI	tolerable daily intake
TERIS	Teratogen Information System
U	sum of expert ranked use code indices
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
UVCB	substance of unknown or variable composition, complex reaction products and biological material
WHO	World Health Organization

PART A: INTRODUCTION

Context

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires categorization (Section 73) of the approximately 23 000 substances on the Domestic Substances List (DSL) prior to a legally mandated deadline of September 14, 2006. The proposed integrated framework described in this document is the second of three proposals related to Health Canada's responsibilities to categorize all substances on the DSL for the "greatest potential for human exposure" (GPE) and a subset of substances for "inherently toxic" to humans (IThuman) under CEPA 1999. It is being released for comment to solicit input on both technical and management aspects.

In considering this proposal, it is important to understand the limited objective of categorization in the overall mandate for Existing Substances under CEPA 1999, which is to identify substances on the basis of either exposure or hazard to be considered further in subsequent phases of assessment. The two named phases of assessment for substances prioritized (categorized) for further consideration under CEPA 1999 are screening assessment (Section 74) and in-depth assessment (Priority Substances; Section 76) (see Figure 1).
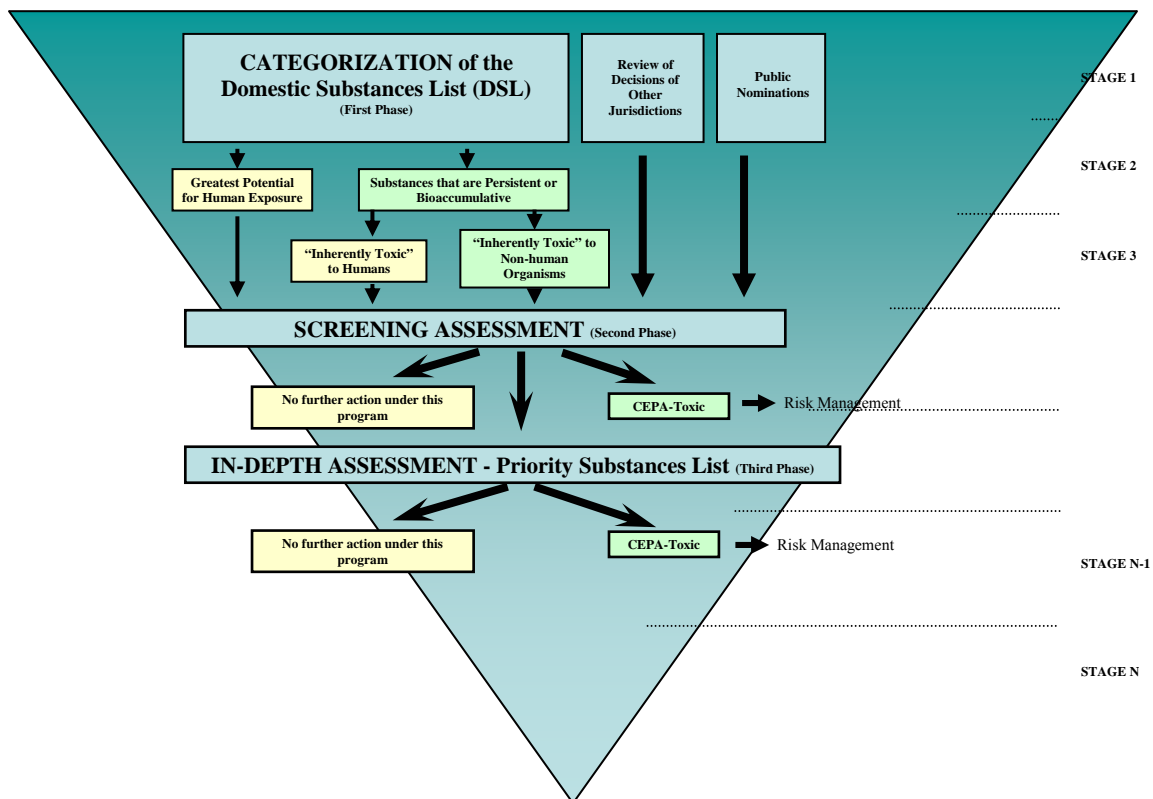

Figure 1. Existing Substances Program under CEPA 1999

In addition to categorization, there are other streams through which substances can be prioritized for assessment: namely, reviews of decisions of other jurisdictions (Section 75), nominations to

the Priority Substances List (PSL) and advice provided to the Ministers of Health and the Environment by expert panels. Thus, while approaches to categorization (priority setting) are necessarily limited due to the requirement to address large numbers of substances, the impact of these limitations is minimized through the potential to additionally prioritize compounds for assessment through other streams in the Existing Substances program. However, the significant contribution of the "tools" described herein and developed to meet the DSL categorization and screening mandate lies in their broad applicability to thousands of substances. It is the application of these tools to consider the relative priority for assessment for all of the approximately 23 000 substances on the DSL which provides the invaluable basis against which the priority of assessment of compounds and mixtures introduced from any stream can be systematically judged.

An important objective of the latter two phases — namely, screening and in-depth assessment — is to determine whether a substance is "CEPA-toxic" as defined in Section 64 of the Act, which may then set the stage for addition of the substance to Schedule 1 (the List of Toxic Substances) and for considering options for controlling risks to human health and/or the environment. In reality, in each of these principal phases or tiers of priority setting or assessment (i.e., categorization, screening and assessment of Priority Substances), there are a number of levels of increasing complexity, indicated here as stages (Figure 1).

These stages are represented by the "simple" and "complex" tools described in this proposal. Application to the entire DSL of the simple tools and partial application of the complex tools to prioritized subsets of substances, as described in this proposal, have resulted in the proposed maximal list of health-related priorities for further consideration in screening. This list is posted separately (http://www.hc-sc.gc.ca/hecs-sesc/exsd/maximal_list.htm).

This maximal list is divided into three subgroups — namely, high, moderate and low likelihood of remaining as priorities for screening (i.e., categorized "in") on the mandated deadline in 2006. Inclusion on this list does not imply that all of these substances are the most hazardous or that exposure should be avoided; it simply indicates that they are high, moderate or low priorities for additional consideration based on the criteria delineated in this proposal.

The complex tools described herein are also critical to efficient screening of priorities subsequent to the 2006 deadline for categorization. To the extent possible, all of the tools described herein take into account exposure and hazard for specific sub-populations or age groups through consideration of, for example, potential variations in the products to which they are exposed and a range of toxicological endpoints relevant to all life stages. The extent to which these aspects is addressed is more refined in the complex tools.

It is also proposed to conduct an annual update of the output of categorization through application of the priority setting tools to the final outcome of Environment Canada declarations of persistence or bioaccumulation and/or to address any additions of Existing Substances to the DSL (through initiatives, for example, such as scheduling of the Food And Drugs Act.

Process

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

Stages of external input include peer input and peer review of technical components of the proposed methodology, the objectives of which 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 (in particular, predictive tools) 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, presentation or input 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 herein.

Critical elements of consultation on the Health Canada components of categorization include public comment on robust proposals and associated preliminary summaries posted at the Existing Substances Division web site (http://www.hc-sc.gc.ca/exsd-dse). Feedback at information sessions with all stakeholders is also critical. The timelines for release of the three proposals on the health-related components of categorization are presented in Figure 2.
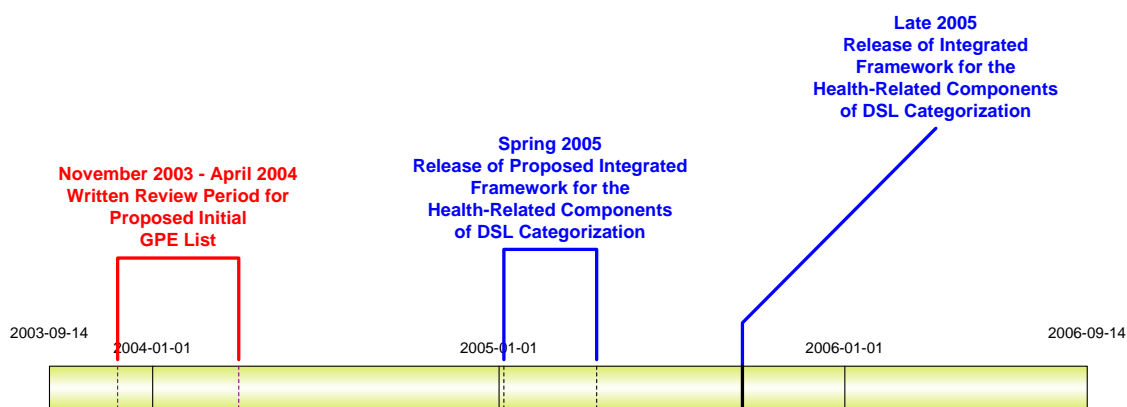
Figure 2. Timeline for release of proposals on health-related components of DSL categorization

The earlier proposal on GPE (see http://www.hc-sc.gc.ca/hecs-sesc/exsd/categorization_dsl_human_exposure.htm) represents essentially the Simple Exposure Tool (SimET) referenced in this proposed integrated framework and revised based on earlier input. Based on comments received in response to this proposal and increasing program experience, a final approach to categorization for both GPE and IThuman will be proposed and issued late in 2005.

Comments and information received in response to the earlier proposal on GPE were taken into account in the development of the integrated framework described in this proposal. The proposal also reflects comments received in response to preliminary summary documentation posted at the Existing Substances Division web site (http://www.hc-sc.gc.ca/exsd-dse) during the summer of 2004. Response to feedback at information sessions held in March and November of 2004 is also incorporated.

Relevant information posted previously included summaries of the simple and complex exposure and hazard tools. Information (principally from industrial stakeholders) was also solicited to assist in decision-making on individual substances (see http://www.hc-sc.gc.ca/hecs-sesc/exsd/info.htm). Extensive information on the Complex Exposure Tool (ComET) has been posted since the autumn of 2004 at http://www.thelifelinegroup.org.

For this proposal, relevant meetings included a peer consultation on genotoxicity held in Ottawa in March 2002 and a peer input meeting on ComET held in Cincinnati, Ohio, in November 2004. Documentation on additional elements of peer input, including two workshops on interpretation of DSL use codes, was included in the previous proposal on GPE.

A web cast of the peer input meeting on this tool held in Cincinnati on November 8, 2004, is available at http://www.tera.org/peer/exposure/exposurewelcome.htm. Reports of the relevant peer input and peer review meetings and information sessions are listed in Part F of this document and are publicly posted and/or are available as supporting documentation to the proposal.
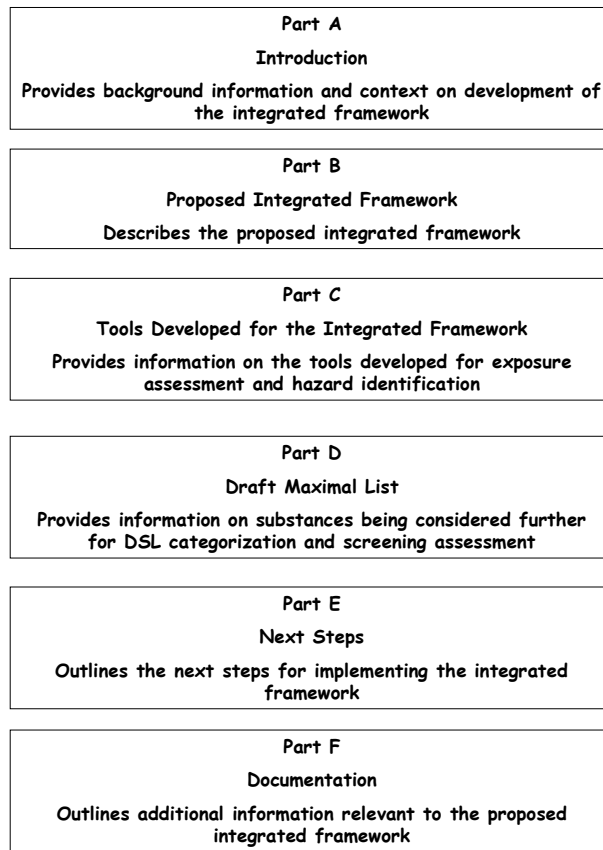
Outline of Document

Information on the overall integrated framework, tools and supporting information for review and public comment is presented in Figure 3.

Part A
Introduction
Provides background information and context on development of the integrated framework

Part B
Proposed Integrated Framework
Describes the proposed integrated framework

Part C
Tools Developed for the Integrated Framework
Provides information on the tools developed for exposure assessment and hazard identification

Part D
Draft Maximal List
Provides information on substances being considered further for DSL categorization and screening assessment

Part E
Next Steps
Outlines the next steps for implementing the integrated framework

Part F
Documentation
Outlines additional information relevant to the proposed integrated framework

Figure 3. Integrated framework document

The appendices of this document provide additional background information on the simple and complex hazard tools as well as on aspects related to development of the framework and the tools themselves.

Call for Comments

The proposal is being released formally for review and written comment.

Views and suggestions are invited on all aspects. However, specific aspects for which input would be helpful are outlined in the questions below:

1) Is the proposed approach sufficiently transparent and discriminating with respect to how substances have been selected for further consideration?

2) Does the proposed approach maximize the use of the available information for all substances on the DSL in identifying those with the greatest potential for human exposure or those that are "inherently toxic" to humans? If not, what other options should be considered?

3) Are there lists of substances considered hazardous or non-hazardous to human health for which transparency and defensibility are sufficient that they should be additionally considered for inclusion in the Simple Hazard Tool (SimHaz)?

4) Is the proposed weighting of various sources of data in the Complex Hazard Tool (ComHaz) appropriate, or can preferred alternatives be identified and justified?

5) Do the proposed criteria for additionally considering substances for each of the endpoints in ComHaz represent a reasonable compromise for establishing initial priorities for further consideration? Can preferred alternatives be presented and justified?

6) Can you suggest specific approaches to additional priority setting in relation, particularly, to hazard to humans for substances within the groups of organics, inorganics, polymers and UVCBs (substances of unknown or variable composition, complex reaction products and biological materials)? Can you identify relevant sources of information or supply relevant data?

Written comments, which will be taken into consideration in revision of the proposal, should be submitted prior to August 30, 2005 via e-mail to: ExSD@hc-sc.gc.ca.

Comments can also be sent by surface mail to the following address:

> Existing Substances Division
> Bureau of Environmental Contaminants
> Safe Environments Programme
> Health Canada
> Environmental Health Centre, Room 145
> Tunney's Pasture
> Postal Locator: 0801C2
> Ottawa, ON K1A 0L2

In providing your comments, please include your name, representation, if any, full mailing and e-mail addresses and telephone and fax numbers.

A summary of the comments provided, the names and affiliations (but not coordinates) of those providing comments and the Department's response to them will be posted at the Existing Substances Division web site (http://www.hc-sc.gc.ca/exsd-dse), along with the finalized integrated framework, later in 2005.

PART B: PROPOSED INTEGRATED FRAMEWORK FOR HEALTH-RELATED COMPONENTS OF DSL CATEGORIZATION

Background

Within seven years of the introduction of CEPA 1999 (i.e., by September 14, 2006), the Ministers of Health and of the Environment are to complete categorization of the approximately 23 000 substances on the DSL. As noted in Part A of this document, categorization of the DSL represents one aspect (albeit the largest and most encompassing) of the overall program for prioritization and assessment of Existing Substances and for the control or management of those considered to pose a risk to human health or to the environment.

As shown in the Figure 4, under this legislative construct, the Minister of the Environment assumes responsibility for identifying substances on the DSL, for subsequent screening assessment by both departments, that are persistent (P) and/or bioaccumulative (B) and "inherently toxic" to non-human organisms (ITeco) (i.e., PBITeco). The Minister of Health is to identify those substances on the DSL, for subsequent screening assessment by both departments, that pose the greatest potential for exposure of the general population in Canada (GPE). The Minister of Health is also to identify those substances for subsequent screening that are "inherently toxic" to humans for a subset of substances considered P and/or B by Environment Canada (PBIThuman).
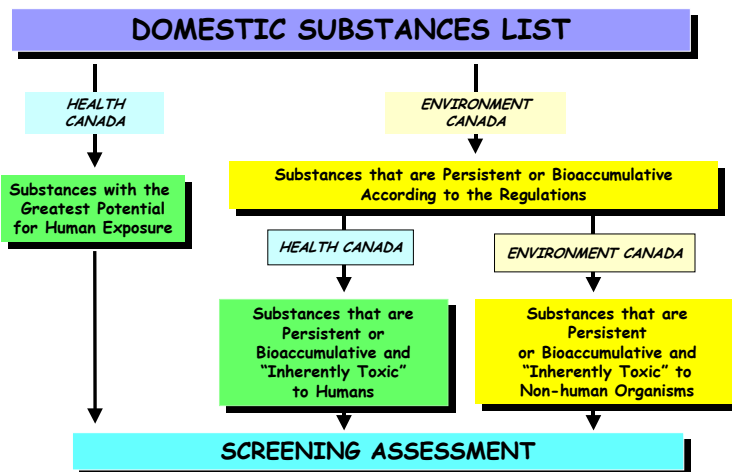

Figure 4. Legislative construct for categorization of Existing Substances on the DSL

This mandate to systematically set priorities for the approximately 23 000 substances on the DSL is technically demanding and precedent setting internationally. It requires significant technical capacity to develop transparent, scientifically defensible and discriminating "tools" for priority setting and subsequent screening assessment.

The Role of Persistent and Bioaccumulative Substances in Human Health

This legislative construct for DSL categorization also poses some challenges with respect to the identification of true priorities for assessment from a human health perspective. This relates principally to the requirement to consider IThuman for a subset of DSL compounds for which the criteria are principally relevant to identification of priorities for the environment (i.e., those substances considered to be P and/or B).

Based on profiling of large numbers of substances, P and B are rarely influential determinants of either potential for human exposure or effects on human health. Rather, they may contribute to the potential for exposure of humans in the general environment ("far-field" exposure), which, for many substances, is secondary to direct exposure in consumer products or indoor air (referred to as "near-field" exposure). It is, then, the use profile for individual substances that is critical in determining potential for exposure.

Even in those cases where humans are exposed principally indirectly through the general environment ("far-field"), P and B contribute to only a limited extent in determining potential exposure, which is a function of the extent of emissions, distribution, degradation and/or metabolism in the principally terrestrial food chain.

In addition to the use profile, toxicokinetics (i.e., how and to what extent a substance is absorbed, distributed, metabolized and eliminated from the body) are also critical in consideration of the potential of P or B chemicals to induce harm in humans. For example, exposure of some age groups may be increased for some bioaccumulative compounds that are fat seeking, since such compounds my be stored in fatty tissue and excreted in breast milk. However, the absorption efficiency of substances with very high octanol/water partition coefficients is actually reduced.

Most importantly, the mere presence of detectable levels of persistent substances in blood or tissue while indicating that there has been exposure, does not necessarily imply potential harm to humans; rather, potential harm is a function of the quantitative relationship between concentrations in critical target organs and those associated with adverse effect. Moreover, it is typically the more chemically reactive compounds rather than those that are persistent that interact with biological materials and induce adverse effects in mammals.

To meet the intent of the provisions of CEPA 1999, the objective of the integrated framework for the health-related components of DSL categorization presented here is to efficiently identify, for additional consideration in screening, substances that are highest priorities in relation to their potential to cause adverse effects on the general population (i.e., those that are highest priorities from a human health perspective). The framework takes into account the often limited potential of P or B to influence potential for human exposure in the context of more influential determinants such as use pattern. Application of the tools within the integrated framework also enables prioritization for additional consideration on the basis of health risk, with output exceeding, therefore, the requirement of categorization simply to identify substances for screening assessment.

The Proposed Integrated Framework

The approach described herein evolved from early recognition that the identification of health-related priorities for additional consideration from among the approximately 23 000 substances on the DSL required multiple stages of increasing complexity. It required also that the tools developed for these various stages were sufficiently robust to address, concomitantly, the several distinct groups of compounds included on the DSL (i.e., organics, inorganics, polymers and UVCBs).

In order to efficiently identify and prioritize, for screening assessment, substances on the DSL that represent highest priorities from a human health perspective, the framework (see Figure 5) is based on iterative application of increasingly discriminating (i.e., simple and complex) tools for consideration of exposure and hazard. The "simple tools" are sufficiently robust to address all substances on the DSL based on the limited information available for many; the "complex tools" are sufficiently discriminating to set true priorities for further work. Application of these tools in stepwise fashion avoids continuing bias to consideration of data-rich compounds, while making optimum and efficient use of available generic and chemical-specific information.
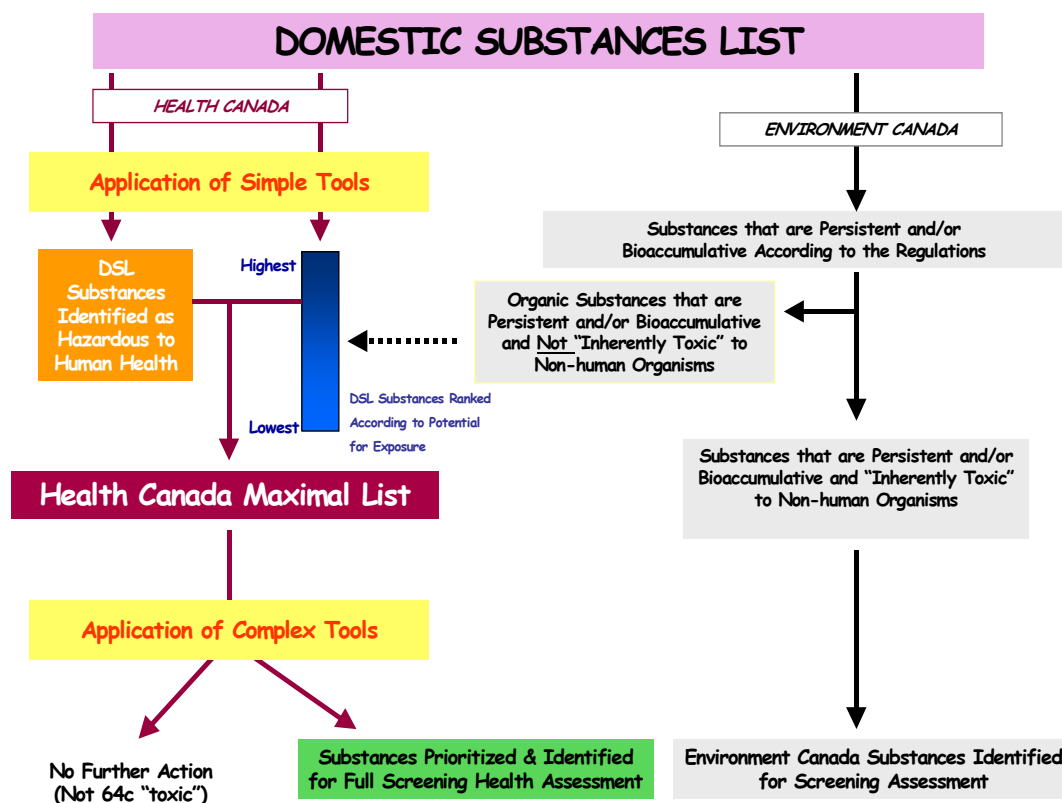

Figure 5. Proposed integrated framework for health-related components of DSL categorization

For both exposure and hazard, then, simple "discriminating" tools are applied initially to focus on highest priorities. Subsequently, more complex tools are applied to additionally refine both

estimates of exposure and identification of hazard. The approach is protective, with conservative choices being made in the absence of data. It identifies priorities for both data generation and assessment and appropriately weights persistence and bioaccumulation in the context of their potential to contribute to human exposure.

Initially, then, as indicated in Figure 6, application of a simple discriminating exposure tool (SimET) results in a relative ranking of exposure potential for the approximately 23 000 substances on the DSL based on limited information for all (number of submitters, quantity and use) supplied to Environment Canada during the initial compilation of the DSL. Although the information on which it is based is limited, this tool allows identification of substances produced or imported in the greatest quantities for which uses could be dispersive in the environment or which are used in products that come into direct contact with the general population. The application of SimET also permits grouping of all substances considered to present the "greatest potential for exposure" (GPE – 849), "intermediate potential for exposure" (IPE – 1779) and "lowest potential for exposure" (LPE – the remainder) (Figure 6) through the application of specified criteria (see the description of the exposure tools in Part C).
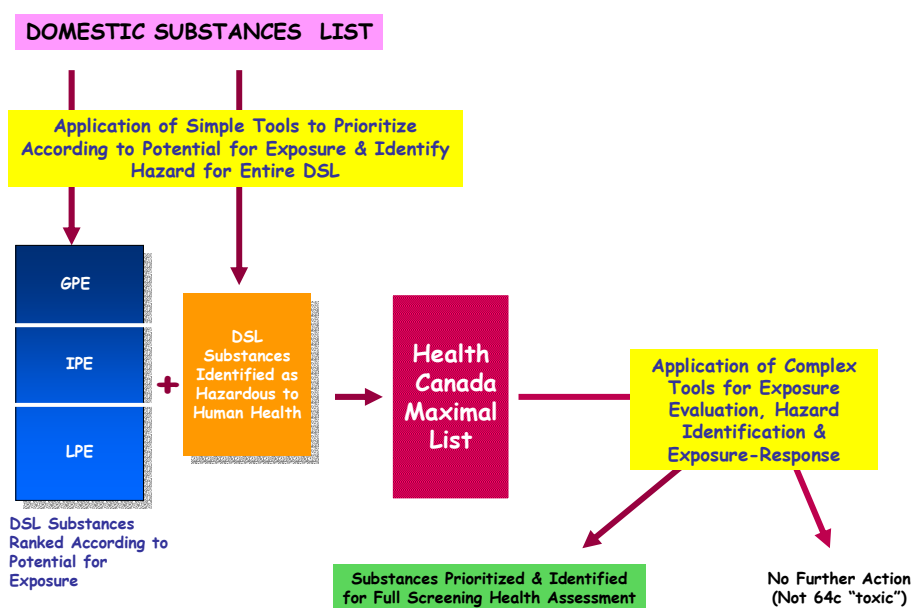

Figure 6. Operationalizing the integrated framework

A simple discriminating hazard identification tool (SimHaz) is also applied to address hazard for all 23 000 substances. This step involves the identification of high- or low-hazard substances by various agencies based upon formal weight of evidence criteria (see the description of the hazard tools in Part C and in Appendices I and II).

The complex hazard tool (ComHaz) involves hierarchical consideration of various sources of information (including data, [quantitative] structure–activity analysis and comparison with analogues) for a range of endpoints of toxicity, which are also considered in stepwise fashion. The first stage is based on a conservative "first hit" approach for data and endpoints based on

specified criteria; the next stage involves consideration of weight of evidence for qualitative endpoints of capture (e.g., cancer, genotoxicity); and the final stage considers dose–response for critical endpoints for comparison with quantitative output of the tool.

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).

Selection of the substances meeting the specified criteria based on application of these tools resulted in the draft maximal list of substances for further consideration in categorization of health-related priorities (see Part D).
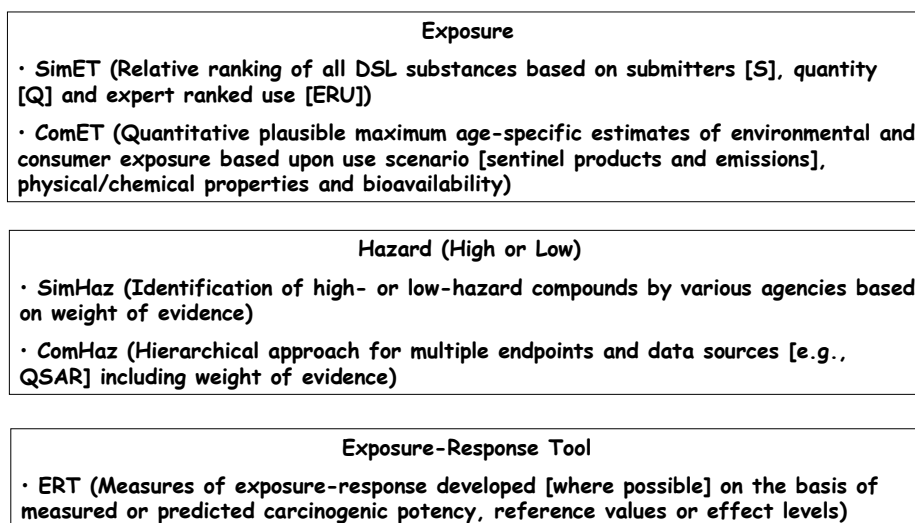
Substances on the maximal list are currently being considered in the additional stages of ComHaz as a basis to focus and efficiently prepare screening assessments post-2006. This includes preliminary consideration of weight of evidence for substances prioritized on the basis of qualitative endpoints. It also includes consideration of exposure–response for critical effects that involve an evaluation of carcinogenic potency (where available) or lowest critical effect level for other endpoints covered in ComHaz for the substance itself or an analogue (identified from similarity searching).

Prioritized substances are also being considered pre- and post-2006 through application of ComET. This tool provides quantitative plausible maximum estimates of exposure of individuals in the general population by age group (based upon use scenario, physical/chemical properties and bioavailability). The tool encompasses estimation of both environmental (far-field) and consumer exposure (near-field), the latter being based on the concept of "sentinel products" — i.e., those yielding highest estimates of exposure for individuals in different age groups of the population.

A summary of the tools developed is presented in Figure 7.

Exposure
· **SimET (Relative ranking of all DSL substances based on submitters [S], quantity [Q] and expert ranked use [ERU])**
· **ComET (Quantitative plausible maximum age-specific estimates of environmental and consumer exposure based upon use scenario [sentinel products and emissions], physical/chemical properties and bioavailability)**

Hazard (High or Low)
· **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., QSAR] including weight of evidence)**

Exposure-Response Tool
· **ERT (Measures of exposure-response developed [where possible] on the basis of measured or predicted carcinogenic potency, reference values or effect levels)**

Figure 7. Tools for the health-related components of DSL categorization and screening

Application of the more discriminating ComET and subsequent stages of ComHaz enables efficient screening post-2006. The feasibility of integrating the complex exposure and hazard tools to additionally contribute to efficiency of screening post-2006 is also being investigated.

For substances that are considered as priorities in screening, in most cases, the minimum dataset considered appropriate as a basis to complete the assessment is the Screening Information Dataset in the OECD High Production Volume Chemicals Program (http://www.oecd.org/about/0,2337,en_2649_34379_1_1_1_1_1,00.html).

The proposed framework described above meets the legal obligation (pursuant to Section 73 of CEPA 1999) to identify substances with GPE and a subset for IThuman taking into account the often limited contribution of P or B to human exposure, and it offers a number of important additional benefits:

- The framework/approach is protective for human health. Priorities are clearly specified, with conservative choices made in the absence of data.
- The framework draws maximally on work completed in other jurisdictions while avoiding continued focus on data-rich compounds.
- The framework results in a list of substances for screening (categorized "in") identified on the basis of exposure or hazard but also *prioritized* on the basis of potential exposure, hazard and/or risk to human health.
- The exposure and complex hazard components of the framework are unbiased in relation to data availability, identifying true priorities for both assessment and data generation.
- The framework also results in development of a list of substances of low priority for further consideration in the program.

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- IThuman is considered for all of the approximately 23 000 substances based on criteria for weight of evidence of hazard consistent with those for Priority Substances or screening health assessment of Existing Substances.
- The framework is sufficiently robust to permit consideration of the wide variety of substances in the four broad groups on the DSL (i.e., organics, inorganics, polymers and UVCBs) concurrently.
- The framework is based on the development of tools that will permit the efficient screening assessment of any Existing Substance introduced from any stream.
- Application of the simple tools and initial stages of ComHaz within the framework has identified the maximum numbers and names of substances for inclusion on the list of substances requiring further assessment in 2006 in a close to final form (the "draft maximal list"). This has provided sufficient time and opportunity for interested parties to submit a limited number of data to reduce the number of substances on the final list, thereby reducing significantly the uncertainty associated with the human health aspects of DSL categorization.

PART C: TOOLS FOR THE HEALTH-RELATED COMPONENTS OF DSL CATEGORIZATION AND SCREENING

The exposure and hazard tools developed for identification and screening of priorities related to human health are presented here in the order of their contribution to development of the maximal list. These include the Simple Exposure Tool (SimET), the Simple Hazard Tool (SimHaz) and the first stage of the Complex Hazard Tool (ComHaz). Information on subsequent iterative stages of ComHaz and the Complex Exposure Tool (ComET) that are relevant to screening post-2006 are also briefly described here.

The Simple Exposure Tool (SimET)[1]

SimET draws on relatively limited information submitted in the compilation of the DSL. However, as for all priority setting and assessment relevant to human health for Existing Substances, it takes into account exposure through both consumer products (near-field or direct exposures to products, generally of a voluntary nature) and all environmental media (far-field or indirect exposures through intake of environmental media into which substances have been released).

SimET provides a relative ranking of the approximately 23 000 substances on the DSL on the basis of limited information submitted at the time the DSL was compiled. This information included the industrial sector in which the substance was used (industrial sector codes) and/or specified broad classes of functional applications (functional use codes). As part of the development of this tool, the potential contribution to exposure of the general population for products within each of the industrial and functional use codes was ranked by experts in several workshops. Each of the approximately 23 000 substances were relatively ranked based on quantity, number of submitters and the sum of expert ranked use codes (Figure 8). Based on specified criteria for each of the three parameters (Table 1), 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. The principles and limitations of SimET are as outlined in the previous GPE proposal (referenced in Part F).

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[1] For additional information, see http://www.hc-sc.gc.ca/hecs-sesc/exsd/pdf/greatest_potential_human_exposure.pdf.
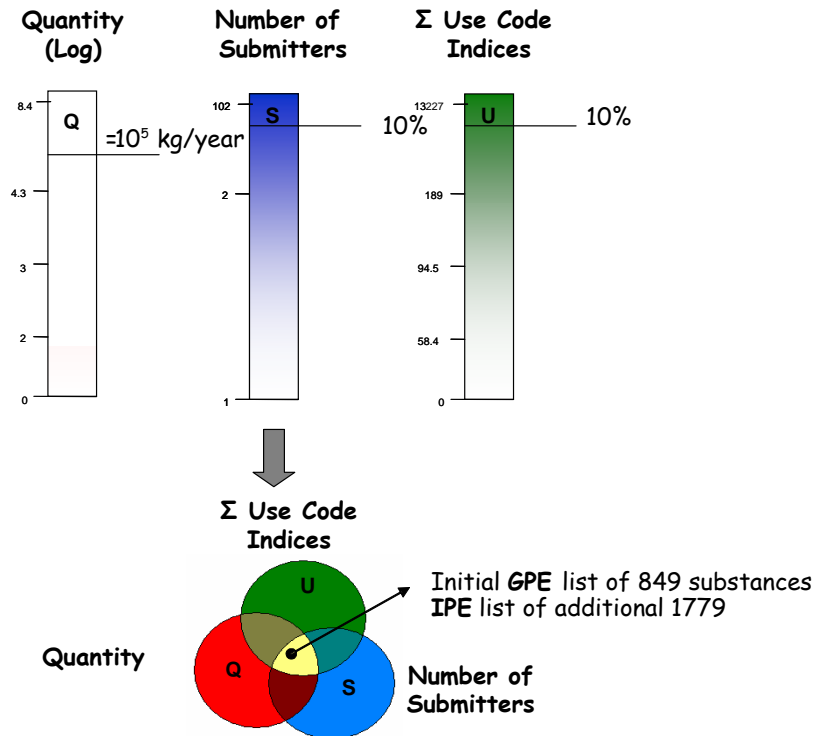
Figure 8. Simple Exposure Tool (SimET): Relative ranking for all DSL substances

Table 1. 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

Relevant supporting documentation for the development of SimET is referenced in Part F.

The Simple Hazard Tool (SimHaz)

SimHaz is a discriminating tool that identifies, among all of the approximately 23 000 substances on the DSL, those 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. Systems developed by national or international agencies in which large numbers of substances have been classified for endpoint-specific hazard based on original review and critical evaluation of data, assessments of weight of evidence and extensive expert peer review have been preferred for inclusion in the high- or low-hazard components of SimHaz (see Table 2).

Table 2. SimHaz Endpoint-Specific Criteria for Identifying High- and Low-Hazard Substances on the DSL

Endpoint	National or international agency	Classification
High-hazard substances		
Carcinogenicity	European Community	• Category 1 (Known to be carcinogenic to humans) • Category 2 (Regarded as if carcinogenic to humans) • Category 3 (Causes concern for humans owing to possible carcinogenic effects)
	Health Canada (Guidelines for Canadian Drinking Water Quality)	• Group I (Carcinogenic to humans) • Group II (Probably carcinogenic to humans) • Groups IIIA and IIIB (Possibly carcinogenic to humans)
	International Agency for Research on Cancer	• Group 1 (Carcinogenic to humans) • Group 2A (Probably carcinogenic to humans) • Group 2B (Possibly carcinogenic to humans)
	National Toxicology Program	• Known to be a human carcinogen • Reasonably anticipated to be a human carcinogen
	United States Environmental Protection Agency (US EPA) 1986 Carcinogenicity Guidelines	• Group A (Human carcinogen) • Groups B1 and B2 (Probable human carcinogen) • Group C (Possible human carcinogen)
	US EPA 2003 Carcinogenicity Guidelines	• Carcinogenic to humans • Likely to be carcinogenic to humans • Suggestive evidence of carcinogenicity, but not sufficient to assess • Human carcinogenic potential
Genotoxicity	European Community	• Category 1 (Known to be mutagenic to humans) • Category 2 (Regarded as if mutagenic to humans) • Category 3 (Causes concern for humans owing to possible mutagenic effects)
Developmental toxicity	European Community	• Category 1 (Known to cause developmental toxicity in humans) • Category 2 (Regarded as if they cause developmental toxicity in humans) • Category 3 (Causes concern for humans owing to possible developmental toxic effects)
Reproductive toxicity	European Community	• Category 1 (Known to impair fertility in humans) • Category 2 (Regarded as if they impair fertility in humans) • Category 3 (Causes concern for human fertility)
Respiratory sensitization	European Community	• May cause sensitization by inhalation

Endpoint	National or international agency	Classification
Low-hazard substances		
Low hazard	Health Canada, Pest Management Regulatory Agency	• Pesticide Formulant 4A List – Formulants of Minimal Toxicological Concern[a]
	Organisation for Economic Co-operation and Development	• Draft list of chemicals that do not need assessment in the High Production Volume Chemicals Programme

[a] Based on US EPA Minimal Risk Inerts List 4A.

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. As presented in Table 2, these include carcinogenicity, mutagenicity, reproductive and developmental toxicity and/or respiratory sensitization. The hazard classification systems considered relevant and appropriate based on the criteria mentioned above for both the high- and low-hazard components of SimHaz are included in Table 2.

There were large numbers of classification systems considered but not included in SimHaz because they did not meet the specified criteria indicated above (i.e., original review and critical evaluation of data, assessment of weight of evidence and extensive expert peer review). These and the basis for their lack of inclusion are presented in Appendix I.

The basis for lack of inclusion in the high-hazard component was often related to the paucity of documentation available to support transparent and robust consideration of weight of evidence. In other cases, identified compilations were simply secondary accounts without documentation of associated criteria and/or process for development.

The lack of applicability of identified systems for the low-hazard component was often a function of their not being restricted to hazard (e.g., taking into account exposure for specific applications such as expected exposure as a food additive used under specified conditions). Since exposure is considered independently in the integrated framework in a more encompassing Canadian multiuse and multimedia context, content of the SimHaz tool is restricted to hazard-based systems. Alternatively, some lists of compounds considered to be of low concern represented assimilations of "grandfathered" substances for which there was no indication of transparent and accountable assessment (e.g., "Generally Recognized as Safe" [GRAS] lists) and as a result, they were not considered to meet the criteria specified above.

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. However, it is biased to identification of substances for which there are a considerable number of data available; while it identifies those substances that are priorities for assessment and, potentially, subsequent control, it is less relevant to the identification of substances for which data generation is required.

Relevant supporting documentation for the development of SimHaz is referenced in Part F.

The Complex Hazard Tool (ComHaz)

ComHaz involves consideration of information on multiple health endpoints in a hierarchical fashion (Figure 9). It also includes several iterative stages, the first of which is based on a conservative "first hit" approach for data and endpoints based on specified criteria; the next stage involves preliminary consideration of weight of evidence for qualitative endpoints of capture (e.g., cancer, genotoxicity); and the final stage compares exposure–response for critical endpoints with quantitative output of the tool.
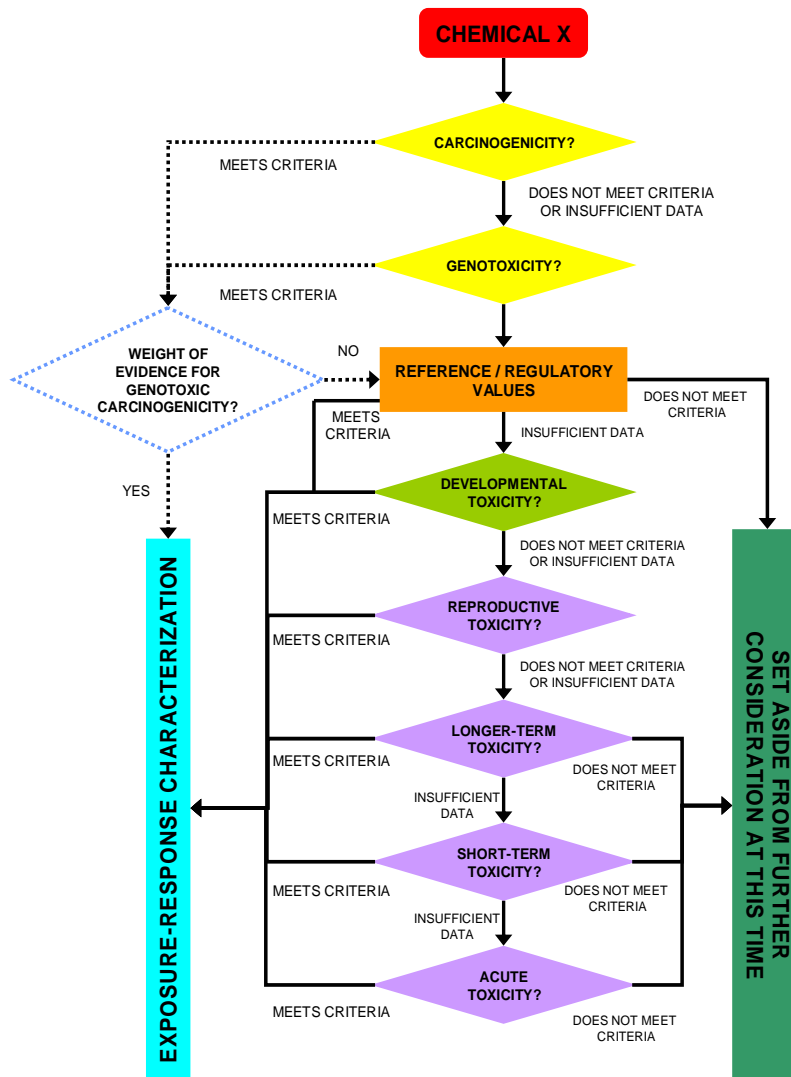

Figure 9. ComHaz endpoint hierarchy

The initial conservative stage of ComHaz was 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 (i.e., organic substances and organic UVCBs that are also persistent or bioaccumulative). This constituted the basis for identification of some of the

substances on the maximal list considered to be low priorities for consideration beyond 2006 (i.e., some of the substances included in the "low likelihood" group).

Substances on the maximal list are currently being considered in the additional stages of ComHaz as a basis to focus and efficiently prepare screening assessments post-2006.

The endpoints in ComHaz were selected based on potential public health impact and the likelihood of available information. For each endpoint in the hierarchy, there are criteria against which identified information is considered to determine whether a specific substance should be prioritized additionally. It is important to recognize that all available identified data are considered within the hierarchy with that on, for example, neurotoxicity and immunotoxicity being considered within the subsets of short or long term toxicity. Endpoints such as endocrine disruption are addressed under subsets such as developmental and reproductive toxicity.

For each substance, relevant data on the specified endpoints are considered sequentially in the order indicated in Figure 9. If the substance meets one of the endpoint-specific criteria based on identified information, it is prioritized for further consideration. If, based on available information, the substance does not meet any of the endpoint-specific criteria, it is set aside from further consideration at this time (e.g., some of the substances in the "low likelihood" group of the maximal list — i.e., those for which the likelihood of their remaining as priorities for screening beyond 2006 is low).

The qualitative and/or quantitative criteria for each of the endpoints included in ComHaz are presented in Table 3. For carcinogenicity and genotoxicity, the criteria are qualitative, while for developmental toxicity, both qualitative and quantitative criteria are proposed, depending upon the source of information. Criteria for regulatory/reference values, reproductive toxicity, longer-term toxicity, short-term toxicity and acute toxicity are quantitative.

Table 3. ComHaz Endpoint-Specific Qualitative and Quantitative Criteria

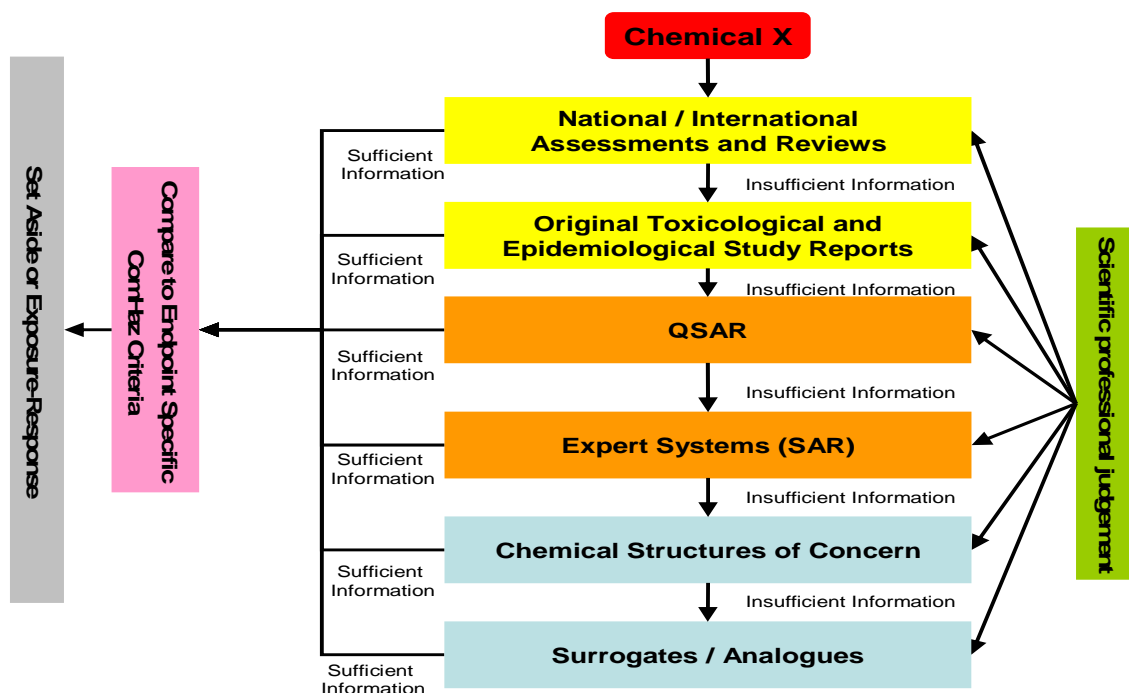| Endpoint	Type of criteria	Sources of information	Description of criteria	
Carcinogenicity	Qualitative	Data or (Q)SAR	First hit, weight of evidence	
Genotoxicity	Qualitative	Data or (Q)SAR	First hit, weight of evidence	
Regulatory/ reference values	Quantitative	Assessments from international/national agencies	Oral: Inhalation: Dermal:	≤ 0.1 mg/kg bw per day ≤ 0.4 mg/m^3 NA
Developmental toxicity	Quantitative	Data	Oral/dermal: Inhalation:	LO(A)EL ≤ 270 mg/kg bw per day NO(A)EL ≤ 90 mg/kg bw per day LO(A)EC ≤ 810 mg/m^3 NO(A)EC ≤ 270 mg/m^3
	Qualitative	(Q)SAR	Sufficient positive evidence[a]	
Reproductive toxicity	Quantitative	Data	Oral/dermal: Inhalation:	LO(A)EL ≤ 30 mg/kg bw per day NO(A)EL ≤ 10 mg/kg bw per day LO(A)EC ≤ 90 mg/m^3 NO(A)EC ≤ 30 mg/m^3
Longer-term toxicity	Quantitative	Data or (Q)SAR (where appropriate)	Oral/dermal:	LO(A)EL ≤ 30 mg/kg bw per day NO(A)EL ≤ 10 mg/kg bw per day

Endpoint	Type of criteria	Sources of information	Description of criteria	
			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: Inhalation: IP injection:[b] IV injection:[b]	$LD_{50} \leq 500$ mg/kg bw $LC_{50} \leq 1500$ mg/m^3 $LD_{50} \leq 219$ mg/kg bw $LD_{50} \leq 154$ 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, with those in which there is greatest confidence being addressed initially (Figure 10). 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.

Figure 10. ComHaz hierarchical consideration of sources of information

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. Unlike SimHaz, there is no bias towards data-rich substances, with the output of ComHaz identifying true priorities for both testing and assessment. While ComHaz is more resource intensive than SimHaz, its application in increasingly discriminating iterative stages allows high throughput and ensures optimum efficiency.

Additional information on ComHaz, including, for example, the nature of output of (Q)SAR modelling and a brief description of the preliminary weight of evidence approach, is included in Appendix II. Relevant supporting documentation for the development of ComHaz is referenced in Part F.

The Complex Exposure Tool (ComET)

Whereas SimET relatively ranks all substances on the DSL in relation to their potential for exposure based on the relatively limited information submitted during compilation of the DSL, ComET provides more refined, quantitative estimates of exposure. Comparison of the output of ComET (i.e., route- and duration-specific or total estimates of exposure of the general population) with measures of exposure–response for relevant critical effects leads to substances being set aside from further consideration or prioritized for additional assessment. Post-2006, ComET will also contribute to efficient screening, delineating the focus of subsequent assessment.

Application of ComET leads to quantitative plausible maximum estimates of exposure of individuals in the general population by age group based on use scenario (sentinel products and emissions), physical/chemical properties and bioavailability. The tool encompasses estimation of both environmental (far-field) and consumer (near-field) exposure, the latter being based on "sentinel products" — i.e., those products yielding the highest estimates of exposure for individuals in different age groups.

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.

The conceptual elements of ComET are presented in Figure 11. Essentially, ComET integrates estimates of exposure to sentinel products ("near field") with estimates of exposure from media in the general environment (e.g., air, water, food, etc.). Coupling of estimated exposures from sentinel products and the ambient environment with age classes and daily intakes of the general population developed for Existing Substances under CEPA 1999 results in route-, duration- and age group-specific estimates of total exposure.
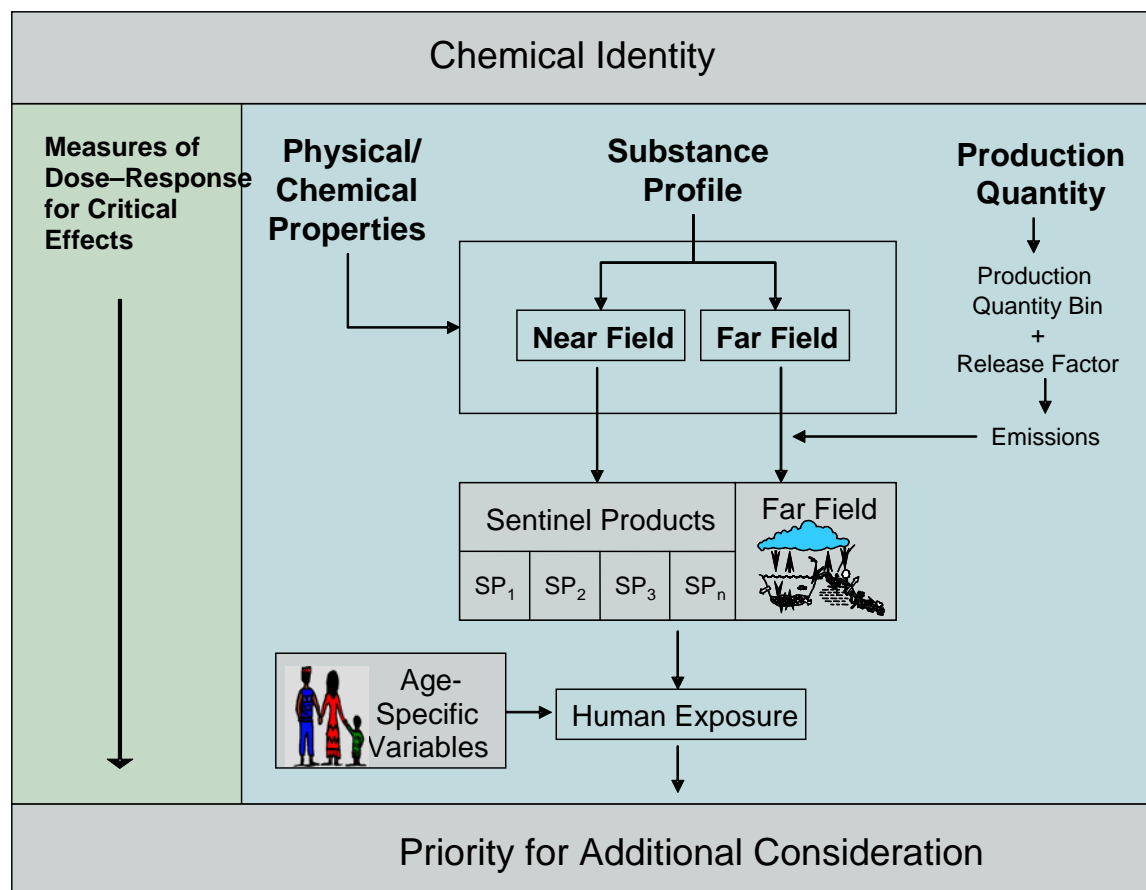
Figure 11. Conceptual elements of ComET

Near-Field Exposures ("Sentinel Products")

Near-field exposures are those that occur through the direct use of a product. The default assumptions used in ComET are based on assumptions about maximum concentrations of substances used for broad functions in products, which are derived from publicly available generic information. Based on this generic information, a library of sentinel products has been developed. Sentinel products are the types of consumer products that are judged to potentially yield the highest exposures of individuals for substances included for specific functions. The library of sentinel products includes, for example, those used every day and frequently throughout the day (e.g., some cosmetics), those in intimate and prolonged contact with the skin (e.g., products used in clothing, swimming pools, bathing water, bedding, jewelry), liquid products prone to be splashed onto the skin during use (e.g., cleaning products, photo-processing chemicals), those providing a large surface area of vaporizing substance (e.g., fresh paint), those in which relatively high concentrations are required for the specified function (e.g., solvent in paint stripper), those with an expected "dusty" application (e.g., polymers used to amend garden soil), those purposely emitted into indoor air (e.g., air fresheners), etc.

For each of the sentinel products within the library, algorithms to estimate exposure for various scenarios of use are developed. For example, for the sample sentinel product "liquid window cleaner," algorithms have been developed to estimate both dermal and inhalation exposure.
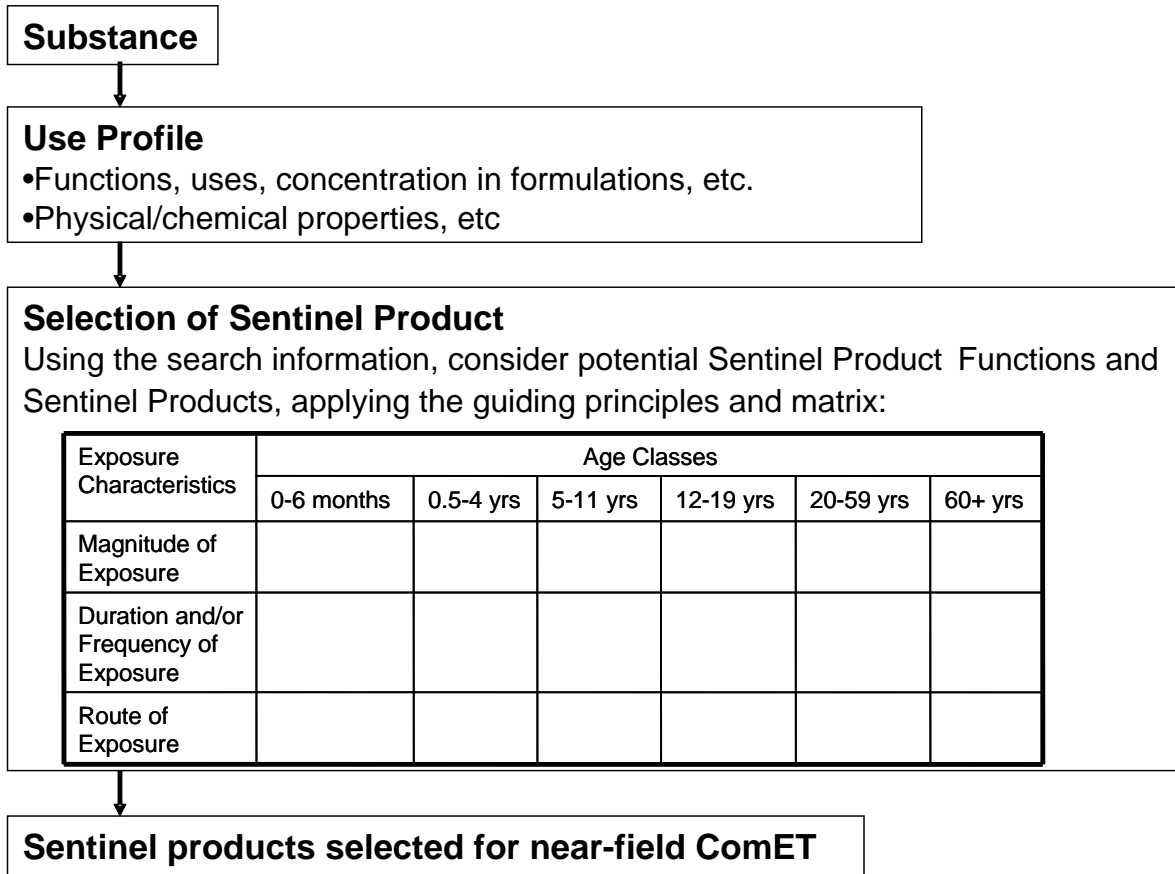
The sentinel products are additionally grouped into broader classes (e.g., "Food items," Paints" and "Tobacco products" for the corresponding sentinel products of "bread, meat, etc.," "latex paints, enamels, varnishes, etc." and "cigarettes, chewing tobacco, etc.," respectively).

Individual or groups of substances are then matched to sentinel products based on generic information about their use for specific functions (i.e., compound- or chemical class-specific use profiles). The selected sentinel products are those believed to present the greatest potential for exposure of either the general population or a subpopulation thereof.

The steps involved in the matching of specific substances to the appropriate sentinel products from among those in the library are presented in Figure 12. Following a robust search of public information to identify generic uses of individual substances (e.g., as a surfactant in detergents or preservative in paints), relevant chemical- or group-specific sentinel products are selected through consensus consideration of experts, taking into account the nature of use of different types of products.

Substance

↓

Use Profile
•Functions, uses, concentration in formulations, etc.
•Physical/chemical properties, etc

↓

Selection of Sentinel Product
Using the search information, consider potential Sentinel Product Functions and
Sentinel Products, applying the guiding principles and matrix:

Exposure Characteristics	Age Classes					
	0-6 months	0.5-4 yrs	5-11 yrs	12-19 yrs	20-59 yrs	60+ yrs
Magnitude of Exposure						
Duration and/or Frequency of Exposure						
Route of Exposure						

↓

**Sentinel products selected for near-field ComET**

Figure 12. Selection of sentinel products for near-field component of ComET

Far-Field Exposures

The conceptual approach to estimation of far-field exposures (an individual's exposure to a
substance from environmental media [air, water or soil] or from consumption of biota [fish,
game or vegetables]) is presented in Figure 13.
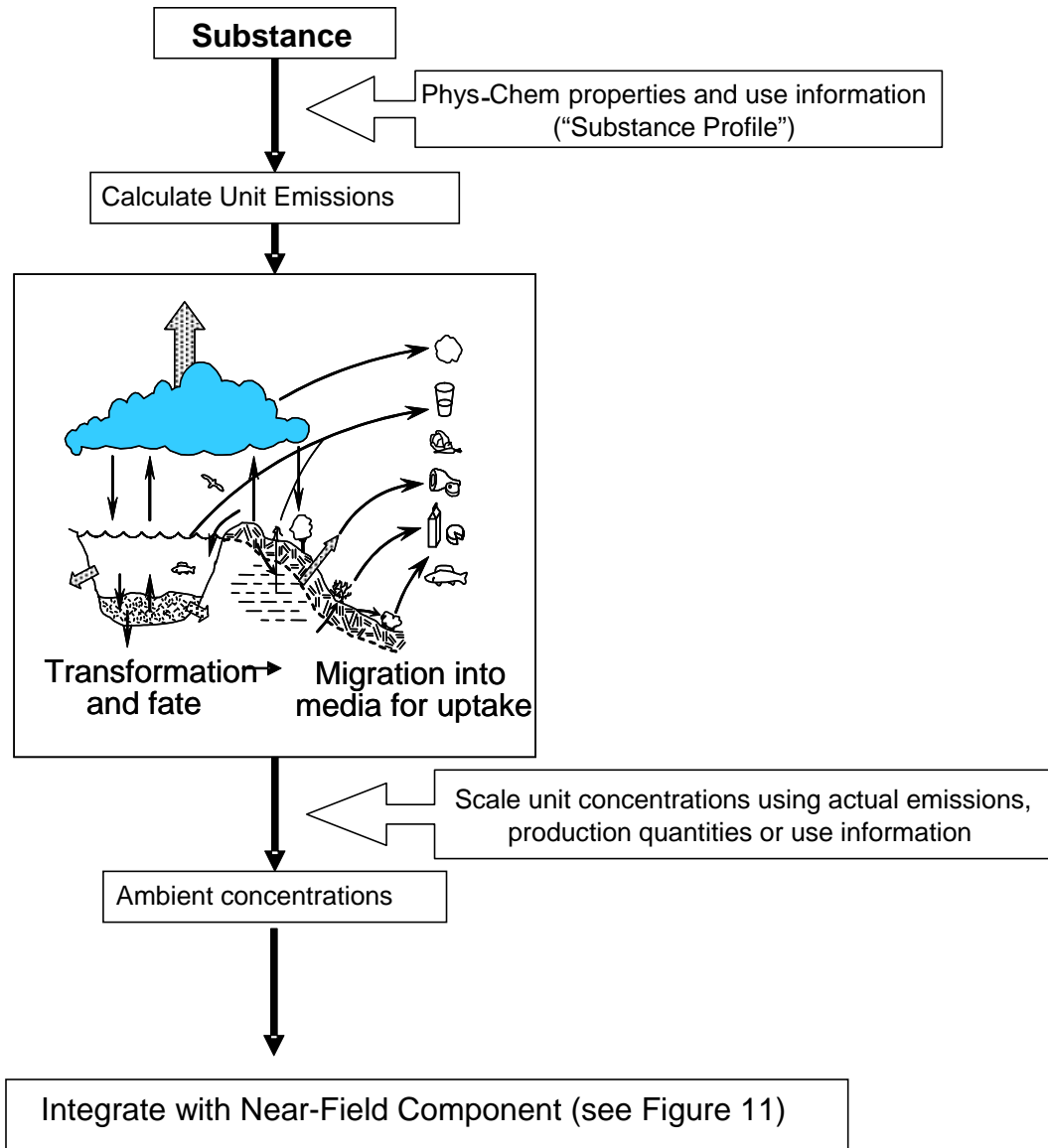
Figure 13. The approach to far-field exposures

Estimation of media-specific concentrations is based on a Level III or steady-state fugacity model, which is essentially identical to ChemCAN in structure. Coupling of model output with generic food webs provides the necessary input for integration with the near-field component of ComET.

As far as possible, estimated environmental concentrations are based on identified data for quantities, emissions, physical/chemical properties, half-lives, etc. In the absence of data, conservative assumptions are made.

PART D: DRAFT "MAXIMAL" LIST OF SUBSTANCES PRIORITIZED BY HEALTH CANADA FOR CONSIDERATION IN SCREENING ASSESSMENT

Based on application of the "tools" to date, a maximum of 1896 substances (i.e., the draft "maximal" list) (Figure 14) has been identified that will be further considered in additional stages of prioritization/screening assessment (i.e., categorization) (see http://www.hc-sc.gc.ca/hecs-sesc/exsd/maximal_list.htm). These substances have been identified on the basis of greatest potential for exposure of the general population in Canada (GPE) (see Table 1) and "inherently toxic" to humans (IThuman), taking into account the potential for persistence (P) and bioaccumulation (B) where such properties may meaningfully contribute to human exposure.
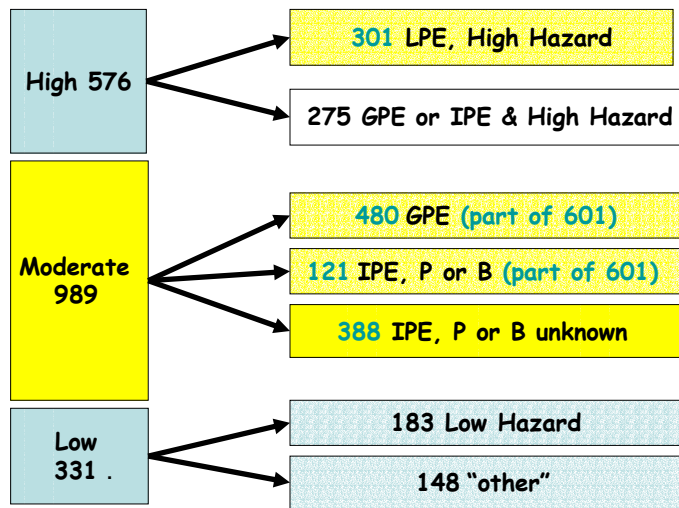

Figure 14. Maximal list

Health Canada released this draft "maximal" list to focus the submission of solicited information (see http://www.hc-sc.gc.ca/hecs-sesc/exsd/info.htm) on the identity, use and/or toxicity of any substance prioritized for further consideration. The early release of this draft "maximal" list has provided 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 the Act. It has also enabled identification of subgroups of substances where submission would be most helpful.

This list has been divided into three groups of substances considered to have a high, moderate or low likelihood of remaining as health priorities following the completion of DSL categorization — that is, as substances for which screening assessments are required.

The "high likelihood" group of 576 substances is composed of 275 substances considered to be either GPE or IPE (using SimET) and high hazard (based upon SimHaz) and 301 substances considered as high hazard (based upon SimHaz) but LPE (using SimET).

For the group of 301 substances considered as high hazard and LPE (see http://www.hc-sc.gc.ca/hecs-sesc/exsd/substance_tables/substances_low_potential_exposure_high_hazard.htm), Health Canada is soliciting from industry information or proposals on the use and extent of current and/or potential options for risk management of substances in this group that would reduce their priority for further consideration in screening assessment.

The "moderate likelihood" group of 989 substances is composed of 480 substances considered GPE (using SimET), 121 substances considered IPE (using SimET) that have also been identified by Environment Canada as either P and/or B and not ITeco (organics and organic UVCBs) and 388 substances considered IPE (using SimET) for which determinations of P or B have yet to be completed.

For these latter 388 substances, submission of information on their persistence or bioaccumulation to Environment Canada and subsequent consideration of this information by Environment Canada (see http://www.hc-sc.gc.ca/hecs-sesc/exsd/substance_tables/substances_intermediate_potential_exposure.htm) could result in their not being additionally prioritized. If any of these 388 substances are deemed to be neither P nor B, they will be moved to the "low likelihood" group of the maximal list and not considered additionally as priorities for screening in 2006.

To the extent possible prior to the 2006 deadline, Health Canada will apply iterative additional stages of ComHaz to the remaining 601 compounds (e.g., 121 + 480) in the "moderate likelihood" group, which may result in their eventually being considered as either high or low priority for screening assessment post September 2006.

The "low likelihood" group is composed of 183 substances identified as low hazard using SimHaz or ComHaz and 148 substances identified as GPE or IPE and potentially P and/or B and not ITeco (organics and organic UVCBs) that are also:
- on the first or second PSL (PSL1 or PSL2); or
- on Schedule 1 or 3 of CEPA 1999; or
- reactants on Schedule X or polyesters in the New Substances Notification Regulations (NSNR); or
- (GPE) polymers with no structural alerts as defined in Schedule IX of the NSNR.

It is most likely that these substances will be omitted from the list of substances prioritized in relation to human health in 2006. However, Health Canada is currently verifying the basis for their lack of prioritization at this time.

PART E: NEXT STEPS

Next steps (Figure 15) associated with refinement of the maximal list as part of implementation of the integrated framework for the health-related components of DSL categorization include:

- Soliciting information on substances on the maximal list. Identified priorities for submission of relevant information include current risk management activities for the specified 301 high-hazard, low-exposure substances in the "high likelihood" group, information on exposure and hazard for the 601 compounds to which the complex tools are being applied[2] and data relevant to P or B determinations for the 388 selected compounds, both of which are in the "moderate likelihood" group.
- Application of ComET and ComHaz to the 601 substances in the "moderate likelihood" group mentioned above.
- Refinement of the framework based on comments received on this proposal.
- Posting of the final framework in late 2005.
- Initiation of compilation of relevant information for planning purposes for screening assessments for substances that are highest priorities for additional consideration from a human health perspective. (This includes a subset of 275 substances that are included in the "greatest potential for exposure" or "intermediate potential for exposure" group and that are also flagged as "high hazard"; Figure 14.)
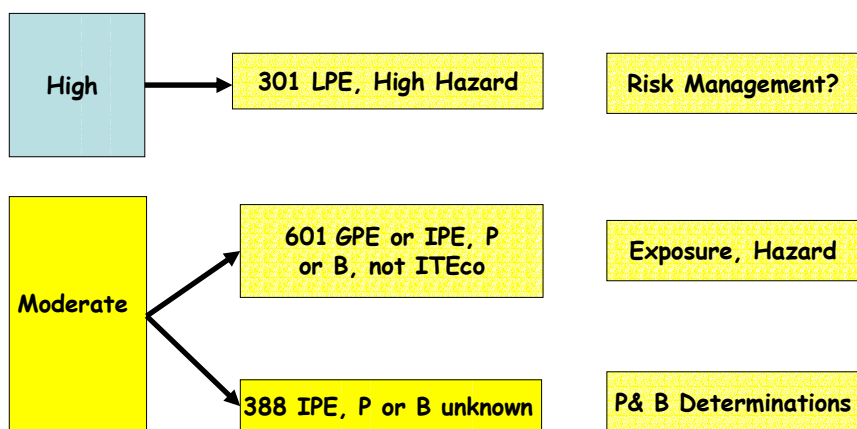

Figure 15. Maximal list: Focus for submission of additional information

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[2] Particularly, UVCBs, polymers and substances with a wide range of use.

PART F: LIST OF SUPPORTING DOCUMENTATION TO THE PROPOSED INTEGRATED FRAMEWORK[3]

SimET

Categorization of the Domestic Substances List for Greatest Potential for Human Exposure (http://www.hc-sc.gc.ca/hecs-sesc/exsd/categorization_dsl_human_exposure.htm).

Report on Workshop to Consider DSL Industrial Sector and Functional Use Codes as Indicators of Potential Human Exposure, 1st Workshop (Government Experts), May 30, 2000.

Report on Workshop to Consider DSL Industrial Sector and Functional Use Codes as Indicators of Potential Human Exposure, 2nd Workshop (Industry Experts), October 18, 2002.

A Study to Determine Currency of DSL Quantity Data for Use in Categorization of DSL Substances, Report prepared by E. Doyle and H. Patterson, Exposure Assessment Section, Existing Substances Division, Health Canada, August 2001.

ComET

Health Canada Hosts Meeting to Invite Submission of Information for the Complex Exposure Tool (ComET) (http://www.tera.org/peer/Exposure/ExposureWelcome.htm).

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/hecs-sesc/exsd/info.htm).

Peer Input Meeting Inviting Submission of Information for the Complex Exposure Tool (ComET) (http://www.hc-sc.gc.ca/hecs-sesc/exsd/tera_peer_input_meeting.htm).

Report on the ComET Peer Input Meeting, November 8, 2004, Toxicology Excellence for Risk Assessment, December 2004.

SimHaz

Criteria for National/International Assessments Used in the Simple Hazard Tool for Prioritization of Substances on the Domestic Substances List, Existing Substances Division, Health Canada, January 2005.

Identification and Review of Toxicity Classification Systems, GlobalTox International Consultants Inc., May 2002.

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[3] Information is available at http://www.hc-sc.gc.ca/exsd-dse, or unpublished supporting documentation is available upon request from: ExSD@hc-sc.gc.ca.

Identification of International and National Agencies' Lists of Substances That Are Considered to Be Toxicologically Inert, to Be of Low Concern or to Not Require Hazard or Risk Assessment, AMEC Earth and Environmental, March 2004.

Identification of Lists of Substances Considered to be Toxicologically Inert and of Low Concern, GlobalTox International Consultants Inc., March 2004.

Safe Substances: Existing Lists, Criteria, Rationale and Use, Report prepared by M.E. Starodub and J. Orr, Human Health and Environmental Toxicology, March 2004.

ComHaz

Categorization of Substances on the Domestic Substances List (DSL) for Inherent Toxicity to Humans: Analysis of the Approach and Criteria for Categorization, TNO BIBRA International Ltd., March 2002.

Documentation of Cutpoints Used for Initial Categorization of Organic Substances for Inherent Toxicity to Humans under Health Canada's Domestic Substances List, Toxicology Excellence for Risk Assessment, October 2004.

Final Report on "Quantitative Structure–Activity Relationship (QSAR) Computer-Based Models for the Prediction of Toxicity," Parts 1 and 2, Report prepared by M. Cronin, Liverpool John Moores University, April 2002.

Peer Consultation on Genotoxicity for Categorization of "Inherent Toxicity" to Humans under CEPA '99, Workshop Report, Report prepared by the International Life Sciences Institute, Risk Science Institute, for the Existing Substances Division, Safe Environments Programme, Health Canada, December 2002.

Search Strategy for the Identification of Toxicological Data Relevant for Categorization on the Basis of Health Hazard, Existing Substances Division, Health Canada, March 2005.

Draft Maximal List

Draft "Maximal" List of Substances Prioritized by Health Canada for Consideration in Screening Assessment under CEPA 1999 (http://www.hc-sc.gc.ca/hecs-sesc/exsd/maximal_list.htm).

Screening Health Assessments

Draft Health Canada Screening Assessments (http://www.hc-sc.gc.ca/hecs-sesc/exsd/screening_assessment.htm).

Screening Assessment of Existing Substances (http://www.hc-sc.gc.ca/hecs-sesc/exsd/screening_assessment_of_existing_sub.htm).

Meeting Reports of Stakeholder Information Sessions

Health-Related Components of Categorization of the Domestic Substances List, Information Session, Holiday Inn Hotel, Toronto, Ontario, Session Report, November 22, 2004.

Report on the Existing Substances Division, Healthy Environments and Consumer Safety Branch, Health Canada, Information Briefing, March 8, 2004, Delta Toronto Airport West, Toronto, Ontario.

Additional Program Information

Existing Substances Division (http://www.hc-sc.gc.ca/exsd-dse).

APPENDIX I: ADDITIONAL LISTS CONSIDERED FOR INCLUSION IN THE SIMPLE HAZARD TOOL

In addition to the classification lists of other agencies accepted for inclusion in the Simple Hazard Tool (SimHaz), a number of lists of other agencies were also considered, but not incorporated. Many of the lists were not comprehensive and were risk based rather than hazard based, related to consideration in the context of specific intended uses. Some lists did not involve primary evaluation of relevant data, but were simply extracted from those prepared by others. In many cases, adequate documentation of the criteria applied in development of specific lists was not available.

The lists considered but not incorporated into the high- and low-hazard components of SimHaz are presented in Table AI-1 and Table AI-2, respectively, along with the rationales as to why they were not considered suitable.

Table AI-1. Lists Not Incorporated into the High-Hazard Component of SimHaz

Organization	Description	Rationale for not including in SimHaz	Reference
Organisation for Economic Co-operation and Development (OECD)	Criteria developed in the context of global harmonization of risk assessments for chemical toxicity Compilation of screening information data sets (SIDS) and SIDS initial assessment reports (SIAR)	No lists of substances classified according to required criteria	OECD (2003) Description of OECD Work on Investigation of High Production Volume Chemicals. Manual for Investigation of HPV Chemicals. Environment Directorate, Organisation for Economic Co-operation and Development. http://www.oecd.org/document/21/0,2340,en_2649_34379_1939669_1_1_1_1,00.html l (accessed July 2004)
California Environmental Protection Agency (EPA)	Proposition 65 List: List of chemicals known to the State of California to cause cancer or reproductive toxicity Regulated under the *Safe Drinking Water and Toxic Enforcement Act* of 1986	Secondary list	California EPA (2004) Proposition 65. The Safe Drinking Water and Toxic Enforcement Act of 1986. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. http://www.oehha.ca.gov/prop65/prop65_list/Newlist.html (accessed June 2004)
Canadian Environmental Law Association and Pollution Probe	Canadian list of substances of concern to children's health based on Scorecard lists of both recognized and suspected toxicants prepared by the Environmental Defense Fund	Secondary list	Canadian Environmental Law Association and Pollution Probe (2004) Toxic Substances — Focus on Children. Developing a Canadian List of Substances of Concern to Children's Health. Environmental Defense Fund. Scorecard — Health Effects.

Organization	Description	Rationale for not including in SimHaz	Reference
			http://www.scorecard.org/health-effects/ (accessed June 2004)
Pest Management Regulatory Agency (PMRA), Health Canada	Lists of pesticide formulants List 1 (Formulants of toxicological concern) and List 2 (Potentially toxic formulants with a high priority for testing)	List 1 is mainly a secondary list and may also contain substances listed solely for ecological considerations List 2 flags formulants that are a high priority for testing based on structural similarity to List 1 formulants or based on data suggestive of toxicity (no weight of evidence assessment)	Health Canada (2004) Formulants Program. Regulatory Directive DIR2004-01. Pest Management Regulatory Agency, Health Canada, Ottawa, Ontario. http://www.hc-sc.gc.ca/pmra-arla/english/pdf/dir/dir2004-01-e.pdf (accessed February 2004) Health Canada (2004) PMRA List of Formulants. Regulatory Note REG2004-01. Pest Management Regulatory Agency, Health Canada, Ottawa, Ontario. http://www.hc-sc.gc.ca/pmra-arla/english/pdf/reg/reg2004-01-e.pdf (accessed February 2004)

Table A1-2. Lists Not Incorporated into the Low-Hazard Component of SimHaz

Organization and name of list	Types of substance on list	Basis of list (hazard/risk/use/ other)	Rationale for not including in SimHaz	Reference
JECFA Compendium of Food Additive Specifications – Flavouring Agents and Food Additive Databases	Food additives, flavouring agents and enzyme preparations – range of substance types	Where possible, ADI is derived; some evaluations are risk or exposure based	Listing may include exposure evaluation or limits on use of substance	Specifications for Food Additives and Flavouring Agents. Joint FAO/WHO Expert Committee on Food Additives (JECFA). http://jecfa.ilsi.org/index.htm (accessed February 2004)
The WHO Recommended Classification of Pesticides by Hazard – Table 5	Technical-grade active pesticidal ingredients – mainly organics	Based on acute hazard (some exceptions)	Principally based on a single hazard endpoint	The WHO Recommended Classification of Pesticides by Hazard (2000–2002) International Programme on Chemical Safety, World Health Organization. http://www.who.int/pcs/docs/Classif_Pestic_2000-02.pdf (accessed February 2004)
EC (European Food Safety Authority) – List of Flavouring Substances	Mainly food additives (organics and mixtures)	Risk assessment based on exposure from food	Use pattern considered (food)	List of Flavouring Substances. European Food Safety Authority, European Commission (EC). http://www.europa.eu.int/comm/food/fs/sfp/addit_flavor/flavourings/index_en.html (accessed February 2004)

Organization and name of list	Types of substance on list	Basis of list (hazard/risk/use/ other)	Rationale for not including in SimHaz	Reference
				http://www.europa.eu.int/comm/food/food/chemicalsafety/flavouring/list_en.pdf (accessed April 2005) Legislated under Commission Regulation No. 1565/2000
European Economic Community (EEC) Lists of Veterinary Products Falling Out of Scope of EC Regulations	Excipients (organics, mixtures); food products (organics, mixtures); and chemically unidentified substances of natural origin (organics, mixtures, etc.)	Based on substances that do not fall under the scope of Council Regulation EEC No. 2377/90, which regulates residues of veterinary medicinal products defined as "pharmacologically active substances, whether active principals, excipients or degradation products, and their metabolites which remain in foodstuffs obtained from animals to which the veterinary medicinal product in question has been administered"	Veterinary use is initial determinant for listing	Substances considered as not falling within the scope of Council Regulation (EEC) No. 2377/90 (Revision 5 – May 2003). European Agency for the Evaluation of Medicinal Products. http://pharmacos.eudra.org/F2/mrl/conspdf/mrl_outofscope_r5_20030527.pdf (accessed February 2004) Legislated under Regulation (EEC) No. 2377/90
EC – List of Permitted Food Colours, Sweeteners and Other Additives	Mainly food additives, food colours and sweeteners, including organics and mixtures of compounds	Rationale of the EC was to establish a list of food additives, colours and substances that were authorized to the exclusion of all others That list was established following the evaluation of	Use pattern considered (food)	List of Permitted Food Colours, Sweeteners and Other Food Additives. Health and Consumer Protection Division, European Commission. http://www.europa.eu.int/comm/food/fs/sfp/addit_flavor/additives/index_en.html (accessed February 2004) http://europa.eu.int/eur-lex/en/consleg/pdf/1995/en_

Organization and name of list	Types of substance on list	Basis of list (hazard/risk/use/ other)	Rationale for not including in SimHaz	Reference
		those substances used in or on foodstuffs in the European Region		1995L0002_do_001.pdf (accessed April 2005) Legislated under Article 1(2) of Directive 89/107/EEC
Health Canada (PMRA) – Lists of formulants List 4B – Formulants of minimal concern under specific conditions of use	Organics, inorganics, salts, UVCBs, polymers	Risk based	Use pattern considered	Health Canada's List of Formulants. Pest Management Regulatory Agency, Health Canada http://www.hc-sc.gc.ca/pmra-arla/english/pdf/dir/dir2004-01-e.pdf (accessed February 2004)
Health Canada (Natural Health Products Directorate) – Non-medicinal ingredients list	Compounds listed generally considered to be organics and mixtures of organics Types of compounds could include herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids and essential fatty acids	List was created to provide information to Canadians and other concerned stakeholders on the types of non-medicinal (as opposed to medicinal) ingredients used in health products that are available to Canadians	Listing based on use as non-medicinal ingredient – not based on hazard assessment	List of Acceptable Non-Medicinal Ingredients. Natural Health Products Directorate, Health Products and Food Branch, Health Canada. http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/nmi_list10_e.html (accessed February 2004)
Health Canada – List of Food Additives Permitted for Use in Canada	Organic and inorganic compounds, including mixtures	Risk based, based on levels in food	Use pattern considered (food)	List of Food Additives Permitted for Use in Canada. Food Additives and Contaminants Section, Chemical Health Hazard Assessment Division, Bureau of Chemical Safety, Health Canada.
Health Canada (PMRA) – Reduced Risk Pesticide Program	Synthetic and natural biopesticide products	Factors that are used and are likely to contribute significantly to the granting of reduced-risk status include human health effects, very low	Reduced risk, but not necessarily low hazard	The PMRA Initiative for Reduced-Risk Pesticides. Regulatory Directive DIR2002-02. Pest Management Regulatory Agency, Health Canada. http://www.hc-sc.gc.ca/pmra-arla/english/pdf/dir/dir2002-

Organization and name of list	Types of substance on list	Basis of list (hazard/risk/use/ other)	Rationale for not including in SimHaz	Reference
		mammalian toxicity, toxicity generally lower than alternatives (10–100×)		02-e.pdf (accessed February 2004)
Health Canada (Bureau of Chemical Safety) – "SURE" List (Safety Universally Recognized) – Unofficial list name	Food additives (e.g., organics, UVCBs, inorganics)	Based on use as food additive Criteria for inclusion on list: 1) Food additive approved for use in Canada 2) Assigned a Not Limited or Not Specified ADI by JECFA 3) Health Canada Bureau of Chemical Safety staff toxicologists concur with Not Limited or Not Specified ADI established by JECFA	Restricted by good manufacturing practice levels of use Majority of substances have a Not Specified ADI Oral exposure only considered	Personal communication with Bureau of Chemical Safety, Health Canada
New Zealand Food Safety Authority (NZFSA) – GRAS Register for Oral Nutritional Compounds	Oral nutritional compounds for agricultural compounds and veterinary medicines	Risk based: "Substances listed on these Registers must have a proven history of safety when used appropriately, in a variety of different products. In order to be listed on the Registers, substances must also not have a potential health risk to animals or food, or be a source of undesirable organisms."	Veterinary and agricultural use are initial determinants for listing	New Zealand Food Safety Authority (NZFSA) (2002) ACVM Information Requirements for Classification of Substances Generally Regarded as Safe (GRAS). Agricultural Compounds and Veterinary Medicines Group, Ministry of Agriculture and Food. Agricultural Compounds and Veterinary Medicines Group (ACVM) (2000) Classification of Substances as Generally Recognised as Safe (GRAS). New Zealand Food Safety Authority (NZFSA).
NZFSA – GRAS Register for Plant Compounds	Plant compounds used in agricultural or veterinary medicines			

Organization and name of list	Types of substance on list	Basis of list (hazard/risk/use/ other)	Rationale for not including in SimHaz	Reference
NZFSA – GRAS Register for Veterinary Medicines	All veterinary medicines (not including oral nutritional compounds)			
NICNAS – Australia's Draft Synthetic Polymers of Low-Concern Programme	Current list includes reactants from which polymers may be made (other substances will be included)	In progress, but will generally include chemicals of low hazard and low or controlled exposure; or substances assessed in other jurisdictions that meet NICNAS requirements	Program is in developmental phase and will focus on New Substances	Low Regulatory Concern Chemicals – A Background Paper (2002) National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australia. http://www.nicnas.gov.au/australia/pdf/lrcc-background.pdf (accessed February 2004)
Japanese Chemical Substance Control Law, New Substances List 3 of "Low-Hazardous" Substances	Variety of new substances	Criteria (any of the following can be satisfied): The substance is biodegradable (BOD over 60%); the substance is an organic polymer without certain functional groups and contains less than 1% of monomer or oligomer with MW of 1000 or smaller; the substance is P but not B and not highly mutagenic; the substance is P but not B, and repeated-dose NOEL is 25 mg/kg bw per day or more without severe toxic effect	Use of P/B criteria and limited hazard criteria In addition, focus is on New Substances only	Personal communication with Office of Chemical Safety, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare of Japan
US FDA – "Everything" Added to Food in the United States (EAFUS) – the	Mixtures of compounds, organic compounds and food-derived products; US FDA	Addition to list is based on use – some substances have undergone risk assessment,	Specific use pattern considered	EAFUS: A Food Additive Database. Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (US

Organization and name of list	Types of substance on list	Basis of list (hazard/risk/use/ other)	Rationale for not including in SimHaz	Reference
Inactive Ingredients List	describes the list as "containing substances added to food and food products which include substances regulated by the FDA as direct, 'secondary' direct, and colour additives, and Generally Recognized As Safe (GRAS) and prior-sanctioned substances"	others have not		FDA) http://vm.cfsan.fda.gov/~dms/eafus.html (accessed February 2004) Regulations posted under U.S. Code of Federal Regulations Title 21
US EPA – Lists of Other (Inert) Pesticide Ingredients: List 4B: Other ingredients for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment	Organics, inorganics, salts, UVCBs, polymers	Risk based – In making a List 4B determination, the US EPA not only evaluates the toxicity of the chemical substance, but also considers the possible exposures that could occur	Specific use pattern considered	Inert (other) Pesticide Ingredients in Pesticide Products – Categorized List of Inert (other) Pesticide Ingredients. Office of Pesticide Programs, U.S. Environmental Protection Agency. http://www.epa.gov/opprd001/inerts/lists.html (accessed February 2004)
US EPA – Registered Biochemical Pesticides	Organics, inorganics, mixtures	In order for a substance to be classified as a biochemical biopesticide, it must be established that the substance is naturally occurring (or is similar in structure or function to a natural chemical) and has a non-toxic mode of action Also considered:	Although a substance may have a non-toxic mode of action to the target pest, it cannot be assumed that the substance also is non-toxic to non-target organisms.	United States Environmental Protection Agency (US EPA). What are Biopesticides? http://www.epa.gov/pesticides/biopesticides/whatarebiopesticides.htm (accessed February 2004) The Biochemical Classification Committee and the Classification of Biochemical Active Ingredients http://ir4.rutgers.edu/RWP/RJones-Bio%20C1%20Com.htm (accessed February 2004)

Organization and name of list	Types of substance on list	Basis of list (hazard/risk/use/ other)	Rationale for not including in SimHaz	Reference
		potential effects on non-target organisms; persistence in the environment; application rates and frequency; and product efficacy		http://www.biobased.com/member/memberdocuments/EPA%20Biopesticide%20Classification%20Process.htm (accessed April 2005)
US FDA – Inactive Ingredient Guide	Mostly food additives and inactive ingredients that are used in pharmaceutical formulations (i.e., organics and mixtures of compounds)	Risk based – Most substances are listed with acceptable ranges of use for various routes of drug administration	Specific use pattern considered US FDA provides a warning stating that these inactive ingredients could be considered active under different circumstances	Inactive Ingredient Guide (Redacted) (1996) Division of Drug Information Resources, U.S. Food and Drug Administration (US FDA). http://www.fda.gov/cder/drug/iig/default.htm (accessed February 2004)
US EPA – Generally Recognized as Safe (GRAS) List	Food additives – mainly mixtures	Risk (exposure/use pattern taken into account)	Specific use pattern considered	Summary of All GRAS Notices (2005) Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (US FDA). http://www.cfsan.fda.gov/~rdb/opa-gras.html (accessed February 2004) GRAS notification occurs under Rule 62 FR 18938 of the US FDA
US FDA – Over The Counter (OTC) Pharmaceuticals	Active OTC ingredients	Some substances on this list are labelled Category I: conditions under which OTC ingredients are generally recognized as safe and effective and are not misbranded	Specific use pattern considered	OTC Drug Review Ingredient Status Report (2003) Department of Health and Human Services, Public Health Service, Food and Drug Administration hnttp://www.fdca.gov/cder/Offices/OTC/industry.htm (accessed March 2004)
US FDA – Colour Additives Approved for Use in Cosmetics	Organic, inorganic, organometallic compounds	Risk based	Specific use pattern considered	Summary of Color Additives Listed for Use in Foods, Drugs, Medical Devices and Cosmetics

Organization and name of list	Types of substance on list	Basis of list (hazard/risk/use/ other)	Rationale for not including in SimHaz	Reference
				(2003) Center for Food Safety and Applied Nutrition, United States Food and Drug Administration (US FDA). http://www.cfsan.fda.gov/~dms/col-toc.html (accessed February 2004) Regulations posted under U.S. Code of Federal Regulations Title 21
Flavor and Extract Manufacturers Association – GRAS List	Primarily organics	FEMA evaluates exposure, pharmacokinetic and toxicological information for the substances and considers whether the GRAS classification is appropriate, based on a weight of evidence approach.	Specific use pattern considered	Smith, R.L., et al. (2003) GRAS Flavoring Substances 21: The 21st publication by the Expert Panel of the Flavor and Extract Manufacturers Association on recent progress in the consideration of flavoring ingredients generally recognized as safe under the Food Additives Amendment. Food Technology 57(5): 46–59. http://www.ift.org/publications/docshop/ft_shop/05-03/05_03_pdfs/05-03-gras21.pdf (accessed April 2005)
Herb Research Foundation – Botanicals GRAS	Extracts, flavours, oils, oleoresins, seasonings and spices	Details regarding the rationale and history of the list could not be located		Herb Research Foundation. Module 19: Botanicals Generally Recognised as Safe. http://www.ars-grin.gov/duke/syllabus/gras.htm (accessed January 2004)
Cosmetic, Toiletry and Fragrance Association – Cosmetic Ingredient Review	Various	Risk assessment	Not necessarily low hazard These substances have undergone assessment (80% were approved for cosmetic use, but some with restrictions)	Cosmetic, Toiletry and Fragrance Association http://www.ctfa.org/ (accessed March 2004) Cosmetic Ingredient Review http://www.cir-safety.org/ (accessed March 2004)

APPENDIX II: COMPLEX HAZARD TOOL (COMHAZ)

1.0 Objective

In the Complex Hazard Tool (ComHaz), information on a variety of types of health effects identified from various sources is considered in a hierarchical manner. The first stage of this tool is described in detail here, since it constitutes the basis for considering a proportion of the greatest potential for exposure (GPE) and intermediate potential for exposure (IPE) persistent and/or bioaccumulative (P and/or B) substances on the Domestic Substances List (DSL) as non-hazardous. As a result, they have been included in the group considered to have low likelihood for additional consideration beyond 2006. The second stage of this tool — namely, the preliminary weight of evidence for qualitative components — is described more generally herein, mainly in the context of its principles, since it is currently being peer reviewed and will be applied principally to efficiently assess priorities in the screening phase. Additionally, exposure–response will be considered for critical endpoints to facilitate efficient assessment in the screening phase.

In the development of this tool, an attempt has been made to balance the requirement to complete the prioritization process for a large number of substances within a mandated time frame with the need for a scientifically credible, defensible, transparent and health-protective approach. Maximum advantage is taken of existing assessments and reviews of available data prepared by other organizations or agencies, thereby minimizing the resource and time demands associated with primary review of original studies. Scientific credibility and defensibility are maintained through extensive searching for relevant available data and the use of empirical data wherever possible; predictions of toxicity from modelling are relied upon only when data are unavailable or inadequate for an endpoint, and the results of modelling are weighted according to the associated degree of uncertainty. Although this tool is designed to be transparent, its application requires technical expertise and scientific professional judgement.

2.0 Hierarchical Consideration of Multiple Health Endpoints

This tool covers a range of toxicological endpoints considered in a stepwise manner and includes criteria specific to each endpoint. These endpoints have been selected based on consideration of potential public health impacts, as well as the likelihood of availability of relevant information. The endpoints, which are listed below, are considered in descending order (see Figure 9, "ComHaz endpoint hierarchy," presented in Part C of this proposal) for prioritization of substances for further consideration. In addition to considering information on these specific toxicological endpoints, the proposed ComHaz incorporates the regulatory or reference values — e.g., acceptable daily intakes (ADIs), tolerable daily intakes or concentrations (TDIs/TDCs), reference concentrations and doses (RfCs/RfDs), etc. — established by other agencies. As indicated in that hierarchical scheme, these values are considered following evaluation of the relevant information on carcinogenicity and genotoxicity, as, in general, such values are established for effects for which there is believed to be a mode of action consistent with a threshold of exposure for induction.

Endpoints included in the hierarchical approach are:

- carcinogenicity;
- genotoxicity;
- regulatory/reference values;
- developmental toxicity;
- reproductive toxicity;
- longer-term toxicity;
- short-term toxicity; and
- acute toxicity.

Definitions and other considerations specific to these endpoints are discussed further in Section 5 of this appendix.

The available information on these effects is considered in sequential order, beginning with carcinogenicity. If any of the information satisfies the criteria for an endpoint, the substance is prioritized for further consideration in subsequent stages, which include a preliminary assessment of weight of evidence for qualitative endpoints and development of measures of exposure–response for critical effects. If the criteria are not satisfied or insufficient data relevant to that endpoint are identified, the available information on the next endpoint is considered. For regulatory/reference values (generally based on longer-term studies), longer-term toxicity, short-term toxicity and acute toxicity, if information is sufficient but does not meet the criteria, it is not necessary to consider steps lower in the hierarchical approach, and the substance can be "Set Aside" for no further consideration at this time. Substances can be "Set Aside" based on regulatory or reference values, because these values are generally based on lowest- or no-effect levels for critical effects identified through comprehensive assessments of the available data. Setting substances aside on the basis of longer-term, short-term and acute toxicity is predicated on the toxicological principle that the amount of a substance required to induce health effects generally decreases with increasing duration of exposure, and more sensitive effects are likely to be discernible in longer-term studies. Thus, if a substance is deemed not to be of concern for longer-term toxicity (on the basis of comparison of adequate information with the quantitative criteria in ComHaz), it is unlikely to be of concern for effects induced following exposures of shorter duration.

Once a substance is prioritized for further consideration on the basis of a given endpoint, there is no need to consider available information on endpoints that are lower in the sequence at this initial stage. This approach permits the initial prioritization of a large number of substances in an efficient and effective manner. While a substance may be prioritized for further consideration without evaluation of the data available for every endpoint in the hierarchy, data on all relevant endpoints will be considered during subsequent phases. If the available information on a substance does not meet the criteria specific to any of the components considered in the hierarchy, the substance is considered to be of low toxicity based on this conservative tool, and it is "Set Aside" at this time, with no requirement for further consideration. However, in some cases, substances "Set Aside" at this time may be reconsidered at some later date in the light of additional data.

Depending on the nature of the endpoint, qualitative, quantitative or both types of criteria are proposed (see Table 3, "ComHaz Endpoint-Specific Qualitative and Quantitative Criteria," presented in Part C of the proposal). For those effects for which there is an assumption of probability of harm at any level — i.e., effects for which the mode of induction indicates that there may not be a threshold of exposure — criteria are qualitative. For the purposes of prioritization, these effects are limited to carcinogenicity and genotoxicity, although it should be noted that investigation of the mode of induction of effects associated with individual substances is beyond the scope of this phase of initial prioritization on the basis of hazard.

Quantitative criteria are applied for those endpoints for which mode of action may be consistent with there being a level of exposure for which there is no probability of harm and for which quantitative measures of exposure–effect are available. For the purposes of priority setting by ComHaz, these endpoints include reproductive toxicity, longer-term toxicity, short-term toxicity and acute toxicity. For these endpoints, effect levels identified on the basis of adequate reviews, original study reports or results of modelling are compared with endpoint-specific cut-off values established following consideration of available relevant information. Similarly, reference or regulatory values established by other national or international organizations are compared with quantitative criteria developed for the purposes of prioritization using ComHaz. For developmental toxicity, both quantitative and qualitative criteria are proposed, depending on the source of information, with quantitative criteria applied when effect levels identified from study reports or reviews are available and qualitative criteria applied when only qualitative predictions of toxicity from models are available.

In general, for components for which quantitative criteria have been developed, the lowest effect level is given precedence in application of ComHaz. For example, if the lowest available NO(A)EL does not meet the criteria outlined, but the lowest available LO(A)EL does meet the criteria, the substance is prioritized for further consideration. If only a NO(A)EL can be identified from the available literature (i.e., there were no effects observed at any level of exposure tested), then the available data are considered as not meeting the criteria for initial prioritization on the basis of this endpoint (unless sufficient information is readily available to determine if the study in question was of sufficiently sensitive design to detect toxic effects), and the next endpoint is considered.

3.0 Hierarchical Consideration of Sources of Information

Various sources of toxicological information are considered to determine if a substance meets the endpoint-specific criteria proposed for ComHaz. These sources of information are also considered in a hierarchical fashion in descending order of degree of confidence, in that acceptable assessments of international or national agencies and secondary reviews are first consulted, followed by original study accounts, predictions of quantitative structure–activity relationship (QSAR) models, information on chemical substructures of concern and analogues or surrogates (see Figure 10, "ComHaz hierarchical consideration of sources of information," presented in Part C of the proposal). These sources are considered in descending order for each component of the ComHaz endpoint hierarchy[4] before proceeding to consider, in similar fashion, sources of information relevant to the next component (with the exception of regulatory or

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[4] See Figure 9, "ComHaz endpoint hierarchy," presented in Part C of the proposal.

reference values, for which only assessments are considered). Each of the sources of information for each endpoint is also considered chronologically, with the most recent being consulted initially, to maximize efficiency in access to inclusive, high-quality data. Therefore, at each endpoint, most recent acceptable assessments or reviews of toxicity data are initially consulted. Acceptability is judged on the basis of availability, comprehensiveness, level of detail presented therein, the traceability of sources of information cited and the nature and extent of peer review. The conclusions of these secondary sources are generally accepted without verification in primary study accounts at this initial stage, unless considered necessary, owing, for example, to observed discrepancies.

If no reviews are identified, original reports of toxicological studies in experimental animals or epidemiological investigations are cursorily examined. Where possible, more recent toxicological data are targeted preferentially by searching in a chronological manner in order to identify studies most likely to be of sound design. Severity or toxicological significance of observed effects is generally not taken into consideration in prioritization, although scientific professional judgement may be required in interpretation of the results of observational or experimental data. Consideration of epidemiological data at this stage is restricted to analytical studies (i.e., case–control, cohort and clinical investigations) or occasionally well-conducted ecological epidemiological studies; case studies, case series and cross-sectional studies are more relevant at a later stage, considered in the context of additional data. Scientific professional judgement may also be required in examining epidemiological studies — i.e., an association between the specific substance in question and the development of a toxic effect must have been established in the study, rather than simply an observation of an increase in the effect in a single study in a population exposed to numerous substances (including the substance being prioritized).

If no relevant toxicological data are identified, QSAR models are used to predict the likelihood that a substance will induce adverse effects on health. Of the various commercially available QSAR models identified, those proposed for use in the first stage of ComHaz currently include the statistically based TOPKAT and/or CASETOX models for carcinogenicity, genotoxicity, developmental toxicity, chronic toxicity and acute toxicity. The models considered for use in prioritization of DSL substances in ComHaz were critically evaluated on the basis of several criteria, including the potential to make predictions for a wide range of diverse chemical structures, the capability to generate quantitative or qualitative predictions for endpoints relevant to initial prioritization, ease of use and interpretation of results, computer requirements, availability, level of technical support and availability of mechanisms for internal "validation" of predictions. In order to ensure consistency in the application of the models, guidelines have been developed for the interpretation of the model predictions in the context of the endpoint-specific criteria in ComHaz. In view of the considerable limitations of the few available QSAR models relevant to the characterization of adverse effect levels for human health, however, decisions to "Set Aside" substances from further consideration on the basis of endpoints in ComHaz for which criteria are quantitative are not based on (Q)SAR output alone. Rather, QSAR contributes most in the subsequent qualitative preliminary weight of evidence component for carcinogenicity/genotoxicity or prioritizing substances for further consideration, based on quantitative criteria. The use of more analytical and metabolic models is being considered in the
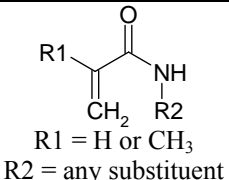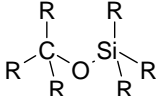
second stage weight of evidence component of ComHaz for carcinogenicity/genotoxicity and potentially for development of estimates of exposure–response for critical effects.

In cases where insufficient information from assessments or reviews of other agencies, primary study accounts or QSAR predictions is available to permit a conclusion with respect to initial prioritization of a substance on the basis of the toxicological endpoints included in the proposed hierarchical scheme (including reference values established by other agencies), substances are examined to determine if they contain chemical structures or structural subfragments that have been correlated with toxicity, based on comparison with other sources of information. These sources include non-quantitative structure–activity relationship (SAR) models (e.g., automated expert systems such as DEREK), lists of chemical substructures of concern compiled by other agencies (excluding those identified by DEREK) (see Table AII-1) and extrapolation of toxicity information on analogue or surrogate substances identified using relevant databases and automated structure or substructure search engines (e.g., Accord, Leadscope). Substances containing substructures of concern associated with endpoints considered relevant in the hierarchical approach described above or for which appropriate analogues or surrogates are associated with these effects are prioritized for further consideration. Although these sources of information are consulted only if the results of QSAR predictions are insufficient, this does not imply that there is greater confidence in predictions from QSAR models versus chemical structures of concern, automated expert systems or extrapolations from analogues. Many of the principles intrinsic to these sources of information are also incorporated into the commercial QSAR models. However, the ease of running and validating predictions from the commercial QSAR models and the range of endpoints (some for which predictions are quantitative) covered by these systems facilitate their direct incorporation into the ComHaz endpoint hierarchy so that large numbers of substances can be more efficiently evaluated.

Consideration of these sources of information in this hierarchical manner by endpoint maximizes efficiency and is optimally health protective (as opposed to, for example, consideration of all empirical data on all endpoints prior to QSAR predictions for any effects). The potentially most serious effects that might be associated with exposure to a substance are efficiently identified in this manner.

Table AII-1. Chemical Substructures of Concern
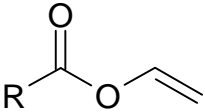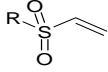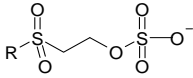
Category[a]	Structure	Description	Potential Endpoint Associated with Structure[b]
Acrylamides	R1 ... O ... NH ... CH₂ ... R2 $R1 = H$ or CH_3 $R2 =$ any substituent	Any chemical with the structure indicated	Carcinogenicity, mutagenicity, reproductive toxicity, developmental toxicity, neurotoxicity
Alkoxysilanes	R ... R ... C ... Si ... O ... R ... R ... R ... R	Any structure containing one or more of the indicated reactive group	Lung toxicity

Anhydrides, Carboxylic acid		Any structure containing one or more carboxylic acid anhydride groups	Developmental toxicity, reproductive toxicity, pulmonary sensitization
Ethylene glycol ethers	 n=1, 2, or 3 R1= alkyl C7 or less or phenyl or alkyl substituted phenyl R2= H or alkyl C7 or less	Indicated structure	Reproductive toxicity, developmental toxicity, systemic toxicity (blood, kidney, liver), immunotoxicity, central nervous system depression
Hydrazines and Related Compounds		Any structure containing one or more of the indicated groups	Carcinogenicity, systemic toxicity (blood, kidney, liver), central nervous system depression
Hindered Amines			Immunotoxicity, systemic toxicity (blood, liver, gastrointestinal tract), reproductive toxicity
Phenolphthalein		Any chemical containing the phenolphthalein structure	Carcinogenicity
Triarylmethane pigments		Derivatives of triphenylmethane or diphenylnaphthylmethane Amine groups (primary, secondary or tertiary) or hydroxyl groups must be present on the aromatic ring positions *para* to the methane carbon	Carcinogenicity, developmental toxicity, reproductive toxicity

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| Vinyl Esters | | A carboxylic acid ester with at least one vinyl group (CH_2=CH-) attached to an organic acid group (RCOO-) | Carcinogenicity, mutagenicity, reproductive toxicity, neurotoxicity |
| Vinyl Sulfones | vinyl sulfone sulfatoethyl-group | Any structure with a vinyl sulfone group or sulfatoethyl-sulfonyl group (typical vinyl sulfone precursors) | Carcinogenicity, mutagenicity |

a   Source: United States Environmental Protection Agency (2002) TSCA New Chemicals Program (NCP) Chemical Categories. http://www.epa.gov/oppt/newchems/cat02.htm (accessed May 22, 2003; last revised October 2002). Structures listed in Table AII-1 exclude those identified by available SAR models (i.e., DEREK) as being associated with effects related to endpoints in the ComHaz hierarchy.

b   Only endpoints relevant to ComHaz are considered.

3.1 Search Strategy

A comprehensive search strategy[5] was developed to efficiently identify relevant toxicity data critical to the initial prioritization of DSL substances using ComHaz. Initially, relevant Internet sites and online databases are searched to determine if another national or international agency has published an assessment or review on a substance. If the assessment or review is deemed acceptable, ensuing journal and database searches would be limited to after the cut-off date for data gathering for preparation of the assessment or, if the latter is not specified, to one year prior to the year of publication. In the absence of — or, if necessary, to supplement — an assessment or review, a comprehensive literature search is conducted of a variety of databases, such as the National Library of Medicine's TOXNET, TSCATS and IUCLID. When possible, more recent reviews and/or toxicological data are targeted preferentially to identify papers most likely to be of sound study design.

3.2 Considerations Relevant to Specific Groups of Substances

3.2.1 Organic and Inorganic Acids, Bases and Salts

The approaches to the application of ComHaz to organic or inorganic acids, bases and salts are dependent upon whether the substance in question is considered to be soluble or not. For the purposes of applying ComHaz, an organic or inorganic acid, base or salt is considered to be soluble if its measured or predicted solubility is ≥ 1 mg/litre. Alternatively, a qualitative determination that an acid, base or salt is soluble or very soluble may be made based on other information such as empirical data, thermodynamic calculations and computer modelling with the application of scientific professional judgement.

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[5] Reference presented in Part F of the proposal.

When applying ComHaz, it is assumed that soluble acids, bases and salts can exist not only as intact substances, but also in alternate forms. For example, a soluble salt could be intact, 100% ionized or exist as the corresponding acid or base. When possible and considered appropriate, the alternate forms of soluble acids or bases and their salts can be grouped in order to take advantage of the data available on all of the substances in the group before making a determination of whether any substance in the group meets the criterion for a specific endpoint in ComHaz. For example, when insufficient information is available to reach a decision for a specific endpoint in the ComHaz hierarchy for a soluble acid, base or salt then data and QSAR model predictions for the alternate forms of the substance may be considered. In addition, when extrapolating from data on an alternate form of an acid, base or salt, previous decisions to either prioritize the alternate form for further consideration or set it aside for no further action based on the application of SimHaz or ComHaz may be taken into consideration

Acids, bases and salts that are not soluble are considered in ComHaz in the same manner as simple organic substances. However, if inadequate data or model predictions necessitates the application of surrogate or analogue approaches, then preference is given to extrapolations based on data from surrogate or analogue substances that are not soluble.

Scientific professional judgement must be considered when determining whether it is appropriate to reach a decision on an acid, base or salt for a specific endpoint in ComHaz based on an extrapolation from an alternate form of the substance, or surrogate or analogue substances.

3.2.2 Mixtures

If ComHaz is applied to a mixture and relevant data on the mixture as a whole are not identified for a given endpoint in the hierarchy, the individual components of the mixture may be considered separately in a manner similar to that outlined above for the alternate forms of a soluble acid, base or salt. Also, similar to the alternate forms of a soluble acid, base or salt, previous decisions to either prioritize a mixture component for further consideration or set it aside for no further action based on the application of SimHaz or ComHaz may be taken into consideration when applying ComHaz to the whole mixture.

As outlined above, the application of ComHaz involves the comparison of information on a series of toxicological endpoints relevant to human health with endpoint-specific criteria that can be qualitative (e.g., carcinogenicity/genotoxicity) or quantitative (e.g., repeated-dose toxicity). For endpoints with qualitative criteria, where possible, in subsequent initial phases of screening, the data will be considered in a preliminary weight of evidence approach, the objective of which is to additionally discriminate priorities for further consideration without imposing undue workload, the latter being more appropriate to subsequent phases of screening and in-depth assessment.

4.0 Preliminary Weight of Evidence Component

The second stage of ComHaz involves consideration, in a preliminary fashion, of the weight of evidence for qualitative components. This will be applied principally to efficiently assess

priorities in the screening phase and is described more generally herein, mainly in the context of its principles.

The three lines of evidence considered in this preliminary weight of evidence approach in screening include empirical data and predictions from QSAR models and SAR models (see Figure AII-1). Currently, this component focuses on carcinogenicity/genotoxicity, principally because confidence in the output of (Q)SAR for these endpoints is highest because of the larger, more diverse training sets for the models, the potential for combining related endpoints and the relevance of some of the assays to specific modes of action.
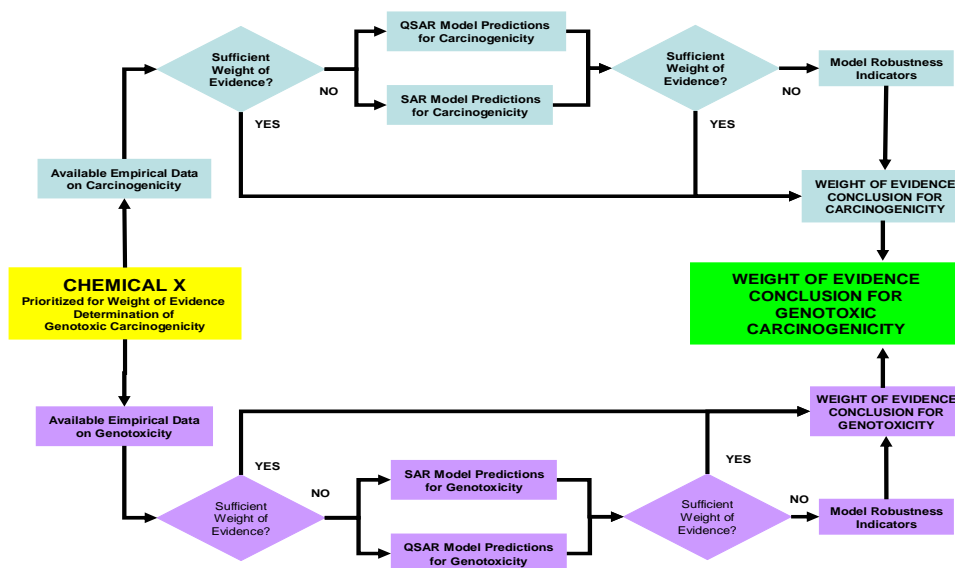
Figure AII-1. ComHaz weight of evidence approach

Preliminary weight of evidence determinations are based on the comparison of the available positive and negative empirical data and the available positive and negative QSAR/SAR model predictions, with data taking precedence. Individual studies are not critically evaluated at this preliminary stage; rather, defensibility relates more to consistency across data and/or modelling output. Currently, the results of individual carcinogenicity and genotoxicity studies and individual (Q)SAR model predictions are weighted based principally on predictive power of the relevant or underlying bioassays. Where weight of evidence from data is equivocal, the output of (Q)SAR is considered. Where output of these latter lines of evidence is inconsistent or equivocal, simple measures of model robustness are proposed to be considered. (e.g., relative sizes of the training sets, numbers of actives versus inactives in training sets, numbers and types of substances in training sets similar to substances being modelled, etc.).

5.0 Detailed Descriptions of Endpoint Components of ComHaz

Development of the criteria for each component of the proposed complex hierarchical tool for initial prioritization of substances on the DSL on the basis of hazard required establishment of

operational definitions or bounds concerning what effects or information would be considered relevant to each component. These aspects are described below, along with other issues specific to interpretation of information relevant to each component beyond the more general considerations.

5.1 Carcinogenicity

Carcinogenicity is the first toxicological endpoint considered in the proposed ComHaz. Available secondary reviews and, if necessary, original accounts of any long-term carcinogenicity bioassays or epidemiological investigations are examined to determine if there is any positive evidence of carcinogenicity. Positive evidence is considered to be a statistically significant increase in the incidence of a specific tumour and an observed exposure–response relationship. If such positive evidence is identified, the substance is prioritized for further consideration. The conclusions of the authors of the studies are generally accepted (e.g., if the authors conclude that tumours observed in an exposed rodent are not related to the substance to which the animal is exposed, these tumours are not considered to be positive evidence of carcinogenicity). At this initial stage, the weight of evidence for carcinogenicity is not critically assessed, nor is individual study quality evaluated.

With respect to studies conducted in experimental animals, preference is given to those conducted by routes of exposure relevant to exposure of humans in the general environment (i.e., oral, inhalation and dermal contact). In the absence of such investigations, studies conducted by less relevant routes (e.g., intraperitoneal or intravenous injection) may be considered for the purposes of prioritization, except when tumours are observed only at the site of injection. Studies in which the potential of a chemical to promote tumour development or possible modes of tumour induction have been investigated are not considered relevant at this initial stage.

If no empirical data on carcinogenicity are available or if the available data are inadequate, the output of QSAR models is considered. QSAR models considered applicable to this endpoint include rodent carcinogenicity models developed for the TOPKAT and CASETOX programs (see Figure AII-2). A valid prediction of sufficiently high probability from any of the relevant models is considered to meet the qualitative criteria for the carcinogenicity endpoint in this initial stage.
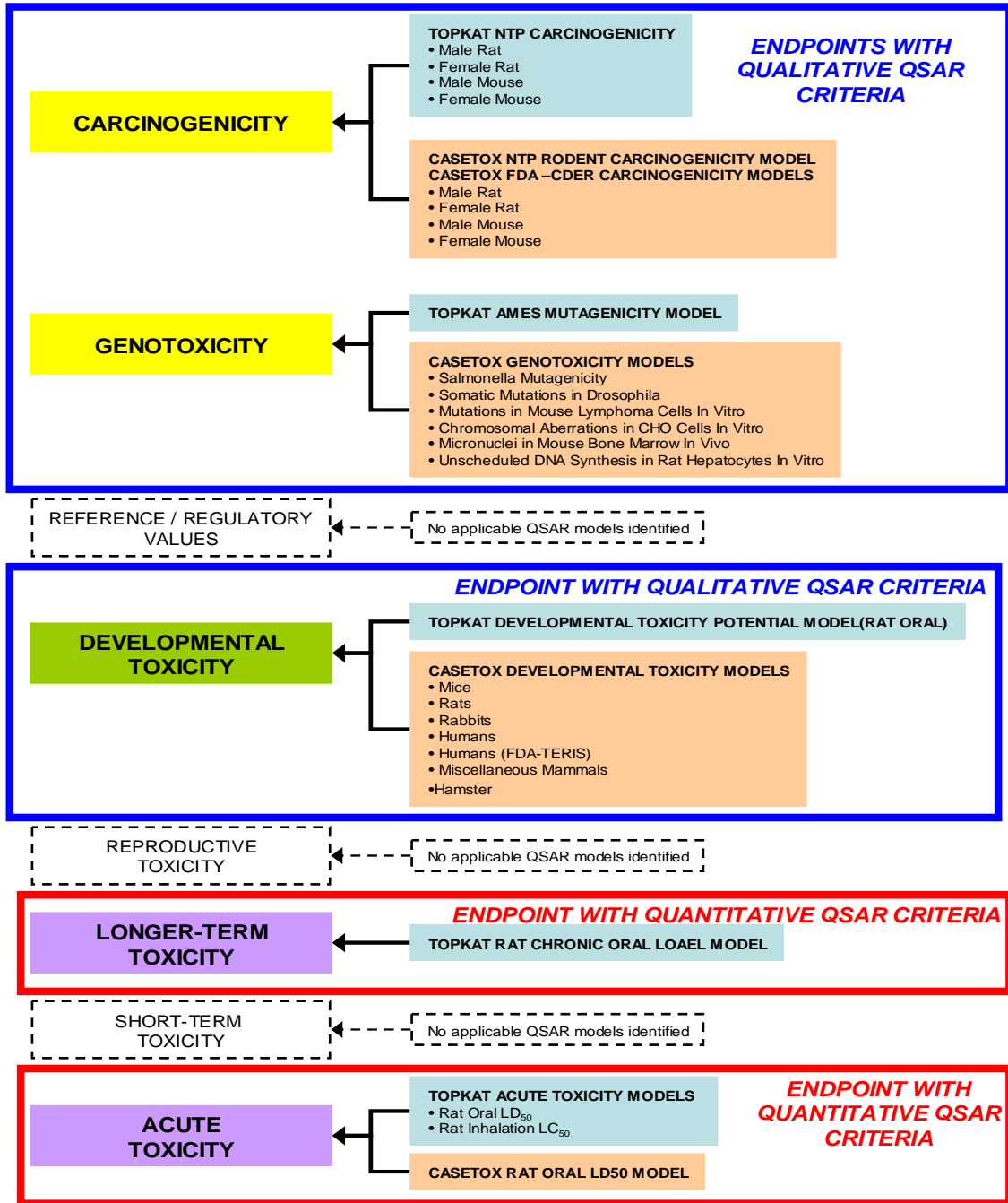
Figure AII-2. QSAR models: ComHaz hierarchy

If no positive evidence is identified, information on the next endpoint in the hierarchy is considered. If positive evidence of carcinogenicity is identified, this, along with evidence on genotoxicity, is considered in a preliminary weight of evidence determination for genotoxic carcinogenicity in a subsequent step at the outset of screening.

5.2 Genotoxicity

Secondary or primary accounts of relevant *in vivo* and/or *in vitro* studies are examined for positive evidence of genotoxicity. The results of available studies are interpreted through application of the criteria outlined in Table AII-2. It should be noted that Table AII-2 is not intended to be a comprehensive listing of all types of assays that could provide evidence of genotoxic potential; rather, this compilation guides interpretation regarding observations of genetic damage commonly encountered in the literature that are considered to be sufficient so as to warrant further consideration of the endpoint for a substance.[6] Tests classified as "indicator assays" (e.g., analyses for sister chromatid exchanges) are not considered in themselves to provide sufficient evidence of genotoxicity to prioritize substances for additional consideration at this initial stage. At this initial stage, the presence or absence of exogenous metabolic activation is not taken into consideration, and study results from *in vivo* or *in vitro* assays that are considered by the author(s) of the article or review to be equivocal do not contribute.

Table AII-2. Criteria for Prioritization of DSL Substances for Further Consideration Based on Results of Genotoxicity Studies

Test type		Examples	Criteria for prioritizing for further consideration
In vivo mammalian tests	Germ cell mutagenicity	Specific locus test Transgenic mutation systems	At least one positive result in a relevant assay
	Germ cell clastogenicity or aneugenicity	Dominant lethal test Heritable translocation test Chromosomal aberrations in spermatocytes or spermatogonia Spermatid micronucleus test (centromere -ve or +ve) Oocyte cytogenetics Sperm FISH assay Abnormal chromosomal segregation	
	Germ cell DNA damage or repair	DNA adducts Unscheduled DNA synthesis Comet assay Strand breaks	
	Somatic cell mutagenicity	Mouse coat colour spot test Transgenic mutation systems Hprt mutations Dlb-1 mutations	

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[6] This list of assays was compiled based, in part, on consultation with several genetic toxicology experts (a report of which is referenced in Part F).

Test type		Examples	Criteria for prioritizing for further consideration
	Somatic cell clastogenicity or aneugenicity	Chromosomal aberrations in bone marrow or peripheral blood of rodents Micronuclei (centromere -ve or +ve) in bone marrow, peripheral blood or liver of rodents Chromosomal aberrations in lymphocytes of exposed humans Non-disjunction using FISH Micronuclei (centromere -ve or +ve) in lymphocytes of exposed humans	
	Somatic cell DNA damage or repair	DNA adducts Unscheduled DNA synthesis Comet assay Strand breaks	
In vivo non-mammalian tests	Mutagenicity	*Drosophila* sex-linked recessive lethal test *Drosophila* wing spot test	At least one positive result in a relevant assay and no sufficient negative evidence from *in vivo* mammalian studies[a]
In vitro tests	Mutagenicity	Bacterial (*Salmonella typhimurium or Escherichia coli*) Mouse lymphoma TK assay Hprt mutations Human TK6 mutations	
	Clastogenicity or aneugenicity	Chromosomal aberrations in human lymphocytes or rodent cells Micronuclei (centromere -ve or +ve) in human or rodent cells Mouse lymphoma assay (small colony mutants) Non-disjunction by FISH in human or rodent cells	
	DNA damage or repair	DNA adducts Unscheduled DNA synthesis Comet assay Strand breaks	

[a] In application of these criteria for the genotoxicity component of ComHaz, sufficient negative evidence from *in vivo* mammalian studies is considered to consist of negative results in two or more *in vivo* tests for different assays in two different tissues (e.g., bone marrow and one other tissue).

If no empirical data on genotoxicity are available or if the available data are inadequate, the potential for genotoxicity is predicted by QSAR models. QSAR models considered to be applicable to this endpoint include a number of genotoxicity models developed for the TOPKAT and CASETOX programs (see Figure AII-2). A valid prediction of sufficiently high probability from any of the relevant models is considered to meet the qualitative criteria for the genotoxicity endpoint at this initial stage of consideration.

If no positive evidence is identified, information on the next endpoint in the hierarchy is considered. If positive evidence is identified, this, along with evidence on carcinogenicity, is considered in a preliminary weight of evidence determination for genotoxic carcinogenicity in a subsequent step at the outset of screening.

5.3 Reference/Regulatory Values

Reference or regulatory values published in acceptable assessments or reviews by international or national agencies for the provision of guidance for regulatory, advisory or risk management purposes are considered in this component of the proposed hierarchical scheme. Such values would include TDIs/TDCs, ADIs or RfDs/RfCs for long-term exposure on the basis of non-neoplastic effects observed in epidemiological investigations or studies in experimental animals. Reference values or regulatory limits established for short-term exposures (due to the smaller number of such values that could provide guidance in developing criteria as well as the lack of standard methodology by which they are established by different agencies), as well as those developed for occupational exposures, are not considered relevant to initial prioritization of DSL substances. The lowest appropriate reference/regulatory value identified is compared with the criteria outlined in Table 3, "ComHaz Endpoint-Specific Qualitative and Quantitative Criteria," presented in Part C of the proposal.

5.4 Developmental Toxicity

For the purposes of initial consideration via ComHaz, developmental toxicity is defined as the induction of effects in the developing organism, either before birth or postnatally. Effects considered include death, morphological malformations, congenital neoplasia, organ toxicity, reduced body weight, altered growth and functional or behavioural toxicity, as well as impaired postnatal mental and physical development up to and including normal pubertal development. These effects may result from exposure of either parent prior to conception or exposure of the offspring *in utero* or postnatally up to the time of sexual maturation. Severity or toxicological significance of effects observed in the developing organism is generally not taken into consideration in this initial stage of prioritization. The presence or absence of maternal toxicity is generally not taken into account at this first stage when comparing the effect level for developmental toxicity with the criteria outlined in Table 3, "ComHaz Endpoint-Specific Qualitative and Quantitative Criteria," presented in Part C of the proposal. This is justified on the basis that it is beyond the scope of this first stage to consider mode of induction of the effects and, hence, relevance of maternal toxicity. It is also health protective. However, if available effect levels for developmental toxicity do not meet the criteria for this endpoint or the available data on developmental effects are inadequate, effect levels for maternal toxicity reported in developmental toxicity studies may be considered in a later component of the complex hierarchical tool (e.g., short-term toxicity). This is based on the assumption that typical developmental toxicity studies involve exposure to a substance for a short period of time during gestation.

If no empirical data on developmental toxicity are identified or if the available data are inadequate, QSAR models are employed to predict whether the substance has the potential for developmental toxicity. QSAR models considered to be applicable to developmental toxicity

include a number of models developed for the TOPKAT and CASETOX programs (see Figure AII-2). A valid prediction of sufficiently high probability from any of the relevant models is considered to meet the qualitative criteria for the developmental toxicity endpoint, although negative predictions are verified on the basis of other information, in view of the considerable limitations of the models for this endpoint. This is also in keeping with the conservative, health-protective approach.

If no positive evidence is identified, information on the next endpoint in the hierarchy is considered. If positive evidence of developmental toxicity is identified, this is considered in a preliminary weight of evidence determination in a subsequent step.

5.5 Reproductive Toxicity

In the reproductive toxicity component of ComHaz, effects considered include morphological effects on reproductive organs as well as effects on libido, sexual behaviour, gestation, lactation, any aspect of spermatogenesis, hormonal activity, any physiological response that would interfere with the capacity to fertilize, effects on fertilization itself or the development of the fertilized ovum up to and including implantation. Effects may result from exposure of either parent prior to mating or during cohabitation. Other toxicological effects observed in investigations of potential reproductive toxicity are considered in later components in the hierarchical approach (e.g., longer-term toxicity or short-term toxicity).

Results of *in vitro* estrogen and androgen receptor binding assays and transcriptional activation assays are not considered in the initial stage of prioritization of DSL substances by ComHaz at this time. Based on the evaluation of the Interagency Coordinating Committee on the Validation of Alternative Methods, there are currently no adequately standardized and validated methods for such *in vitro* assays; there is also little consistency among available protocols, and assay protocols are considered inadequately detailed or standardized (ICCVAM, 2003). Therefore, results of currently available *in vitro* binding assays and (Q)SAR being developed to estimate estrogen or androgen receptor binding potential are not considered in prioritization via ComHaz at this time.

5.6 Longer-Term Toxicity

For the purposes of initial prioritization, longer-term studies are considered to include those investigations in which experimental animals are exposed to a substance for a significant portion of their life span (e.g., approximately 90 days or longer in rodents[7]). Effects observed in longer-term studies considered relevant may include statistically significant changes in survival, body weight or organ weights, morphological or histopathological changes, as well as alterations in hematological, neurological, immunological or biochemical parameters. As noted above, the biological adversity or severity of effect is generally not taken into account during the initial stage of prioritization. However, decisions regarding whether certain effects observed in studies

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[7] For the purposes of prioritization of DSL substances on the basis of hazard, there are no absolute definitions with respect to the duration of longer-term and short-term toxicity studies. Values presented here should be considered as approximate examples only; case-by-case judgement may be required.

are relevant to ComHaz may require application of scientific professional judgement on a case-by-case basis.

If no empirical data on longer-term toxicity are identified or if the available data are inadequate, QSAR predictions are considered. The only QSAR model considered to be applicable for longer-term toxicity is the TOPKAT rat (oral) chronic LOAEL model (see Figure AII-2). A valid prediction of a LOAEL from this model can be compared with the quantitative criteria for the longer-term toxicity endpoint,[8] although predictions of less than the relevant quantitative criterion are verified on the basis of other information, in view of the considerable limitations of the models for this endpoint, prior to setting aside any substance from further consideration.

5.7 Short-Term Toxicity

Short-term studies are considered to be those in which experimental animals are exposed repeatedly to a substance for several days (e.g., less than approximately 70 days in rodents). Effects observed in short-term studies considered relevant are the same as those for longer-term toxicity (i.e., statistically significant changes in survival, body weight or organ weights, morphological or histopathological changes, as well as alterations in hematological, neurological, immunological or biochemical parameters). Again, biological adversity or severity of effect is generally not taken into account during this initial stage of prioritization, although scientific professional judgement may be required in some cases.

5.8 Acute Toxicity

Lethality is the only acute effect for which criteria are proposed for this initial stage of prioritization of DSL substances in ComHaz. The lowest identified LD_{50} for oral or dermal exposures or LC_{50} for inhalation exposures is compared with the values outlined in Table 3, "ComHaz Endpoint-Specific Qualitative and Quantitative Criteria," presented in Part C of the proposal. If no values for acute toxicity via the oral, dermal or inhalation routes are available, LD_{50} values obtained from studies in which experimental animals were exposed by intraperitoneal or intravenous injection may be considered; however, values obtained by the routes of exposure considered more relevant to human exposure are given precedence over those obtained from injection studies.

If no empirical data on acute toxicity bioassays are identified or if the available data are inadequate, QSAR predictions are considered. Relevant QSAR models include the TOPKAT rat oral LD_{50} and rat inhalation LC_{50} models (see Figure AII-2) and the CASETOX rat oral LD_{50} model. A valid prediction of an oral LD_{50} or inhalation LC_{50} from any of the relevant models is compared with the quantitative criterion for the acute toxicity endpoint (see Table 3, "ComHaz Endpoint-Specific Qualitative and Quantitative Criteria," presented in Part C of the proposal), although predictions of less than the relevant quantitative criterion are verified on the basis of other information, in view of the considerable limitations of the models for this endpoint, prior to setting aside any substance from further consideration.

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[8] See Table 3, "ComHaz Endpoint-Specific Qualitative and Quantitative Criteria," presented in Part C of the proposal.

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