Report of Peer Consultation on Dermal Exposure for Assessment of Existing Substances under the Canadian Environmental Protection Act of 1999 (CEPA '99)

March 7 and 8, 2002

Ottawa, Ontario, Canada

Participants

Sponsor:

Existing Substances Division, Safe Environments Programme, Health Canada

Presenters:

Ms. Bette Meek, Existing Substances Division, Safe Environments Programme, Health Canada

Mr. Ray Beauchamp, Existing Substances Division, Safe Environments Programme, Health Canada

Chair:

Dr. Gail Charnley, HealthRisk Strategies

Consultation Panel:

Mr. Thomas Brennan, U.S. Environmental Protection Agency

Dr. Annette Bunge, Colorado School of Mines

Dr. Michael Dellarco, U.S. Environmental Protection Agency

Ms. Catherine Petito Boyce, Gradient Corporation

Dr. Michael Roberts, University of Queensland

Dr. Peter Robinson, ManTech Environmental Technology, Inc., Wright-Patterson Air Force Base

Dr. John Ross, infoscientific.com, Inc.

***TERA* Staff:**

Dr. Dan Briggs
Dr. Bert Hakkinen

Ms. Jacqueline Patterson

Introduction and Background

An independent panel of expert scientists, including skin penetration researchers and dermal exposure and risk assessors, met in Ottawa to review an early draft of dermal exposure guidance being developed by Health Canada's Existing Substances Division, Safe Environments Programme, for assessment of existing substances under the Canadian Environmental Protection Act (CEPA, as amended in 1999). The meeting was not open to the public; however, observers from Health Canada were present.

Toxicology Excellence for Risk Assessment (*TERA*) organized the peer consultation under contract to Health Canada. *TERA* also provided some technical assistance to Health Canada prior to the meeting on both the content and presentation of the materials. The members of the peer consultation panel donated their time and talents to provide an evaluation of the draft documentation. The objective was a comprehensive overall review of the draft documentation as provided by the combined experience of all the panel members.

After brief introductions, the meeting began with a discussion of conflict of interest. Each panel member certified in writing that he or she did not have a conflict (real or apparent) with the material covered by the peer consultation or with the sponsor, or identified the potential for such conflicts. T*ERA* staff discussed possible conflicts with each panel member to determine if measures were needed to manage a potential conflict (or appearance of conflict). Options included exclusion from a particular discussion, or allowing the panel member to participate in the discussion. Panel members each indicated that he or she did not have a real or perceived conflict of interest (see Appendix 1).

This peer consultation meeting followed a standard *TERA* process, beginning with a request to the panel members to conduct a close examination of the supporting documentation in the several weeks prior to the meeting. Pre-meeting written comments were provided by panel members. At the meeting, the author of the draft documentation presented an overview of his work. The panel then discussed the documentation, focusing on the fourteen questions posed to the panel as part of the charge to the Panel. Full discussion and participation were encouraged.

The panel was provided with the following materials:

1. Documents for Review

    - Preliminary Proposal to Assess Dermal Exposure for Existing Substances
    - (Draft) Study Notes – Supporting Documentation for the Preliminary Proposal to Assess Dermal Exposures to Existing Substances
    - Supporting Documentation – Case Studies
    - Supporting Documentation – Excerpt on Exposure from "Approach to Human Health Risk Assessment for Priority Substances Under CEPA"
    - A list of additional references not included in the above documents

2. Background and Charge Questions developed by Health Canada with assistance from *TERA* staff (Appendix 2)

The Chair discussed the format and goals for the meeting, and the charge to the Panel, noting that the objective of this peer consultation was to provide pragmatic suggestions for modification of the preliminary proposal based on the current state of common understanding of factors affecting dermal absorption.

Ms. Meek briefly presented background information and the context for the development of the draft guidance under review by the panel.

Mr. Beauchamp briefly introduced the decision trees that form the base of the Health Canada guidance and presented two case studies.

Panel Discussion and Suggestions

Following the Health Canada presentations, the panel discussed each charge question. Overall, the panel members were impressed with the work that Health Canada had done. They noted that the decision trees and associated documentation are comprehensive and transparent, and the documents have done a good job of summarizing the current knowledge. The following summarizes the key outputs of panel discussions relevant to revision of the draft guidance and its decision trees. A more comprehensive summary of the panel discussions on the charge questions is in a separate document provided to Health Canada.

- Each decision tree should be reviewed from the viewpoint of "can this tree be simplified?" Simplification techniques such as using key words (with explanatory narrative in footnotes) and collapsing branches were suggested.

- Other simplification techniques suggested: (a) for finite dose situations, assume 100% absorption; (b) for infinite dose situations, assume maximum flux exists (discussed further below).

- Assuming 100% absorption for the chemical being evaluated (with finite doses only) is a reasonable alternative to working through the decision trees. If the estimated exposure determined by complete absorption is below the level of concern, one need not use the decision trees for further refinement.

- Two types of decision trees might be prepared: one type for screening and the other for full assessment. The trees intended for screening could be much simpler than the current decision trees. For example, they could be based on easily obtainable data such as octanol/water partition coefficients.

- In Decision Tree 6, the use of "Is the liquid medium at least 99% water" as a decision point was not supported by the panel. Instead, the Panel favors use of dermal absorption equations as discussed below in the "Rules of Thumb."

- Decision Trees 15 (Part 2) and 16 might be simplified by using just one model, rather than listing both the Robinson and the Potts and Guy models.

- Decision Trees 20-23 are very similar in that they all consider dermal exposure from materials associated with substrates (e.g., soil, dust, paper, fabric). A simplifying alternative is to list the types of media covered, and then use the one decision tree.

- Many consumer products contain skin penetration enhancers. Several Panel members volunteered to provide Health Canada with a list of those enhancers judged to be most relevant to consumer products, so that this information may be factored into the decision tree exposure assessments.

In response to one of the charge questions, the panel developed a list of criteria that Health Canada may use to evaluate the quality of *in vitro* studies intended for decision tree use:

- Skin integrity (confirm integrity exists with standard methods and criteria; specify what methods and criteria were used).
- Appropriate receptor solution.
- Split thickness is better than full thickness for evaluating lipophilic materials (those chemicals with log K_{ow} greater than 3), but both may be overly conservative.
- Length of study (loss of skin viability may occur if duration is too long and if preservatives are not used)
- Source of skin should be reported (cadaver skin has more variability, but is better than some animal skin; pig skin is better than rat skin.)
- The region of the body from which the skin is obtained should be specified.
- Dose characterization (e.g., volatile materials may evaporate if the site of application is not occluded)
- Validated or consistent results, with regression lines.
- Occlusion of test chambers (however, the potential negative effects of skin hydration caused by occlusion also should be considered and weighed against the potential benefits of occluding the chambers)
- Use of preservatives (possible effects on absorption should be considered)
- Avoidance of contaminants (e.g., stop cock grease)
- Diffusion cells (flow-through cells are better than static cells for maintaining metabolic activity)

During the panel discussion, panel members suggested some "Rules of Thumb" regarding dermal exposure assessment, which Health Canada might find useful in considering revisions of the Decision Trees. The panel discussed a number of possibilities and offered the following for consideration:

Rule #1: If the log Kow is less than three, then "B" is virtually zero
Page 33 of the draft Study Notes discussed "B," which Cleek and Bunge (1993) defined as the ratio of the permeability coefficient for a substance in the stratum corneum to the permeability of the same substance in the viable epidermis (assuming the same vehicle in each case). The rationale for this rule is that if the log Kow for a chemical is less than

three, then the viable epidermis will not be a significant barrier. This simplifies the calculation of uptake, with "B" being virtually zero if used in dermal uptake equations (see Pages 33 – 39 of the draft Study Notes). In some cases, compounds with large Kow's may be excluded from further consideration because they will not be absorbed through intact skin. Two major mechanisms are involved: (1) uptake into the stratum corneum, and (2) subsequent transfer through the skin into the body.

Rule #2: Maximum flux: Estimate by (Kp) x (water solubility).
Use maximum flux for a complex vehicle. If it is not known, use a permeability coefficient in water. With no other information, one can estimate the maximum flux using the permeability coefficient from water and water solubility.

Rule #3: Flux equals [(maximum flux) x (concentration in formulation)] divided by solubility in formulation
A good estimate of flux for a compound in a vehicle can be made from its solubility and concentration. This approach is not necessarily conservative. A refinement can be made by assuming the concentration in the formulation should be less than the solubility in the formulation. To address Health Canada's concern that information on the formulation might not be available, using water solubility was recommended as a conservative assumption. Only occasionally will there be consumer product ingredients that decrease solubility. One panel member suggested considering the fraction of solubilities. For example, the maximum flux for pure benzene should be the maximum flux for benzene in water.

Rule #4: A pure compound's flux is approximately equal to the maximum flux based on water solubility. Using water solubility is a default conservative assumption. It is not necessary to have at least 99% water solubility as is stated in Decision Tree #6

Rule #5: The maximum flux from any vehicle approximately occurs at the solubility limit in that vehicle. This is true unless supersaturation exists, such as occurs with micelle formation; however, supersaturation occurs rarely.

Rule #6: A pure compound with reasonable solubility in water (>10%) is more likely to be corrosive, leading to enhanced penetration.

Rule #7: Differentiate between flux and exposure.
For screening purposes assume maximum flux for infinite doses and total (100%) absorption for finite doses. Also, assume that everything in the skin will eventually get into the body. Determine the maximum amount that can be absorbed given the amount contacting the skin. Then, determine the toxicity for this maximum amount.

Several panel members raised a general issue regarding whether approaches used for screening the different exposure pathways included in the Existing Substances screening process are addressing uncertainties and conservatism in comparable ways, and whether the various pathway-screening processes identify potential hazards in an equivalent way. Specifically, these panel members thought Health Canada should consider the overall impact on the screening

process of the combined assumptions included in the dermal screening component, including consideration of the conservativeness of the assumptions used, and the sources and magnitude of the uncertainty inherent in them.

Summary of Key Discussion Points

At the conclusion of the meeting, Mr. Beauchamp of Health Canada noted the following as key points from the panel's discussions. The panel agreed.

- Separate sets of exposure decision trees might be developed for screening-level assessments and for full assessments.
- Explain to decision tree users the need to use YES or NO responses at tree branch points, even though doing so will add uncertainty.
- Developing a range for acceptable exposures is often better and more useful than providing single numbers (even though many users may then resort to the default of taking the most conservative value in the range to assure enough conservatism).
- The documents should be less prescriptive.
- Provide more transparency by clarifying the rationale and explanation for decisions: such as eliminating the consideration of vapour exposures, and identifying the criteria used for selecting and recommending specific modeling approaches.
- Follow-up on suggested "SPE/Micro-fiber" approaches to bounding level estimates of dermal exposure to substances in formulations. The goal should be a quick method of developing partition coefficient data as an estimate to predict skin penetration rates.
- Further explore recent information developed with regard to the (expanded) Flynn database. The goal should be to improve substance/group/category-specific predictive capability, i.e., improve predictions in terms of scope (domain), accuracy, and confidence.
- Remember the importance of distinguishing between finite and infinite dose scenarios, in particular for the screening type approach.

References

Cleek, R. L. and A. L. Bunge. "A New Method for Estimating Dermal Absorption from Chemical Exposure. 1. General Approach" Pharmaceutical Research 10 (4): pp. 497-506 (1993)

Appendices

1. Managing Potential Conflicts of Interest: *Dermal Exposure Peer Consultation Meeting*
2. Background and Charge Questions

Appendix 1

Managing Potential Conflicts of Interest
Dermal Exposure Peer Consultation Meeting
March 7 and 8, 2002

All panel members are donating their time and talents to this review. They were selected based upon their expertise and qualifications and are employed by many types of organizations. Toxicology Excellence for Risk Assessment (*TERA)* strives to create a balance of expertise and affiliations for each panel. However, individual panel members are representing their own expertise and views, not the views of their employers.

To identify potential conflicts of interest, each panel member was asked by *TERA* to answer a number of questions and disclose any potential conflicts of interest he or she might have related to the review of the Health Canada document "Preliminary Proposal to Assess Dermal Exposure for Existing Substances." Questions included whether --

1. The panel member (or spouse or dependents) has any financial stake in the outcome of the panel meeting

2. The panel member has personal beliefs or values that would preclude him or her from an objective scientific evaluation of the materials

3. The panel member (or spouse or dependents) has made public statements or taken positions relevant to the subject matter to be considered by the panel*, or

4. The panel member is aware of any other factors which may create potential conflict of interest or bias issues

Each panel member answered these questions and signed a form attesting to his or her answers. *TERA* reviewed these forms and did not identify any conflict of interest issues. While the actual forms are kept confidential, the following summarizes the issues noted by the panel members.

Thomas H. Brennan –Mr. Brennan is a Chemist with the U.S. Environmental Protection Agency, Office of Pesticide Programs. No conflict or bias issues identified.

Annette L. Bunge – Dr. Bunge is a Professor in the Chemical Engineering Department of the Colorado School of Mines. No conflict or bias issues identified.

Gail Charnley – Dr. Charnley is with HealthRisk Strategies. She served as Chair for the panel. No conflict or bias issues identified.

Michael Dellarco – Dr. Dellarco is with the U.S. Environmental Protection Agency, Office of Research & Development. No conflict or bias issues identified.

Catherine Petito Boyce – Ms. Boyce is a Principal Scientist with Gradient Corporation. No conflict or bias issues identified.

Michael Roberts – Dr. Roberts is a Professor in the Department of Medicine at the University of Queensland. No conflict or bias issues identified.

Peter J. Robinson – Dr. Robinson is a Principal Scientist with ManTech Environmental Technology, Inc. at Wright-Patterson Air Force Base. No conflict or bias issues identified.

John H. Ross – Dr. Ross is a Senior Consultant with infoscientific.com, Inc. No conflict or bias issues identified.

* For this question, *TERA* defined "subject matter" to include dermal exposure policies and practices of Health Canada.

Appendix 2

Background and Charge Questions (see .pdf file)

Peer Consultation on Dermal Exposure for Assessment of Existing Substances under CEPA '99

Ottawa, Ont.
March 7th – 8th, 2002

Background and Charge
(Essential Initial Reading by the Panel)

Existing Substances Division
Safe Environments Programme
Health Canada

Draft, 11/02/02

Introduction

Purpose/Documentation

This peer consultation is being convened to provide expert input into revision of an early draft of documentation which outlines approaches to estimation of dermal exposure for Existing Substances in Canada. Based on this and other input, this documentation which was prepared by staff of the Existing Substances Division of Health Canada[1] will be revised, refined and ultimately finalized as part of the resource materials which outline approaches to assessment of risks to human health for the Existing Substances Program. The purpose of this documentation is twofold. It will be used by staff of the Existing Substances Division to ensure consistency in assessment. In addition, this documentation (or a summary of a subsequent version thereof) will be made publically accessible as part of the continuing commitment to accountability for methodology adopted within the program.

In this document ***("Background and Charge"),*** initially, background information is provided in the interest of clarifying the nature, scope and purpose of exposure estimation in the Existing Substances program to provide context for the consultation. This is followed by a description of the Charge to the peer consultation, which highlights specifically those issues on which the peer consultation is being asked to focus. Issues and areas considered outside of the scope of this peer consultation are also outlined.

The documentation for review at this consultation (namely decision trees as a basis for estimation of exposure in screening and full assessment, and associated glossary and references) is included in a separate document entitled "***Preliminary Proposal to Address Dermal Exposure for Existing Substances"***. This documentation delineates 12 pathways (relating sources to the activities of circumstances which may bring them into contact with human skin) considered to be the most important in relation to dermal exposure and deserving attention in assessments of Existing Substances. Several to numerous exposure scenarios are described in the decision trees as a basis for estimation of the external dermal exposure or the dermally absorbed dose per exposure event, as data permit, and taking into account distinction between "finite" and "infinite dose" conditions.

Additional "***Supporting Documentation"*** has also been provided. Review and/or submission of comments on this documentation is ***not*** being solicited from panel members. Rather, this documentation is being provided in the interest of clarifying aspects of the decision trees, their application or the current approach to exposure estimation for Existing Substances. It is envisaged that panel members would consult this documentation only when they have need for

[1] Dr. Bert Hakkinen, TERA, provided comments and relevant text in the preparation of the current draft

additional clarity on specific points. This includes ***"Study Notes***" for the decision trees, several ***"Case Studies"*** illustrating application of the decision trees and an ***"Update to the Approach to Estimation of Exposure for Priority Substances".***

Context - the Existing Substances Program[2]

The *Canadian Environmental Protection Act* (CEPA), proclaimed in 1988, and amended in 1999 authorizes the Ministers of the Environment and of Health to investigate a wide variety of substances that may be present in the environment and cause adverse effects on the environment or on human health.

"Existing Substances" are those that appear on the **Domestic Substances List (DSL)** under the Canadian Environmental Protection Act (*CEPA*). Under CEPA, the definition of **substance** is very broad and encompasses discrete chemical compounds, classes of chemicals, emissions and effluents, and products of biotechnology, including microorganisms.

The DSL is an inventory comprising some 23,000 chemicals and biological agents that were in commerce in Canada between January 1984 and December 1986 and includes several groups including discrete organic and inorganic chemicals, polymers and substances of unknown or variable composition, complex reaction products or biological material ("UVCBs").

Previously, as has been the case in most other jurisdictions, effort in assessment on Existing Substances has been focussed on small numbers of substances, often high production volume chemicals utilized in a broad range of industrial applications. Focus on this limited number of substances for which there is considerable available data has permitted preparation of **full** assessments of high complexity, incorporating, for example, full weight of evidence determinations for hazard assessment and in some cases physiologically based pharmacokinetic or biologically based dose-response modelling for dose-response analysis. In this context, since 1988, for Existing Substances under *CEPA*, the Ministers of Health and Environment have assessed 69 substances (including a number of complex mixtures) on the first and second Priority Substances Lists, deemed to be of highest priority with respect to health or to the environment.

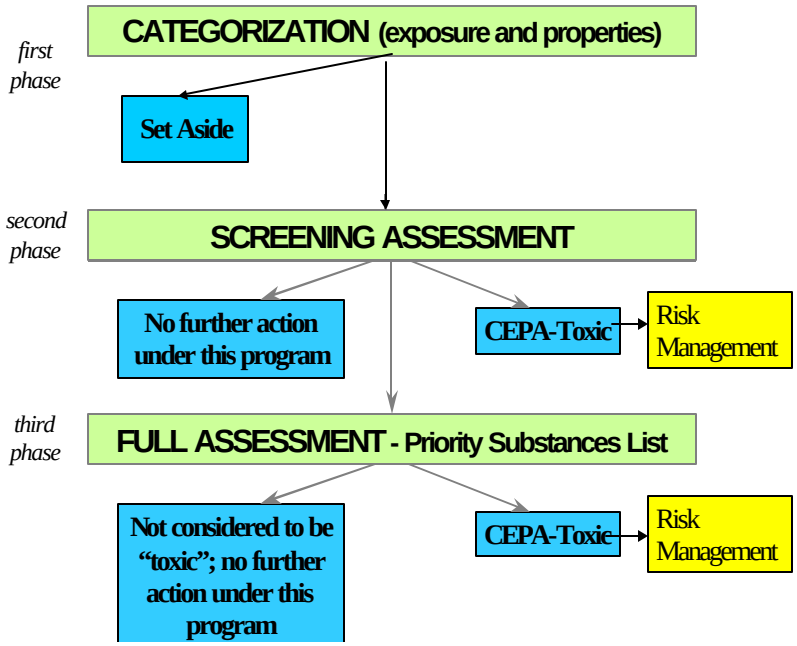
However, in Canada as in other jurisdictions, the need to systematically consider the potential for adverse health and environmental impacts of all or most of the large numbers of Existing Substances in commerce is a recognized priority. This prioritization has been prompted in part by the introduction of systematic consideration of potential and health implications of all **New Chemicals** (those not used in Canada between 1984 and 1986) under CEPA and similar legislation

[2] For additional information on the context and content of the program, see ***www.hc-sc.gc.ca/hecs-sesc/exsd***

in other countries. This has prompted consideration of potential adverse effects of the much larger numbers of likely more hazardous substances already in commerce, for which environmental and health effects have never been systematically assessed.

As a result, the mandate respecting Existing Substances has been vastly expanded under the recently renewed Canadian Environmental Protection Act ***(CEPA '99).*** In addition to the continuing requirement to establish and assess lists of Priority Substances, *CEPA '99* requires that the Ministers of Health Canada and Environment Canada complete categorization for all of the 23,000 substances on the DSL by September 2006 with subsequent screening and full assessment, where warranted, in an iterative approach to priority setting for risk management for all Existing Substances in Canada (Figure 1).

Figure 1-PRIORITY SETTING – EXISTING SUBSTANCES



The three iterative stages for priority setting for risk management of Existing Substances specified under CEPA '99 as presented in Figure 1 are **"categorization", "screening assessment"** and **"full (Priority Substances) assessment"** representing increasing levels of complexity**.**

This requirement to systematically prioritize all Existing Substances for assessment and management is precedent setting internationally, though schemes whose intent is similar (i.e., to systematically consider the health and environmental impacts of most or all Existing Substances), are being considered in other jurisdictions such as Europe.

CEPA '99 – Priority Setting for Existing Substances - Categorization

In the first of the three stages of iterative priority setting for risk management, substances are being "categorized" to identify those that:

a) may present to individuals in Canada, ***the greatest potential for exposure***, or

b) are persistent or bioaccumulative and inherently toxic to human beings or to non-human organisms

Operational definitions for the aspects of categorization for which Health Canada has responsibility including "potential for human exposure" are currently being developed. Since categorization constitutes only the first of three possible iterative stages of priority setting for risk management, these options are necessarily pragmatic, recognizing the limitations of information likely to be available for the large numbers of substances included on the DSL. The simplest option being considered for potential for human exposure involves systematic analysis of limited information on volumes and use (i.e., use codes) provided at the time the Domestic Substances List was compiled, though hierarchical approaches informed by more robust data where they exist, have not been ruled out. Though the approach to "categorization" of potential for human exposure has not yet been finalized, it is unlikely to involve quantitative estimates of exposure by route. Rather, it is the subsequent iterative stages of screening and full assessment to which the current documentation related to estimation of dermal exposure applies.

CEPA '99 – Priority Setting for Existing Substances – Screening and Full Assessments

As indicated in Figure1, the objective for the latter two phases, namely screening and full assessment is to determine whether a substance is **"toxic"** or can be "set aside" (i.e., requiring no further action)**.** Designation of a substance as "toxic" under the Act sets the stage for adding the substance to Schedule I of CEPA (the "List of Toxic Substances") and for reviewing options for controlling risks to human health and/or to the environment (i.e., risk management). According to the legislation,

"... a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions

> (***c***) constituting or that may constitute a danger in Canada to human life or health."

This legal definition of "toxic" under CEPA may be equated with risk since it embodies the concept that harm to the environment or to human health is a function of both the intrinsic toxicity (i.e., toxicity in the traditional sense) and the extent of exposure

As indicated in Figure 1, the second iterative stage of assessment, namely screening, will be conducted for substances that meet criteria for various aspects of categorization. The exact form and content of screening assessments is still under development. However, since as indicated in Figure 1, the principal objectives of these screening assessments are rather limited (i.e., to determine whether substances can be set aside, requiring no further action or should be prioritized for full (i.e., Priority Substances) assessment[3], decisions will likely be based on comparison of worst case estimates of exposure and effect. If margins are wide, there would be no further action on the compound at this stage. If, however, margins are small, the substance would be nominated for inclusion on the Priority Substances List for preparation of an in-depth assessment, for which additional data will be sought and/or generated.

There are several substantive differences between “categorization” and the subsequent iterative risk assessment phases in the program (i.e., screening and full assessment). One is that categorization will be based on available data; only in the subsequent screening and full assessment stages are the information gathering provisions of the legislation being invoked to access existing information and to require testing by industrial stakeholders (the latter when Ministers “suspect” that a substance is “toxic” under the legislation).

Since operational definitions for the various streams of categorization have not yet been finalized, the number of substances likely to require screening assessments is unknown, at this time (Though larger numbers of compounds may be “categorized” in, initial steps in screening may indicate their lack of current use in Canada and hence, no need for additional assessment). However, the rate of production of assessments will almost certainly exceed that for completion of assessments conducted previously for Priority Substances Lists (i.e., 69 substances in an approximately 10 year period), and may be in the range of hundreds for comparatively shorter periods[4]. CEPA does not impose a statutory deadline for completion of the screening assessments, though expectations are high. There is a five year mandated timeframe for full Priority Substances assessments from the time of their addition to the Priority Substances List to completion.

Hence, exposure estimation is a critical component of all stages of the iterative approach to priority setting for risk management, with the current documentation

[3] Currently the only cases envisaged where the compound might be considered “toxic” to human health on the basis of a screening assessment are those where there are serious and irreversible effects – e.g., teratogenicity at relatively low exposure levels.

[4] There are currently 123 substances in the pilot phase for screening.

being relevant to the last of these two stages, namely screening and full (i.e., Priority Substances) assessments.

CEPA incorporates several information gathering provisions which are being, and will continue to be, invoked to solicit necessary information to permit the systematic prioritization and assessment of Existing Substances mandated by the recently renewed legislation. Notices are being issued under Section 71[5] of the legislation requiring those producing or importing the substance during a specified period to provide information to which they reasonably have access relevant to the assessment of both exposure and effects. This includes information on physical/chemical properties, functional uses, emissions and discharges, actual products and concentrations, studies on environmental fate, including data on bioaccumulation and persistence and investigations of biological effects on human and non-human organisms. The first of these Notices was published in the Canada Gazette on November 17, 2001. Based on experience in the pilot phase, these Notices will be modified as appropriate in subsequent stages of the program. The objective in refining the Notices is to solicit information most critical to assessment while minimizing reporting onus on industry.

Under Section 71 of the legislation, those who import or produce the compounds may also be required to generate appropriate data for assessment of either exposure or effects. For exposure, it is likely that this provision would be exercised only at the third iterative stage of assessment, namely full (i.e., that for Priority Substances).

Scope – Exposure Assessment in the Existing Substances Program

The current approach to assessment of Priority Substances including estimation of exposure is presented in documentation posted at the Existing Substances website ***(www.hc-sc.gc.ca/hecs-sesc/exsd)*** and a more recent update (see excerpt included in Supporting Documentation, provided to set context, only. Comments on this documentation are not being solicited from Panel members). For all Existing (including Priority) Substances assessed under CEPA, to the extent possible, exposure is estimated for non-occupationally exposed populations from all sources in the general environment. This sets the stage for subsequent development of measures (if prioritized for risk management) which effectively reduce risk from the most important sources. Therefore, exposure to environmental substances by numerous routes including inhalation, ingestion and/or dermal absorption from air, water, food, soil and through the use of consumer products is relevant to assessment of Existing Substances.

While estimation of exposure for Existing Substances under CEPA focusses primarily on populations exposed in the ambient environment, where relevant

[5] Notices for the 123 substances in the pilot phase have been issued, with a deadline for reporting of March 8, 2002.

and data are sufficient, exposure in the vicinity of industrial point sources is also addressed. Assessment of exposure in the vicinity of contaminated sites (as a basis, for example, for remediation measures) is not considered in the assessment of "toxic" for Existing Substances under CEPA (the objective of which is to set priorities in a national rather than local context).

For human health, exposure through environmental media is the focus of CEPA; consumer products are addressed additionally under other legislation administered by Health Canada (e.g., the Hazardous Products Act). However, operationally, it has been agreed that systematic consideration of exposures to existing chemicals in consumer products for the general population (not mandated under HPA) are best addressed through the provisions of CEPA to ensure that any subsequent risk management measures to minimize exposure of the general population address the most important sources of exposure.

Scope - Purpose of the Current Documentation in the Context of the Existing Substances Program

The potential for dermal exposure from both environmental media and consumer products is acknowledged in the approach to assessment of Existing (including Priority) Substances referenced above. However, owing principally to the nature of the majority of substances included on the first and second Priority Substances Lists, current documentation of the approach to estimation of dermal exposure for Existing Substances is not explicit. Rather, it is limited to the following general text in the "Approach Paper" (See "Supporting Documentation"):

> *Upper bounding estimates of dermal exposure are based on the assumption that all of the substance present in a thin film of product contacting the skin is available for dermal absorption by the user. More refined estimates of dermal absorption through human skin are based on a measured or predicted permeability coefficient of the substance. Caution is necessary when extrapolating permeability data for a substance in aqueous medium to other (e.g., organic) solvents or vehicles. Actual product testing in carefully designed and controlled experiments is recommended for obtaining the most reliable estimates of potential dermal absorption of an ingredient from the use of consumer products, since the vehicle/formulation that a substance is applied in can be more important in regulating skin absorption than the physical-chemical characteristics of the ingredient.*

For several substances on the second Priority Substances List (including ethylene glycol and the glycol ethers), dermal absorption from consumer products potentially contributed significantly to total exposure. In addition, it is likely that consumer products constitute an important source of exposure to many of the substances included on the Domestic Substances List which may be

prioritized through categorization for screening and/or full assessments under the expanded mandate for CEPA ‘99.

In order to ensure consistent application and to facilitate understanding by the scientific and stakeholder communities, it is timely, therefore, to document developments in the approach to estimation of dermal exposure to Priority Substances and to expand it further to address likely issues in the context of the significantly increased mandate for Existing Substances under CEPA ’99. In view of this expanded mandate and the larger numbers of compounds to be categorized and possibly assessed in iterative fashion, it is also critical that this approach be sufficiently pragmatic to accommodate both screening and full assessments, permitting compounds to be “set aside” (i.e., not requiring additional assessment) at a point where additional evaluation should not be considered a priority (i.e., where margins between estimated exposure and effect are large).

Focus/Coverage of Documentation for the Peer Consultation

References consulted in the preparation of the “proposal” are listed in the bibliography of the attached documentation and are those identified as of the date of completion of the draft (i.e., “***Preliminary Proposal to Address Dermal Exposure for Existing Substances”).*** Sections of the documentation addressing exposure from environmental media build on critical previous work by the U.S. EPA (1992, 2001) and incorporate in large measure the symbols included therein. However, approaches to estimation of exposure from consumer products are universally less well documented/developed and while drawing on a number of important references (ECETOC, 1993; ECETOC, 1994; OECD, 1993; Smith and Surbur, 1999; U.S. EPA, 1997), those included in the “Preliminary Proposal” derive largely from experience acquired in the assessment of substances included on the second Priority Substances List under CEPA.

The approach outlined in the decision trees does not address nor obviate the need for consideration of the quality of specific data or assumptions on a case-by-case basis. For example, in the interest of ensuring a pragmatic and hence, useful approach in the context of the considerably expanded mandate for Existing Substances under CEPA, considerations of individual study quality are not addressed herein. This is based on the premise that it is not possible to generically specify criteria by which the quality of individual studies may be judged as a basis for estimation of dermal exposure, since this necessarily will be dependent upon a number of compound, pathway, scenario and event specific considerations.

2. Charge to the Reviewers for the Peer Consultation

Purpose of the Peer Consultation

As acknowledged above, approaches to estimation of exposure from consumer products are universally less well documented/developed than those for environmental media. As a result, many of the questions posed to reviewers for this consultation relate to further development of approaches to assessment of exposure to consumer products, which are critically important sources of uptake for significant subsets of the general population.

While it is recognized that there are significant gaps in relevant knowledge, the ***objective*** of this consultation is to ensure that the current draft of the preliminary approach (as delineated in the draft decision trees) reflects the state of the art of current understanding of the factors that influence dermal absorption. In this context, it is important that the review panel offers pragmatic suggestions for improvement of the current scheme.

This input will enable refinement of the draft scheme to permit its subsequent early adoption in the expanded Existing Substances program in order to acquire operational familiarity to permit informed, iterative refinement.

Recommendations for further research on dermal exposure are ***not*** the focus of this peer consultation. Assessment of the applicability/utility of this draft approach in meeting program objectives is also ***not*** the responsibility of peer reviewers since it necessarily falls within the exclusive purview of Health Canada. However, specific suggestions to revise the current approach based on experience in developing or implementing methodology to assess dermal exposure in other programs are welcome.

The ***"Case Studies"*** in the ***"Supporting Documentation"*** have been included simply to provide illustration and promote understanding of application of the principles outlined in the decision trees; the content of these specific examples is ***not*** being solicited from reviewers; rather, they are being provided as a basis to suggest revisions to the current scheme, through consideration of practical aspects related to application of the preliminary scheme.

Charge to the Peer Consultation

Reviewers are asked to consider the following questions in formulating their comments and as a basis for discussion. While reviewers need not restrict their input to responses to the items below, additional input should be based on mindful consideration of the objectives and scope of the peer consultation described above (pragmatic suggestion for modification of the preliminary proposal based on the current state of common understanding of factors affecting dermal absorption).

Priority of accessing input from the panel on the questions that follow has been assigned on the basis of their relevance to pragmatic revision of the decision trees to permit their subsequent early adoption. As their ***top priority***, then, the Panel is asked to consider the inclusiveness and defensibility of the current content of the decision trees included in the "***Preliminary Proposal to Address Dermal Exposure for Existing Substances" (i.e., Questions 1-7).*** As a second priority, reviewers are asked to identify critical sources of data relevant to the essential content of the decision trees and that would be additionally meaningfully informative in the estimation of dermal exposure for specific use scenarios or event frequencies ***(Question 8).***

Finally, reviewers are also asked to consider (as time permits), questions related to the defensibility of specific assumptions proposed in various sources related to the estimation of dermal permeability coefficients and/or their appropriate development ***(Questions 9 to 14).***

Inclusiveness and Defensibility of Decision Trees - "Preliminary Proposal to Address Dermal Exposure for Existing Substances"

1. Is the content of the decision trees sufficiently inclusive?

> -Are you aware of pathways/scenarios for dermal absorption that potentially significantly contribute to total exposure of the general population that are not included? If so, please indicate how these additional scenarios/pathways might be addressed in the context of the content of the current draft decision trees.
>
> -Are you aware of products that have potential to contribute significantly to dermal absorption of the general population which are not adequately addressed? If so, please indicate how these products might be more appropriately addressed in the context of the content of the draft decision trees.
>
> -Are you aware of (types of) chemicals for which there is potentially significant dermal absorption which are not addressed adequately by the current draft decision trees? What revisions/additions to the content of the draft decision trees would you suggest to ensure their adequate consideration in the draft decision trees?

2. Can the decision trees be simplified without sacrificing scientific integrity (i.e., while still addressing the critical sources of dermal exposure of the general population)?

3. Can additional distinction be made concerning the relevance of various aspects of the decision trees to screening versus full (e.g., Priority Substances) assessment?

4. Are the uncertainties associated with any aspect of the current draft of the decision trees so large that any component is not considered potentially meaningful even in a priority setting context (i.e., screening as a basis for prioritisation for setting the compound aside or conducting further, full assessment)?

5. Is there "generic" guidance (or considerations that should be taken into account) that could be provided in evaluating different types of individual studies (e.g., *in vivo* studies of percutaneous absorption) in the assessment of dermal exposure, without unnecessarily complicating further the draft decision trees? Could these considerations be incorporated or referenced in the current draft decision trees or are they best considered on a case-by-case basis, in view of the number of relevant factors that need to be considered?

6. Is it possible to include additional generic considerations within the draft decision trees of relative weighting of data (e.g., % absorption *in vivo* versus % absorption *in vitro* versus permeability coefficients based on phys/chem. parameters). If so, please suggest specific revisions to the draft decision trees to address this aspect.

7. Would you suggest any modifications to the assumptions relating to distinction of "finite" versus "infinite" dose scenarios (see Table in ***"Introduction"*** to ***"Preliminary Proposal to Assess Dermal Exposure for Existing Substances")***?

Sources of Data on Use Scenarios and Event Frequencies

8. Are there important additional data sources relevant to the critical content of the decision trees? For example, are you aware of critical additionally informative compilations of relevant product use scenarios (T-18) or event frequencies (T25). If so, please provide a copy of the relevant reference(s) or citation thereof.

Defensibility of Assumptions – Dermal Permeability Coefficients

9. Under what conditions is estimation of the dermal permeability coefficient for a substance from an organic solvent based on its dermal permeability coefficient from aqueous solution justified (equation 4.7, page 4-7, USEPA 1992)?

10. Under what conditions is the K_p value of a substance from aqueous solution a reasonable estimate of the product-specific K_p when a water-based product includes ingredients other than the substance of interest?

11. Can reasonable upper limits of concentration of a substance in a medium be specified (e.g., 10%, 50%, 90%, limit of solubility?) above which a K_p value measured or estimated at lower concentrations should not be assumed? Could this be specified on the basis of whether or not the substance and the medium are miscible (i.e., mutually soluble in all proportions)?

12. Cleek and Bunge (1993) have proposed an approach which is further developed by Reddy et al. (2000) and U.S. EPA (2001) (pages 3-1 to 3-8) to estimate the mass of substance absorbed through the area of exposed skin (M/A) depending on whether or not the exposure period is shorter or longer than the unsteady-state period of the flux of chemicals through the skin? Do you agree that this approach is defensible? If so, what are the finite lower limits to the durations of the external skin contact below which an estimate of amount of substance absorbed calculated from a steady state flux can reasonably be assumed? Is the assumption that all substance absorbed into the skin is ultimately available for systemic uptake reasonable (recognizing that metabolism and irreversible binding within the skin layer can contribute to "losses" in some cases).

13. Are the only defensible estimates of the extent of dermal absorption of a substance from a product formulation those obtained from *in vivo* or *in vitro* testing of the actual formulation? If not, can the panel suggest defensible alternatives (e.g., 100% absorption of the substance in the vehicle contacting the external skin surface?)

14. Based on lack of applicability of compound-specific estimates of % absorbed under specific finite dose to dissimilar exposure conditions, Robinson (1998) (page 211) suggests that an estimate of K_p be estimated and then extrapolated to other exposure conditions using this normalized parameter. Relevant operational equations [% absorbed = 100% • (amount absorbed)/applied dose], defined on the basis of parameters applied surface area, exposure time, applied concentration and applied dose volume do not address decrease over duration of the experiment of an assumed finite applied dose. Is this approach defensible, in the absence of an experimentally determined K_p value? If not, are there defensible alternatives? If so, should there be qualifications about ranges of applicability?