Consideration of endocrine-related effects in risk assessment

Fact sheet series: Topics in risk assessment of substances under the *Canadian Environmental Protection Act, 1999* (CEPA)

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The endocrine system

The endocrine systems (also called hormone systems) of living organisms, including humans, are highly specialized and intricately timed systems that control critical physiological processes. The endocrine system consists of a network of specialized cells and glands distributed throughout the organism, which release signaling molecules called hormones. The hormones act through receptors in target organs and tissues that are specialized to recognize and respond to specific hormones. Glands in the endocrine system of humans and other mammals include the hypothalamus, pituitary gland, thyroid gland, adrenal glands, ovaries, testes, pancreas, pineal gland, parathyroid gland, and thymus.

The endocrine system regulates a variety of biological processes in the body at all life stages. Dozens of hormones and hormone classes involved in these processes have been identified in humans and other living organisms. Some examples of the biological processes controlled by endocrine systems and the hormones involved include:

- development and functioning of reproductive organs (for example, estrogen and testosterone)
- regulation of metabolism and nutrient balance (for example, insulin and thyroid hormones)
- co-ordination of circadian rhythms, hibernation, and insect metamorphosis (for example, melatonin)
- response to stress and changing environments (for example, cortisol and adrenaline)

Endocrine-related effects of substances

CEPA defines a hormone disrupting substance as a substance having the ability to disrupt the synthesis, secretion, transport, binding, action or elimination of natural hormones in an organism, or its progeny, that are responsible for the maintenance of homeostasis, reproduction, development or behaviour of the organism.

Certain substances (natural or synthetic) can interfere with the function of endocrine systems. Such effects, referred to as endocrine-related (or hormone-related) effects, can occur when substances mimic natural hormones, prevent hormones from reaching their targets, or change hormone metabolism. In some instances, interference with the function of the endocrine system can be a mode of action by which substances may cause adverse effects in living organisms. Substances that cause changes in endocrine function that result in adverse effects to an organism are referred to as endocrine disruptors.

Given the fundamental role of hormones in the lifecycle of humans and other living organisms, the biological effects of endocrine-disrupting substances can be of concern. Studies have shown an association between exposure to certain endocrine-disrupting substances and a range of effects in humans and other living organisms. Adverse effects may include: delayed, altered or impaired intellectual, sexual, immune or nervous system development; impaired ability to reproduce or produce healthy offspring; and increased susceptibility to certain cancers. Endocrine-disrupting substances may have the most pronounced effects during early developmental periods (such as, prenatal and early postnatal development) when hormone-sensitive systems are developing. Further, such exposures during critical periods of development may result in long-term and possible multigenerational changes in function.

Use of data on endocrine-related effects in assessment

Consideration of endocrine-disrupting properties and endocrine-related effects continues to be an important aspect of chemicals management under CEPA, both in prioritizing substances for assessment, and in characterizing the hazard of those substances. For example, potential for hormone receptor binding was considered when prioritizing substances for assessment through the Ecological Risk Classification of Organic Substances Approach.

Information on endocrine-related effects has been considered in the risk assessments of many substances including: perfluorooctanoic acid (PFOA) and its salts, polybrominated diphenyl ethers (PBDE), hexabromocyclododecane (HBCD), nonylphenol and its ethoxylates, bisphenol A (BPA), and certain flame retardants.

Endocrine properties and endocrine-related effects data used in assessment can come from standard (in vivo) laboratory toxicity studies using animals. Data can also come from laboratory studies that document effects at the gene and cellular level in a controlled environment such as a test tube, culture dish, or elsewhere outside a living organism (in vitro). Endocrine disruption data may also come from predictive computer models (which are based on chemical structures), and to a lesser extent, from field studies or epidemiological studies that consider exposures and effects to wildlife and humans, respectively. Currently, most internationally-standardized in vitro laboratory studies focus on a limited number of endocrine pathways, namely the estrogen, androgen, thyroid, and steroidogenesis pathways.

Standard laboratory toxicity studies primarily provide information on endocrine-related effects that occur at the whole-organism level, and typically include endpoints such as growth and development/maturation, reproduction, carcinogenicity, neurotoxicity, thyroid or other organ effects, or changes to blood biochemistry. Effects observed in these types of tests may occur through various modes of action. It is not always known whether these effects are a result of interference with the normal functioning of the endocrine system or some other mode of action such as effects related to cell regulation or development (such as effects on cell membranes or on certain genes). In vitro tests and predictive models can help identify whether endocrine systems may be involved. These types of information are considered within assessments carried out under CEPA. However, a full understanding of the mode of action is not required in order to take into account potential endocrine effects in an assessment.

Risk assessment includes consideration of the adverse effects of a substance (including those caused by endocrine-disrupting substances) as well as the potential exposure. The ratio of exposure to the no adverse effect level is estimated in order to determine if substances may be harmful. In human health risk assessments, uncertainty factors are considered in the risk calculation which take into account the particular sensitivity of the endocrine system and the potential for irreversible adverse effects. The acceptability of the resulting ratio, referred to as the margin of exposure, is determined by taking into consideration the magnitude of the margin in the context of uncertainties in the health effects and exposure information. In ecological risk assessment, information on endocrine-related effects is one line of evidence that is considered in the overall weight of evidence, and can be used in the determination of the predicted no effect concentration in the environment. Weight of evidence and precaution are applied in both human health and ecological risk assessments.

Advancing the consideration of endocrine-disrupting chemicals in risk assessment was discussed at a Chemicals Management Plan Science Committee meeting in July 2018; observations and recommendations are provided in the Committee's report.

Research on endocrine-disrupting substances and endocrine-related effects

CEPA, in subsection 44(4), places mandatory obligations on the Minister of Health and the Minister of the Environment with regard to research on hormone disrupting substances.

Health Canada and Environment and Climate Change Canada maintain active scientific research programs that contribute internationally to advancements in the field of endocrine disrupting substances through various research activities. This research includes the development of toxicity test methods through the Organisation for Economic Co-operation and Development (OECD) to assess substances for endocrine disruption and resulting effects. This research routinely informs the identification of new priorities for further action and assessments carried out under CEPA.

Canadian researchers and regulators are also collaborating with international partners on the development and use of novel technologies and approaches to test substances for endocrine activity and related effects. The aim is to use data from these tests, commonly referred to as New Approach Methodologies (NAM), for prioritization of substances and in risk assessment. For example, Health Canada and Environment and Climate Change Canada are active in conducting case studies to explore modern risk assessment approaches, including for substances with endocrine modes of action, under the OECD Integrated Approaches for Testing and Assessment Case Study Project and the Accelerating the Pace of Chemical Risk Assessment (APCRA) initiative.