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Children's Health Priorities within the Pest Management Regulatory Agency

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Pesticides are carefully regulated in Canada through a coordinated federal and provincial regulatory network that delivers a program of pre-market scientific assessment, enforcement, education, and information dissemination. To prevent the use of pesticides from adversely affecting Canadians' health or their environment, the Pest Management Regulatory Agency (PMRA) assesses the human health and environmental safety of pest control products prior to their use in Canada. The PMRA's assessments allow the identification of potential hazards and risks to health and the environment. Once a pesticide has been registered, monitoring and compliance programs, by both the PMRA and the Canadian Food Inspection Agency (CFIA), ensure the proper use of pesticides and the safety of our food supply.

The PMRA has recently published a document describing the framework that guides the assessment and management of risks from pesticides, Science Policy Notice SPN2000-01 (Technical Paper): *A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency*, December 22, 2000. It can be found at www.hc-sc.gc.ca/pmra -arla or by contacting the Publications Coordinator.

The PMRA's human health risk assessments address the Canadian population in general and subpopulations such as women of child-bearing age, pregnant and nursing women, infants and children. Infants and children have been a special consideration in our risk assessments for many years. Recent advances in scientific understanding reaffirm that children are not "little adults" and must be considered as a discrete subgroup. Two elements distinguish infants and children from the adult population:

1) Biological considerations. The developing fetus, infants, and children are in a state of rapid growth with cells dividing and organ systems developing. Some organ systems mature in early childhood and others are not fully developed until adulthood. Children have a higher ratio of skin surface area to body weight than adults and on a weight for weight basis, children eat more food, drink more water, and breathe more air, than adults. As a result of these biological differences, children may absorb, metabolize, and excrete chemicals differently than adults do, potentially resulting in differing levels of susceptibility to chemical hazards.

2) Unique exposures. In addition to exposure through minute residues that may remain on some food, such as fruits and vegetables, children may be exposed to pesticide residues in breast milk, formula, through skin contact with treated surfaces while crawling and playing, and through incidental ingestion from behaviours such as hand to mouth transfer.

In all cases where the use of a pesticide could result in exposure of children, the PMRA considers the unique biological characteristics and exposure patterns of children in its risk assessments.

Key child-specific considerations are:

1. When assessing risks from pesticide residues in food, additional safety factors for infants and children are applied where warranted. This is to ensure protection of vulnerable subpopulations.
2. Available information on aggregate exposure from a single pesticide is considered. This includes exposure through dietary and drinking water sources and other non-occupational exposures such as arise from use in and around homes.
3. Available information on cumulative effects of pesticides with a common mechanism of toxicity is considered.

Assessment of Risks to Human Health

The primary reason for conducting an assessment of risks to human health is to ensure that the pesticide will not cause adverse effects on human health. All pathways of children's exposure, including dietary, drinking water, and residential exposures, are considered in the risk assessment. The following steps are undertaken in a risk assessment.

Hazard Identification

The first step in the health risk assessment process is the hazard identification, which provides a thorough understanding of the toxicological profile of the pesticide. Animal toxicity studies are the main source of information for identifying hazards (toxic end points or adverse health effects) and for determining the relationship between dose and response. Extensive toxicity studies conducted in laboratory animals must be submitted by the manufacturer to support pesticide registration. Scientists at the PMRA perform a comprehensive evaluation of these studies. The evaluation assesses the possible adverse health effects that may result from a single, multiple, or lifelong exposure. These studies are designed to allow the assessment of acute, short-term, and long-term toxicity, including the potential for causing cancer, genetic alterations, neurotoxicity, reproductive effects (including endocrine disruption), and effects on pre- and post-natal development. All routes of exposure are considered, including ingestion, skin absorption, and inhalation. All studies must be conducted according to internationally accepted guidelines and are subject to strict quality controls.

In order to fully understand any potential impact relating to child health, the effects of a pesticide are studied in laboratory animals from pre-conception through to adulthood. Reproductive toxicity studies, which are conducted over at least two generations, are designed to generate information on possible effects on offspring growth and development and on reproductive parameters such as fertility. Animals are typically fed diets containing the pesticide prior to and during mating and throughout pregnancy and lactation; offspring receive the pesticide through the maternal milk supply, until weaning, following which they also receive the treated diet before and during mating and throughout pregnancy and lactation.

Pesticides are also tested in two species of laboratory animals to determine whether they may cause adverse effects in the developing fetus. In these developmental or teratology studies, the test substance is administered to pregnant animals during the most sensitive stages of development of the embryo and fetus. These studies provide evidence regarding toxicity to the embryo and fetus, as well as to the pregnant animal. The reproductive toxicity studies and the developmental studies provide essential information on potential sensitivity of the young. This information is considered in the risk assessment. Potential sensitivity of the young or evidence of neurotoxicity will trigger the requirement for submission of a developmental neurotoxicity study. This type of study is designed to specifically investigate potential effects on the developing nervous system, and allows any potential risk to the developing nervous system to be evaluated.

All experimental toxicity studies are designed to define toxic effects, i.e., which dose levels cause effect and which levels do not. The highest doses used in the studies are generally several orders of magnitude higher than what humans are exposed to.

The No Observed Adverse Effect Level (NOAEL) refers to the highest dose of a pesticide at which no adverse effect was observed in animal toxicity studies.

Dietary Risk Assessment

Before a pesticide is registered for use on food crops, the PMRA must determine whether there would be unacceptable adverse effects if people were exposed to residues that might remain on the food. Three pieces of information are needed to conduct this assessment. The first is the level that could be ingested without causing adverse effects, the second is the amount of residue that would remain on the food when the pesticide is applied according to label directions, and the third is the amount of pesticide a person would consume if the pesticide were registered.

To determine the level that could be ingested safely, the PMRA establishes reference doses for acute and chronic exposure. The starting point for calculating the reference dose is the No Observed Adverse Effect Level (NOAEL) from an animal toxicity study that is representative of the route, frequency, and duration of human exposure. For an acute reference dose (ARfD), the end points typically chosen are ones that are seen in a single-dose toxicity study or, although detected in a repeat-dose toxicity study, could possibly be induced by a single exposure. For a chronic reference dose, which is called an Acceptable Daily Intake (ADI), the NOAEL is typically selected from a repeat-dose toxicity study and reflects an end point usually associated with prolonged or continuous exposure. A reference dose must take into account uncertainties arising from the extrapolation of effects observed in animals to potential effects in humans. It also considers that some humans in the population are more sensitive to potential effects than others. Reference doses therefore incorporate a 10-fold safety factor to account for extrapolation from animals to humans (i.e., interspecies) and an additional 10-fold safety factor to account for the variation within the human population (i.e., intraspecies). In this way, the calculated reference dose for humans (NOAEL divided by the safety factors) is a minimum of 100 times lower than the dose that caused no adverse effects in animals.

Acute Reference Dose (ARfD) is the amount of a pesticide that can be consumed in a single day with no adverse effect in humans.

Acceptable Daily Intake (ADI) is the amount of a pesticide that can be consumed daily for a lifetime with no adverse effect in humans.

In addition to the two 10-fold safety factors, additional safety factors are often applied to address the severity of the toxicology end point, sensitive subpopulations, and any concern or uncertainty about the precision of toxicity and exposure estimates. The increased sensitivity to a pesticide experienced by the young, as well as the exposure of infants, children, and pregnant women, are considered during the risk assessment process. This is done in order to provide additional protection where warranted and is consistent with the practice established by the U.S. *Food Quality Protection Act* (FQPA) of 1996. Where reliable scientific data are available, a case-specific determination as to the size of the additional safety factor is used. This approach is consistent with that of the U.S. Environmental Protection Agency (EPA).

The second piece of information, i.e., the amount of residue remaining on food after pesticide is correctly applied, is determined from residue trials that are conducted and submitted in support of registration. From these data, the PMRA determines the type and quantity of pesticide residues that could remain on crops at the time of harvest or after processing, and in meat, milk, or eggs. These potential residue levels vary from undetectable to a few parts per million, depending on the use pattern and nature of the pesticide.

The third piece of information is the amount of pesticide a person might ingest. To establish this, current food consumption data are used to determine the quantity of various food commodities (e.g., fruits, vegetables, grains, meat, milk, and eggs) eaten by different age groups. The unique food consumption patterns of infants and children, including breast milk, formula, and fruit juice, are used in the risk assessment.

Most food has no detectable pesticide residue. Therefore, the comparison of "maximum potential exposure" with the reference dose is a conservative means of determining the acceptability of risk. It is done to ensure safety.

The estimated total consumption of the residues from all food uses for which the pesticide would be registered is used to determine the maximum amount of dietary exposure. All dietary risk assessments are based on the calculated maximum potential exposure through all sources in the diet, including drinking water. The determination of whether the exposure is acceptable is made by comparing the estimated human dietary exposure to the reference dose. Exposures that fall below the reference dose are considered to provide sufficient margins of safety and are unlikely to be associated with unacceptable risk to health. Dietary risk assessments are conducted for various age groups as shown in the following table and include child-specific determinations.

Age-specific groupings for the dietary risk assessments

Infants	<1 year
Children	1–6 years
Children	7–12 years
Females	13–19 years
Males	13–19 years
Females	20+ years
Males	20+ years
Seniors	55+ years

Residential Risk Assessment

Some pesticides can be used in and around homes and schools. For these uses the PMRA assesses potential exposure to women of child-bearing age, pregnant and nursing women, infants and children, as well as the general population. Infants' and children's exposures from all routes and pathways are considered, as well as their unique behavioural and activity patterns. These assessments factor in potential exposures from inhalation, skin contact, and incidental ingestion resulting from behaviours such as ingestion of soil after transfer from hand to mouth. Scientists at the PMRA conduct a critical review of exposure studies or estimates based on surrogate studies, submitted by the manufacturer, to assess potential exposures. The data/studies used for exposure estimates include pesticide use data, activity pattern survey data, passive dosimetry and biological monitoring studies, transferable residue studies, dermal absorption studies, data from validated databases and models, and packaging integrity data.

Internationally accepted guidelines for conducting these exposure studies and deriving exposure estimates for infants and children are followed. Guidelines for conducting exposure studies are being refined as the science evolves. For example, through the North American Free Trade Agreement (NAFTA) and the Organisation for Economic Co-operation and Development (OECD), progress is being made on developing an internationally harmonized guidance document for assessment of post-application exposure.

The health risk assessment for residential scenarios compares the human exposure estimates to the most relevant end points and NOAELs from the animal toxicology studies, ensuring all appropriate uncertainty and safety factors are applied. The results of the exposure and risk assessment provide the PMRA with important information on ways to reduce potential exposures to infants and children (e.g., child-resistant packaging, longer reentry intervals), and such measures are factored into the PMRA decisions and recommendations, wherever appropriate.

Aggregate Risk Assessment

For each single pesticide, the PMRA also considers the potential risks arising from exposure from multiple pathways and relevant routes. This type of assessment, known as an aggregate assessment, includes exposure from all food residues, drinking water, and other non-occupational exposure sources such as arise from use in and around homes and schools. The PMRA and the U.S. EPA have cooperated in the development and implementation of methods for aggregating dietary, drinking water, and residential exposures in health risk assessments; there is ongoing cooperation to refine these methods.

Cumulative Risk Assessment

The combined effects (cumulative risk) to human health that can result from exposure to pesticides with a common mechanism of toxicity must now be considered. A standardized approach and appropriate methods to conduct cumulative risk assessments for pesticides with a common toxic mechanism are under development in the PMRA and the U.S. EPA, and will be implemented as the science allows.

International Activities

The PMRA is working with the U.S. EPA under the umbrella of the NAFTA Technical Working Group on Pesticides to refine approaches in assessing residential residues. Together with the U.S. EPA scientists, the PMRA scientists provide expert guidance to several task forces which have been created to generate data to refine residential exposure estimates for infants and children. For example, the Outdoor Residential Exposure Task Force (ORETF) has developed and validated methodology to generate transferable residue data on treated grass, has conducted a comprehensive survey of residential use of lawn and garden pesticides, and is investigating approaches to refine exposure estimates for children playing on treated grass. Other task forces are focusing on the indoor environment. The culmination of these efforts will be improved methods and data for deriving exposure estimates for infants and children.

As mentioned earlier, the PMRA and the U.S. EPA are working to further develop and refine methods for aggregating dietary, drinking water, and residential exposures in their health risk assessments, and the capacity to consider any cumulative risks from chemicals with common mechanisms of toxicity.

Internationally, toxicology study protocols and requirements are continually being refined to keep up with scientific advancements. Even though the registration of new pesticides requires extensive studies on reproduction and long-term toxicity, additional new screening studies will further enhance our capacity to identify potentially adverse effects of pesticides in their pre-market assessments. For example, specific screening tests for detecting endocrine disruptors have been developed and are in the process of being validated. These new tests will enhance the ability to detect any potential for interfering with normal endocrine function. The PMRA participates in the development of international guidelines for the conduct of toxicity studies via the OECD, a key international body.

Federal Government Initiatives

Several federal departments play an important role in children's environmental health, and various activities are underway to ensure coordination of these activities. The PMRA participates in an Interbranch Working Group on Child Health, which meets regularly to exchange information and to ensure a coordinated response to emerging issues. Membership includes representatives from key Health Canada branches as well as from Environment Canada. The working group is currently involved in conducting an inventory of existing departmental activities related to children's environmental health, to determine whether there are gaps that need to be addressed.

The PMRA also participates in a Working Group on Children's Environmental Health (WGCEH), established under the federal Memorandum of Understanding on Science and Technology for Sustainable Development. The purpose of the WGCEH is to ensure that consideration of children's special vulnerability to environmental risks is incorporated into the federal government's environmental protection regime. The WGCEH promotes cooperation and coordinated action among the five natural resources departments, on needs, opportunities, collaborative science, and related policy issues with respect to child health and environmental contaminants. In May, 2000, the working group sponsored a workshop to identify emerging needs and gaps in federal activities on children's environmental health, and to strengthen coordination and collaboration among federal departments and agencies on children's environmental health.

A Coordinated Approach

Providing input to research, developing new policies on considering children's health in risk assessments, and staying abreast of all children's environmental health issues continue to be priorities for the PMRA. Our everyday decisions from both dietary and residential standpoints give key consideration to the uniqueness of children. The involvement with initiatives both intra- and inter-departmentally will ensure we remain strongly linked with emerging issues and policies. Internationally, scientists from the PMRA are working to define and refine state-of-the-art methodology to make certain our decisions are fully protective of children.