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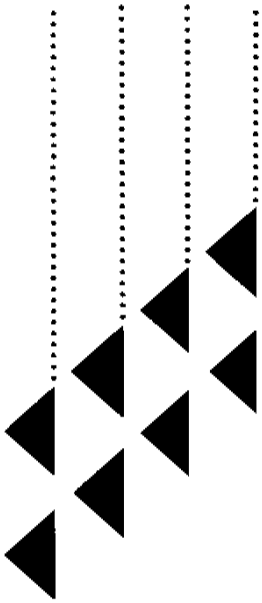
Canadian Environmental Protection Act

Human Health Risk Assessment for Priority Substances



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CANADA'S GREEN PLAN

Canadian Environmental Protection Act

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Health Canada

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The approach to assessment of potential risks to human health under paragraph 11(*c*) of CEPA will be revised periodically to incorporate new developments in risk assessment methodology. Final revisions to the technical content of this version of the document were made on April 21, 1994. Copies of this Report may be obtained from:

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1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA), proclaimed on June 30, 1988, and amended on June 30, 1989, 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.

Under CEPA, "substance" means "any distinguishable kind of organic or inorganic matter, whether animate or inanimate, and includes:

> ... any mixture that is a combination of substances ...,
>
> ... any complex mixtures of different molecules that are contained in effluents, emissions or wastes that result from any work, undertaking or activity."

This definition of a "substance" encompasses discrete chemical compounds, classes of chemicals, emissions and effluents, and products of biotechnology, including microorganisms. Therefore, all of the above are candidates for assessment under the legislation.

According to a definition in section 11 of the Act:

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

> (***a***) having or that may have an immediate or long-term harmful effect on the environment;
>
> (***b***) constituting or that may constitute a danger to the environment on which human life depends; or
>
> (***c***) constituting or that may constitute a danger in Canada to human life or health."

Under Part II of CEPA ("Toxic Substances"), there is a legal framework for assessing and controlling substances that may already be present in the Canadian environment (existing substances). Both Ministers (Environment and Health) must publish and may amend a Priority Substances List, respond to public nominations for additions to the List within 90 days, and conduct an assessment to ascertain whether or not each listed substance is "toxic". If the report of the assessment is not published within 5 years of a substance being added to the List, this could lead to the establishment of a Board of Review. The Ministers must also publish a summary of the Assessment Report in the *Canada Gazette* along with an indication of whether they **intend to recommend** the development of regulations to control the substance.

The first Priority Substances List, published in the *Canada Gazette* in February 1989, comprised 44 substances including discrete chemicals, classes of substances and complex mixtures. Priority must be given to these substances in assessing whether they are "toxic or capable of becoming toxic" under section 11 of CEPA.

The determination of "toxic", under paragraph 11*(c)* of CEPA (i.e., with respect to direct effects on human health), for Priority Substances is the responsibility of the Bureau of Chemical Hazards of Health Canada, and is based on careful consideration of the principles outlined in this report. Though developed specifically to ensure consistency of approach for Priority Substances, some of the aspects addressed herein also apply to other substances being assessed under CEPA.

In scientific parlance, toxicity is the inherent capability of a substance to cause harm, which does not take into account exposure. However, the definition of "toxic" under section 11 of the Act is a legal one which 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. In addition, the inclusion of the word "may" in the definition with respect to both entry into the environment ("a compound may enter the environment in a quantity or concentration or under conditions") and effects ("that may constitute a danger in Canada to human life or health") allows the approach to designation of "toxic" with respect to human health 11*(c)* to be developed in a manner which is consistent with current principles of health risk assessment. Assessment under paragraph 11*(c)*, for which there are three endpoints (i.e., designation of "toxic", "not considered to be toxic", or "insufficient information to conclude whether or not the compound is toxic") does not address any aspects of risk management, which are not considered at this stage. 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. Provisions concerning the need for controls on a substance that is deemed to be "toxic" are included under other sections and paragraphs of the Act (for example, paragraph 13(l)*(c)* and sections 33 and 34). It should be noted that the designation of a substance as "toxic" under CEPA does not necessarily mean that controls will be imposed. Such decisions can only be made in a subsequent risk management phase that includes a judicious balancing of the risks and benefits associated with continued use of the substance (that is, based on subsequent analysis of social and economic as well as scientific factors).

In this report, initially, a brief description of aspects considered in the evaluation of data relevant to assessment of "toxic" under paragraph 11*(c)* of CEPA is presented. This is followed by a description of the principles used in the assessment of exposure and the approach to evaluation of effects for different types of substances ("non-threshold toxicants", "threshold toxicants", "possible threshold toxicants" and mixtures). More detailed information is included in the Appendices.

Although there may be uncertainty in the available scientific data used as the basis for determination of whether or not a substance is "toxic" under paragraph 11*(c)* of CEPA, every effort is made to take these uncertainties into account in the approaches described here. It should also be emphasized that fundamental to these assessments is the application of sound scientific judgement on a case-by-case basis. Moreover, these approaches are subject to change, to incorporate new developments in risk assessment methodology.

2.0 Database for Assessment of " Toxic" under paragraph 11*(c)* of CEPA

Initially in the determination of whether a substance is "toxic" under paragraph 11*(c)* of CEPA, information on levels in the general (non-occupational) environment to which the population of Canada is exposed, and on the intrinsic toxicological properties of the substance, is collected and critically evaluated.

2.1 Exposure

To the extent possible, information on concentrations of Priority Substances acquired in national surveys of ambient air, drinking water, soil, foodstuffs and consumer products within Canada is used as the basis for the assessment of exposure of the general (non-occupationally exposed) population. Concentrations in various tissues or biological fluids (e.g., adipose tissue or breast milk) of the general population are also used as a basis for estimation of human exposure. In those cases where relevant Canadian data are lacking or inadequate, information on the levels of Priority Substances in various environmental media, foods, consumer products, or biological tissues and fluids in the general population from other countries (primarily the United States) is used as a basis for assessment of the exposure of the general population of Canada. In addition to size (i.e., number of samples and locations) and representativeness (i.e., range of locations sampled) of available surveys, the sensitivity, precision and accuracy of the analytical methodology employed is also considered in the selection of data as a basis for estimation of exposure. In general, mean concentrations in various environmental media used in estimating exposure are those reported by the authors of relevant accounts, although, wherever possible, the values which have been assigned to non-detectable concentrations in the calculation of means are indicated. Where it is necessary to calculate mean concentrations from raw data, the concentration in samples in which the compound has not been detected is considered to be the limit of detection, though it is recognized that this will lead to an overestimate of exposure. Where appropriate, information on concentrations of Priority Substances in specific locales is also used as a basis for estimation of exposure of some "high exposure subgroups" in the general population.

In some cases where data on concentrations of Priority Substances in environmental media within Canada or elsewhere are not available or are inadequate, where appropriate, population exposure is estimated based on levels in air, water, soil and food (fish) predicted by modelling of information on use patterns and physical/chemical properties (e.g., fugacity modelling). However, owing to the considerable uncertainty in values predicted by these models, they are only relied upon in the determination of "toxic" in cases where estimated total daily intake is markedly less (i.e., by many orders of magnitude) than intakes, considered on the basis of available data, to which it is believed that a person can be exposed over a lifetime without deleterious effect. In cases where total daily intake estimated on the basis of concentrations in the environment predicted by modelling are only somewhat less than or exceed that to which it

is believed that a person can be exposed over a lifetime without deleterious effect, acquisition of monitoring data on actual concentrations in the environment may be required, prior to reaching a conclusion that the substance is “toxic”.

Information on the duration and frequency of exposure is also important in assessing the total daily intake of Priority Substances by the general population under CEPA. Relevant data on behaviour and activity patterns are also considered, therefore, in the development of estimates of exposure of the general population.

2.2 Effects

Effects of exposure to existing substances are generally classified in the following broad categories: organ-specific, neurological/behavioural, reproductive/developmental, immunological, carcinogenic and mutagenic. These effects are manifested at the biochemical, cellular, histopathological and morphological levels. Such effects vary depending upon the dosage, route of exposure (e.g., ingestion, inhalation or dermal absorption), frequency and/or duration of exposure, species (and strain in the case of animals), physiological state, sex and age of the exposed population. Toxicological effects resulting from exposure to chemical substances may be brief or prolonged, reversible or irreversible, immediate or delayed. The nature, number, severity, incidence and/or prevalence of specific toxicological effects in populations (of either humans or animal species) exposed to chemical substances generally increase with increasing dose or level of exposure; this is commonly referred to as the exposure- or dose-response relationship.

For most existing substances, data on the toxicological effects resulting from exposure are restricted to information obtained from studies involving laboratory animals. Occasionally, information derived from studies of human populations (principally epidemiological investigations) forms an integral part of the database upon which the assessment of “toxic” under paragraph 11*(c)* of CEPA is based. Clearly, data on effects in humans are preferred as a basis of assessment of “toxic” under CEPA since such information obviates the need to extrapolate across species; however, in most cases, such data are limited or inadequate.

Often, there are case reports on the health of exposed individuals included in the literature; however, they are not weighted heavily in assessments for Priority Substances, owing to the nature of and general lack of quantitation of exposure (generally short-term exposure to concentrations much greater than those in the general environment) and lack of statistical reliability. In some cases, information from clinical studies in human volunteers is also available. Although such investigations are generally reliable for the establishment of exposure-response relationships, they are most often restricted for ethical reasons to the examination of mild, temporary effects (e.g., neurobehavioural or biochemical changes) of short-term exposures in a limited number of subjects. Therefore, such results are often of limited value in assessment of the potential effects of long-term exposure in the general environment.

Epidemiological studies of populations exposed to chemical pollutants in the general environment are most often limited to descriptive epidemiological studies, also referred to as ecological or correlational studies. Generally, in such investigations, mortality or morbidity rates for various diseases in populations in different geographical areas are examined in relation to data on concentrations of pollutants in environmental media (e.g., air or drinking water). Although it is possible to examine large populations in this manner, the lack of data on the exposure of individuals in the population makes it difficult to adjust rigorously for possible confounding factors such as lifestyle factors, which may be as or more important than pollutants in the general environment in the causation of disease. In addition, in such studies, it is difficult to adequately take into account population mobility (that is, movement into and out of the areas under study) or to examine temporal relationships. Although such investigations are useful in generating hypotheses for further testing, they are seldom adequate for identifying cause and effect relationships and are, therefore, not weighted heavily in the determination of "toxic" under paragraph 1l*(c)* of CEPA.

Analytical epidemiological studies (that is, cohort and case-control studies) in which exposure and outcome are examined in individuals rather than in populations, are more reliable since it is possible to adjust more rigorously for confounding factors. Still, such studies are relatively insensitive in detecting the likely small risks to health which may be associated with exposure to low levels of pollutants in the general environment. Available cohort and case-control studies on the health risks associated with exposure to chemical pollutants are often confined to investigations in the occupational environment, where exposures and potential health risks are greater than those in the general environment. These studies are relevant to the assessment of the weight of evidence for particular effects and for characterization of the exposure-response relationship. The results of such studies are assessed based on several features of study design including estimation of exposure, the role of confounding variables and the measurement of outcome. Assessment of causality of associations observed in such epidemiological studies is evaluated against traditional criteria which include consistency, strength, specificity, exposure-response, the existence of a temporal relationship and biological plausibility.

Owing to the lack of adequate epidemiological data for most existing substances, assessment of "toxic" under paragraph 11*(c)* of CEPA is most often based on the results of toxicological studies in animal species. In identifying the critical studies for assessment of "toxic", several features of study design are considered including the purity of the compound administered, the size of the study (i.e., how many exposed and control animals there were), whether the study adhered to the principles of good laboratory practice, the relevance of the route of exposure to that of humans, duration of exposure, the number and suitability of the dose levels administered, the extent of examination of various toxicological endpoints and the statistical analysis of the data. The types, site, incidence and severity of effects and the nature of the exposure- or dose-response relationship are also taken into account. Where data indicate that there are significant differences in absorption, distribution, metabolism and elimination of the compound in different animal species, wherever possible, studies in which the species and strain of animal are most similar to man in this regard are used (where relevant human data are

available). The consistency of the results of the principal studies are also considered in the assessment of the weight of evidence for an effect (for example, have similar effects been observed in studies in other species or would such effects have been expected based on the structure or properties of the chemical?).

Commonly, the general (i.e., non-occupationally exposed) population in Canada is exposed for a prolonged period (i.e., a lifetime) to low (sometimes non-detectable) concentrations of Priority Substances in the general environment. During the lifetime, there may be especially critical periods where sensitivity is increased (for example, during pregnancy or old age). Consequently, it is the potential for adverse effects on health following the long-term (chronic) exposure or exposure during critical periods (e.g., pregnancy) which are most important in assessing whether substances are "toxic" under paragraph 11*(c)* of CEPA. Chronic studies in which the chemical has been administered for a considerable portion of the animal's lifespan, or studies in the most sensitive subpopulation (e.g., the embryo or foetus of an exposed mother in developmental studies) are, therefore, preferred as a basis for assessment of "toxic" under paragraph 11*(c)*. Though data on acute or short-term studies in laboratory animals provide useful background information (for identification of target organs or species differences in sensitivity, for example), they are generally not considered sufficient in themselves to assess "toxic" under paragraph 11*(c)* of CEPA (i.e., a study of subchronic duration or longer is required), unless observed effects in longer term studies are expected to be similar. In some cases where data on the adverse effects of exposure to a Priority Substance are not available from either epidemiological or toxicological studies, potential toxicity may be predicted on the basis of modelling of structure activity relationships, for the purposes of providing information for prioritization of recommendations for additional research.

Information on molecular, biochemical and cellular mechanisms of toxicity as well as metabolic pathways is also collected and evaluated for the assessment of "toxic" under paragraph 11*(c)* of CEPA. Information on the metabolism of chemical substances (including data on the toxicological effects of potential metabolites) and mechanisms of toxicity is extremely important in assessing the relevance of effects observed in laboratory animals to man. Effects observed in experimental studies may not be relevant to humans if the metabolic pathway or mechanism involved in mediating the toxicity of a particular substance is operative in one or more species of animals but not (or to a much lesser degree) in humans.

3.0 Approaches for the Assessment of "Toxic" under paragraph 11*(c)* of CEPA – Single Substances

3.1 Assessment of Population Exposure

Exposure to environmental substances may occur by inhalation, ingestion and/or dermal absorption from air, water, food, soil and through the use of consumer products. Estimation of the total daily intake (usually expressed as μg/kg body weight/day) from all sources is critical in assessing the true magnitude of risk associated with exposure to substances in the general environment. This "multimedia" approach also sets the stage for any subsequent development of measures which are most effective for human health protection by identifying the relative magnitude of the contribution of each pathway of exposure to total daily intake.

Standardized reference values for body weights, the volume of air breathed, quantities of food, water and soil ingested and, to the extent possible, information on behavioural patterns of the exposed population(s) form an integral part of the estimation of exposure from all sources. A description of the reference values for these parameters, used in estimating the total daily intake of Priority Substances by five discrete age groups in the general population in Canada, and the rationale for their selection are presented in Appendix A.

It should be emphasized that the reference values tabulated in Appendix A and concentrations in environmental media used in the population exposure estimates are representative for **average members of the general population of Canada.** Owing to the often considerable variation in mean concentrations of chemical substances in environmental media measured at different locations, the estimated daily intakes from various media for each of the age groups are generally expressed as a range of mean values. Exposure of a significant proportion of the population will be incorporated within these ranges. In addition, exposure of some segments of the population which may be greater than those for the population at large (i.e., "high-exposure subgroups"), is also taken into account, where considered appropriate and where sufficient data are available. For example, exposures via one or more routes to some substances may be elevated for persons living in the vicinity of point sources (such as industrial emissions), depending on the form in which these substances are released and their subsequent environmental transport and transformation. The intake of some substances by subsistence hunters or fishermen may also be elevated due to accumulation in the game species which they consume. It should be noted, however, that although relevant data concerning occupational exposure, paraoccupational exposure (for hobbyists, for example), substance abuse and smoking are sometimes reviewed and presented in assessments for Priority Substances, they are not considered in the estimation of total daily intake, since such exposures are highly variable, often not typical of most of the general population and more appropriately addressed under statutes other than CEPA. Exposure from consumer products is taken into account, however, primarily through estimation of intake from indoor air.

Selection of "high-exposure subgroups" for which total daily intakes are estimated is determined on a case-by-case basis. In addition to the magnitude of the estimated intake for various subgroups, the most important factor weighted in this determination is the size of the exposed population. For example, elevated levels to which few individuals are exposed in isolated locales as a result of intermittent spills or leakage are not considered relevant to estimation of exposure for the general population. Additional factors considered in the selection of relevant "high-exposure subgroups" are use patterns, environmental partitioning of the substance, the major routes of exposure, and availability of quantitative data on concentrations in relevant media and consumption.

In general, information on the toxicokinetics of a Priority Substance is not incorporated into the estimated total daily intakes since, in the assessment of "toxic", they are generally compared to tolerable daily intakes or quantitative estimates of cancer potency that are based on nominal doses to which animals or humans in the critical toxicological or epidemiological studies are exposed.

3.2 Assessment of Effects

Different approaches have been adopted to assess whether a Priority Substance is "toxic" under paragraph 11*(c)* of CEPA, depending on whether the critical effect is considered to have or not to have a threshold ("threshold toxicants" or "non-threshold toxicants", respectively). (The critical effect is defined as the biologically significant effect expected to occur at the lowest dose or concentration). For many types of toxic effects (i.e., organ-specific, neurological/behavioural, immunological, epigenetic carcinogenesis, reproductive or developmental), it is generally considered that there is a dose or concentration below which adverse effects will not occur (i.e., a threshold). For other types of toxic effects it is assumed, but not proven, that there is some probability of harm at any level of exposure (i.e., that no threshold exists). At the present time, the latter assumption is generally considered to be appropriate only for mutagenesis and genotoxic carcinogenesis.

Chemical substances are classified, therefore, with respect to their potential carcinogenicity and mutagenicity to humans; this is accomplished on the basis of rigorous examination of the quantity, quality and nature of the results of available toxicological and epidemiological studies. The criteria by which Priority Substances are classified based on their weight of evidence of carcinogenicity and mutagenicity are outlined in Appendices B and C, respectively.

3.2.1 "Non-Threshold Toxicants"

For those substances for which the critical effect is assumed to have no threshold (i.e., currently restricted to mutagenesis and genotoxic carcinogenesis), it is assumed that there is some probability of harm to human health at any level of exposure, and consequently it is not appropriate to calculate a dose below which adverse effects are not expected to occur.

Therefore, substances classified in Groups I ("Carcinogenic to Humans") or II ("Probably Carcinogenic to Humans") in Appendix B are considered to be "toxic" under paragraph 11(c) of CEPA.

Substances classified in Groups I ("Human Germ Cell Mutagen") or II ("Probable Human Germ Cell Mutagen") of Appendix C for which the weight of evidence of carcinogenicity is weak, may be considered to be "toxic" under paragraph 11(c) of CEPA.

For such substances, mathematical models are often used to extrapolate data on the exposure- or dose-response relationship derived from experimental studies in animal species or epidemiological studies (generally in workers) to estimate the risk at concentrations to which the general population is exposed. There are numerous uncertainties in this approach, which generally involves linear extrapolation of results over several orders of magnitude, often in the absence of relevant data on mechanisms of tumour induction or differences in toxico-kinetics and -dynamics between the relevant experimental animal species and humans.

For assessment of "toxic" under paragraph 11*(c)* of CEPA for non-threshold toxicants, it is considered inappropriate to specify a concentration or dose associated with a negligible or *de minimis* level of risk (such as a lifetime cancer risk of 1 in 1 million) by low-dose extrapolation procedures, primarily since this would involve inclusion of considerations other than those based on science at this stage (i.e., making a societal judgement about what level constitutes *de minimis* risk). There is no single "correct" value which adequately characterizes *de minimis* risk associated with a concentration or dose below which risks are acceptable and above which they are not; rather, the risk at low doses or concentrations is assumed to be a continuum, with reduction of exposure leading to an incremental reduction of risk and increases in exposure leading to incremental increases in risk. In addition, in view of the considerable uncertainties of current low-dose extrapolation procedures, it is also considered inappropriate to specify risks in terms of predicted incidence or numbers of excess deaths per unit of the population.

However, it is recognized that the incremental risks associated with exposure to low levels of such substances, although difficult to characterize, may be sufficiently small so as to be essentially negligible compared with other risks encountered in society and that on this basis, control action to reduce exposure may not be justified. Decisions concerning the need for, and development of, control strategies may be made only following a judicious balancing of the estimated risks against the associated costs and feasibility of controls, and/or benefits to society (i.e., in stages subsequent to assessment of "toxic" under the Act such as strategic options analysis).

To characterize risk and provide guidance in establishing priorities for further action following assessment of "toxic" under the Act, where possible, quantitative estimates of the carcinogenic and mutagenic potency of compounds classified in Groups I and II of Appendices B and C are compared to the estimated daily intake of the Priority Substance by the general population (or certain high-exposure subgroups) in Canada, or to concentrations in specific relevant environmental media (referred to as the Exposure/Potency Index or EPI). Potency is

expressed as the concentration or dose which induces a 5% increase in the incidence of, or deaths due to, tumours or heritable mutations considered to be associated with exposure[1]. It may be based on tumours observed in epidemiological studies (generally) in occupationally exposed human populations or those considered relevant to humans as observed in bioassays in laboratory animals. The estimates of potency are generally restricted to effects for which there has been a statistically significant increase in incidence and a dose-response relationship, characterized using appropriate mathematical models (e.g., multistage).

Any model which fits the empirical data well is likely to provide a reasonable estimate of the potency; choice of the model may not be critical since estimation is within the observed dose range, thereby avoiding the numerous uncertainties associated with low-dose extrapolation. The value of 5% is arbitrary; selection of another value would not impact on the relative magnitudes of the Exposure/Potency Indices (EPIs) for each of a range of compounds. The priority for further action (i.e., analysis of options to reduce exposure) is considered to be high for EPIs of approximately 2.0×10^{-4} or greater; for EPIs within the range of greater than or equal to approximately 2.0×10^{-6} to less than approximately 2.0×10^{-4}, it is considered to be moderate and for EPIs less than approximately 2.0×10^{-6}, it is considered to be low. That is, when estimated exposure is only a very small proportion of the concentration or dose which induces a 5% increase in tumours, the priority for analysis of options to reduce exposure is low.

Wherever possible and if considered appropriate, information on pharmacokinetics, metabolism and mechanisms of carcinogenicity and mutagenicity is incorporated into the quantitative estimates of potency derived particularly from studies in animals (to provide relevant scaling of potency for human populations).

Obviating the establishment of a single *de minimis* risk level enables the assessment of "toxic" for "non-threshold toxicants" to be based to the extent possible on scientific considerations. This approach is also consistent with the objective that exposure to "nonthreshold toxicants" should be reduced to the extent possible.

3.2.2 "Threshold Toxicants"

The approach to assessment of "toxic" for substances classified in Groups IV ("Unlikely to Be Carcinogenic to Humans"), V ("Probably Not Carcinogenic to Humans"), or VI ("Unclassifiable with Respect to Carcinogenicity in Humans") based on the criteria in Appendix B, is that adopted for "threshold toxicants" as described in this section. Threshold toxicants are those for which the critical effect is not considered to be cancer or a heritable mutation. It is recognized, however, that for at least one of these categories (Group VI), adoption of this approach is sometimes a function more of the lack of available data on carcinogenicity

1. The $TD_{0.05}$ is not based on the confidence limit but rather, is computed directly from the curve. This was considered to be appropriate in view of the stability of the data in the experimental range and to avoid unnecessarily conservative assumptions. Also, use of a point estimate or confidence limit does not affect the relative magnitude of the potency estimates for different compounds.

than certain knowledge of the critical effect. Though this may appear to be less than conservative, tolerable daily intakes for compounds in this group are developed on the basis of very large uncertainty factors (to account for inadequacies of the database), with the objective of providing protection for potential carcinogenicity.

Where possible, a dose (or concentration) of a chemical substance that does not produce any (adverse) effect [i.e., "no-observed-(adverse)-effect-level" (NO(A)EL)[2]] for the critical endpoint is identified, usually from toxicological studies involving laboratory animals, but sometimes from epidemiological studies of human populations. If a value for the NO(A)EL cannot be ascertained, a lowest-observed-(adverse)-effect-level (LO(A)EL) is used. The nature and severity of the critical effect (and to some extent, the steepness of the dose-response curve) are taken into account in the establishment of the NO(A)EL or LO(A)EL. For example, the concentration or dose which induces a transient increase in organ weight without accompanying biochemical or histopathological effects would generally be considered a LOEL. If there are accompanying adverse histopathological effects in the target organ, the concentration or dose at which these effects were observed would be considered a LOAEL.

An uncertainty factor is applied to the NO(A)EL or LO(A)EL to derive a Tolerable Daily Intake or Concentration (TDI or TDC)[3], the intake or concentration to which it is believed that a person can be exposed daily over a lifetime without deleterious effect[4]. Ideally, the NO(A)EL is derived from a chronic exposure study involving the most relevant or sensitive species (where possible, determined based on data on species differences in pharmacokinetic parameters or mechanism of action) or on investigations in the most sensitive subpopulation[5] (e.g., the embryo or fœtus in developmental studies) in which the route of administration (in studies with laboratory animals) is similar to that by which humans are principally exposed. Tolerable Daily Intakes or Concentrations are not generally developed on the basis of data from acute or short-term studies (unless observed effects in longer term studies are expected to be similar), although they are occasionally based on data from subchronic studies in the absence of available information in adequately designed and conducted chronic toxicity studies, in which case an additional factor of uncertainty is included. Exceptionally, in cases where a NO(A)EL or LO(A)EL cannot be identified in studies by the route of exposure by which humans are principally exposed, a NO(A)EL or LO(A)EL from a bioassay by another route of exposure may be used where appropriate, incorporating relevant pharmacokinetic data.

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2 See Appendix D for definitions.

3 NO(A)ELs or LO(A)ELs are also modified by an additional factor for conversion of intermittent to continuous exposure in the development of TDIs.

4 Reference values for intakes and body weights of various species used in derivation of the TDI are presented in Appendix E.

5 "Sensitive subpopulations" do not, however, include the small number of individuals who are considered hypersensitive, for which extraordinary control measures are required.

The uncertainty factor is derived on a case-by-case basis, depending principally on the quality of the database. Generally, a factor of 1 to 10 is used to account for intraspecies variation and interspecies variation[6]. An additional factor of 1 to 100 is used to account for inadequacies of the database which include but are not necessarily limited to, lack of adequate data on developmental, chronic or reproductive toxicity, use of a LO(A)EL versus a NO(A)EL and inadequacies of the critical study. An additional uncertainty factor ranging between 1 and 5 may be incorporated where there is sufficient information to indicate a potential for interaction with other chemical substances commonly present in the general environment. If the chemical substance is essential or beneficial for human health, the dietary requirement is also taken into consideration in derivation of the Tolerable Daily Intake or Concentration. Exceptionally, in deriving a TDI or TDC for severe effects (e.g., teratogenicity), an additional uncertainty factor of 1 to 10 may be incorporated. Numerical values of the uncertainty factor normally range from 1 to 10,000. Uncertainty factors greater than 10,000 are not applied since the limitations of such a database are sufficient to preclude development of a reliable TDI or TDC. In some cases, where the uncertainty factor is less than 10,000 but there are limitations in the protocol of the critical study, a "tentative TDI" or "tentative TDC" may be established.

The value of the TDI, TDC, "tentative TDI" or "tentative TDC" is compared to the estimated total daily intake of a chemical substance by the various age groups of the population of Canada and, in some cases, certain high-exposure subgroups or to concentrations in relevant environmental media.

If the estimated total daily intake of a chemical substance by the various age groups of the Canadian population (or certain subgroups) or concentrations in relevant environmental media exceed(s) or could exceed the TDI, TDC, "tentative TDI" or "tentative TDC", the substance is considered to be "toxic" under paragraph 11(c) of CEPA; if the estimated daily intake or concentrations in relevant environmental media are less than the TDI, TDC, "tentative TDI" or "tentative TDC", the substance is not considered to be "toxic" under the Act.

For those "threshold toxicants" considered to be "toxic" under paragraph 11*(c)* of CEPA, the estimated total daily intake of the substance by the general population in Canada or concentrations in relevant environmental media are compared to the NO(A)EL or LO(A)EL on which the TDI or TDC is based, to provide guidance in establishing priorities for further action following assessment of "toxic" under the Act.

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6 Where there are sufficient data, the factors for interspecies and intraspecies variation are subdivided to address separately kinetic and dynamic differences. For example, it has been proposed that for intraspecies variation, a factor of 2.5 be assigned to dynamics and 4 for kinetics; for interspecies variation, respective factors of 3.2 and 3.2 have been proposed (Report of IPCS Discussions on Deriving Guidance Values for Health-Based Exposure Limits, International Programme on Chemical Safety, Geneva, 1992). As a result, incorporation of data on toxico-kinetics and -dynamics, when available, would generally lead to a reduction in the uncertainty factors applied.

An alternative approach, which may be used where data permit, involves estimation of the "benchmark dose", a model-derived estimate of a particular incidence level (e.g., 5%) for the critical effect. More specifically, the benchmark dose is the effective dose (or its lower confidence limit) that produces a certain increase in incidence above control levels. The benchmark dose is derived by modelling the data in the observed range and selecting the point on the curve (or its upper confidence limit) corresponding to a specified increase in the incidence of an effect. Any model which fits the empirical data well is likely to provide a reasonable estimate of the benchmark dose and choice of the model may not be critical since estimation is within the observed dose range. The advantages of the benchmark dose are that it takes into account the slope of the dose-response curve, the size of the study groups and the variability in the data in establishment of the true threshold.

3.2.3 "Possible Non-Threshold Toxicants"

Substances classified as "Possibly Carcinogenic to Humans" (Group III in Appendix B) are generally assessed in a manner similar to "threshold toxicants"; the determination of "toxic" under CEPA is made by comparing the total daily intake by the various age groups of the Canadian population or concentrations in relevant environmental media with the value derived for the TDI or TDC as described for Groups IV to VI above. Exceptionally, however, in deriving the TDI or TDC for substances classified as "Possibly Carcinogenic to Humans", an additional uncertainty factor (ranging between 1 and 10) may be incorporated to account for the limited evidence of carcinogenicity. In some cases where considered appropriate[7], quantitative estimates of the carcinogenic potency of these substances (or the potency to induce heritable mutations) are compared to the estimated daily intake by the general population in Canada, or to concentrations in relevant environmental media, to characterize risk and provide guidance in establishing priorities for further action following assessment of "toxic" under the Act.

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7 For example when there are convincing data that the compound is genotoxic or mechanistic information which indicates that it is likely to be carcinogenic, but there is insufficient evidence of carcinogenicity in chronic bioassays, due probably to the limitations of the studies.

4.0 Approaches for the Assessment of "Toxic" under paragraph 11(*c*) of CEPA – Simple Mixtures

The approach to assessment of whether or not a simple mixture of chemical substances is "toxic" under CEPA is dependent upon the nature of the available data. Occasionally, the chemical composition of a mixture, levels of exposure of the general population to the mixture, and toxic effects of the mixture itself or its components, may be well characterized. Generally though, not all components of the mixture are known, and information on the levels of exposure and toxicological data either of the mixture itself or the components are limited and/or inadequate. Examples of some relevant approaches to the assessment of "toxic" under paragraph 11*(c)* of CEPA are provided below, though owing to the variation in the types and compositions and relevant toxicological data available, assessment on a case-by-case basis is especially critical.

4.1 Mixture-Based Approach

For those cases in which information is available on exposure of the general population to and the toxicological effects produced by the exposure of animals or humans to the simple mixture itself, the approach to assess whether or not it is "toxic" under paragraph 11*(c)* of CEPA is similar to that outlined above for single "threshold" or "non-threshold toxicants".

4.2 Component-Based Approach

An assessment of whether or not simple mixtures of chemical substances are "toxic" under paragraph 11*(c)* of CEPA can sometimes be based on the effects of some or all of the components present in the mixture. For those cases in which the components in the simple mixture have similar effects due to similar modes of action, and there is little indication for interaction between components, effects are generally considered to be additive.

One component-based approach for "threshold toxicants" involves expressing the total daily intake of the mixture as toxic equivalents [summing of the concentrations of individual compounds multiplied by the potency of that substance relative to that of the reference (generally most potent) substance]. This composite measure of intake is compared to a Tolerable Daily Intake for the reference substance, derived as presented above for "threshold toxicants".

In another approach for simple mixtures for which the components are classified in Groups III to VI in Appendix B, and for which the mechanisms of toxicity for the critical effect are similar, a "Hazard Index" (HI) can be derived as follows:

$$HI = E_1/TDI_1 + E_2/TDI_2 + ... + E_i/TDI_i$$

where: E_i = estimated total daily intake of the ith toxicant;
TDI_i Tolerable Daily Intake for the ith component of the mixture.

The HI is derived from the dose addition presented above but substitutes 1/TDI for the relative potency factor.

If the numerical value of the hazard index exceeds or could exceed one, the simple mixture is considered to be "toxic" under paragraph 11(c) of CEPA; if the numerical value of the index is one or less, the simple mixture is not considered to be "toxic" under the Act.

In cases where the simple mixture contains a high proportion of substances classified in Groups I or II of Appendices B and C ("Carcinogenic to Humans" or "Probably Carcinogenic to Humans"; "Human Germ Cell Mutagen" or "Probable Human Germ Cell Mutagen"), the mixture as a whole may be considered to be "toxic" under paragraph 11(c) of CEPA.

Such a determination is based on consideration of factors such as the extent of characterization of the chemical composition and toxicological effects of the simple mixture and the proportion of the total mixture which is composed of components classified in Groups I or II. For simple mixtures considered to be "toxic" owing to the classification of a major proportion of components in Groups I or II in Appendix B and/or C, where possible, the estimated daily intake of the components by the general population in Canada or concentrations in relevant environmental media are compared to quantitative estimates of carcinogenic or mutagenic potency (Exposure/Potency Index or EPI) to characterize risk and provide guidance in establishing priorities for further action following assessment of "toxic" under the Act.

Appendix A – Reference Values for Assessing Total Daily Intake of Priority Substances by the General Population in Canada

The general principles and recommended values for body weights, inhalation of indoor and outdoor air, consumption of drinking water, foodstuffs and soil, and use of consumer products in the calculation of total daily intake of Priority Substances by the general population in Canada[8] are presented in this Appendix. These values are recommended to provide consistency in approach; however, the need for the application of sound scientific judgement on a case-by-case basis is fundamental to the estimation of exposure for assessment of "toxic" under paragraph 11*(c)* of CEPA.

1.0 Age

Exposure to environmental substances may change substantially over the course of an individual's lifetime, as a result of variations in medium-specific intakes, activities and physical attributes with age. Consequently, exposure of the general population of Canada is estimated for several defined periods of life: for infants (0-6 months), pre-school children (7 months-4 years), elementary school children (5-11 years), teenagers (12-19 years), and adults (20 years of age and older). These categories are intended to reflect more-or-less discrete stages of life in terms of varying potential for exposure to environmental substances. Hence, the period up to 6 months of age is when many infants may be exposed to substances present in breast milk. Also, preschoolers' exposure to contaminants in soil may be significantly higher than that for other age groups. Children of all ages have relatively high intakes of food per unit of body weight. Adulthood is a period of long-term lower-level exposure via most environmental media, with relatively high potential exposure to some substances through activities such as the use of consumer products.

2.0 Body Weights

Estimates of body weights presented in Table 1 are based on the most recent Canadian surveys; available data indicate that body weights have increased since earlier surveys. The body weights for teenagers and adults are taken from the 1981 Canada Fitness Survey of 16,000 individuals, while those of infants, pre-schoolers and grade school children are derived from the 1970-1972 Nutrition Canada survey of over 13,000 individuals (EHD, 1992).

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8 It should be noted that although relevant data concerning occupational exposure, para-occupational exposure (for hobbyists, for example), substance abuse and smoking are sometimes reviewed and presented in Supporting Documents and Assessment Reports for Priority Substances, they are not considered in the estimation of total daily intake since such exposures are highly variable, often not typical of most of the general population and more appropriately addressed under statutes other than CEPA.

3.0 Inhalation of Indoor and Outdoor Air

Since there are no quantitative data on amounts of air inhaled by Canadians in a range of age groups, the recommended age-specific intakes presented in Table 1 for school-age children and adults are the weighted means of the values calculated by the Environmental Health Directorate Working Group on Reference Values (EHD, 1992). These values were derived from estimates contained in the International Commission on Radiological Protection (ICRP) report of the Task Group on Reference Man (ICRP, 1975), corrected for the difference in height between the average Canadian and the ICRP Reference Man [using the formulae in the Intermountain Thoracic Society Manual (Morris *et al*., 1984)]. When data on concentrations of a substance in both indoor and outdoor air are available, it is assumed that intake of indoor and outdoor air are in proportion to the average amount of time spent indoors (approximately 20 hours) and outdoors each day [4 hours, divided evenly between time spent out of doors and in a motor vehicle, if data on concentrations in the latter case are available] (U.S. EPA, 1985).

4.0 Consumption of Drinking Water

The recommended values for the ingestion of drinking water presented in Table 1 are based primarily on the 1977-1978 survey of Canadian tap water consumption conducted by the Environmental Health Directorate of the Department of National Health and Welfare (NHW, 1981). This survey was conducted utilizing questionnaires and individual water consumption diaries of 970 people from 295 households. Distribution of the selected subjects was based on a representative sample of the Canadian population. The results of a similar survey from the United Kingdom (Hopkin and Ellis, 1980) have been used to distinguish the daily tap water consumption for persons aged from 6 to 17 years of age in the EHD survey into the 5-to-11- and 12-to-19-year age classes.

There are no data available on the consumption of drinking water by Canadian infants. It has been assumed, therefore, that infants are exclusively breast-fed and do not consume drinking water (exclusively breast-fed children do not require supplementary liquids). In the absence of data on the levels of a chemical substance in breast milk, or if the consumption of food or drinking water appear to be more important routes of exposure, it is assumed that infants are exclusively formula-fed for the first 6 months of life, consuming an average 0.75 litres/day. This estimate is based on the use of drinking water in the preparation of powdered infant formulae for exclusively formula-fed infants, discussed in the next section. For infants consuming other foods (see section 5.0 of this Appendix), the recommended intake of drinking water is 0.75 litres/day; if data on the concentration of chemical substances in foods include tap water added to beverages (i.e., the concentrations represented those in “table-ready” beverages), the volume consumed as drinking water (0.2 litres) reported for this age class in the U.S. Nationwide Food Consumption Survey (NCI, 1989) is used in the assessment of total daily intake.

5.0 Consumption of Food

The estimates of food consumption are based on the Nutrition Canada Survey (NCS)[NHW, 1977], conducted between 1970 and 1972, which involved detailed dietary surveys of over 13,000 Canadians, based on the 24-hour recall method. Data on food consumption for the recommended age classes represent the general food groups used in the NCS Food Consumption Patterns Report (Table 2), and the individual composites compiled by staff of the Food Directorate of the Department of National Health and Welfare (Table 3). The NCS is now approximately 20 years old, and there have been significant changes in the types of foods consumed by Canadians. Most notable among these are reductions in the consumption of eggs and whole milk, and increases in the amounts of poultry, fish and low-fat milk consumed (Caputo and Poutanen, 1990). Any errors introduced by these changes in these dietary intakes are likely to be relatively small in relation to other uncertainties associated with estimating the average total daily intake of Priority Substances by the general population.

Where available data on the level of substances do not correspond exactly to those for which consumption data are presented in Tables 2 and 3, it may be necessary to assume that data for a limited number of individual food items apply to the broad food groups presented in Table 2, or to consider (as a minimum estimate) intakes only from the foodstuffs for which monitoring data are available. The approach which is taken is based on professional judgement concerning the likely distribution of chemical substances among various foodstuffs and is dependent upon factors such as use patterns of the substance, or its partitioning among food component groups (e.g., fats).

Information on various components may be useful in assessing the intake of chemical substances from foods; the intake of lipophilic chemicals may be derived from information on the fat content and consumption of food products. The composition of a large number of Canadian foods has been compiled in the report “Nutrient Value of Some Common Foods” (NHW, 1988), and the intakes of fat, calories, protein, etc. by various age classes are presented in the NCS “Food Consumption Patterns Report” (NHW, 1977).

In Canada, infant feeding practices have changed dramatically over the last 30 years (Tanaka *et al.,* 1987; NHW, 1990). Recent studies indicate that a majority of Canadian mothers breast-feed; breast-feeding initiation rates are close to 80%, with 30% still breast-feeding their infants after 6 months. The intake of breast milk peaks between 4 to 6 months of age. Solid foods are introduced to approximately 50% of infants by 4 months of age, and 89.5% by 6 months of age. To reflect these practices, estimation of total daily intake is generally based on the assumption that a typical infant is exclusively breast-fed up to 6 months of age, after which foods are consumed in the quantities determined in the NCS. No Canadian data on the volume of breast milk consumed have been identified, but the average intake of breast milk over this period has been estimated to be 0.75 litres/day (or kg/day), based on studies of well-nourished mothers in Sweden and the United States (NHW, 1983); this intake is similar to that reported in a number of other studies of exclusively breast-fed infants (Butte *et al.,* 1991, and references therein).

In the absence of data on the concentration of a substance in breast milk, or where other food types are a more important source of exposure to a substance, it is assumed that infants are exclusively formula-fed for the first 6 months of life and consume on average the same volume as breast-fed infants (i.e., 0.75 litres/day). (Comparative studies indicate that bottle-fed infants consume similar or slightly higher volumes than breast-fed infants). Alternatively, in those cases in which table foods appear to be an important source of exposure to a chemical substance, the food intakes for infants compiled through the NCS may be used (Tables 2, 3, and Table 2.1 in NHW, 1977). At the time at which this survey was conducted, solid foods were generally introduced to infants' diets at a much earlier age than at present; hence, the food intakes from the NCS likely overestimate the current consumption of solid foods by infants.

6.0 Ingestion of Soil

The intake of soil by the various age groups of the population of Canada presented in Table 1 are based on recent studies from the United States and the Netherlands, in which tracer elements have been used to estimate the amount of soil ingested (Binder *et al.*, 1986; Clausing *et al.*, 1987; Calabrese *et al.*, 1989; van Wijnen *et al.*, 1990).

7.0 Consumer Products

In most cases, direct exposure to Priority Substances from consumer products is not estimated. However, such products generally contribute to concentrations in indoor air for which information is often included in estimates of total daily intake.

Exceptionally, however, estimates of intake from consumer products may be calculated. In view of the diverse range of consumer products and applications, exposure to chemical substances present in consumer products is estimated on the basis of plausible upper bound assumptions regarding the intensity, frequency and duration of exposure. Data and approaches for estimating exposures from consumer products (e.g., exposure to volatile organic compounds while filling a gas tank) have been reported by the U.S. EPA (1987a, 1987b, 1987c) and Wallace *et al.* (Wallace, 1986; Wallace *et al.*, 1986, 1987, 1988, 1989).

TABLE 1

RECOMMENDED VALUES FOR BODY WEIGHT AND INTAKES OF AIR, WATER AND SOIL BY AVERAGE CANADIANS

AGE (yr)	BODY WEIGHT[1] (kg)	AIR INTAKE[2] (m^3/d)	WATER INTAKE[3] (L/d)	SOIL INTAKE[4] (mg/d)
0-6 mo	7	2	BF-0/0 NBF-0.2/0.75	35
7 mo-4	13	5	0.2/0.8	50
5-11	27	12	0.3/0.9	35
12-19	57	21	0.5/1.3	20
20+	70	23	0.4/1.5	20

1 For infants, pre-school children and elementary school children, weighted average from Nutrition Canada Survey; for teenagers and adults, weighted average from Canada Fitness Survey (data taken from EHD, 1992; average for adults is 69 kg, but traditionally 70 kg has been used).

2 For infants, estimated from linear regression between values of 0.8 m^3 (newborn) and 3.8 m^3 (1-year-old) from ICRP (1975), estimate at 0.25 years (mid-range); for pre-schoolers, from linear regression between 3.8 m^3 [1-year-old] (ICRP, 1975) and 9.25 m^3 [7-year-old, both sexes] (EHD, 1992), estimate at 2.25 years (mid-range); other values are weighted average from EHD (1992), based on sample sizes from Canada Fitness Survey for 7-11-year-olds, 12-19-year-olds, and adults.

3 Water intakes presented separately as tapwater/tapwater+tapwater-based beverages (water, tea, coffee, reconstituted soft drinks); exclusively breast-fed infants (BF) do not require supplementary liquids (NHW, 1983); estimates for non-breast-fed infants (NBF) are based on NCI (1989) for volume consumed as drinking water, and on consumption of 750 mL/day of formula made from powdered formula and tap water for total drinking water (see text for discussion); for pre-schoolers, weighted mean of < 3 and 3-5-year classes from NHW (1981); for elementary school children and teenagers, from NHW (1981) for 6-17-year class (0.3/1.1 L/d), adjusted by ratio of consumption for 5-11 years (0.54 L/d) and 12-17 years (0.77 L/d) to mid-range (0.66 L/d) from Hopkin and Ellis (1980); for adults, mean of persons 18 and over from NHW (1981).

4 For infants, value from van Wijnen *et al.* (1990) for children less than 1 year, for pre-schoolers, average of 4 estimates of soil intake by 1-4-year-olds (Binder *et al.,* 1986; Clausing *et al.,* 1987; Calabrese *et al.,* 1989; van Wijnen *et al.,* 1990); for teenagers, assume same intake as for adults; estimate for adults from EHD (1992); estimate for 5-11-year-olds is midpoint between 1-4-year-olds and adults.

TABLE 2

MEAN CONSUMPTION OF VARIOUS FOOD GROUPS BY CANADIANS, FROM NUTRITION CANADA SURVEY

FOOD GROUP	COMPOSITE[1]	CONSUMPTION (g/person/d)				
		0 - 6 mo[2]	7 mo - 4 yr	5 - 11 yr	12 - 19 yr	20+ yr
DAIRY PRODUCTS	1-10	545	670	609	573	283
MEAT, POULTRY, FISH, EGGS	12-27, 110	37	90	120	169	183
CEREAL PRODUCTS	32-50, 107	53	168	300	325	247
FRUIT AND FRUIT PRODUCTS	74-91, 109	112	189	202	160	186
VEGETABLES	51-73, 112	42	125	198	250	250
FATS	11, 92, 93	0.8	11	21	29	25
NUTS AND DRIED LEGUMES	94, 108	0.2	6	13	19	12
FOOD, PRIMARILY SUGAR	95-101, 111	25	46	57	67	57
MIXED DISHES AND SOUPS	28-31	5	71	82	89	100
SOFT DRINKS, ALCOHOL	104-106	2	102	196	264	255
SAMPLE SIZE		132	1,199	2,086	2,342	7,037

1 Derived from table of consumption of individual food composites (Table 3).

2 These data will be used if it is assumed that the infant is not exclusively breast-fed or not exclusively formula-fed (see text for discussion).

TABLE 3

MEAN CONSUMPTION OF INDIVIDUAL FOOD COMPOSITES BY CANADIANS, FROM NUTRITION CANADA SURVEY

FOOD COMPOSITE		CONSUMPTION (g/person/day)				
		0-6 mo[1]	7 mo-4 yr	5-11 yr	12-19 yr	20+ yr
1.	MILK, WHOLE	274.16[2]	377.88	323.16	255.65	138.24
2.	MILK, 2%	188.60	194.50	185.61	194.75	60.64
3.	MILK, SKIM	21.20	59.67	55.57	72.56	30.83
4.	EVAPORATED MILK, CANNED	59.78	12.04	6.54	7.06	11.46
5.	CREAM, 10-12% BUTTER FAT	0.00	1.63	2.83	2.65	10.19
6.	ICE CREAM	1.37	15.35	25.59	25.78	12.80
7.	YOGURT	0.00	0.78	0.48	0.87	1.54
8.	CHEESE	0.11	2.56	3.18	5.66	8.33
9.	CHEESE, COTTAGE	0.00	1.73	1.33	1.74	5.35
10.	CHEESE, PROCESSED CHEDDAR	0.06	3.59	4.92	6.43	3.81
11.	BUTTER	0.73	7.06	12.94	16.67	13.61
12.	BEEF, STEAK	0.07	3.09	7.37	10.89	17.38
13.	BEEF, ROAST AND STEWING	0.27	6.49	12.21	23.27	27.00
14.	BEEF, HAMBURG	31.36	20.05	19.23	30.84	21.61
15.	PORK, FRESH	0.00	7.24	11.98	22.74	22.73
16.	PORK, CURED	0.00	1.95	3.96	4.40	7.78
17.	VEAL	0.00	0.50	0.33	1.79	2.16
18.	LAMB	0.00	0.03	1.80	1.20	0.78
19.	POULTRY, CHICKEN AND TURKEY	0.00	13.24	16.72	20.32	21.17
20.	EGGS	4.67	24.16	21.05	21.50	32.29
21.	ORGAN MEATS, LIVER, KIDNEY	0.00	0.91	1.85	2.27	2.81
22.	COLD CUTS AND LUNCHEON MEATS	0.00	5.72	7.85	11.27	9.27
23.	LUNCHEON MEATS, CANNED	0.00	0.88	0.97	2.20	2.10
24.	FISH, MARINE, FRESH OR FROZEN	0.50	1.52	4.81	5.00	6.59
25.	FISH, FRESH WATER, FRESH OR FROZEN	0.00	1.12	1.08	1.09	1.26
26.	FISH, CANNED	0.00	0.43	1.84	4.13	4.07
27.	SHELLFISH, FRESH OR FROZEN	0.00	0.28	0.64	1.00	1.93

TABLE 3 (cont'd.)

FOOD COMPOSITE		CONSUMPTION (g/person/day)				
		0-6 mo[1]	7 mo-4 yr	5-11 yr	12-19 yr	20+ yr
28.	SOUPS, MEAT, CANNED	3.37	39.23	42.77	35.94	54.76
29.	SOUPS, PEA, CANNED	1.09	14.52	19.97	37.58	30.41
30.	SOUPS, TOMATO, CANNED	0.37	7.70	11.66	7.39	7.02
31.	SOUPS, DEHYDRATED	0.00	10.02	7.98	7.92	7.65
32.	BREAD, WHITE	2.12	34.00	76.80	94.88	67.45
33.	BREAD, WHOLE WHEAT AND RYE	0.00	5.49	6.47	7.43	19.76
34.	ROLLS AND BISCUITS	0.00	3.64	11.63	15.92	10.00
35.	FLOUR, WHEAT	0.28	3.86	10.38	5.17	6.93
36.	CAKE	0.19	8.59	25.62	42.52	20.37
37.	COOKIES	1.50	18.87	26.00	23.08	15.58
38.	DANISH AND DONUTS	0.00	3.60	5.39	9.53	5.49
39.	CRACKERS	0.04	4.83	5.14	5.67	3.45
40.	PANCAKES	0.00	2.16	2.93	3.37	2.04
41.	CEREALS, COOKED WHEAT	13.50	13.94	5.72	4.73	6.53
42.	CEREALS, OATMEAL	33.12	20.86	19.95	12.26	16.44
43.	CEREALS, CORN	1.07	3.42	5.37	3.40	1.82
44.	CEREALS, WHEAT AND BRAN	0.09	3.37	3.37	3.35	2.31
45.	RICE	0.00	6.73	13.98	14.56	15.14
46.	PIE, APPLE	0.00	2.02	3.87	3.71	9.25
47.	PIE, OTHER	0.08	3.68	10.35	10.77	11.70
48.	PIZZA	0.00	0.12	3.09	5.09	1.74
49.	PASTA	0.00	17.67	36.90	46.99	15.81
50.	PASTA, ORDINARY	0.00	10.85	26.24	10.32	13.47
51.	CORN	0.56	9.90	17.60	12.02	8.16
52.	POTATOES, RAW	0.00	0.25	0.00	0.00	0.04
53.	POTATOES, BAKED	0.00	2.08	2.95	3.05	4.92
54.	POTATOES, BOILED, SKINS ON	0.00	2.13	1.81	3.54	5.43
55.	POTATOES, BOILED, SKINS OFF	7.51	45.22	77.66	100.98	82.11
56.	POTATOES, FRENCH FRIED, FROZEN	0.01	18.46	22.78	33.02	20.68
57.	POTATOES, CHIPS	0.00	1.64	5.18	7.81	1.31

TABLE 3 (cont'd.)

FOOD COMPOSITE		CONSUMPTION (g/person/day)				
		0-6 mo[1]	7 mo-4 yr	5-11 yr	12-19 yr	20+ yr
58.	CABBAGE	0.00	2.69	5.05	6.21	10.26
59.	CELERY	0.03	1.59	2.43	3.45	8.34
60.	PEPPERS	0.00	0.05	0.27	0.43	1.28
61.	LETTUCE	0.00	2.37	4.49	8.21	12.70
62.	CAULIFLOWER	0.00	0.26	0.11	1.11	1.46
63.	BROCCOLI	0.87	0.34	1.34	0.20	2.19
64.	BEANS	0.32	2.66	4.27	4.49	6.82
65.	PEAS	31.10	6.10	6.09	7.66	9.34
66.	CARROTS	1.39	8.14	10.34	11.08	14.19
67.	ONION	0.00	0.89	2.45	3.05	6.15
68.	RUTABAGAS OR TURNIP	0.58	2.40	3.51	3.29	5.69
69.	TOMATOES	0.00	3.19	7.47	11.16	17.90
70.	TOMATO JUICE, CANNED	0.00	5.28	4.52	5.64	10.02
71.	TOMATOES/SAUCE, CANNED & KETCHUP	0.00	4.91	7.15	8.88	6.40
72.	MUSHROOMS, CANNED	0.00	0.47	0.86	2.11	1.63
73.	CUCUMBERS	0.00	3.47	8.27	11.27	11.37
74.	CITRUS FRUIT, RAW	0.00	11.47	24.70	22.29	33.25
75.	CITRUS FRUIT, CANNED	0.00	0.00	0.17	0.04	0.16
76.	CITRUS JUICE	3.46	34.61	22.54	32.98	35.01
77.	CITRUS JUICE, CANNED	11.82	9.69	12.96	11.05	13.38
78.	APPLES, RAW	1.15	26.79	41.38	33.85	20.52
79.	APPLE JUICE, CANNED, UNSWEETENED	14.98	44.21	26.66	9.65	13.30
80.	APPLESAUCE, CANNED, SWEETENED	1.45	3.91	8.81	3.16	5.97
81.	BANANAS	3.25	12.98	21.42	11.19	12.82
82.	GRAPES	0.00	0.82	1.52	2.67	2.94
83.	GRAPE JUICE, BOTTLED	0.00	5.27	2.52	5.02	2.15
84.	PEACHES	0.50	12.25	10.27	6.56	10.17
85.	PEARS	73.53	18.10	6.70	4.06	7.73
86.	PLUMS, DRIED PRUNES & CANNED PLUMS	0.95	2.15	2.72	2.64	4.74

TABLE 3 (cont'd.)

FOOD COMPOSITE		CONSUMPTION (g/person/day)				
		0-6 mo[1]	7 mo-4 yr	5-11 yr	12-19 yr	20+ yr
87.	CHERRIES	0.00	0.90	1.15	0.88	1.64
88.	MELONS	0.00	1.18	7.39	3.82	9.53
89.	STRAWBERRIES	0.00	3.01	7.56	5.39	7.75
90.	BLUEBERRIES	0.67	0.67	1.00	1.51	1.99
91.	PINEAPPLE	0.00	0.70	1.68	1.66	2.22
92.	COOKING FATS & SALAD OILS	0.00	1.23	2.21	3.97	4.95
93.	MARGARINE	0.02	2.65	6.13	8.34	6.23
94.	PEANUT BUTTER & PEANUTS	0.16	2.98	6.08	6.60	3.52
95.	SUGAR, WHITE	1.54	7.08	11.66	14.46	19.20
96.	SYRUP	3.13	2.89	6.45	5.59	4.94
97.	JAMS	0.28	3.55	6.76	9.63	6.14
98.	HONEY	1.30	0.86	2.02	1.88	2.17
99.	PUDDINGS	18.13	13.16	8.85	10.59	8.78
100.	CANDY, CHOCOLATE BARS	0.16	3.14	5.45	8.10	3.58
101.	CANDY, OTHERS	0.01	5.36	8.47	10.39	4.58
102.	COFFEE	0.00	6.48	11.99	83.95	347.77
103.	TEA	0.00	8.47	22.20	81.64	354.13
104.	SOFT DRINKS	2.39	100.33	193.57	240.70	109.91
105.	ALCOHOLIC DRINKS, WINE	0.00	0.02	0.73	1.84	23.54
106.	ALCOHOLIC DRINKS, BEER	0.00	1.22	1.93	21.44	121.05
107.	MUFFINS	0.00	0.39	0.53	2.12	1.56
108.	BAKED BEANS	0.00	3.11	7.27	12.14	8.12
109.	RAISINS	0.00	0.50	0.53	1.08	0.62
110.	WIENERS	0.00	2.26	6.35	5.45	2.41
111.	GELATIN DESSERT	0.09	9.59	7.49	5.98	7.80
112.	BEETS	0.00	0.43	1.26	1.00	1.80
TOTAL		821.05	1,492.48	1,833.10	2,109.28	2,299.30
SAMPLE SIZE		132	1,199	2,086	2,342	7,037

1. These data will be used if it is assumed that the infant is not exclusively breast-fed or not exclusively formula-fed (see text for discussion).

2 Includes 90.50 g of infant formula per day.

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Appendix B — Criteria for Classification of Carcinogenicity

Chemicals are classified into six categories on the basis of the following criteria[9] (modified from those of the International Agency for Research on Cancer):

Group I — Carcinogenic to Humans

Group I — Data from adequate epidemiological studies indicate that there is a causal relationship between exposure to a substance and an increased incidence of cancer in humans (i.e., the observed association is unlikely to be due to bias, confounding or chance). Confidence in inferring a causal relationship is increased when the association is strong and observed in several studies, when there is a dose-response relationship, when a reduction in exposure is followed by a reduction in the incidence of cancer or when there are supporting data which indicate that the association is biologically plausible.

Group II— Probably Carcinogenic to Humans

Group II — Data from epidemiological studies are inadequate to assess carcinogenicity either because there are few pertinent investigations or because chance, bias or confounding cannot be excluded as a possible explanation for the results. However, there is sufficient evidence of carcinogenicity in animal species (i.e., there is an increased incidence of malignant tumours in multiple species or strains, in multiple experiments with different routes of exposure or dose levels, or the incidence, site or type of tumour or age of onset is unusual). Confidence in the sufficiency of the data from animal studies is increased when there is evidence of a dose-response relationship, supporting results from in vitro studies or a number of limited carcinogenicity bioassays, evidence of structure-activity relationships, genotoxic effects and/or supporting data on a mechanism of carcinogenicity which is operative in humans and animal species. Exceptionally, a compound for which the evidence of carcinogenicity is limited but for which there is a strong supporting dataset (on genotoxicity, for example) which indicates that the compound is likely to be carcinogenic would be included in this category.

9 Though criteria for several subgroups of each category are specified, they are presented **as representative examples only** of possible combinations of results and are not exhaustive. This does not preclude inclusion of a compound in the category for which available data do not precisely fulfil the exact criteria specified in one of the subgroups.

Group III — Possibly Carcinogenic to Humans

Group III.A — Data from epidemiological studies indicate an association between exposure and human cancer but alternative explanations such as chance, bias or confounding cannot be excluded.

Group *III.B* — Data from epidemiological studies are inadequate to assess carcinogenicity. There is some evidence of increased tumour incidence in animals but the data are limited because the studies involve a single species, strain or experiment; study design (i.e., dose levels, duration of exposure and follow-up, survival, number of animals) or reporting is inadequate; the neoplasms produced often occur spontaneously and have been difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumours in mice). The weight of limited evidence indicates that the compound is genotoxic or results are mixed.

Group III.C — Data from epidemiological studies are inadequate to assess carcinogenicity. There are sufficient data which indicate that the substance is carcinogenic in long-term animal experiments but there are data available which indicate that the aetiology of tumour induction may be epigenetic (for example, there is evidence that tumours occur only at very high doses as a result of tissue damage, that the administered compound acts as a tumour promoter perhaps by increasing the proliferation rate of pre-neoplastic cells and the weight of evidence from a variety of short-term tests indicates that it is not genotoxic).

Group III.D — Data from experimental studies in animal species indicate that the compound is carcinogenic in one species only and there is suspicion that the results are species- specific but available data on mechanisms of toxicity are insufficient to conclude unequivocally that this is the case.

Group IV — Unlikely to Be Carcinogenic to Humans

Group IV.A — There is no evidence of carcinogenicity in sufficiently powerful and well-designed epidemiological studies. There is some evidence of carcinogenicity in well-designed and well-conducted carcinogenicity bioassays in animals, but the results are limited (i.e., they are confined to a single study or single species, sex or strain of animals and/or exposure produces a non-statistically significant increase in tumour incidence, compared to unexposed controls).

Group IV.B — There is no evidence of carcinogenicity in sufficiently powerful and well-designed epidemiological studies; there is evidence of carcinogenicity in well-designed and well-conducted carcinogenicity bioassays in animals, but the increased tumour incidence can be confidently (but not necessarily unequivocally) ascribed to species- specific mechanisms of toxicity and/or metabolism which do not appear to be operative in humans. (Generally the weight of evidence indicates that such compounds are not genotoxic).

Group IV.C — Data from epidemiological studies are inadequate to assess carcinogenicity; there is evidence of carcinogenicity in well-designed and well-conducted carcinogenicity bioassays in animals, but the increased tumour incidence can be confidently (but not necessarily unequivocally) ascribed to species-specific mechanisms of toxicity and/or metabolism which do not appear to be operative in humans. (Generally the weight of evidence indicates that such compounds are not genotoxic).

Group IV.D — Data from epidemiological studies are inadequate to assess carcinogenicity; there is no evidence of carcinogenicity in well-designed and properly conducted carcinogenicity bioassays in two species of animals.

Group V — Probably Not Carcinogenic to Humans

Group V.A — There is no evidence of carcinogenicity in sufficiently powerful and well-designed epidemiological studies; there is no evidence of carcinogenicity in adequate studies in two animal species and available data indicate that the compound is not genotoxic.

Group V.B — There is no evidence of carcinogenicity in sufficiently powerful and well-designed epidemiological studies; data in animal species are inadequate.

Group V.C — There is inadequate evidence of carcinogenicity in humans but evidence of a lack of carcinogenicity in two species of laboratory animals is strongly supported by a broad range of other relevant data.

Group VI — Unclassifiable with Respect to Carcinogenicity in Humans

Group VI.A — Data from epidemiological and/or animal studies are inadequate (i.e., because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of carcinogenicity).

Group VI.B — There are no data on carcinogenicity available for evaluation.

Group VI.C — Results of epidemiological studies in human populations and experimental studies in animal species are conflicting, without an identifiable mechanistic basis.

Appendix C — Criteria for Classification of Mutagenicity in Germ Cells

Chemicals are classified into six categories on the basis of the following criteria[10]

Group I — Human Germ Cell Mutagen

Group I — Data from adequate epidemiological studies indicate that there is a causal relationship between exposure of humans to a substance and an increased incidence of inherited mutations in live or dead offspring.

Group II — Probable Human Germ Cell Mutagen

Group II — Data from epidemiological studies to assess germ cell mutagenicity are inadequate: however, there is sufficient evidence of germ cell mutagenicity in animal species (i.e., there is an increased incidence of gene mutations, structural or numerical chromosomal aberrations, or inherited congenital malformations in the live offspring of exposed animals; or an increase in dominant lethal mutations in the potential offspring of exposed animals).

Group III — Possible Human Germ Cell Mutagen

Group III.A — Data from epidemiological studies indicate an association between exposure and human germ cell mutagenicity, but alternative explanations such as chance, bias, or confounding cannot be excluded.

Group *III.B* — Data from epidemiological studies to assess germ cell mutagenicity are inadequate: however, there is sufficient evidence of somatic cell mutagenicity (*in vivo* gene mutations or chromosomal aberrations) in humans or animal species, and sufficient evidence of exposure to germ cells in humans or animal species.

Group III.C — Data from epidemiological studies to assess germ cell mutagenicity in humans are inadequate or lacking. There is sufficient data in animals to indicate that the chemical is a germ cell mutagen, but available data indicate that the induction of mutations occurs through an epigenetic threshold-based mechanism.

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10 Though criteria for several subgroups of each category are specified, they are presented **as representative examples only** of possible combinations of results and are not exhaustive. This does not preclude inclusion of compound in the category for which available data do not precisely fulfil the exact criteria specified in one of the subgroups.

Group III.D — Data from epidemiological studies to assess germ cell mutagenicity in humans are inadequate. There is sufficient evidence of mutagenicity of somatic cells in humans or animal species *(in vivo* gene mutations or chromosomal aberrations), but evidence of exposure to germ cells is inadequate or lacking.

Group IV — Unlikely to Be a Human Germ Cell Mutagen

Group IV.A — There is no evidence of human germ cell mutagenicity in sufficiently powerful and well-designed epidemiological studies. There is evidence of mutagenicity of somatic cells in well-designed and well-conducted studies in humans or animals, but there is no evidence of exposure of human or animal germ cells in well-designed studies.

Group IV.B — Data on germ cell mutagenicity in epidemiological studies in humans are inadequate; there is no evidence of mutagenicity *in vivo* in germ or somatic cells in well-designed and properly conducted studies in animals.

Group V — Probably Not a Human Germ Cell Mutagen

Group V.A — There is no evidence of germ cell mutagenicity in sufficiently powerful and well-designed epidemiological studies; there is no evidence of germ cell mutagenicity in animal species.

Group V.B — There is no evidence of germ cell mutagenicity in sufficiently powerful and well-designed epidemiological studies; data in animal species are inadequate.

Group V.C — Data from epidemiological studies to assess germ cell mutagenicity in humans are inadequate, but evidence of the lack of germ cell mutagenicity in animal species is strongly supported by other data on mutagenicity *in vivo.*

Group VI — Unclassifiable with Respect to Germ Cell Mutagenicity in Humans

*Grou*p *VI.A* — Data from epidemiological and/or animal studies are inadequate (i.e., because of major qualitative limitations, the studies cannot be interpreted as showing either the presence or absence of germ cell mutagenicity).

Group VI.B — There are no *in vivo* mutagenicity data available for evaluation.

Group VI.C — Results of epidemiological studies in human populations and experimental studies in animal species are conflicting, without an identifiable mechanistic basis.

Appendix D — Definitions

Critical Effect: the effect of biological significance expected to occur at the lowest dose or concentration.

LOEL — Lowest-observed-effect-level: the lowest dose in a toxicity study that results in an observed effect (usually one dosage level above the NOEL).

LOAEL — Lowest-observed-adverse-effect level: the lowest dose in a toxicity study that results in an observed adverse effect (usually one dosage level above the NOAEL). (An adverse effect is a change in the morphology, physiology, growth, development or lifespan of an organism that results in impairment of its capacity to compensate for additional stress or an increase in its susceptibility to the harmful effects of other environmental influences.)

NOEL — No-observed-effect level: the highest dose in a toxicity study that results in no observed effects.

NOAEL — No-observed-adverse-effect level: the highest dose in a toxicity study that does not result in any observed adverse effect. (An adverse effect is a change in the morphology, physiology, growth, development or lifespan of an organism that results in impairment of its capacity to compensate for additional stress or an increase in its susceptibility to the harmful effects of other environmental influences.)

TDI — Tolerable Daily Intake: the intake to which it is believed that a person can be exposed daily over a lifetime without deleterious effect.

Appendix E — Reference Values for Intakes and Body Weights of Laboratory Animals

Wherever possible, values reported by the authors in the critical study are used to calculate doses on a body weight basis. Where such data are not provided, the following reference values are used:

TABLE 1

REFERENCE VALUES FOR BODY WEIGHTS AND INTAKES IN LABORATORY ANIMALS[1]

Species	Body Weight (kg)	Inhalation Rate (m^3/day)	Water Consumption (L/day)	Food Consumption (g/day)	Dose Conversion (1 mg/m^3 in air Equals X in mg/kg b.w./day)	Dose Conversion (1 ppm (mg/L) in water Equals X in mg/kg b.w./day)	Dose Conversion (1 ppm in food Equals X in mg/kg b.w./day)
Mouse	0.03[2]	0.04[2]	0.006[2]	4[2]	1.33	0.20	0.13
Rat	0.35[2]	0.11[4]	0.05[2]	18[2]	0.31	0.14	0.05
Hamster	0.14[2]	0.13[2]	0.03[2]	12[2]	0.93	0.21	0.09
Guinea Pig	0.84[2]	0.40[2]	0.20[2]	34[2]	0.48	0.24	0.04
Rabbit	3.8[2]	2.0[2]	0.41[2]	186[2]	0.53	0.11	0.05
Rhesus Monkey	8.0[2]	5.4[2]	0.53[2]	320[2]	0.68	0.07	0.04
Dog	12[2]	4.3[2]	0.61[2]	300[2]	0.36	0.05	0.03
Cat	1.5[3]	0.75[3]	0.15[5]	168[5]	0.50	0.10	0.11
Pig	80[5]	—	5.5[5]	2,250[5]	—	0.07	0.03

1 In most cases, values have been rounded to two significant figures.

2 Calabrese and Kenyon (1991).

3 Flecknell (1987). (Values are averages of the ranges reported).

4 Calculated from the minute volume of 220 mL/kg b.w. reported by Flecknell (1987).

5 Canadian Council on Animal Care (1980-1984). (Values are averages of the ranges reported).

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