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The Application of Uncertainty Factors and the *Pest Control Products Act* Factor in the Human Health Risk Assessment of Pesticides

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This document describes how Health Canada's Pest Management Regulatory Agency (PMRA) addresses uncertainty and variability in the mammalian toxicity database in the human health risk assessment of pesticides. The application of uncertainty factors to the most relevant endpoints in the mammalian toxicity database ensures that there is a protective margin between the dose levels that elicit toxicity in laboratory animal studies and the anticipated human exposure. This document also describes how the PMRA addresses the additional 10-fold margin of safety required under certain conditions as specified in the new *Pest Control Products Act* (PCPA). This margin of safety, herein referred to as the PCPA factor, is intended to provide additional protection for infants and children in the risk assessment. This document describes the relevant factors and provides a framework for the application of these factors.

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1.0 Introduction

On 28 June 2006, the new PCPA came into force. The revised PCPA significantly amends the PCPA of 1969. In the new PCPA, health or environmental risk is deemed acceptable "if there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions or proposed conditions of registration."[1] The new PCPA directs the PMRA, the federal regulator, to apply this standard to applications for new active ingredients, registration amendments that may result in significantly increased health or environmental risk, the establishment of maximum residue limits, re-evaluations and special reviews.

The new PCPA specifies that a science-based approach be used in evaluating the health risk of a pest control product. Ensuring a reasonable certainty of no harm to human health with respect to a pesticide exposure requires, in most cases, a quantitative risk assessment. One aspect of this assessment is the application of uncertainty factors to animal toxicity data to ensure that there is a protective margin between the levels known to cause no adverse effects in animal studies and the anticipated human exposure. In accordance with current practice, the new legislation requires that these margins take into account, among other relevant factors, the use of animal experimentation data and the different sensitivities to pest control products of major identifiable subgroups. The PCPA states that major identifiable subgroups include pregnant women, infants, children, women and seniors.

The new PCPA gives specific consideration to pest control products that are currently used or proposed for use residentially (i.e. in and around homes or schools) as well as to those pest control products where residues could be in the diet. In these scenarios, an additional 10-fold margin of safety (herein referred to as the PCPA factor) is to be applied for threshold effects. This takes into account potential prenatal and postnatal toxicity and completeness of the data with respect to the exposure of and toxicity to infants and children. A different margin of safety may be determined to be appropriate on the basis of reliable scientific data.[2]

Similar provisions were enacted in 1996 in the United States under the *Food Quality Protection Act* (FQPA), which significantly amended the *Federal Insecticide, Fungicide, and Rodenticide Act* and the *Federal Food, Drug, and Cosmetic Act*. The additional 10-fold margin of safety has become known in the regulatory community as the FQPA safety factor provision. The United States Environmental Protection Agency's (USEPA) Office of Pesticide Programs generated guidance on the implementation of the FQPA safety factor following input from other USEPA offices, the USEPA Scientific Advisory Panel and the American public.[3]

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1 Section 2(2). *Pest Control Products Act*, 2006, c.28

2 Sections 7(7), 11(2) and 19(2). *Pest Control Products Act*, 2006, c.28

3 USEPA. 2002. *Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment. Office of Pesticide Programs*. Washington, D.C. 28 February 2002. www.epa.gov/oppfead1/trac/science/determ.pdf

In response to the enactment of the new PCPA and other considerations, the PMRA sought the input of stakeholders on the use of uncertainty and safety factors. A public consultation document entitled "Use of Uncertainty and Safety Factors in the Human Health Risk Assessment of Pesticides" was released on 25 July 2007.[4] The purpose of this document was to provide stakeholders with an overview of historical and current Canadian pesticide regulatory practices concerning the application of uncertainty and safety factors to mammalian toxicology data. It was also intended to solicit feedback from interested stakeholders on issues and considerations regarding the future application of uncertainty and safety factors by the PMRA. A public information and consultation session regarding this document was held on 10 September 2007. A more in-depth second public consultation followed on 10 December 2007. These collaborations, along with the written responses received on the consultation document, were considered in the development of a revised policy on the use of uncertainty factors and the PCPA factor in human health risk assessment. This revised policy is presented in this document.

While considerable effort has been expended to make the selection of factors more objective and transparent in this policy, a certain degree of subjectivity is unavoidable and necessary due to the ultimate reliance on scientific judgement. It is anticipated that a transparent and disciplined framework for the selection of appropriate factors, as outlined in this document, will enhance the PMRA's consistency and predictability in its scientific decision-making process.

The implementation of uncertainty factors and the PCPA factor is one element in the PMRA's approach to exercising precaution in its regulatory activities on pesticides. Furthermore, the use of these factors is consistent with actions taken by the PMRA to take into account the precautionary principle during re-evaluation or special review. The framework described herein embodies the precautionary approach required as a matter of sound science and law.

It should be noted that this policy only addresses the statutory provisions of the new PCPA; it does not apply to any of Health Canada's other regulatory programs or risk assessment processes that are carried out under different statutory authorities.

2.0 Primer on Risk Assessment

Human health risk assessment is a fundamental cornerstone of the pesticide regulatory system in Canada. When estimating what is likely to be a human exposure that is without harm, it is necessary to assess the risk posed by a pesticide in different situations. This would include assessing the risks of a pesticide from exposure via the diet and drinking water, exposure from the workplace and other non-occupational exposures such as from uses in and around the home.

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[4] PMRA. 2007. Regulatory Proposal PRO2007-01. *Use of Uncertainty and Safety Factors in the Human Health Risk Assessment of Pesticides*. Ottawa, Canada. http://www.pmra-arla.gc.ca/english/pdf/pro/pro2007-01-e.pdf

The basic framework for the process of risk assessment is well accepted internationally[5] and consists of four key activities: hazard identification, hazard characterization, exposure assessment and risk characterization.

Hazard identification involves understanding the inherent properties of a substance that may lead to adverse responses. The assessment of the hazard of pesticides is based primarily on toxicity studies conducted in laboratory animals. Toxicity studies that address different durations of toxicity (acute, short-term or chronic exposure), different routes of toxicity (oral, dermal and inhalation) and different endpoints of toxicity (neurotoxicity, developmental toxicity, carcinogenicity, genotoxicity, etc.) are required for conventional chemical pesticides. The current toxicity data requirements are further elaborated in Regulatory Directive DIR2005-01, *Guidelines for Developing a Toxicological Database for Chemical Pest Control Products*.[6]

Hazard characterization involves defining the relationship between the dose of a substance administered to or received by the test species and the qualitative and quantitative response to the substance. This document focuses only on the processes for those substances determined at the hazard identification and characterization stages to demonstrate a threshold response. For these substances, it is assumed that there is a dose level below which the substance will not elicit a response, i.e. there is a threshold for the response. Most responses elicited by a substance, including acute toxicity, chronic toxicity, neurotoxicity, irritation, developmental toxicity and reproductive toxicity, are considered threshold in nature. Endpoints deemed to lack a threshold response (e.g. genotoxicity, carcinogenicity) are assumed to result in an increase in risk at any level of exposure and hence are subject to different risk assessment methodologies that do not use uncertainty or safety factors.

The experimental dose level at which no adverse effects are detected in a given study is deemed the no observed adverse effect level (NOAEL). The lowest dose level in a study that elicits an adverse effect is referred to as the lowest observed adverse effect level (LOAEL). An adverse effect is commonly defined as "a change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences."[7] Application of this definition is not straightforward; expert judgement is required to distinguish adverse effects from those effects that merely reflect the ability of an organism to adapt to a biological or chemical insult.

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5 International Programme on Chemical Safety. 1999. Environmental Health Criteria 210. *Principles for the Assessment of Risks to Human Health from Exposure to Chemicals*. Geneva, Switzerland, World Health Organization, International Programme on Chemical Safety. www.inchem.org/documents/ehc/ehc/ehc210.htm

6 PMRA. 2005. Regulatory Directive DIR2005-01. *Guidelines for Developing a Toxicological Database for Chemical Pest Control Products*. Ottawa, Canada.

7 International Programme on Chemical Safety. 1994. Environmental Health Criteria 170. *Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits*. Geneva, Switzerland, World Health Organization, International Programme on Chemical Safety. www.inchem.org/documents/ehc/ehc/ehc170.htm

An alternative approach to defining the lower end of a dose-response curve in the area of the observed threshold involves the establishment of a benchmark dose (BMD). The BMD is the effective dose (or its lower confidence limit) that produces a specific increase in incidence of effect above control levels and is derived by modelling the data with little or no extrapolation outside the experimental dose range. Although this method has seen little use in the international pesticide regulatory community in the past, the BMD approach is gaining ground as a tool when adequate dose-response data are available.

The evaluation of a mammalian toxicological database for a specific pesticide will yield numerous NOAELs for different toxicological endpoints. The selection of the most appropriate study, endpoint and NOAEL for risk assessment takes into consideration which human subpopulations may be exposed, the route of exposure and the anticipated duration and/or frequency of exposure. The endpoint selected for risk assessment, known as the critical effect, is typically the first adverse effect that occurs in the toxicity database with increasing dose. On occasion, the critical effect may be an effect that, although observed at a higher dose level than the first adverse effect, may result in a lower reference dose when appropriate factors are applied.

The goal of exposure assessment is to quantify, either directly or indirectly, the extent of exposure to the substance with respect to route, magnitude, duration and frequency. Exposure estimates are inherently subject to variability, and in some cases, high uncertainty. The PMRA characterizes uncertainty and variability related to exposure estimation either qualitatively or quantitatively (i.e. probabilistic assessments) as the data allow. This document is not intended to address exposure uncertainties.

Risk characterization represents the integration of hazard and exposure information to determine the level of risk. Consideration of the uncertainty, variability and conservatism of both the hazard information and the exposure information is a fundamental component of this process. It is during the risk characterization stage that factors are employed in relation to the toxicity data to ensure that there is a protective margin between the NOAEL (or BMD) seen in animals and the anticipated human exposure. This margin is intended to provide a reasonable certainty that no harm to human health will result from exposure to or use of the product taking into account its conditions or proposed conditions of registration. Although a comprehensive scientific database is available for most pesticides, one cannot prove scientifically that something is safe with absolute certainty. Absolute certainty of safety is not attainable in view of the requisite extrapolation of the results of toxicity studies conducted in a homogeneous laboratory animal population to a heterogeneous human population. Although the risk assessment process strives to use the best scientific information available, the use of factors to account for uncertainties in the assessment or concerns for human health is critical in securing assurances of reasonable certainty of no harm to human health.

In conducting a risk assessment for a pesticide, the PMRA typically establishes a regulatory standard (i.e. a reference dose) that is considered to represent a level of exposure or intake for which there is reasonable certainty of no harm. With this approach, the most relevant NOAEL (or BMD) from the database for a specific pesticide is divided by a multiple of factors (described in this document) to generate a regulatory standard. This standard is then compared to an estimate of exposure. Dietary risk assessments are conducted this way; regulatory standards include an acute reference dose (ARfD) and an acceptable daily intake (ADI). The ARfD is the dose to which an individual could be exposed on any given day and expect no adverse health effects. This term is equivalent to the acute population adjusted dose (aPAD), the term used by the USEPA. The ADI is the dose to which an individual could be exposed over the course of a lifetime and expect no adverse health effects. The USEPA's equivalent term for the ADI is the chronic population adjusted dose (cPAD). The ARfD is typically a larger value than the ADI, reflecting the fact that individuals often can tolerate a higher dose of a substance over a shorter time period. Risk is deemed acceptable if the potential peak one-day and average lifetime dietary intake are less than the ARfD and the ADI respectively, that is, the acceptable maximum intake has not been exceeded.

For assessing non-dietary risk such as that associated with exposures in the workplace (occupational) or in and around the home (residential), a different approach is typically used. With this approach, the ratio of the NOAEL (or BMD) to the estimate of exposure is calculated. This ratio is commonly referred to as the margin of exposure (MOE). The adequacy of the magnitude of the MOE is assessed in light of the uncertainties and findings of the database. An adequate MOE is one considered to be sufficiently large to ensure reasonable certainty of no harm to human health. The factors that determine the magnitude of the desired MOE are the same as those involved in the standard setting (i.e. reference dose selection) described above. The MOE approach is also useful when estimating aggregate risk from all sources of exposure, including residues in the diet and drinking water and exposure from residential activities.

3.0 Application of Uncertainty Factors

3.1 General

Consistent with other regulatory authorities, the PMRA applies factors to account for various sources of uncertainty and variability within a toxicology database. The term "uncertainty factor" is used to denote factors associated with interspecies extrapolation, intraspecies variation, extrapolation from a LOAEL to a NOAEL where no NOAEL is available, extrapolation for duration of dosing and database deficiencies. In the recent past, the term "safety factor" was used by the PMRA to reflect concerns relating to severity of endpoint or age sensitivity. These concerns are now addressed through the PCPA factor; hence, the term "safety factor" has been abandoned.

Figure 1 provides an outline for the consideration of uncertainty factors in a human health risk assessment for pesticides. Elaboration of the various uncertainty factors is provided in the following sections. Uncertainty factors are relevant in three main areas of risk assessment that pertain to pesticide use: dietary, occupational and residential risk assessment. Risk assessments

are scenario-specific and take into account the route of exposure and duration of exposure and in some cases population-specific exposure (e.g. children or women of child-bearing age). Accordingly, for any given pesticide, different uncertainty factors may be selected to reflect the relevant toxicology data and varying parameters associated with each scenario-specific risk assessment.

3.2 Interspecies Extrapolation and Intraspecies Variability

The uncertainty factor for interspecies extrapolation (UF_A) addresses the uncertainty inherent in the extrapolation of information from experimental animal species to humans and is based on the assumption that humans are more sensitive than experimental animals. Consistent with the practices of most regulatory authorities, the PMRA will continue to apply a default factor of 10-fold for extrapolating results from animal studies to humans.

The uncertainty factor for intraspecies variability (UF_H) addresses the potential variability in response within the human population. This variability may result from differences in parameters such as genetic makeup, age, gender, lifestyle or health status. Accordingly, this factor accounts for differences in response between the average person and a sensitive person within a population. Consistent with other regulatory authorities, the PMRA will continue to apply a default factor of 10-fold to account for potential human variability. The derivation of a reference dose based on application of these default uncertainty factors is illustrated below.

Standard application of uncertainty factors

$$\text{Reference Dose} = \frac{\text{NOAEL for Critical Endpoint of Concern}}{(UF_A \text{ of } 10) \times (UF_H \text{ of } 10)}$$

The PMRA recognizes that validation of the 10-fold interspecies and intraspecies factors is an ongoing field of research. Furthermore, there are numerous initiatives in the scientific community to develop alternate approaches to cross-species scaling and characterizing variability. It will be important for the Agency to stay abreast of this research to adapt or refine its approach to the use of these factors as warranted by the supporting science. One such example is the refinement of the interspecies and intraspecies uncertainty factors through the use of chemical-specific adjustment factors (CSAFs).

Recent advances in methodology suggest that it is possible to develop CSAFs in lieu of default 10-fold factors to reflect differences in the toxicokinetic and toxicodynamic processes. Toxicokinetic processes refer to the uptake, distribution, biotransformation and elimination of a substance in the body whereas toxicodynamic processes refer to the interaction of a substance with target sites and the subsequent reactions leading to adverse effects. One of the more recognized methods of generating CSAFs recommends that the 10-fold factor for interspecies extrapolation is divided into a factor of 4-fold ($10^{0.6}$) for toxicokinetic differences and 2.5-fold

($10^{0.4}$) for toxicodynamic differences.[8] Similarly, potential refinement of the 10-fold factor for intraspecies variability lies in the generation of chemical-specific factors to replace the default factor of 3.2-fold ($10^{0.5}$) for each of the contributors to human variability, namely toxicokinetic and toxicodynamic differences.[9] The generation of compound-specific information in humans and animals allows biology-based comparisons and potential replacement of these default kinetic and dynamic factors.

Generally speaking, kinetic and dynamic data in humans are rarely available for pesticides. Furthermore, given the multiple routes of exposure of a pesticide (i.e. oral, dermal and inhalation), the varying exposure durations of interest and the scientific and ethical constraints of human testing, the development of such data is likely limited. This is most problematic with respect to generating CSAFs for intraspecies variability given the ethical implications of testing in vulnerable populations (e.g. children, pregnant women, etc.). Such data may be available in situations where a pesticide may also have therapeutic application. Notwithstanding the challenges of generating CSAFs for pesticides, the PMRA will consider using chemical-specific data to reduce, increase or confirm these 10-fold uncertainty factors where the data are adequate in terms of quality and sufficiency. The consideration of CSAFs for pesticides will also be contingent upon PMRA policy regarding the use of human toxicity studies for regulatory purposes.

3.3 Use of a LOAEL

In situations where a NOAEL has not been achieved in a key study for risk assessment (i.e. adverse effects are observed at the lowest dose tested), it may be necessary to rely on the LOAEL for deriving a reference dose. The margin between the LOAEL and what would have been the NOAEL is often unclear. Consequently, an uncertainty factor (UF_L) may be employed for extrapolating from a LOAEL to a NOAEL to account for this uncertainty in risk assessment. The PMRA will use a factor of 1- to 10-fold for this extrapolation when necessary. When well-defined NOAELs are available for the critical endpoint of concern, no such factor is warranted. This approach is consistent with that of other regulatory jurisdictions, where the upper limit of this factor ranges between 3- and 10-fold.

The magnitude of the selected factor will be based upon the level of response at the LOAEL, the nature of the effect and the steepness of the dose-response curve. Based on the known progression of effects (both incidence and severity) with increasing dose, it is reasonable to consider level of response and nature of the effect in determining the size of the uncertainty factor. For example, a mild or moderate response or effect at the LOAEL would suggest

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[8] World Health Organization/International Programme on Chemical Safety. 2001. *Guidance Document for the Use of Data in Development of Chemical-Specific Adjustment Factors (CSAFs) for Interspecies Differences and Human Variability in Dose/Concentration–Response Assessment*. International Program on Chemical Safety, WHO/UNEP/ILO, WHO, Geneva, Switzerland. www.who.int/ipcs/publications/methods/harmonization/en/csafs_guidance_doc.pdf

[9] Ibid.

application of a 3-fold uncertainty factor[10] whereas a severe or serious response or effect could warrant a higher factor of 10-fold. A one-fold uncertainty factor could be invoked under certain circumstances. For example, a toxicological finding that is marginal in terms of level of response (i.e. close to the threshold) as well as consideration of the nature of the effect could warrant application of a one-fold uncertainty factor. With regards to the shape of the dose-response curve, a very shallow dose response would be of concern due to less precision about the likely threshold for effects. A very steep dose-response curve would dictate the need for a greater level of certainty and therefore a larger uncertainty factor since a small increment in exposure could dramatically increase the response rate.

The derivation of a reference dose based on application of the uncertainty factor for extrapolating from a LOAEL to a NOAEL is illustrated below.

A NOAEL for the critical endpoint of concern has not been identified.

$$\text{Reference Dose} = \frac{\text{LOAEL for Critical Endpoint of Concern}}{(UF_A \text{ of } 10) \times (UF_H \text{ of } 10) \times (UF_L \text{ of } 1 \text{ to } 10)}$$

In some cases, it may be possible to use the benchmark dose as an alternative method of defining the lower end of the dose-response curve. The main advantage of this approach is that it uses all information from the dose-response data. It is important to note that the benchmark dose approach is appropriate only when the data are adequate for modelling (i.e. observable response data available in the appropriate dose range). The benchmark dose approach is increasingly replacing the need to conduct a LOAEL to NOAEL extrapolation. The PMRA has started using this approach in situations where the data are well suited to this modelling.

3.4 Extrapolation for Study Duration

An uncertainty factor (UF_S) may be applied to the NOAEL if extrapolation from studies of shorter duration to a longer-term exposure scenario is necessary due to lack of relevant data for risk assessment. Chronic studies might reveal relevant health effects not detected in short-term studies. In addition, critical effects seen in short-term studies may progress with chronic exposure such that the resultant NOAEL would be lower.

[10] Note that a value of 3 is often used in place of ½ power, i.e. $10^{0.5}$. The PMRA uses these half-power values as whole numbers when they occur singly but as powers or logs when they occur in tandem, e.g. a composite factor of 3-fold and 10-fold would be expressed as 30 (3×10^1), whereas a composite factor of 3-fold and 3-fold would be expressed as 10 ($10^{0.5} \times 10^{0.5} = 10^1$).

Long-term toxicology studies are required for pesticides to support an assessment; therefore, this factor would rarely be required. However, there may be certain situations where this factor could be employed such as where existing chronic data have been determined to be inadequate during re-evaluation, where a tiered approach to data requirements may have been undertaken (e.g. industrial antimicrobials) or where route-specific, long-term information (i.e. dermal or inhalation) was lacking. The PMRA's regulatory counterparts are generally harmonized in applying additional factors to extrapolate for this uncertainty.

The PMRA will use a 1- to 10-fold factor for the extrapolation from short-term studies (e.g. 90-day studies) to longer-term scenarios where necessary. The magnitude of the value for a given risk assessment will be determined through scientific judgement. Factors such as the bioaccumulation potential, toxicokinetics, absorption and mechanism of action (maximum concentration [C_{max}] or area-under-the-curve mediated) will be considered in the determination of this factor. The nature of the response (i.e. likeliness to progress in severity, frequency, etc.) and the effect of duration in alternate studies are also key determinants in assessing the magnitude of the factor. As an example, a 10-fold uncertainty factor would likely be invoked for a long-term risk assessment of a pesticide demonstrating bioaccumulation potential but lacking chronic data.

The derivation of a reference dose based on extrapolation for study duration is illustrated below.

Extrapolation from a short-term study to a chronic scenario is required

$$\text{Reference Dose} = \frac{\text{NOAEL for Critical Endpoint of Concern}}{(UF_A \text{ of } 10) \times (UF_H \text{ of } 10) \times (UF_S \text{ of } 1 \text{ to } 10)}$$

3.5 Data Deficiency

The application of uncertainty factors for database deficiencies (UF_{DB}) in a risk assessment can be prompted by varying sources of uncertainty. The issues of LOAEL-to-NOAEL extrapolation and subchronic-to-chronic extrapolation, described above, could be considered database deficiencies but for the purpose of this policy are considered separately. Hence, the use of a factor for database deficiency primarily reflects the absence of key data in the hazard component of the risk assessment for a given pesticide.

Key data could include missing or inadequate core studies (i.e. carcinogenicity studies in two different species, one chronic toxicity study, prenatal developmental toxicity studies in two different species or a multigeneration reproduction study). A deficiency in a core data requirement would rarely occur with a new registration application as these studies would be requested prior to consideration of a registration application. An uncertainty factor for data deficiency pertaining to a core data requirement is more likely to be invoked during re-evaluation since this activity could identify missing studies or inadequate studies by current standards. Key data could also include specialized studies to address an endpoint of concern; this

would be of relevance to both new pesticide evaluation as well as re-evaluation activities. Database deficiency factors are intended to be applied as an interim measure until relevant data can be produced.

The PMRA will use a 1- to 10-fold factor for database deficiencies. This approach is comparable to other regulatory jurisdictions. The magnitude of the factor will be influenced by the level of concern generated by the database and the potential impact of the missing information. A higher factor of 10-fold would be warranted if missing data are considered critical to understanding the potency of a pesticide, have a good possibility of revealing a sensitive subpopulation, or are likely to affect the point of departure (by identifying new effects or effects at lower dose levels). Consideration of the uncertainty factor would generally occur only when a study is being required "for cause," that is, if a significant concern is raised based on a review of existing information. Consideration of the uncertainty factor would not generally occur simply because a data requirement has been levied to expand the PMRA's general knowledge of the pesticide. Multiple database deficiencies would also likely invoke a higher factor of 10-fold. A lesser factor would typically be considered by the PMRA when supplementary data ameliorates the concern for a database deficiency (e.g. available information on the toxicity of structurally similar chemicals, available information on existing but deficient studies, etc.).

On rare occasions, deficiencies within a study (e.g. analytical problems, low sample size, poor dose selection) or other database considerations (e.g. insensitivity of the test organism, shape of the dose response, etc.) may warrant consideration of the database deficiency factor. Application of the uncertainty factor in these cases reflects low confidence in the available hazard information needed to derive a reliable assessment of risk. As with the other database deficiencies, consideration of the factor would generally occur "for cause" based on existing information.

The derivation of a reference dose reflecting a data deficiency is illustrated below.

Database deficiency is present

$$\text{Reference Dose} = \frac{\text{NOAEL for Critical Endpoint of Concern}}{(UF_A \text{ of } 10) \times (UF_H \text{ of } 10) \times (UF_{DB} \text{ of } 1 \text{ to } 10)}$$

4.0 Application of the *Pest Control Products Act* Factor

4.1 General

Under the new PCPA, the PMRA must apply a default 10-fold factor (the PCPA factor) unless the PMRA concludes, based on reliable data, that a different factor is appropriate for the protection of infants and children. Determination of the magnitude of the factor involves evaluating the completeness of the data with respect to exposure of and toxicity to infants and

children as well as potential for prenatal or postnatal toxicity (see Figure 2). Incomplete toxicology databases are not equally incomplete and all prenatal and postnatal toxicities are not of equal concern. For these reasons, the PMRA makes specific case-by-case determinations as to the size of the PCPA factor if reliable data permit. An integrative approach is taken to optimize use of all available information. A PCPA factor less than or equal to 10-fold or, in very rare circumstances, greater than 10-fold may be employed in an assessment. Given the extensive data typically available for a given pesticide, the PMRA believes that in most instances, there will be sufficient reliable data to conduct an individualized assessment of the factor necessary to assure the safety of infants and children.

The PMRA interprets the new PCPA provisions as requiring a presumptive application of the 10-fold factor for the protection of infants and children. In other words, the onus is on the PMRA to provide a reliable scientific rationale in those cases where the 10-fold PCPA factor is reduced, as opposed to the past regime in which the PMRA provided scientific justification for why any additional factors beyond those for intraspecies and interspecies differences were used. For any given product, each risk assessment scenario may warrant a different PCPA factor. Separate decisions on the magnitude of the PCPA factor may be necessary for different routes of exposure, different durations of exposure or different subpopulations.

The PCPA clearly specifies the use of the PCPA factor for the protection of infants and children in dietary risk assessment as well as in risk assessment for products used residentially (i.e. used in or around homes or schools). The PCPA factor is also applied to protect fetuses and nursing infants that may be exposed indirectly as a result of placental or lactational transfer from women who receive dietary or residential exposure. The PCPA does not specifically require the application of the PCPA factor in occupational risk assessment. Regardless, those exposed occupationally could include pregnant or lactating women; therefore, there is the potential for indirect exposure of their offspring to a pesticide. In keeping with the spirit of the legislation, it is necessary to protect these indirectly exposed young to a similar degree as their counterparts that are afforded protection through the application of the PCPA factor. Consequently, where warranted, an additional uncertainty factor will be applied to worker exposure scenarios if available data identify concerns for potential effects on the young or if appropriate data are not available to adequately address the concerns.

Some within the regulated community may view the PCPA factor as a policy-based factor, required by law, as opposed to a science-based factor. While the introduction of the PCPA factor into the pesticide regulatory framework may have been a policy choice, the refinement of the PCPA factor is determined solely upon the scientific considerations outlined below. Others may regard the uncertainty factors that address use of a LOAEL versus a NOAEL, extrapolation for duration of dosing and database deficiencies as components of a PCPA factor. While one could argue that the PCPA codified the use of these uncertainty factors, the PMRA will characterize these factors separately for transparency and to reflect the traditional usage of these factors. Nevertheless, where these uncertainty factors have been deployed, the PCPA factor may be modified accordingly to avoid double counting. Double counting could occur if the same concern were relied upon to justify both an uncertainty factor and a PCPA factor. Appropriate review procedures and documentation will serve to minimize the potential for double counting (see Section 5.0). The PCPA factor is explained in more detail in the following sections.

4.2 Completeness of the Data

While the new PCPA provisions focus attention on the safety of infants and children, it was the PMRA's practice, prior to and after enactment of the PCPA, to assess the completeness of the pesticide database for hazard identification and quantification. In light of this, there is overlap between the use of an uncertainty factor to account for database deficiencies (UF_{DB}) and a PCPA factor to account for the completeness of the data with respect to the toxicity to infants and children. Accordingly, it is anticipated that most uncertainties relating to the completeness of data with respect to the toxicity to infants and children (or for any subpopulation) will have been addressed through the application of an appropriate uncertainty factor for database deficiency.

It is critical that each pesticide assessment address the completeness of data with respect to identifying available studies specific to the life stages associated with the young animal or human (i.e. embryo, fetus, neonate, infant, child, juvenile). The PMRA will ensure that data gaps, particularly those that pertain to evaluating risk to children and other sensitive subpopulations (i.e. the prenatal developmental studies or the multigeneration reproduction study), are adequately accounted for through the use of the database deficiency uncertainty factor. Any residual uncertainty relating to completeness of data with respect to infants and children (i.e. concerns that remain unaccounted for following the application of uncertainty factors) would become a critical determinant in retaining all or a portion of the PCPA factor.

Scientific judgement is used to determine the appropriate magnitude of the factor in a pesticide risk assessment. This determination is based on the toxicology data as well as the anticipated impact of missing or inadequate information in characterizing the potential toxicity to infants and children. If adequate data are available, there would be reliable data with respect to the completeness of the toxicity data to support establishing a lower factor than that specified in the PCPA provisions. This approach is generally similar to the USEPA's approach with respect to application of the FQPA provision.

As an example, if all relevant studies were available but a critical study had some methodological issues, a PCPA factor could be retained in full or in part to address residual uncertainties relating to the completeness of the data with respect to toxicity of the young. The PMRA could request further data, but depending on the scenario, the PMRA may not ask for a new study in consideration of animal welfare issues. However, the applicant or registrant would still have the option to address this residual uncertainty through data development followed by a new submission. In some cases where residual uncertainties are identified, it may not be possible for the registrant or applicant to address or generate data due to practical considerations or lack of appropriate testing models. These cases would support retaining the PCPA factor in full or in part.

4.3 Prenatal and Postnatal Toxicity

It is generally recognized in the scientific literature that the 10-fold intraspecies factor is adequate to address variability within the population for the majority of chemicals. However, there are chemicals for which there is a greater range of variability; sometimes that variability is age-related. Accordingly, the new PCPA provisions require the application of an additional 10-fold factor in the risk assessment for certain scenarios (i.e. dietary, use in and around homes or schools) to take into account, in part, potential prenatal and postnatal toxicity.

As part of the toxicological considerations, the PMRA evaluates prenatal and postnatal toxicity on a case-by-case basis taking into account all pertinent information. The level of concern for such effects will be assessed considering several lines of evidence, including the degree to which protection for infants and children is provided by the standard application of uncertainty factors. The principal components in determining the level of concern are the sensitivity of the young noted in the database and seriousness of the prenatal or postnatal endpoint(s), although other factors can influence the assessment (see Figure 3).

If toxicity data indicate no prenatal or postnatal toxicity or the level of concern is low (and the data is considered complete), then the presumption for use of the 10-fold PCPA factor will be obviated with respect to the potential for prenatal and postnatal toxicity (i.e. the PCPA factor would be reduced to one-fold). If the level of concern is high, the 10-fold PCPA factor will be retained. A different PCPA factor could be used based on the level of uncertainty regarding the potential for prenatal and postnatal toxicity. Key lines of evidence or considerations that would influence the degree of concern for prenatal or postnatal toxicity are outlined in Table 1 and discussed below. This approach is similar to that used by the USEPA with respect to application of the FQPA provision.

It should be noted that Table 1 is for illustrative purposes and should not be interpreted as all-inclusive. Furthermore, these considerations are used in a weight-of-evidence approach for making scientific judgements about the level of concern; no single consideration determines the overall level of concern for the young. This integrative approach maximizes the use of all available information rather than relying on findings in isolation.

Table 1 Considerations for Evaluating Degree of Concern for Prenatal and Postnatal Toxicity from Human Information and/or Animal Data— A Weight-of-Evidence-Approach

Considerations	Degree of Concern	
	High	**Low**
Sensitivity or susceptibility of the young	Qualitative or quantitative sensitivity.	Absence of sensitivity.
Seriousness of the endpoint(s)	Serious as per definition (causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death).	Less serious.
Dose response	Steep dose response (small increment in exposure can have significant impact). Shallow dose response (less certainty about precision of NOAEL).	Good data on dose response (allows for confident identification of NOAEL or BMD).
Toxicokinetics and/or metabolism	Metabolic profile indicates higher internal dose of active moiety in young compared to adult or in humans compared to animals. Animal or human evidence of significant placental or lactational transfer.	Metabolic profile indicates lower internal dose of active moiety in young compared to adults or in humans compared to animals. Evidence of no significant placental or lactational transfer in animals or humans.
Mode of action	Mode of action supports relevance to humans. Evidence that humans are more sensitive than the animal model. Mode of action may lead to several adverse consequences in offspring.	Evidence that mode of action is species-specific and thus not relevant to humans. Evidence indicates that humans are less sensitive than the animal model.
Confidence in study and/or endpoint	Low quality database. Study limitations. Poorly defined NOAEL.	High quality database. Well-conducted study. Well-defined NOAEL.
Human information	Effects found in humans related to exposure.	No adverse human effects associated with exposure.

4.3.1 Sensitivity or Susceptibility of the Young

When results of animal testing reveal unique effects in the young (e.g. a different pattern of effects of concern) relative to adults, this is referred to as susceptibility or qualitative sensitivity. Evidence of quantitative sensitivity of the young arises when the effects in the young are similar to those seen in adults, but occur at doses lower than those causing effects in adults, occur more quickly, or occur with greater severity or duration than those observed in adults. While the demonstration of increased susceptibility or sensitivity of the young in the toxicology database would be a critical determinant for retention of the PCPA factor, other evidence would also be factored into determining the overall level of concern. For example, if all other lines of evidence were to show a low degree of concern for prenatal or postnatal toxicity and the point of departure were based on the critical endpoint in the sensitive population, the PCPA factor could be obviated with respect to prenatal and postnatal toxicity.

4.3.2 Seriousness of the Endpoint

The term “severity of effect” is well used in regulatory toxicology; however, it should be noted that the term “severe” is not synonymous with serious. By definition, “severe” is used to describe the intensity of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor toxicological significance. In determining the level of concern for a pesticide with regards to the seriousness of the endpoint, it is necessary to have a working definition for a serious effect. Components of the definition of serious adverse reaction as described in the Food and Drug Regulations[11] can be adapted for this purpose. Thus, for a threshold response, a serious toxicological effect for a pesticide is one that causes congenital malformations, results in persistent or significant disability or incapacity, is life-threatening or results in the death of exposed animals.

If the critical endpoint is based on a serious toxicological effect, a high degree of concern would be identified. The temporal nature of the effect (e.g. time of onset, persistence, recovery, etc.) will influence the determination of the degree of concern, with irreversible findings eliciting greater concern. Examples of serious endpoints of concern include, but are not limited to, reduced viability of offspring, the occurrence of malformations and changes in brain morphometrics (size or weight). Less serious endpoints of concern could include transient effects such as cholinesterase inhibition or organ weight changes with no or minimal associated histopathological changes.

4.3.3 Dose Response

The shape of the dose-response curve can influence the degree of concern. There is a lower degree of concern when the dose-response relationship is well characterized. A steep dose response could heighten concern since a small increment in exposure could have a significant impact. A shallow dose response also gives way to higher concern, as there is less certainty about the precision of the NOAEL in this case. Dose level selection plays a critical role in

[11] Section C.01.001. Food and Drug Regulations, Part C Drugs, Division 1, 4 December 1997.

adequately characterizing the dose-response curve. Information on the comparative dose responses of young animals and adults can also play a role in determining the degree of concern.

4.3.4 Toxicokinetics/Metabolism

Knowledge of age-specific differences in absorption, distribution, excretion or metabolism can have a major impact on the degree of concern. For example, a higher degree of concern may be elicited by findings that the young achieve a higher internal dose compared to adults with equivalent administered doses, or by findings that the young have a lesser capability to detoxify the parent compound or active metabolite. A compound that is persistent in body tissues or bioaccumulates will generally have a higher level of concern than one that is rapidly excreted, due to the prolonged possibility of interacting with sensitive tissues or organs.

There is often little information available on the toxicokinetics associated with indirect exposure of the fetus or nursing infant to a pesticide as a result of direct exposure of the mothers. Animal or human evidence of significant placental or lactational transfer is a key consideration in the degree of concern analysis. As regulatory science evolves to integrate physiologically based pharmacokinetic models into risk assessment, such information on placental and lactational transfer will be required to derive age-appropriate models.

4.3.5 Mode of Action

Mechanistic or mode of action information can be critical to understanding the relevance of animal findings to humans. Human relevance frameworks such as the one developed by the International Programme on Chemical Safety[12] are useful tools for characterizing the mode of action of a compound and consideration of life stage. Two important components of this analysis are the degree to which developmental processes are similar in humans and the animal model(s), and the phase specificity or relative timing of developmental processes in humans and the animal model(s). A species-specific response that is not relevant to humans would obviously decrease the level of concern. Significant differences in developmental ontogeny between humans and the animal model could also play a role in the overall weight of evidence.

[12] Boobis, Alan R. et al. 2008. “IPCS Framework for Analyzing the Relevance of a Noncancer Mode of Action for Humans.” *Critical Reviews in Toxicology*, 38: 2, 87–96.

4.3.6 Confidence in Study and/or Endpoint

Consideration of the degree of confidence or reliability in the data is intended to account for the quality of information available. It is not intended to address data deficiencies as these would have already been accounted for through the application of an uncertainty factor for database deficiencies. Concerns can arise in consideration of the database as a whole, or in consideration of a study or endpoint(s) within a study. A low degree of concern would be associated with well-conducted studies with well-defined NOAELs in a high-quality database. Less confidence, resulting in a higher degree of concern, could be characterized by situations where there is a poorly defined NOAEL, where there are limitations in study design, measurement or reporting, or where the overall database is considered to be of low quality.

4.3.7 Human Information

Product-specific human information, although rarely available, is considered highly relevant in determining degree of concern. Concern is heightened if sufficient human data are available to judge that an adverse developmental effect is related to exposure. Such information could arise from the literature and include epidemiological information or clinical trial data if the product has potential therapeutic application. Incident reporting databases are also a source of information relevant to humans. Biomonitoring information can play a role in characterizing age-related differences in body burden or in identifying compound or metabolite uptake in developmentally sensitive compartments such as the placenta or breast milk. It would be concluded that there is a low degree of concern if there is sufficient human evidence to demonstrate a lack of prenatal or postnatal toxicity. However, it is acknowledged that this burden of proof is difficult to meet because of the wide range of data and measured endpoints necessary to confirm the absence of effects.

5.0 Further Considerations

It is recognized that application of this framework relies heavily on scientific judgement. Moreover, characterizing uncertainties within a risk assessment is not an exact science, and challenges are anticipated for the risk assessor in attributing the uncertainty to a discrete factor (e.g. specific uncertainty factor or PCPA factor). The risk assessor must guard against accounting for the same area of insufficiency or “double counting” among the uncertainty factors.

For instance, the lack of a study with a well-defined NOAEL could prompt the use of an uncertainty factor for extrapolating from a LOAEL to a NOAEL or the use of an uncertainty factor for database deficiency. Similarly, the absence of a required chronic study could prompt the use of an uncertainty factor for extrapolating the results from a short-term study to a chronic study or the use of an uncertainty factor for a data deficiency. There is also potential for “double counting” among the uncertainty factors and the PCPA factor. For example, the absence of some critical information relating to developmental toxicity could be reflected as an uncertainty factor for database deficiency or as a PCPA factor resulting from residual uncertainty relating to the

completeness of the database. Instead of focussing on differentiating between these factors with precision, it is more important that the rationale supporting the use of additional factors be transparent and that care be taken not to double count or multiply uncertainty factors that are clearly not independent of one another.

Following a comprehensive analysis of the available information, the risk assessor must derive the total uncertainty factor (UF_{TOTAL}). This factor is the product of all the applicable uncertainty factors in a given risk assessment ($UF_{TOTAL} = UF_A \times UF_H \times (UF_L \times UF_S \times UF_{DB}$ if required). In the case of occupational risk assessment, this would also include any additional factors employed for concerns relating to prenatal or postnatal toxicity. For non-occupational risk assessment, the magnitude of the PCPA factor, where applicable, is determined subsequent to the derivation of the UF_{TOTAL} on the basis of scientific judgement. After assignment of the appropriate uncertainty factors and PCPA factor, it is necessary to derive a composite assessment factor (CAF) reflecting the totality of factors applied in a given risk assessment (CAF = UF_{TOTAL} × PCPA factor). Figure 4 illustrates the framework described above.

Regardless of whether a CAF has been derived for dietary or residential risk assessment or a UF_{TOTAL} has been derived in the case of occupational risk assessment, an upper limit of 3000 has been adopted. This limit is deemed reasonable given the potential for overlap and compounding conservatism associated with the application of numerous factors. This approach is consistent with that of many regulatory counterparts, who employ an upper limit ranging from 3000 to 10 000. One would have low confidence in a database where the uncertainty in the risk assessment would prompt the use of a total factor in excess of 3000. In such a situation, the risk assessor should refrain from quantifying the uncertainty and from deriving reference values. Instead, the uncertainties should be addressed in a qualitative manner and the pesticide should be handled accordingly at the risk management phase of the assessment.

6.0 Conclusion

To date, the application of uncertainty factors in risk assessment has been influenced to a large extent by historical practice. Despite this, it is apparent that practices are evolving to reflect increased scientific knowledge and changing laws and regulations. This guidance document is intended to provide a transparent and disciplined basis for the application of uncertainty factors and the PCPA factor for pesticide regulation in Canada. It should be noted that deviations from this guidance would be considered on the basis of developments in science or risk assessment methodologies or changes in policy approach; however, such deviations would require sound scientific justification.

List of Abbreviations

ADI	acceptable daily intake
aPAD	acute population adjusted dose
ARfD	acute reference dose
BMD	benchmark dose
CAF	composite assessment factor
cPAD	chronic population adjusted dose
CSAF	chemical-specific adjustment factor
FQPA	*Food Quality Protection Act*
IPCS	International Programme on Chemical Safety
LOAEL	lowest observed adverse effect level
MOE	margin of exposure
NOAEL	no observed adverse effect level
PCPA	*Pest Control Products Act*
PMRA	Pest Management Regulatory Agency
UF	uncertainty factor
UF_A	uncertainty factor for interspecies extrapolation
UF_{DB}	uncertainty factor for database deficiency
UF_H	uncertainty factor for intraspecies variability
UF_L	uncertainty factor for LOAEL to NOAEL extrapolation
UF_S	uncertainty factor for extrapolation of study duration
UF_{TOTAL}	total uncertainty factor
USEPA	United States Environmental Protection Agency

Figure 1 Determination of Uncertainty Factors

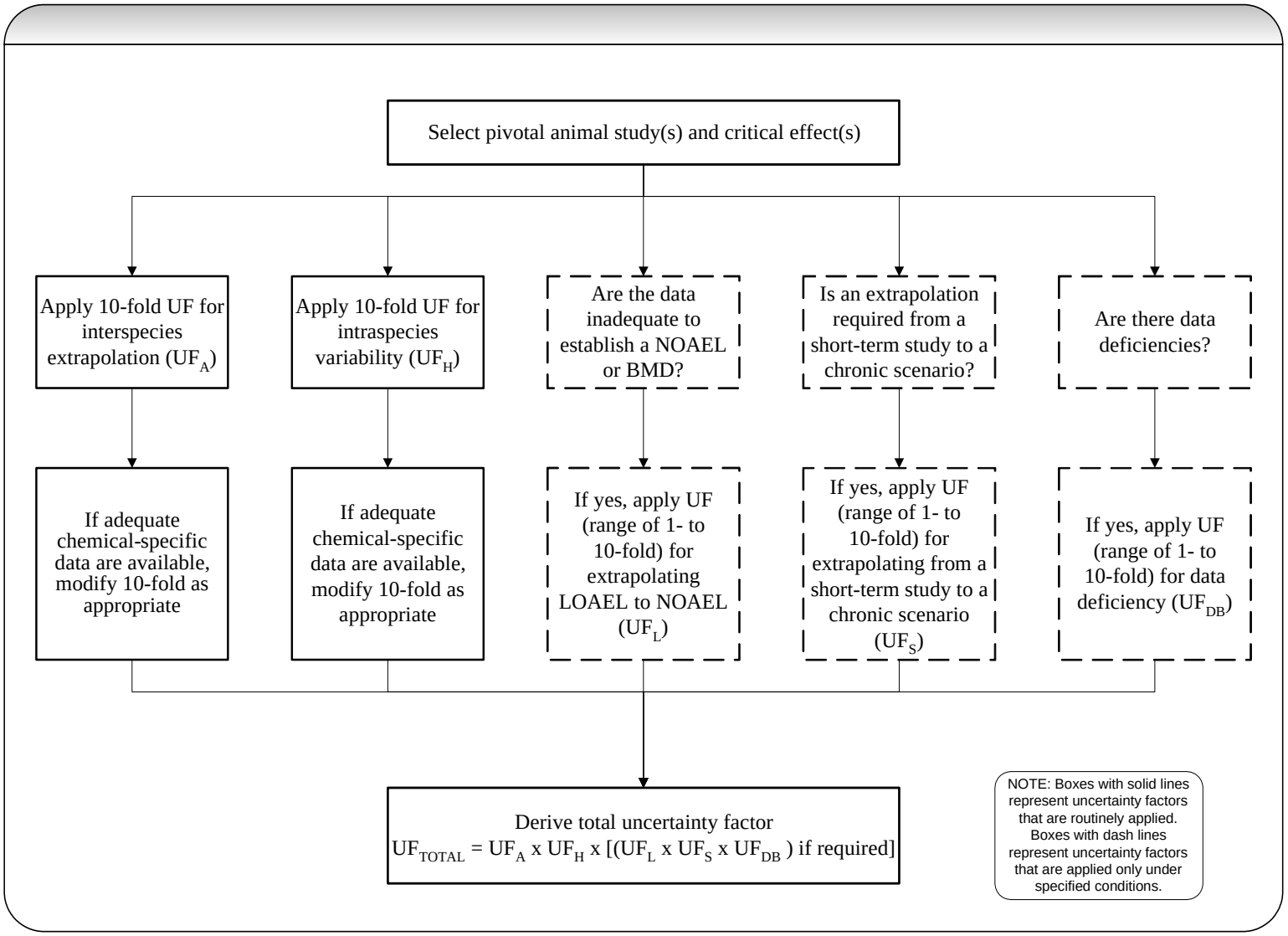

Figure 2 Determination of *Pest Control Products Act* Factor

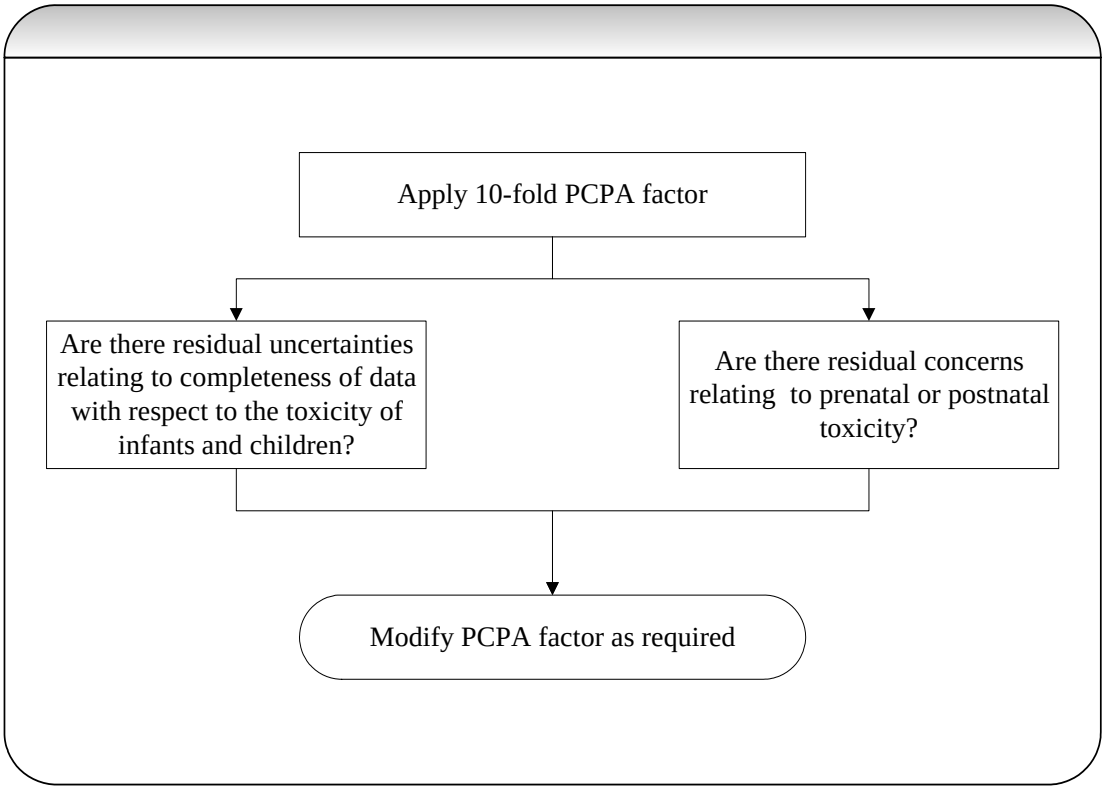

Figure 3 Prenatal and Postnatal Toxicity Considerations

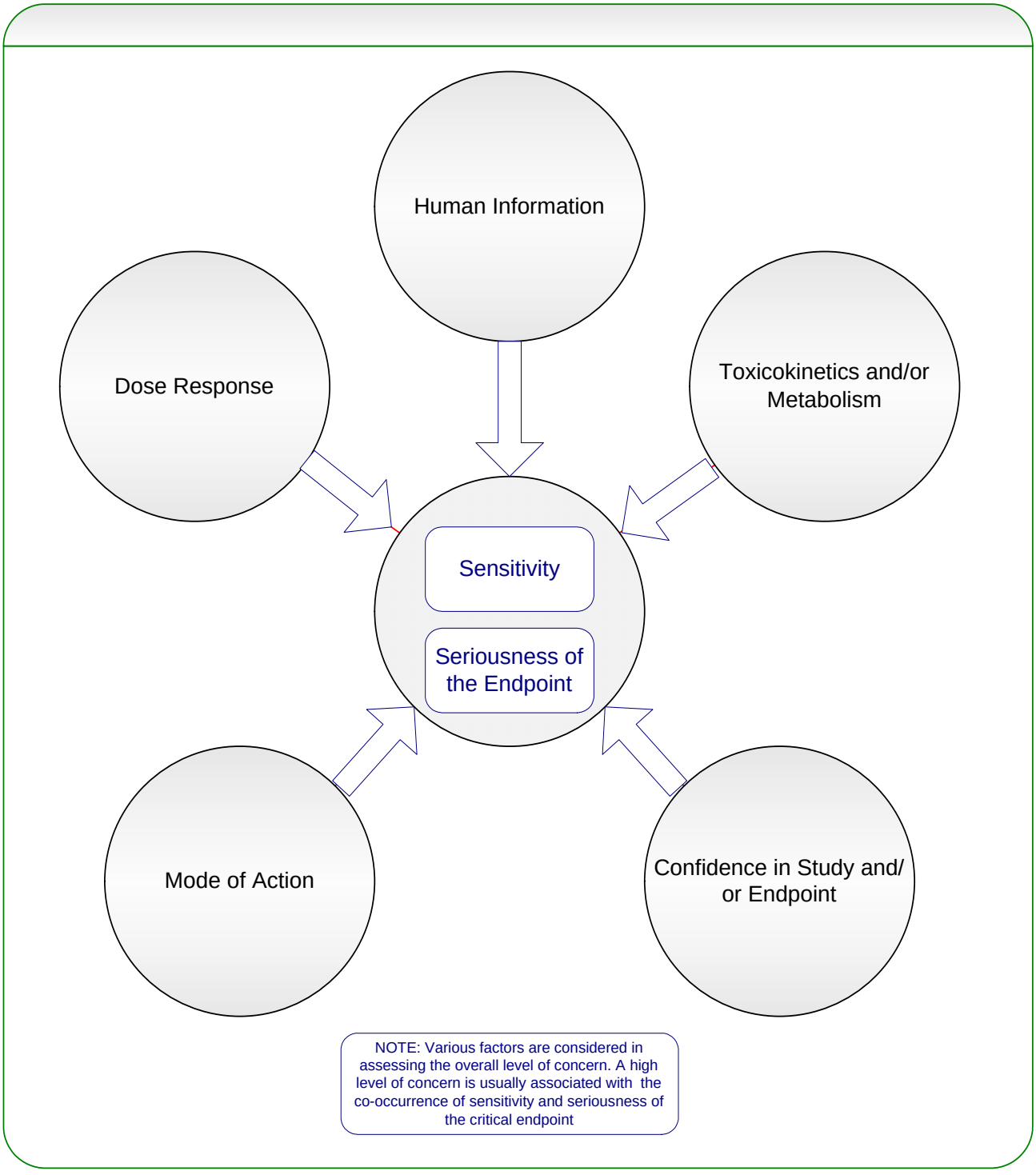

Figure 4 Framework for Determination of Uncertainty Factors and *Pest Control Products Act* Factor