Response to 2.1.1 Additional Clarification

***Note:** Canadian Pest Control Product legislation requires application of additional uncertainty factors to the endpoints that are selected for assessing health risks from potential pesticide residues in food, as well as for handling the pesticide, or from products used in or around homes or schools. In addition to factors that account for inter-species extrapolation and intra-species variation (typically 100-fold combined), the Pest Control Products Act requires the application of an additional 10-fold factor to threshold effects. This factor takes into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre- and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

Refer to: The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides, which describes how Health Canada's Pest Management Regulatory Agency addresses uncertainty and variability in the mammalian toxicity database in the human health risk assessment of pesticides.

http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/spn2008-01/index-eng.php

Other statutes/risk assessment programmes of Health Canada have a similar risk-based approach.

Examples 1 & 2:
NOTE: The following 2 examples provide links and background information to risk assessment documents for compounds that have endocrine activity and/or reproductive toxicity, but indicate acceptable health and environmental risk.

(1) Re-evaluation of Atrazine (Health Assessment):
http://www.hc-sc.gc.ca/contact/order-pub-commande-eng.php?title=PMRA (PACR2003-13) Re-evaluation of Atrazine

Human health reference doses for atrazine were based on no observed adverse effect levels (NOAEL) for the most relevant endpoints, namely attenuation of the LH surge, estrous cycle alterations and developmental effects. These reference doses incorporated uncertainty factors to account for extrapolation between rats and humans and for variability within human populations, as well as an additional safety factor (see above) to provide an extra level of protection for the potential neuroendocrine modulating effects of atrazine.

Dietary and non-dietary exposures were well below the reference levels - no health risks of concern were identified.

Re-evaluation of Atrazine (Environmental Assessment):
http://www.hc-sc.gc.ca/contact/order-pub-commande-eng.php?title=PMRA (PACR2007-05) Re-evaluation of Atrazine (Environmental Assessment)

The re-evaluation of atrazine identified a potential risk to salmon smolts during their sensitive migration period from freshwater to seawater.

Additional information was provided and a refined assessment examining salmonids undergoing smoltification and migration was conducted using water monitoring data from tributaries located in areas of use.

The environmental risk assessment was based upon an evaluation of a registrant sponsored study as well as published studies relevant to assessing the exposure risk of salmon smolts to atrazine during the sensitive smolt migration period, that were not available for the initial atrazine re-evaluation. The PMRA determined an appropriate endpoint for the atrazine aquatic risk assessment for migrating salmon smolts; this endpoint is based on significant reduction in growth rate observed during the first month in seawater (Nieves-Puigdoller et al. 2007), an effect that could potentially result in reduced survivorship and reproduction due to increased predation and/or a reduced ability to compete for food sources.

Environmental monitoring data showed that environmental concentrations were below this endpoint and the resulting conclusion was that atrazine is not expected to pose an unacceptable risk to salmonids undergoing smolt migration in those areas.

Outcome of Quantitative Risk Assessment for Atrazine: Continue Registration

(2) Re-evaluation of Myclobutanil (Health & Environment Assessment):
http://www.hc-sc.gc.ca/contact/order-pub-commande-eng.php?title=PMRA (PRVD2010-14) Myclobutanil

Reference doses for human health risk assessment were based on NOAELs for the most sensitive indicators of toxicity, namely testicular effects (atrophy and decreased weight), and fetal effects (increased resorptions/litter and decreased viability index) in rats. Reference doses incorporated uncertainty factors to account for extrapolating between laboratory animals and humans (100-fold), and in the case of females 13-49 years of age (for dietary and occupational exposure), a further 10-fold PCPA factor (see above) was retained to account for the demonstrated fetal sensitivity and seriousness of the endpoint (fetal deaths in rat developmental study) in the presence of minor maternal effects.
ARfD = NOAEL from rat developmental study & 1000-fold Uncertainty Factor
ADI = NOAEL for testicular effects in chronic rat study & 100-fold Uncertainty Factor, which was protective of the more significant testicular effects in the rat reproduction study.

Dietary and non-dietary exposures were well below the reference levels - no risks of concern were identified.

Note: There were no environmental issues with myclobutanil.

Outcome of Quantitative Risk Assessment for Myclobutanil: Continue Registration

Example 3:
NOTE: The following example provide links and background information to the risk assessment document for a neurotoxic endocrine active compound that indicated unacceptable health and environmental risk.

(3) Re-evaluation of Lindane - Health and Environmental Risk Assessment:
http://www.hc-sc.gc.ca/contact/order-pub-commande-eng.php?title=PMRA (REV2009-08) Lindane

Reference doses for human health risk assessment were based on concerns regarding endocrine modulation, neurotoxicity (damage to the central nervous system and altered hormone levels in developing animals at doses that were not toxic to the mother), and the overall evidence that suggested increased toxicity following repeated exposure. For repeated exposures (dietary and occupational), the 10-fold PCPA factor* (see above) was retained - (i.e., target =1000)

The environmental risk assessment was based on adverse reproductive / developmental effects in fish and small wild mammals (skewed sex ratio, smaller testes, lower levels of testosterone, lower number of sperm and spermatid, reduced sexual behaviour and absence of ejaculation in male offspring). The risk quotients (RQs) based on endocrine-disrupting effects ranged from 15 to 404 indicating that the level of concern was exceeded.

Outcome of Quantitative Risk assessment for Lindane: Registration discontinued