



**Comments on the Pest Management Regulatory Agency's  
Use of Uncertainty and Safety Factors in the  
Human Health Risk Assessment of Pesticides**

**By**

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## **Executive Summary**

The Environmental Health Committee of the Ontario College of Family Physicians is pleased to contribute to this important consultation. Pest Management Regulatory (PMRA) requests for public commentary including comments from the OCFP, and ongoing consultation through the Pest Management Advisory Committee as well as the planned December 10, 2007 consultation meeting, point favourably towards improving transparency and broader consideration of determinants of human and environmental health in pesticide assessment.

### ***The bottom line for protection of public health***

The Ontario College of Family Physicians believes that Canada should be moving from the present framework of registration of all pest control products that meet prescribed requirements, to an approach whereby Canadians use methods and products with the least risk to health and the environment. The least-toxic model is somewhat similar to the decision-making model in Sweden, where there is the Substitution Principle, along with the Precautionary Principle. Basically, for whatever you want to do, produce, etc., you must use the methods/chemicals that are of the lowest known toxicity and least known environmental impact; not merely those with an “acceptable risk”.

This is a model for using only best practices, and for continual improvement. Sweden has instituted this approach in order to reach its goal of achieving a non-toxic environment within a generation. We believe that only this type of approach can achieve the requirement under Canada’s Pest Control Products Act (2002) (PCPA 2002) of “reasonable certainty that *no* harm to human health, future generations or the environment will result from exposure to or use of the product ...” (emphasis added).

A public discussion of the cut-off for “reasonable certainty” would assist the public in understanding that, when using chemicals meant to be toxic, even with agreement on what “reasonable certainty” should be, a small percentage of people will still be affected. What is this percentage? How does it compare with the percentage of people with environmental sensitivities and other complex, chronic conditions?<sup>1</sup>

No matter what the driving philosophy, any regulatory framework requires that pesticides be assessed. One must start somewhere, and the present risk assessment system may be as good (or bad) as other possible starting points to assess toxic chemicals. However, the system only provides a means to extrapolate from laboratory animal data, using arbitrarily determined extrapolation factors, to hypothesize that a chemical when used in a particular manner will or will not cause harm in humans with widely varying susceptibilities or in the environment.

There is an ongoing difficulty that the results of epidemiological studies of potential human health effects of exposure to pesticides do not appear to be consistent with pesticide risk assessment study conclusions.<sup>2-4</sup> Thus, limitations in extrapolation of animal test results under experimental laboratory conditions must be recognized and the reliability of such extrapolations ought not to be overstated. Other information must continually be sought and used to provide “reality checks,” to validate or disprove the hypothesis that use of a particular product in a particular manner will not harm present or future generations, or the environment. Investigation of hypotheses is the heart of science, and must be central to pesticide regulation. Until the hypotheses generated by toxicological risk assessment are validated by monitoring of human and environmental contamination, epidemiological research and other basic science studies, Canada’s regulatory system is not truly “science-based.”

Low dose effects are one of several reasons postulated for the incongruity between conclusions reached through epidemiology reported in peer-reviewed literature, and regulatory toxicology-based

assessments. Within single-chemical assessment, more testing is needed to investigate whether low dose effects are being “missed.” Pesticide toxicity in animals is typically measured at relatively high doses, assuming that lower doses will engender the same effect to a decreasing degree, and that a low enough (non-zero) dose will have a zero effect (the “no observed adverse effect level” – NOAEL). However, present knowledge indicates that effects (particularly hormonal/endocrine disruption) may be different at low doses compared to high doses, and become increasingly apparent at lower doses. Thus, doses at least an order of magnitude below the NOAEL as well as environmental exposure levels should be studied. It is possible that high-dose experiments are identifying the nadir of a U-shaped dose-response curve as a NOAEL, while lower environmental levels engender overt toxic effects. Furthermore, when a NOAEL was *not* measured, the need to extrapolate from a lowest observed adverse effect level (LOAEL) suggests strongly that low dose effects may be significant.

As this document affirms, workers should not be second-class citizens when it comes to protection of their health from toxic chemicals, including pesticides. Any extrapolation factor deemed appropriate for the population at large should apply to workers. Foetal development is a time of particular concern, and pregnant workers should not be risking their offspring because of their employment.

***The bottom line for the PMRA - whether or not to register a pesticide.***

Toxicological risk assessment as outlined in the consultation document is a limited examination of some of the relevant science; complementary scientific issues are discussed in this submission.

Pesticides should be used only when absolutely necessary, and when less toxic or hazardous solutions (strategies, agronomic solutions, etc. as well as chemical products) with lower impacts on human and environmental health are not available. Special provisions for areas such as residences, hospitals, schools, clinics, etc. with sensitive populations (e.g. children, the elderly and pregnant women) deserve consideration.

In the name of precaution, pesticides should *not* be registered when the uncertainties are too great. This would include extrapolation from a LOAEL, and lack of core studies. Many details in this regard are included in responses to the PMRA questions in this submission. Knowledge of vulnerabilities of various populations is developing rapidly, making it increasingly clear that understanding of important areas of science may not be sufficient to set extrapolation factors (i.e. the more we know, the more we know we don't know). We can say, however, that the range of magnitude of potential effects may frequently exceed 10-fold across the human population.

Toxicological risk assessment hypotheses must be tested for validity alongside epidemiological and other data not presently considered during assessments. As well, evidence of persistence or bioaccumulation of a pesticide, breakdown product(s) and/or contaminant in the environment, wildlife or people should be grounds for refusal to register (e.g. lindane).

If pesticide assessment continues to be driven by registrant-sponsored research, resistance to low-dose testing is to be expected. There is a concern that pesticide data may not be forthcoming if it is not favourable, so it is recommended that a system similar to clinical trial registration for medications be instituted, open at least to the regulator. A potential registrant would inform the PMRA before commencing work of the experimental details and the laboratory conducting the studies, and the PMRA could access the data directly from the researchers.

***Once registered, what next?***

If the PMRA is acting upon the hypothesis that no harm will ensue from use of a particular pesticide in a particular manner, it must then carry out adaptive management. Data regarding pesticide uses, concentrations of parent and daughter compounds in people and the environment, harms, and reports in all areas of related public-domain research should be comprehensively gathered, monitored and

reviewed to validate or disprove this hypothesis. Interim precautionary measures should include restricting pest control products to the most essential applications, away from vulnerable populations.

It should be highlighted that the European Union is now considering legislation that would dramatically change the way that pesticides are managed in that jurisdiction (see <http://www.europarl.europa.eu/oeil/file.jsp?id=5372322>). The EU is moving towards banning of aerial spraying, banning of use around vulnerable populations such as children, and strong support of organic agriculture. Many pest control ingredients are being de-registered. As such it is moving from the difficult grey science of risk assessment and management, to risk avoidance. This will be necessary for the PMRA to meet the new higher bar of protection of the health of people, wildlife and the environment mandated by the PCPA 2002.

### ***Consultation questions posed by the PMRA***

We are concerned that the questions posed by the PMRA do not address essential systemic problems with risk assessment. However, they do raise some interesting issues. The following are highlights of responses to the specific questions posed:

- “Uncertainty” or “safety” factors should be called “extrapolation factors,” as a general term that is more informative than other options. If one wishes to be more specific, factor names could reflect their objective – interspecies extrapolation factor, intraspecies extrapolation factor, etc.
- Chemical-specific theoretical analyses should not be used to reduce extrapolation factors, but could certainly justify much greater factors. This is evident given rodents’ and other animals’ abilities to live in environments that are inhospitable to humans, and the wide variability among the human population in sensitivities to chemicals, and abilities to detoxify and excrete toxins;
- If there is a need to extrapolate from a LOAEL to a NOAEL it should lead at most to a temporary registration of short duration, with no option for renewal. NOAELs should be interpolated rather than extrapolated. The PMRA should require data for at least three dose levels covering an order of magnitude below the NOAEL, and this should include typical environmental exposures (more dose levels may be needed to include levels in the environment);
- Pesticide assessments for chemicals that have effects on the same type of cell or organ (e.g. insecticides that affect nerve cells, or pesticides that affect the liver) should consider potential exposures to all other chemicals known to affect the same cell type or organ, in a manner that addresses outcomes when exposures occur concurrently or cumulatively;
- Risks of pesticides of a common class (e.g. phenoxy herbicides) have common modes of toxicity on target species, so should be considered to pose potentially additive or synergistic toxicities to non-target species;
- Information from the PMRA feeds into development of Drinking Water standards, so it would seem that the PMRA is indeed required to assess cumulatively effects of pesticides with different but related effects (complementary, additive, antagonistic or synergistic).
- Metabolic pathway information should be determined, and included in standard package inserts;
- Dose-response curves over low doses and environmental levels should be determined in the course of assessment.

## Summary of the Pesticide Assessment Process in Canada

The PCPA 2002 sets a very high bar for protection of health and the environment, requiring a “reasonable certainty that *no* harm to human health, future generations or the environment will result from exposure to or use of the product ...” (emphasis added). It is unclear that this high protective bar is met with “an acceptable risk when the product is used as directed,” which is the current standard cited by the PMRA.

The “reasonable certainty” provision has been and is proposed to be addressed with traditional risk assessment. This integrates exposure and effects assessments, the latter based largely on laboratory exposure studies involving “model” organisms. According to the consultation document, an acceptable dose determined in animal models is then used to derive an acceptable human dose by dividing the animal dose by numerical factors to account for:

- Interspecies differences;
- Intraspecies differences among people;
- Extra sensitivity of the young (as stipulated in the PCPA 2002 – other sub-populations such as people who are ill or the elderly are not singled out);
- Database deficiencies (e.g. lack of a multi-generational or developmental neurotoxicity study);
- Extrapolation of dosing duration (e.g. from subchronic to chronic exposure);
- Use of a LOAEL instead of a NOAEL;
- Severity of endpoint (e.g. irreversible effects such as carcinogenicity or birth defects are considered severe, triggering a 10-fold factor; endocrine disruption and immunotoxicity are “less severe,” triggering a 3-fold factor).

The first step is to derive a NOAEL or LOAEL for a non-human “model” organism under controlled laboratory exposures. From this, a reference dose (RD) for humans is generated, below which the risk to human health is deemed to be “acceptable.” All safety/uncertainty factors are attempts to capture the uncertainty associated with extrapolating from specific endpoints measured in the laboratory, to what is actually of concern, overall human health. There are two aspects to this extrapolation. Both scientific effects (toxicities measured in the model animals), and a value judgement (“acceptability of risk” (previous PCPA) or “degree of certainty” (PCPA 2002)) contribute to the final extrapolation factors. This was not discussed in the PMRA document, but must be explicitly addressed to ensure that the statutory requirement has been met of “reasonable certainty that no harm...” It is suggested in a review of this subject by the Swedish Chemicals Inspectorate<sup>5</sup> that if potential extrapolation factors are considered as distributions, the value judgement entails where on the distribution the factor is chosen, to be more or less protective. This document contains interesting discussions of many issues raised by the PMRA in the present consultation, and we highly recommend that it be considered in the PMRA review and subsequent discussions.

If each consideration in the list above may trigger a 10-fold factor, the maximum conceivable factor under this paradigm might be 10,000,000, although the highest factor used by the PMRA to date is 3,000.

## Scientific Framework

Irrespective of how “acceptable risk” or “reasonable certainty of no harm” are characterized, RDs should be regarded as scientific hypotheses from which one derives the prediction: if people (or the environment) are exposed to pesticides at levels less than the RDs, the probability of observing a harmful effect should be less than X, where X is one minus “reasonable certainty.” Once “reasonable certainty” is defined, the hypotheses then become testable, at least in principle.

Once an RD is established, the next step is to *test the hypothesis*. If results are inconsistent with the hypothesis, the RD should be revised accordingly. It is important that to the extent that scientific information/data is used to *determine* RDs, the *same* data/information cannot then be used to *test* the hypothesis, as doing so would violate the basic scientific principle of independent validation. This iterative process of hypothesis formulation, independent testing and revision is, after all, what science (including regulatory science) is, or ought to be.

This perspective provides some insight into the extrapolation factors issue. The scientific evidence for: (a) the selected set of issues for which factors are required; (b) the magnitude of the factors themselves; and (c) the multiplicative form of the RD function is scanty at best. Nonetheless, the outcome of this present solicitation is predictable, with those of the view that pesticides pose substantial risks to human health advocating for many, large factors (this will ensure that the reference dose is so small that no pesticide will be registered); those of the view that the risks to human health from pesticides are overblown advocating for a minimal number of factors, each as close to unity as possible (thus reference doses will be comparatively high to allow registrations); and those who are concerned with potential impacts of pesticides on human health or the environment, but who also recognize that some pesticides may be of considerable value, will have difficulties responding. They will understand that the proposed safety/uncertainty factors are highly arbitrary, and that even the form of the extrapolation function – let alone the magnitude of its component parameters – merely represent hypotheses. As such, the distribution of the three classes of responses will depend on the number of people who cleave to positions (a) – (c) (for whatever reason), among those who have decided to respond. In what way, then, can responses to the specific queries be construed as providing epistemological support for a particular policy choice?

Biological science is now showing that assumptions inherent in the toxicological model (e.g. monotonic dose-response relationships, threshold responses) are not always sound. Coupled with the scanty scientific evidence supporting the predictive value of the risk assessment paradigm, the most important issue is not whether the suggested magnitudes of proposed factors, or functional forms, is “reasonable.”

The real issue is: given that RDs – however estimated – are merely hypotheses, how does PMRA intend to test them? It is our view that, hitherto, PMRA (along with almost all other pesticide regulatory agencies) has been far too concerned with *hypothesis formulation*, and far too little concerned with *hypothesis testing*.

## Inadequacy of existing methods for Reference Dose (RD) estimation

As noted above, the starting point for estimation of the RD is classical ecotoxicological risk assessment. All such assessments rely on controlled exposure experiments over a range of doses using a defined set of measurement endpoints, and from these baseline data the RD estimation procedure begins. It is therefore useful to ask, even before addressing the issue of extrapolation factors, whether the starting point is itself adequate and appropriate. There is some evidence to suggest that caution may be warranted even here.

### ***Non-monotonic dose-reponses.***

An assumption in toxicological risk assessment is that the dose-response curve is monotonic. Studies for pesticide assessment are carried out with relatively high doses of chemicals compared to what would be expected under conditions of use. However, it is now increasingly recognized that low dose effects may be different, even opposite, and at least as serious as high dose effects (some peer-reviewed studies are summarized at: <http://www.environmentalhealthnews.org/sciencebackground/2007/2007-0415nmdrc.html>).

Since pesticide assessment includes extrapolating a NOAEL to an acceptable human dose, it may be expected that manufacturers would only wish to explore animal doses that are high enough such that the use would be allowed after application of extrapolation factors. Discovery of low dose effects would mean that the pesticide could not be registered according to the current paradigm. Nevertheless, current science indicates that biologically active substances must be tested over many orders of magnitude of doses to adequately assess the entire spectrum of their effects. It is possible that a NOAEL would be measured at the nadir of a U-shaped response curve, while environmental exposures would trigger significant adverse effects.

It is stated in the consultation document (p 3) that a variety of toxicities are threshold in nature, but these “truisms” are challenged by current knowledge. On the same page, it is noted that “*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.*” On what basis and with what expertise does the PMRA make this complex health-based judgement? How is reliance upon the abilities of organism to adapt to biological or chemical insults consistent with the legislative requirement of “reasonable certainty that *no* harm ...,” since adaptation is almost invariably at a cost and results in increased vulnerability to other insults?

### ***Adequacy of measurement endpoints***

At present, registrants are obliged to provide PMRA with genotoxicity studies. However, pesticide exposure may also lead to epigenetic changes. These epigenetic changes determine which DNA is going to be expressed (and how), and it is now understood that at least some forms of epigenetic variation are heritable, producing multi-generational effects.<sup>6,7</sup>

Neurological outcomes are also difficult to assess and are sometimes not required to be fully explored,<sup>8</sup> although implications are serious for our society.<sup>9</sup>

### ***Cumulative assessments – pesticides in combination or sequence***

The PCPA now requires that cumulative assessments be conducted for pesticides with a common mechanism of toxicity, and this is a work in progress for cholinesterase-inhibiting insecticides. The groundbreaking work of York scientists further highlights the complexity of this topic. They recently demonstrated that exposure to two pesticides had different effects on mortality of *Gammarus pulex* (small shrimp), depending upon the **order of exposure**.<sup>10</sup>

Cumulative toxicities may contribute to inconsistencies between toxicological and epidemiological studies. Although not specifically required under the PCPA, given that information from the PMRA feeds into the Drinking Water considerations, an argument could be made that **the PMRA is indeed required to assess cumulatively effects of pesticides with related effects** (complementary, additive, antagonistic or synergistic). One example might be insecticides that affect nervous systems. Pyrethins affect sodium transport along nerve fibres, and cholinesterase inhibitors affect nerve impulse transmission across the synapse, so it is conceivable that the combined insults to the nervous system

may be much more problematic. **Pesticides that have effects on the same type of cell or organ should be assessed in a cumulative manner.**

Other classes of pesticides such as phenoxy herbicides are not being assessed in a cumulative manner, in spite of the fact that they belong to a common class and are applied as mixtures for a synergistic killing effect. This is not because the chemicals do not have common, complementary or synergistic mechanism of toxicities, but because the mechanism(s) of toxicity are not well understood. However, materials that are chemically similar and have common mechanisms of toxicity in the target organisms may indeed share other toxic effects in non-target organisms. **The risks of pesticides of a common class should be considered to be cumulative.**

*Estimation of exposure* is a major source of uncertainty in epidemiological studies, and contributes to the PMRA opinion that epidemiological studies are not reliable enough to determine whether or not present practices are protective of human health. Significantly however, estimation of human exposure is also key information that contributes to toxicological assessment. The chief improvement in “certainty” between toxicological and epidemiological studies arises from the use of homogeneous populations of animals in controlled environments as opposed to humans of mixed ages, genetics, environments, co-exposures, co-morbidities, etc. This is mentioned in support of our **strong recommendation that epidemiological studies be used in pesticide assessment, or as they become available in subsequent adaptive management of hypotheses.**

Animals in cages are not exposed to sporadic contaminants (e.g. 2,7-DCDD in 2,4-D), or breakdown products (e.g. the plethora of compounds arising from imidacloprid), so toxicology does not assess these important components of the total toxicity and outcomes of pesticide use. Only other research such as epidemiological and environmental evidence will assess these aspects. This research should be supported and carried out.

It is stated on p15, “*It is generally accepted that in the current deterministic model, multiplication of the factors results in a substantial magnification (positive bias) of conservatism.*” This view is not shared by the medical community, given that detoxification abilities of humans may vary more than 10-fold for many reasons, including genetic variability and enzyme levels, with observable consequences as a result of pesticide exposure.<sup>11-20</sup> It is possible that the simplistic, historical approach is overlooking many substantial considerations that actually render it overly optimistic about pesticide safety and underestimate risk. The Swedish Chemicals Inspectorate suggests that factors greater than 10-fold may be appropriate for certain cases, and discusses expansion of intraspecies extrapolation factors into several factors.<sup>5</sup>

**Probabilistic assessment** of a generic sort may be helpful to determine the range of fates of a droplet emanating from a nozzle for instance, but it is a lot less clear how it could be appropriate for estimation of hazard. The consultation document did not specify the methodology for this assessment. However, with reference to methodologies discussed by the Swedish Chemicals Inspectorate,<sup>5</sup> an extensive database is required. Complex mathematics cannot overcome uncertainties inherent in extrapolation from limited animal testing to human health. This methodology would need extensive validation before becoming a primary risk assessment tool, and should not be used to justify human exposures that are substantially lower than exposure estimated using the deterministic model.

## Human Data

Although "*the use of human data in pesticide risk assessment warrants further policy development and will not be dealt with in this document*" p22, **this question is integral to the present considerations.**

Just as it is unethical to condone or encourage dosing of humans with pesticides (e.g. the Children's Environmental Exposure Research Study<sup>a</sup> that was cancelled in the US - <http://www.epa.gov/cheers/>), it seems unethical *not* to consider existing data arising from human poisonings and occupational exposures, to incorporate actual human health effects in decision-making. Even if it is difficult to understand how to use data, it cannot be ignored. Use of such data would not violate the Nuremberg, Geneva and Tokyo Conventions on human experimentation.

Reference lists in reassessment documents lack recent human epidemiological studies and are frequently devoid of reference to human studies. The 2,4-D example<sup>2</sup> has been discussed extensively with the PMRA (private communications through MS - please ask for more information if required), with the Chair of the Canadian Leukemia Studies Group (communications from Dr. Richard van der Jagt <[rvanderjagt@ohri.ca](mailto:rvanderjagt@ohri.ca)> to Dr. Karen Dodds and to MS) and many other physicians now believing, for instance, that there is ample evidence that 2,4-D is linked to cancers, yet it remains in use even for weeds in lawns where children play. A recent example is the dicamba Proposed Acceptability for Continuing Registration document that did not mention recent research linking this specific pesticide to cancers<sup>21</sup> among its handful of references. Other relevant areas of research, such as *in vitro* evidence of endocrine disruption, hormone mimicking, genetic damage and epigenetic effects should also be considered in the course of pesticide (re)assessments.

Humans are exposed to pesticide breakdown products that are not necessarily assessed in laboratory systems. For instance, imidacloprid has a very complex, slow pattern of breakdown, and metabolites/breakdown products may be more toxic than the parent compound.<sup>22</sup> Extrapolation factors cannot capture the harms or substitute for assessment of these daughter chemicals, that aren't necessarily present at environmentally relevant levels in laboratory cages.

Another example is the lack of assessment of malaaxon from malathion. The chemical reaction occurs slowly under laboratory conditions but is rapid in volatilized drift in sunshine. Example #6 does not mention that malathion was reapproved at a *higher* application rate, despite a long history of complaints and even protests in the streets of Winnipeg over harms (e.g. environmental sensitivities and cancers) ascribed to its use. This chemical should be the subject of public health investigations, due to the large number of complaints of health effects, and the high volume of its use in some urban communities. The response of public health officials in Winnipeg, supported by the industry, to complaints about dursban and malathion is basically that the PMRA would not register the chemicals if anyone could be harmed, so the people claiming ill health corresponding to spraying must be wrong.

### Availability of metabolic data

In order for clinicians to have meaningful data to guide clinical decision-making, the main metabolic pathways and enzymes (eg CYP2D6, CYP1A2, PON1) for every pesticide should be known and in the public domain. This would allow for clinicians to assess whether use of specific drugs such as warfarin, and other factors such as smoking, could be contributing to the toxicity of a pesticide in an individual. **We strongly suggest the inclusion of this information on standard package inserts**, as is now occurring frequently with new drugs. If pesticides have common binding sites and/or are metabolized

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<sup>a</sup> The two-year, \$2.1M Children's Environmental Exposure Research Study (CHEERS) was to monitor infants in low-income families to determine how chemicals are ingested, inhaled or absorbed by children up to age 3, as well as the health effects that ensued. Study participants were to receive up to \$970, a T-shirt, a baby bib, a calendar, a newsletter, a framed certificate of appreciation and a video camcorder. Visits and payments were to correspond to pesticide applications. Controls were to represent 10% of participants, who would have lower exposures to pesticides.

by common pathways, it would allow for anticipation and maybe even mathematical modelling of synergistic effects. Knowledge of metabolic pathways in animals would either lend credibility to interspecies extrapolation, or alert regulators and physicians to possible difficulties with human metabolism of a pesticide or breakdown products.

The superficiality of the science relied upon for pesticide assessment is illustrated in the atrazine example #4. The hypothalamic-pituitary function is a fundamental, albeit complex process in the body. It should be of grave concern that a pesticide affects this function. A 3-fold factor was used due to the effect on luteinizing hormone and estrus cycles. Without knowing more details about the mechanisms involved, it is impossible to know how profound this effect will be on people and subsequent generations, and whether or not the factors imposed are protective. It is worrisome that Ottawa tap water contained enough atrazine to interfere with experimental controls in studies of hermaphroditic changes in frogs at the University of Ottawa (personal communication to MS. For more information, please contact Dr. Vance Trudeau <[vtrudeau@science.uottawa.ca](mailto:vtrudeau@science.uottawa.ca)>).

*We are concerned that the questions posed by the PMRA do not address essential systemic problems with risk assessment, but they do raise some interesting issues. The following are responses to the specific questions posed.*

## **1. Nomenclature**

*a) Please comment on the PMRA's proposal to use the terminology "uncertainty factor" to describe factors associated with interspecies extrapolation, intraspecies variation, use of a LOAEL versus a NOAEL, extrapolation for duration of dosing and database deficiencies.*

*b) Please comment on the PMRA's proposal to use the terminology "safety factor" to describe factors applied for the protection of infants and children under the new PCPA provisions (PCPA safety factor) as well as for severity of endpoint considerations.*

All factors are being used to extrapolate from what is known about a homogeneous population of animals under controlled laboratory conditions to humans in the "real world." Thus, we recommend "extrapolation factor" as a general term that is more informative than other options. In addition, factor names could reflect their objective – interspecies extrapolation factor, intraspecies extrapolation factor, etc.

The use of the word "safety" in relation to factors applied to infants and children is inappropriate and unsupported by medical evidence. We note that there are many populations in addition to children also in need of recognition for their individual susceptibilities, such as the elderly or people with otherwise compromised physiology (e.g. from medications, illnesses and environmental sensitivities).

The PMRA has ceased using "safe" in other contexts and should not use it in this context either.

## **2. Interspecies Extrapolation**

*a) Please comment on the PMRA's use of a default factor of 10-fold for interspecies extrapolation.*

There is little more than historical precedent to justify the use of a 10-fold interspecies extrapolation factor. An empirical assessment of the adequacy of a 10-fold default factor would require that the variation in a number of relevant endpoints be explored over a wide range of species. This type of assessment was discussed in the Swedish document,<sup>5</sup> including results that higher factors would frequently be appropriate, depending upon animal model and type of substance. Certainly for some physiological endpoints, which may or may not be relevant to pesticide toxicity, interspecies variation can extend over several orders of magnitude, as many such processes obey power-law scaling relationships with, for example, body size. Ability to excrete pesticides varies between species. For example, it is unclear to us how appropriate it was that 2,4-D data on dogs was not used in the reassessment, because of dogs' relatively lower ability to excrete it.<sup>23</sup> Had that data been used, the pesticide may not have passed the reassessment process. Certainly many people, particularly the elderly, suffer from decreased renal capacity.

Moreover, we know that detoxification enzymes in test animals may be entirely absent in humans, and if such an enzyme was critical for detoxification, the appropriate factor would be 1/0 or infinity.

It is our view that present knowledge is insufficient to conclude that a default factor of 10-fold to extrapolate from laboratory animals to humans is protective for all outcomes. Again, we suggest that the Swedish document<sup>5</sup> should help inform the present deliberations by the PMRA.

*b) When adequate chemical-specific data are available, is it reasonable to generate chemical-specific factors for interspecies extrapolation?*

It is difficult to comment on this proposal without further scientific details. What constitutes “adequate”? To be done thoroughly, this would be a formidable array of knowledge to have and to model, including adequate knowledge of all relevant biochemical pathways, and potential physiological effects and consequences, at all stages of life and in subsequent generations, in all species involved. Such methods would need substantial experimental verification.

The Swedish review mentioned above<sup>5</sup> indicated that such analyses would frequently result in higher extrapolation factors. Chemical-specific theoretical analyses should not be used to reduce the 10-fold factor, but could certainly be used to justify much greater factors, particularly given rodents’ and other animals’ abilities to live in environments that are inhospitable to humans.

### 3. Intraspecies Variation

*a) Please comment on the PMRA’s use of a 10-fold default factor for intraspecies variability.*

A 10-fold factor is not always adequate to cover variability in human responses to pesticide exposures. An intraspecies extrapolation factor should capture the variability of a population’s responses to the toxin. However, the 10-fold intraspecies factor is inadequate to account for individual differences in rates of metabolism of xenobiotics, let alone physiological effects. This factor is less than the factor of genetic polymorphism difference between genetically slow and normal metabolizers.<sup>11-20,24</sup> For example, genetic predisposition to slow metabolism of pesticides is linked to diseases including lymphoma,<sup>25</sup> environmental sensitivities,<sup>11,26</sup> Parkinson’s disease with dementia<sup>27</sup> and childhood leukemia.<sup>20</sup> Moreover, in populations taking medications (particularly the elderly), and even as a consequence of eating some foods such as grapefruit,<sup>28</sup> the metabolic pathways may be completely “saturated” or blocked, leading to a complete shutdown of the pathway and rapid accumulation of phase I metabolites, or the unmetabolized chemical. Compromised excretory pathways, such as renal insufficiency, may also contribute to increased susceptibility to pesticide toxicities. Again, the Swedish document has a large review and commentary, parsing susceptibilities into several areas.<sup>5</sup>

A 10-fold factor is also inadequate to capture sensitization to a pesticide. This happens all too commonly, and is even noted on some labels. For example, the label for an organophosphate insecticide Rabon® states, “Chronic exposure may produce kidney and liver damage. ... Tetrachlorvinphos is a cholinesterase inhibitor. **Repeated exposure to cholinesterase inhibitors may, without warning, cause prolonged susceptibility to very small doses of any cholinesterase inhibitor.** Allow no further exposure until cholinesterase regeneration has occurred as determined by blood test.” (emphasis added)<sup>29</sup> Pyrethrins are also common sensitizers.

Given the wide variability among the human population in susceptibilities to toxicities at various ages and stages, it is our view that current knowledge is insufficient to use a default factor of 10-fold for intraspecies variability. Again, we suggest that the Swedish document<sup>5</sup> should help inform the present deliberations by the PMRA.

*b) When adequate chemical-specific data are available, is it reasonable to generate chemical-specific factors for intraspecies variability?*

As with the above, it is difficult to comment on this proposal without further details, including what would constitute “adequate.” Theoretical analysis should not be used to reduce the 10-fold factor. Such analysis could be used to justify much greater factors as mentioned above, given some people’s limited abilities to metabolize and excrete chemicals resulting from other exposures (drugs, foods, other chemicals), superimposed upon the wide natural variability of abilities to metabolize chemicals between individuals, at various ages and stages of life.

In our opinion, given the current, generally inadequate knowledge of health impacts of individual chemicals, let alone the profound lack of understanding of health effects of interactions of multiple chemicals, it is not reasonable to use chemical-specific factors to justify lower extrapolation factors for intraspecies variability. However, this line of inquiry may highlight needs for higher factors.

#### **4. Use of a LOAEL Versus a NOAEL**

*a) Please comment on the PMRA’s use of a factor of 3- to 10-fold for extrapolating from a LOAEL to a NOAEL.*

In engineering, extrapolation is viewed with great suspicion (e.g. low flow laminar flow patterns and high flow turbulent patterns, or discontinuous reactions of materials to shear or strain render extrapolation meaningless), and is not something upon which one would base a major decision. Interpolation, estimation of a point between two known data points is associated with much greater confidence than estimation of a point beyond the experimental range, particularly without evidence of a monotonic continuous function. Given rapidly expanding knowledge of low-dose effects and non-monotonic dose-response curves, if there is a need to extrapolate from a LOAEL to a NOAEL it should lead at most to a temporary registration of short duration, with no option for renewal. NOAELs should be interpolated rather than extrapolated. The PMRA should require data for at least three dose levels covering an order of magnitude below the NOAEL, and this should include typical environmental exposures (more dose levels may be needed to include “real life” levels in the environment).

*b) Is it reasonable to consider the dose-response curve and the severity of effect in determining the magnitude of this factor?*

If it is necessary to carry out LOAEL-to-NOAEL extrapolation, by definition the dose-response curve is not completely known. We have not examined how this approach has been used by the PMRA but we fear that dose-response curves over low doses and environmental levels are not completely known for most pesticides. LOAEL-to-NOAEL extrapolations may represent serious deficiencies in pesticide assessment, and we would be interested in statistics regarding this practice.

*c) Is it reasonable for the PMRA to use the benchmark dose approach in those situations where the data are well-suited to this modelling?*

Again, the question arises as to the type of model being proposed (there are many) and the meaning of “well-suited.” Models carry with them intrinsic uncertainties, which may be substantial. A parameter estimated via a modelling procedure is a much weaker basis upon which to base a decision, versus one that is directly (or even indirectly) empirically estimated.

This is also the concern that if the criteria for “well-suitedness” of the data to the benchmark dose approach are relatively modest, and the expense of obtaining these data comparatively modest, there will be little incentive for registrants to invest resources to acquire rigorous empirical estimates.

Some benchmark dose approaches model pesticide metabolism, including recovery from the toxicities of pesticides. The question arises that since the model involves calculation of recovery from measurable toxicity, does it fit with the legislative requirement of reasonable certainty of *no* harm to humans ...?

If the legislation were to require merely that there not be lifelong harm but that transitory harm is acceptable, one must ask how it is determined that for all life stages harm is not permanent (e.g. insecticide exposure in utero that is asymptomatic for the mother may cause permanent alterations in the foetus’ brain<sup>9</sup>).

The bottom line is that people, wildlife and the environment are highly complex. The entire range of abilities to metabolize, excrete, produce new enzyme (e.g. acetylcholinesterase), etc. must be modelled, including for the unborn. Some effects cannot be accounted for by primary pathways of toxicity.<sup>9</sup> Thus modelling should not be used to justify decreases in extrapolation factors, and would need to be thoroughly validated.

## 5. Extrapolation of Data for Duration

*a) Please comment on the PMRA’s use of a factor of 1- to 10-fold for extrapolating from a short-term study to a chronic scenario.*

The uncertainties involved in this type of extrapolation are akin to extrapolation from LOAEL to NOAEL. If this is necessary, it should be accompanied with a high extrapolation factor, and lead at the most to a temporary registration of short duration, with no option for renewal.

*b) Is it reasonable to consider factors such as toxicokinetics, toxicodynamics, the nature of the response and ancillary information on durational responses in determining the magnitude of this factor?*

This information might be considered if several conditions were met. What might contribute to strong evidence that effects might be the same over the longer period of time?

- The pesticide and metabolites are very rapidly and completely (>99.9%) degraded in the environment (water, air, soil and indoors) to basic molecules such as carbon dioxide and water. Degradation to more complex chemicals such as 6-chloronicotinic acid (reported to the PMRA for imidacloprid) should not be considered adequate.
- Pesticide and metabolites are degraded/excreted in test animals within less than a small fraction (maybe 10%) of the duration of the chronic study.
- Toxicities were minor and did not involve genotoxicity, endocrine effects including hormones such as pituitary, thyroid, insulin, corticosteroid, androgen and estrogen, other endocrine disruption, effects on the nervous system or nerve cells in vitro, or immunotoxicity.

Note: This is a very preliminary discussion of this issue, presented only as suggested ideas.

## 6. Database Deficiencies

*a) Please comment on the PMRA’s use of a factor of 3- to 10-fold for data deficiencies.*

*b) Is it reasonable for the PMRA to use this factor when missing a “core” study or when missing a study whose need has been triggered by the existing data? (Note: core studies for conventional chemical pesticides include carcinogenicity studies in two different species, one chronic toxicity study, two prenatal developmental toxicity studies and a multigeneration reproduction study).*

We have grave misgivings regarding pesticide registration when there are data deficiencies. The PMRA has been severely criticized in the past for re-approving conditional registrations when important data was lacking.

The proposal to use an extrapolation factor for database deficiencies is epistemologically unsound. It necessarily implies that the results of one study have positive predictive value with respect to the results of *any* (missing) study. This is equivalent to the assertion that every assessable endpoint in a missing study must be positively correlated with at least one endpoint assessed in existing studies. This is a strong statistical condition, one which is, *a priori*, highly unlikely to be true.

While on the topic, another form of data deficiency that is not in the proposal document is the toxicity of breakdown products. It is assumed in some assessments that studies using the parent compound will necessarily expose the animals to all the breakdown products. This is not the case if the pesticide is excreted unchanged and the cages are cleaned. Some assessments include tests of some metabolites, but the rationale for choices of metabolites is unclear, and within a single assessment there may be no consistency between the number or identities of metabolites included in various experiments. This issue could amount to considerable work so resistance from manufacturers must be expected, but unless it is addressed there can be little assurance that no harm will ensue from use of pest control products with complex, prolonged breakdown such as the neo-nicotinoid insecticides.<sup>22</sup>

## **7. Severity of Endpoint**

*a) Please comment on the PMRA’s use of a factor of 3- to 10-fold for severity of effect.*

A finite extrapolation factor for any chemical implies that there is a level at which there is “acceptable risk” or “reasonable certainty of no harm.” In the European Union, legislation is being read that would require that a pesticide that has any of the effects listed in 7(b) be rapidly phased out (see <http://www.europarl.europa.eu/oeil/file.jsp?id=5372322>). The reasoning is that there is no “safe” exposure to chemicals that cause irreversible or severe effects such as reproductive toxicity, developmental toxicity, nongenotoxic carcinogenicity or mortality.

*b) Is it reasonable for the PMRA to use this factor, as described above, for irreversible or severe effects such as reproductive toxicity, developmental toxicity, nongenotoxic carcinogenicity or mortality?*

*c) Is it reasonable for the PMRA to use this factor, as described above, for less severe effects such as endocrine disruption or immunotoxicity?*

Endocrine disruption and immunotoxicity can have severe chronic repercussions, and are common non-genotoxic mechanisms promoting development of cancers. We are unaware of scientific justification for this distinction in “severity.” This distinction is not made in Europe. Application of a lower factor for these outcomes is not justified.

## **8. Multiplication of Uncertainty and Safety Factors as well as Upper Limit of Factors**

*a) Please comment on the PMRA's proposal of an upper limit of 3000 for an overall assessment factor.*

We concur with the opinion that if an extrapolation factor is too high, that the process is not credible. However, the answer is not to impose an arbitrary cap on the factor. Pesticides with so much data lacking and/or reasons for concern that they would incur a larger extrapolation factor simply should not be registered until the data gaps have been filled in. The factors that are unavoidable within the PMRA's current methodology under discussion, are due to scientific limitations and uncertainties in the application of animal toxicology to human health. These are the interspecies, intraspecies, and vulnerable populations factors. This amounts to a 1000-fold factor. Any additional factors represent serious data deficiencies and/or severe outcomes.

*b) Please provide any guidance relevant to minimize "double-counting" or to address the compounding conservatism of multiplying factors.*

As described above, current extrapolation factors (interspecies, intraspecies, etc.) do not cover the range of metabolic abilities and responses to toxic exposures of vulnerable populations. Further factors reflecting data deficiencies should trigger more study. Serious endpoints should trigger deregistration. We do not see that conservatism in terms of health protection necessarily ensues from the present model; indeed in some cases the opposite may be the case.

## **9. Factors for the Protection of Infants and Children under the New PCPA Provisions**

*a) The PMRA interprets the new PCPA provisions as requiring a presumptive application of the 10-fold factor for the protection of infants and children. Please comment on whether this presumptive application satisfies the obligations of the new PCPA provisions.*

The new PCPA requires a very high degree of protection, and the 10-fold factor for children is one way to implement that. However, given the uncertainties in the science it is not possible to state that the obligations of the new PCPA are being met using only toxicological risk assessment.

When toxicological science leaves us with excessive uncertainties, we must complement that area of science with other disciplines and bodies of knowledge, such as epidemiology and basic scientific studies.

When there are doubts, the new PCPA would seem to require that vulnerable populations be given greater protection whenever possible, such as restricting use to only industrial/farm settings and further restricting or prohibiting uses in the vicinity of schools, hospitals, residences etc. The new PCPA provisions would be better met if pesticide registrations were restricted to fewer least-toxic approaches to pest control.

*b) Please comment on the PMRA's use of the PCPA safety factor as it relates to completeness of the data with respect to the toxicity of infants and children.*

We do not recommend that pesticides be approved without complete data regarding infants and children. However, if it is determined that the pesticide assessment will proceed without this data, a very high extrapolation factor should be applied. To do otherwise would be to assume that the results will be favourable before the fact, and would act as a disincentive to developing the data. As explained in the proposal document p 28, extrapolation factors due to data deficiencies may be an incentive for a company to produce data, only if that factor is reduced as a consequence of the research. This highlights a systemic problem with the program of manufacturer-produced data. The most effective incentive to fill in data gaps would be not to register (this is recommended) or at least to put a strict time-limit on the registration. There

should also be the equivalent to trial registration for drugs, to attempt to reduce non-disclosure of unfavourable findings. Certainly pesticides lacking information regarding infants and children should not be used in areas they may frequent.

*c) Please comment on the PMRA's use of the PCPA safety factor as it relates to prenatal or postnatal toxicity concerns.*

At this point, we should explain that there are three areas of concern to be captured by extrapolation factors addressing human health.

Firstly, there are well known vulnerabilities of children due to their immature metabolic systems, developing bodies, thinner skins, crawling and hand-to-mouth behaviour, etc. These are discussed in relation to the 10-fold factor in a).

The uncertainties discussed in b) relate to essential data, and this data should be developed and examined before a product is registered, particularly if it is to be used frequented by children or on foods.

Known additional prenatal or postnatal concerns are not covered in the above two sub-questions. If there are known concerns and still important data gaps this might strongly suggest that the pesticide should not be registered, or at a minimum a substantial additional extrapolation factor is justified, with the same discussion as in b) above.

*d) Is the PMRA's revised assessment scheme (see Appendix 1) reasonable, transparent, and consistent with the new PCPA provisions?*

No. As described above, children's vulnerabilities, data gaps, and known prenatal and post-natal concerns are independent issues and merit separate studies and therefore independent extrapolation factors.

## **10. Application of Uncertainty and Safety Factors to the Working Population**

*a) Is it reasonable for the PMRA to apply uncertainty factors for interspecies and intraspecies variation, LOAEL-to-NOAEL extrapolation, extrapolation for study duration and database deficiencies to occupational risk assessment?*

The PCPA rightfully does not distinguish between occupational and non-occupational exposures. Workers have as much right for their health to be protected in the course of their duties as anyone else. Workers include pregnant women, and their foetuses must be protected as any others. Some of the most sensitive developmental windows for the foetus occur while the woman may be unaware that she is pregnant, so the highest level of protection is required for workers as for other citizens.

Workers may be required to use pesticides, whereas it is the choice of a homeowner to use or not to use a pesticide. Any user of a pesticide is required by law to follow label instructions including personal protection, but it is well known that pesticide residues are brought home on the clothes and boots, and in and on vehicles, by professional applicators and on the farm. Children and spouses may be exposed in homes and vehicles, and washing the laundry.

Bystanders of any pesticide application will not be taking the same protective measures as applicators, and they must also be protected. They may be unaware of the pesticide use, and children and animals cannot read signs to avoid re-entry of properties. Homes and workplaces may be contaminated over long periods of time as pesticides degrade extremely slowly indoors.

Whether exposure is intentional or incidental, in the course of work, play or just plain day-to-day living, all humans deserve the high level of protection required by the PCPA.

Thus, yes the same factors should be applied, as a minimum.

*b) Is it reasonable for the PMRA to apply the 10-fold factor in the new PCPA provisions to the pregnant/nursing worker in those cases where there is incomplete data to characterize the hazards to the fetus/infant or where a prenatal or postnatal concern has been identified?*

*c) Is it reasonable for the PMRA to apply a safety factor for severity of effect to occupational risk assessment?*

As discussed in a), yes, as a minimum

## Conclusions and Recommendations

The Ontario College of Family Physicians believes that Canada should be working towards use of only least-toxic, lowest environmental impact, best practice methods and products for pest control. The present pesticide risk assessment process is intended to ensure that there is “reasonable certainty” that use of a pesticide under particular conditions will cause no harm to human populations, future generations or the environment.

The essence of science is to test hypotheses. Until and unless the risk assessment hypotheses are scrutinized as to their validity using independent data (e.g. epidemiology and basic scientific chemical effects studies), Canada cannot claim to have a “science-based” pesticide assessment system.

Some uncertainties inherent in pesticide assessment are meant to be captured in independent extrapolation factors (“safety” is no longer used by the PMRA in other contexts and should not be used in this context either).

- Extrapolation factors may be used to extrapolate from animal to human data, with the caveat that when animals have detoxification enzymes which humans do not possess, this extrapolation may be suspect.
- Extrapolation factors are used to attempt to account for variation amongst human susceptibilities at various ages and stages, from the foetus to the elderly, from the most robust to those with genetic predispositions to poor metabolism of pesticides.
- We are concerned that some serious effects such as epigenetic changes are not examined at all.
- Intra- and various inter-species susceptibilities each can vary over much more than an order of magnitude. Thus, it is clear that 10-fold factors do not envelop the range of susceptibilities to toxic effects seen between laboratory species and humans, amongst adult humans, or amongst humans over the course of a lifetime.
- Workers certainly may be pregnant or nursing, and workplace daycares are common; these people deserve the levels of protection afforded all others.

Given the large uncertainties arising from current limited knowledge of health science, other data deficiencies should be minimized to the greatest extent possible.

- Due to possible non-monotonic dose effects, RDs should be within the range rather than outside of the range of dose-response data. This data should also include environmental levels. LOAEL-to-NOAEL extrapolation should not be used in full registrations if at all.
- Extrapolation from short-term to long-term data should at most be considered for a one-time brief temporary registration, subject to a large extrapolation factor, *and* subject to strict criteria.
- Endocrine disruption and genotoxicity should be considered to be equally serious as carcinogenicity. Traits that contribute strongly to development of cancers as well as other common chronic conditions should be treated as seriously as cancer. These traits are not nuanced as to seriousness in Europe, where they may lead to deregistration. This should be the case in Canada.
- Interpretation of PCPA 2002 requirements for cumulative assessments should be expanded. Pesticides that affect a common type of cell or tissue should be assessed such that the combined effects are examined (e.g. insecticides that affect nerve cells). As well, pesticides that exert a common mode of toxicity on target organisms (e.g. phenoxy herbicides) should be assessed such that total doses are not excessive within the risk assessment process.

The vast majority of data for pesticide assessment is generated by the registrants.

- Metabolic pathway information should be determined, and included in standard package inserts
- The PMRA should institute the equivalent to trial registration for drugs, to ensure direct access to complete data sets, and to address potential non-disclosure of unfavourable findings.

Only with such a system, with measures adopted or proposed in large measure in many European countries, can the PMRA implement the PCPA 2002, and can Canada claim to have a robust system protecting Canadians, second to none.

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