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A Primer on Scientific Risk Assessment at Health Canada

Prepared by Dr. Marc Saner
Executive Director, Regulatory Governance Initiative, Carleton University, Ottawa

Canada

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Contents

Sophie's Story

The extent to which Health Canada's scientific assessments of risks and benefits permeate everyday life might surprise many Canadians. Consider our fictional character, Sophie, who lives in a Canadian city. When Sophie gets up, she rises from her foam pillow that was manufactured with an antimicrobial treatment; showers and uses shampoo, toothpaste and other cosmetic products; puts on clothes that are treated with stain guard; opens her vinyl blinds; then eats her breakfast while perusing the nutritional facts on the cereal box. Like every other day she takes a natural multivitamin; today she also takes a painkiller, she tidies up her son's toys and packs her water bottle.

At this early point in the day, Sophie has already been protected numerous times from potential risks in her surroundings. She has been informed about risks that she is expected to manage on her own, but for the rest she puts her trust in the work done by scientists and risk managers at Health Canada and other health agencies around the world. In fact, every noun in the above story has something to do with the risk and policy work carried out at Health Canada, as will be shown below.

Sophie may not think about all of the risks surrounding her but she now lives in what sociologists call a **risk society**. People have always thought about risks and are naturally capable of evaluating personal risks and benefits. Modern society, however, is also characterized by an increasing awareness of technological and global risks, and an increasing demand for more protection. The fact that Canada harbours many cultures and lifestyles raises the complexity of protecting Canadians from health risks.

About this Primer

This Primer provides an introduction to **how science is used at Health Canada to assess and manage health risks**, particularly risks that may be associated with products regulated by Health Canada. Corporate, ethics, legal and economic risks are not covered in this Primer. The focus of the Primer is on the use of the natural sciences in decision making (which is not intended to imply that other themes such as risk communication, governance and societal implications are of lesser importance). This Primer has been written for interested professionals and casual readers who want to immerse themselves in the world of concepts used by risk assessors at Health Canada – these concepts are highlighted in boldface throughout this Primer. The main purpose of this Primer is to introduce these concepts in the context of their use.

The scientific assessments carried out at Health Canada require sophisticated technical skills and a complex system of cooperation between players in the public and private sectors. In this Primer, this activity is called *Risk Assessment*.[1] The use of this technical information in decision making is called *Risk Management*. The term *Risk Governance* is used for issues related to communication, public engagement and accountability.

The Primer addresses three fundamental questions that represent the basic elements of a risk management system. The question "Who is at risk?" is addressed first. It is followed by the questions "What causes the risks?" and "How does Health Canada deal with the risks?"

1 Semantic confusion abounds in this discipline and not even the most basic terms are universally used. For example, the term *risk analysis* is sometimes used instead of either risk assessment *or* risk management.

Who is at Risk?

The Person and Population Perspective

Risk thinking can have two different starting points. One can either start from the perspective of the *value at risk* (the well-being of persons, populations and the natural environment) or from the perspective of the *agent that may cause the risk (or produce a benefit)*. This chapter deals with perspective from the *value at risk*. Health Canada's mandate covers the management of health risks and benefits to individual persons, human populations and the natural environment. Reviewing Sophie's Story provides a description of the **exposure** to agents that potentially could pose a risk, as shown in **Figure 1**, below.

Figure 1: Some Sources of Exposure to Agents that Could Potentially Pose Health Risks (and Benefits) and Examples of Health Canada's Scientific Risk Assessment Activities

Antimicrobial-treated Pillow	**Shampoo and Cosmetics**	**Clothes with Stain Guard**	**Vinyl Blinds**
The safety and efficacy of antimicrobials are assessed in detail, including their environmental impact	Ingredients of cosmetics are monitored for their human health and environmental safety	Ingredients in stain guards are assessed for both human health risk and long-term environmental impact	The substances in vinyl miniblinds (including lead) are assessed for their human health and environmental safety
Breakfast	**Multivitamin**	**Painkiller**	**Children's Toys**
The safety and quality of food are assessed; Nutritional labels help Canadians managing their personal risks	The safety, efficacy, and quality of natural health products are assessed	The risks and benefits of drugs are assessed in detail and their label instructions are scrutinized	The safety of toys and other consumer products are assessed and monitored

Sophie's perspective will differ for the various items dependent on the benefits she derives, her expectations of governments and her risk tolerance. For example, she may expect the federal government to ensure that her pillow, cosmetics, clothes, blinds, food are completely free of harmful chemicals. For her painkiller, she may tolerate a minor side effect in exchange for the benefit. With respect to her food, her multivitamin selection, she likely will accept some responsibility of her own and not expect governments to be overly involved. On the contrary, she may resent the feeling that Health Canada, or another level of government, may curtail her liberties. But she would probably expect Health Canada to step in if her natural multivitamin is contaminated with a chemical. As for her child's toys, she assumes the safety is closely assessed.

Finally, Sophie will expect the various levels of government to make decisions with her best interests in mind–decisions that are rooted in sound science and that stand up to scrutiny and the test of time. She would likely espouse the following underlying **principles** that are stated in the *Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks* issued in 2000:

1. Maintaining and Improving Health is the Primary Objective
2. Involve Interested and Affected Parties
3. Communicate in an Effective Way
4. Use a Broad Perspective
5. Use a Collaborative and Integrated Approach
6. Make Effective Use of Sound Science Advice
7. Use a "Precautionary" Approach
8. Tailor the Process to the Issue and its Context
9. Clearly Define Roles, Responsibilities, and Accountabilities
10. Strive to Make the Process Transparent

Satisfying Sophie's tall order of expectations requires that the regulatory system and the risk assessment practices are tailored to the various situations. This point is explicitly stated in the above Principle 8. The full **standardization** of assessment methods across all product classes would prevent the adaptation of the regulatory system to the various contexts at hand, for example, food, drugs or consumer products. At the same time, the application of the regulations has to be reasonably predictable for manufacturers of products. One simply cannot expect a manufacturer to enter a market that is governed by wildly unpredictable or erratic rules. Health Canada balances this need for simultaneous flexibility and consistency in the same way as similar agencies located in jurisdictions such as the U.S. and the E.U. Health Canada has adopted a system that streams the products entering the market into a number of different product classes, typically guided by use patterns or label claims. It is possible that the same substance or even product ends up in more than one product class. For example, an antibiotic could be a drug and also a pesticide. The same chemical may be used as an ingredient in paints and food. Aspects of risk management approaches differ considerably between product classes (the scope, for example) but are kept as consistent as possible within a class.

The issue of **risk governance** is very important but can only be addressed here as it pertains to the science context. Risk governance encompasses issues such as accountability, transparency, risk communication and the shared responsibility to manage risks. Most risk management decisions in the human health context become shared responsibilities of the manufacturer, regulators, distributors and users, including health care professionals and the public at large. As a result, information of any kind–product labels are just one example–become important components of the risk management system. Risk assessments provide scientific insights that are

essential to the creation of this information. Different users such as medical personnel, users of over-the-counter medicines, pesticide applicators, laboratory personnel, the transportation industry, etc., have different needs when it comes to labels and other product information. This provides another argument for the value of separating the risk management of different product classes.

Another aspect of risk governance that relates to science is access to data. Essential scientific data is often owned by the proponent of a product. The public demand for transparency raises the issue of how to provide interested parties with reasonable access to proprietary risk assessment data. Finally, access to indigenous and local knowledge is sometimes important in the science context, especially in environmental risk assessments. These points demonstrate some of the linkages between risk governance and science.

More needs to be said about the scientific assessment of **exposure**. The estimation of exposure is a key ingredient in risk assessments because it is required to estimate the probability by which an adverse effect will take place. As Paracelsus is attributed with saying some 400 years ago: "All things are poison and nothing is without poison, only the dose permits something not to be poisonous." Deliberate exposures to chemicals in the human or veterinarian health context are called **doses**. Otherwise, exposures to chemicals or micro-organisms are normally expressed as **concentrations**.

The scientific assessment of exposure is an in-depth investigation into the deliberate use or incidental and accidental release of a product. It charts the subsequent transportation and transformation (or "degradation") that may take place in a human body or in the environment. In the human or veterinarian health contexts, exposure of the individual as a whole and the exposures of specific organs or even different cell types are of interest. Routes of exposure such as ingestions, inhalation, uptake through the skin, or direct injection into the bloodstream or into muscle tissues are distinguished in risk assessments.

Cultural differences, lifestyles and age can make a huge difference in the level of exposure. Sophie's Story, for example, could read very differently if she had been chosen to represent a child or a member of a non-urban community. In some contexts, for example food, exposure depends much on age or lifestyle. In other contexts, for example, prescription drugs, the variability can be managed through the product labels. The important point is to think of exposure as being linked to different **scenarios** which, in turn, depend on an array of variables.

In the environmental context, the goal is to understand the entire path from the point of release to the final "resting ground" of a product and the possible transformation of the product along its path. For substances of priority environmental interest, such as pesticides, the exposures of different species are assessed. Repeated exposures can be common and are taken into account in both the human and environmental contexts. The surrounding conditions can influence exposure; it may matter if a stomach is empty or full; if a drug is taken with alcohol or not; if the weather is hot or cold; if a chemical is released on the coast of Newfoundland or in Saskatchewan. In short, there are many variables that affect the estimation of exposure and every scenario will result in a specific exposure level.

Exposures can be **deliberate**, as is the case when Sophie takes a painkiller, or **incidental**, as may be the case if Sophie ingests chemical residues in her food. We should note that the word "exposure" sounds out of place in the context of a deliberate use, or in the case of an object such as a toy. It may be better to simply choose the word **use** in these cases.

Another important component of risk assessment needs to be introduced in this section. Sophie's Story focuses on a single individual which obscures the important fact that different persons vary in their **susceptibility** to a given risk. Most risks assessed and managed by Health Canada are estimated at the **population** level.

Like exposure, the estimation of susceptibility is a key ingredient in risk assessments because it is required to estimate the consequences of an adverse effect. In the human health context, differences in sex, age or medical conditions have to be taken into account and the effects on health and well-being, reproduction and development of children are assessed.

Differences in susceptibilities are even more important in the environmental protection context due to the diversity of species that are exposed. For example, a typical environmental risk assessment of a pesticide will include an assessment of the susceptibility and exposure of two species of each of mammals, birds and fish, plus an assortment of other important or highly susceptible species including honey bees, earthworms and water fleas.

The "person and population perspective" described in this section is very useful to explain the relevance of risk assessments. The scientific assessment of risk, however, uses a different starting point, and is focused on the agent of the risks, that is to say, on the product under regulatory consideration. This perspective will be shown in the next section.

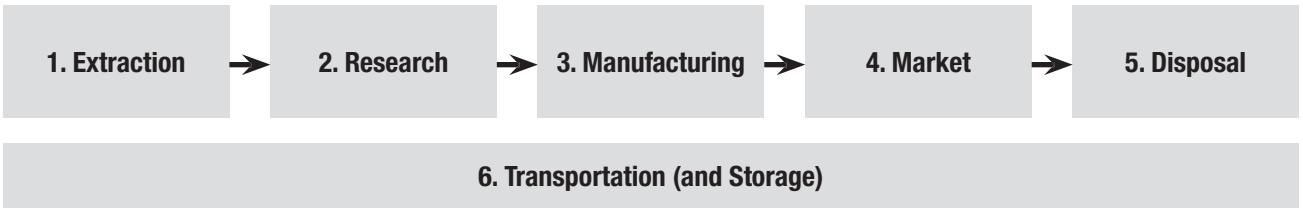
What Causes the Risks?

The Product Perspective

Product Life Cycles

Increasingly, Health Canada regulators are interested in the entire **life cycle** of the products under review. **Figure 2**, shows the simplified path of a product from its "cradle to grave":

Figure 2: Simplified "Cradle to Grave" Product Path



1. Dependent on exposures, risks to human health and the environment can occur during the extraction of raw materials. Workplace and environmental safety are particularly important at this step in the product life cycle. We should note that workplace safety is predominately a provincial mandate.
2. From a risk perspective, research can be a complex step. This is particularly true when clinical trials are involved or when there is an open field test of a genetically engineered organism. Clinical trials are only permitted if a preliminary assessment of risk and benefit is in place; they are designed to fine-tune an assessment and to improve the understanding of differences in susceptibilities between patients. Due to the potential of a genetically engineered organism to become permanently established in the Canadian environment, such open field tests require special attention from a risk assessment perspective. Research ethics boards play a regulatory function during the planning of clinical trials and may question the benefit and validity of a research project, although this is not their main function.
3. Like the extraction step, the manufacturing step is primarily a workplace and environmental safety issue. The selection of a manufacturing site will be under the purview of local government and the issue of multi-jurisdictional integration of rules and standards can arise. In some cases, the risks associated with a product depend to a large extent on the conditions at manufacturing. Examples are vaccines or insulin production.
4. The market step follows. Users and professionals such as health care providers become implicated in the management of risk. Risks can be reassessed based on the reporting of adverse effects or problematic performance.

5. Attention to the final disposal step is growing. The incidental exposure of the natural environment to the disposal of unused drugs is one example.
6. Transportation (and storage) can lead to exposures of numerous environments, each with its own susceptibilities to the risk agent.

Within each product class, existing regulations will focus on the step in the risk context that carries the greatest weight of concern. For example, the long-term fate of the stain guard on Sophie's pants requires more attention than the disposal of her unused natural health products. Or, it is more important to determine any side effects of Sophie's painkiller than those of her shampoo because the components of shampoos are in most instances already well understood.

In Canada and internationally, regulatory systems use a triage system and balance the **pre-market** and **post-market** surveillance and assessment of risks. The judgment over the appropriate approach is based on the basic characteristics and uses of the products that may cause the risks. If a product is relatively unfamiliar or expected to be biologically highly active, as is the case with pesticides and drugs, then a lot of attention will be given to pre-market assessments. Also, a product that is highly persistent will receive more pre-market attention because

Table 1: Health Canada's Six Key Product Classes: An Overview of the Legislative Basis, Products Assessed and Scope of the Scientific Risk Assessment

	Drugs, Devices, Biologics	Foods	Pesticides
Legislative Basis	The *Food and Drugs Act* and, when applicable, the *Controlled Drugs and Substances Act*	The *Food and Drugs Act* and the *Department of Health Act*	The *Pest Control Products Act*
Products Assessed	Pharmaceutical drugs, natural health products, medical devices, biological drugs, radiopharmaceuticals, blood and blood products, cells, tissues and organs, as well as vaccines and veterinary drugs.	Food, including food ingredients and components and production processes related to safety and nutritional qualities.	Pest control products (including, for example, herbicides, insecticides, fungicides, animal repellents, wood preservatives, swimming pool algicides, material preservatives, certain disinfectants and sanitizers).
Scope of Scientific Risk Assessment	**Risks and benefits, includes efficacy.** (Predominantly risk in some cases, such as the post-market assessment of possible contaminants). Focus is on risk to human health with some attention to environmental consequences. Risks are normally assessed at the population or sub-population level. Detailed pre-market assessment (including clinical trials for some products) combined with post-market surveillance (e.g., through reporting of adverse reactions). Risks associated with manufacturing are assessed and Good Manufacturing Processes (GMPs) are required.	**Risks and efficacy.** Estimates of risk are normally based on exposure patterns for a population. Vulnerable sub-populations are identified for additional protection (i.e., infants). Pre-market risk assessment combined with post-market surveillance through inspection (via the Canadian Food Inspection Agency).	**Risks and efficacy (value).** Human health and environmental assessments at the individual and population level. Pre-market risk assessment, assessment of risks during use, post-market monitoring of pesticide residues (via the Canadian Food Inspection Agency), and incident reporting. No assessment at the manufacturing step. Cyclical re-evaluation.

Note: This table is not meant to be an exhaustive list of legislative basis and products assessed at Health Canada.

persistence limits the ability to mitigate risks later on. For example, some commercial chemicals are highly persistent and some products, such as pacemakers, are hard to recall when a problem is discovered after market launch. Strong arguments can also be made in favour of post-market assessments because the information gathered in inspections or surveys, or through the reporting of adverse effects, reflects real-world conditions. Needless to say, the risk assessment methods between pre-market and post-market assessment can be quite different because different scientific approaches are applied to predict risks compared to those used in the study of adverse effects.

This triage approach provides a much higher level of safety to Canadians compared to spreading resources evenly across all product classes. It also optimizes the timely access to products since the delay that a pre-market risk assessment causes will only be experienced in those product classes where such assessments provide a key value.

Six Key Product Classes

An overview of the six key product classes used by Health Canada, including their legislative basis, the products assessed and the scope of the scientific risk assessment undertaken for each class, is included in **Table 1**, below.

New Substances	Existing Substances	Consumer Products (including cosmetics)
The *Canadian Environmental Protection Act*, 1999 (in cooperation with Environment Canada) and the *Food and Drugs Act*	The *Canadian Environmental Protection Act*, 1999 (in cooperation with Environment Canada)	The *Hazardous Products Act* and the *Food and Drugs Act* (for cosmetics)
New substances (e.g., chemicals, polymers, products of biotechnology, nanomaterials) imported and manufactured in Canada that are not already listed in the Domestic Substances List (DSL), or for which there is a significant new activity notice (often this refers to a new use, an increase in quantity or concentration, or changes in the manner or circumstances of use). Environmental assessment of *Food and Drugs Act* products. Screening assessment of living organisms listed in the DSL.	The approximately 23,000 chemical substances used, imported or manufactured in Canada (at a quantity greater than 100 kg) that are included in the DSL.	Consumer products, (e.g., household chemicals and cleaning products, bedding, pyjamas and cosmetics).
Risks. Human health and environmental assessments often based on "structure-activity relationship" methods (for chemicals; more on this below). Assessments are done at the population or sub-population level. Pre-market risk assessments may be followed up by enforcement activities, which could include inspections (via Environment Canada). Risks from effluents at the manufacturing step are assessed.	**Risks.** Benefits may be considered in the risk management phase. Human health and environmental assessments. Acute exposure is evaluated at the individual level; chronic exposure at the population level. By definition, assessment is post-market. No formal assessment at the manufacturing step.	**Risks.** Consideration of benefits occurs predominantly during development of risk management options. Focused on human health assessment at the population level plus some attention to environmental consequences. Post-market surveillance regime, with triggers for human health and safety.

Scientific Risk Assessment

Let us now review how risk assessors approach the review of a novel product. The risk assessment process often starts with a regulatory **trigger**. A trigger can be a label claim, for example, the intent to sell a product as a medicine or pesticide. The regulatory system can also be triggered by a new substance that is not yet listed on Canada's Domestic Substances List, or when the production of a substance is ramped and a production quantity specified in the regulations is surpassed. Risk assessment can also be initiated when surveillance of food or the monitoring of adverse reactions in consumers give rise to a concern. In some instances, such as pesticides, cyclical re-evaluations are mandated by law. In addition, products are sometimes assessed outside of the normal procedures. A brand new issue may arise, for example, the issue of UV radiation from fluorescent lamps, or a new technology yields products that may not fit into the existing regulatory system. Nanotechnology is a pertinent example. In these cases, a process of **hazard characterization** may replace regulatory triggers as the start of a risk assessment process.

The risk assessment of a chemical starts with an understanding of its basic **physical and chemical properties**. These are relatively easy to measure and provide a basis for the understanding of more complex information. For example, if a product is highly soluble, then it likely will move quickly through the bodies of humans and other organisms, or move rapidly through sandy soil in the environment. Other properties may indicate that the chemical may become "bio-magnified" as it moves through the food chain in the environment and concentrated in human tissues.

The rise of information technology has made it possible to carry out a rudimentary risk assessment of a new chemical via comparison to the information available for known, similar substances. This risk assessment method is based on the chemical structure and basic properties of the new chemical and is called "structure-activity relationship" or **SAR**. The SAR program produces a visual comparison between the chemical structure of the new substance and those of existent substances for which risk-relevant data exists. A risk assessor visually compares these chemical structures, and judges if data on biological activity, mobility and persistence of the known substances can be generalized to the new substance under investigation. SAR is used in particular in those contexts where no other data is available, for example, in the context of new substances.

Similarly, the concept of **familiarity** (or the flipside, "novelty") is used in the assessment of a biological product such as a new strain of food crop derived either by traditional breeding or genetic engineering. **Novel traits** are of particular interest as they may introduce a new element of risk. For instance, a genetically modified plant may carry a novel trait that must be assessed for its potential to cause an allergic reaction. Some novel foods, however, may be judged familiar (or "substantially equivalent") by risk assessors and, thus, will not be further investigated. The regulation of cosmetics and other consumer products also use the familiarity concept. An understanding of the **mode of action** of a chemical, biological or consumer product raises the level of familiarity of a new product.

In those cases where a complete risk assessment is triggered or requested, a suite of data requirements will feed into a risk assessment. It is common that these data are provided by the proponent of a product. To ensure quality, these data are usually generated according to guidelines, many of which are international. There are also oversight procedures in place, for example, internationally accepted **Good Clinical Practices** and **Good Laboratory Practices**.

There are three main scientific methods used to generate data: **mathematical models**, ***in vitro*** experiments and ***in vivo*** or field experiments. *In vitro* experiments (which literally means "in glass") are laboratory experiments that are not based on entire organisms. *In vivo* experiments ("in life") are based on entire living organisms. For reasons of animal welfare, cost and reproducibility, there is an international trend to replace *in vivo* data with *in vitro* and model data when possible. However, because of a lack of trust in unproven methods, and the need for comparative assessments, change is slow and animal experiments are still very commonly required by regulators.

The product perspective is based on two key components of risk, commonly called **fate** and **hazard**. The assessment of the **fate** of a product examines the ways in which exposures of persons, populations, or the environment to chemicals and biologics occur. One can think of fate as *the journey* and exposure as *the arrival*. In some product classes, the use pattern is all that needs to be known to estimate exposure and the probability of an adverse effect. In other cases, the transportation and transformation of an agent needs to be studied in detail. The transport of agents in humans may be predicted based on *in vivo* animal studies that are concluded with measurements taken in the dissected animal. In the environmental context, single or multi-year open field experiments may be required, and complex mathematical models may be used to calculate the movement of chemicals or biologics. Many chemicals will transform within an organism, or in the environment, which renders the assessment much more complex. Transformation is not always equivalent to "degradation" from a risk perspective because it can happen that a transformation product is more potent than the parent product. Risk assessors will follow the fate of transformation products as far as practically possible.

In the typical case, risk assessors are guided by the **endpoints** that are specified in regulations or guidelines. One can think of endpoints as indicators used in risk assessment. Examples of endpoints in the assessment of the fate of a product are values that describe the speed of transformation or the persistence of a product. Another endpoint may be the likelihood of transportation to groundwater levels. There are many more. An understanding of the triggers and endpoints – the start and the goal provides a good snapshot of a regulatory requirement and can be used to compare requirements between product classes or jurisdictions.

The assessment of the **hazard** of a product or ingredient is of key importance, of course. "Hazard" is a technical term that describes the inherent potency of a product, or its potential for consequences if an exposure takes place. The previous section discussed differences in the susceptibilities of different persons, populations or portions of the natural environment. Due to these differences, the hazard assessment of an agent may require a wide array of endpoints. One can think of hazard as the inherent *effect of* a product and susceptibility as the *effect to* an individual, population or species.

Examples of endpoints in the human health context are changes in key organs, impacts on human development, potential to cause cancer, immunological or neurological effects. Different routes of exposure such as inhalation, ingestion, intravenous applications, etc., may be tested. In the environmental context, these endpoints are evaluated within a suite of species. Finally, risk assessors distinguish between **threshold** and **non-threshold** effects. Threshold effects are those that occur only at a specific level of exposure while non-threshold effects are assumed to occur at any level of exposure to a substance. This distinction is particularly important in the context of priority risks such as cancer. For example, during the evaluation of existing chemicals under the *Canadian Environmental Protection Act*, a non-threshold cancer risk automatically leads to the designation of the substance as "toxic." In summary, different endpoints will be handled differently in risk assessments.

Most of these endpoints are initially derived from the extrapolation of data from other mammals including rats, mice and dogs. When the data from these animal species are used to estimate hazards to humans, then it is necessary to be conservative and to modify estimates by an **uncertainty factor** (or "safety factor"). This factor ensures that humans are protected even if our species is more susceptible than the surrogate species, or if human susceptibility varies. In the context of drugs, clinical trials to assess safety, efficacy and dose ranges remove the need to extrapolate from other species.

The same basic logic is used in the environmental protection context, but the array of tested species is much wider and covers birds, fish, invertebrates and plants, as indicated in the previous section. It is also possible to derive some data on hazard from SAR and from *in vitro* testing.

In some contexts, the assessment of efficacy and benefits accompanies the assessment of hazard. For example, benefits of novel drugs are assessed and pesticides are tested for their efficacy.

We are now well equipped to bring the perspectives and components together and discuss the logic of a risk assessment in the following section.

How Does Health Canada Deal with the Risks?

The Process Perspective

At a high level, the logic underlying a risk (or benefit) assessment is identical for all contexts, including organizational, financial, engineering, personal, and the health and environmental risks discussed here. It can be expressed in the following formula:

Risk = Probability of Event × Seriousness of Consequences

(Benefit = Probability of an Event × Yield from the Consequences)

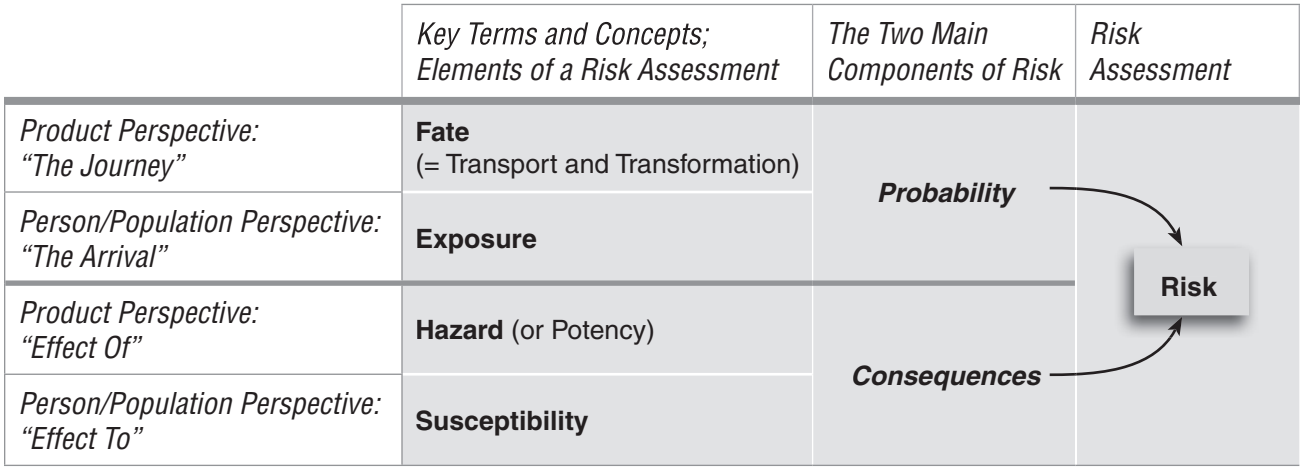
This risk formula can also be shown in a graphical way as shown in **Figure 3**, below. This matrix can be used to carry out a rudimentary risk assessment (the darker the background of the cells, the higher the concern; replacing "seriousness of consequences" with "yield from the consequences" would result in a tool for benefit assessment):

Figure 3: Risk Matrix: A Tool for Priority-setting

		*Seriousness of **Consequences***		
		Low	Medium	High
***Probability** of Event*	High			**Top Concern**
	Medium			
	Low	Little Concern		

The concepts introduced in the sections "Who is at Risk?" and "What Causes the Risks?" can be mapped quite easily onto the risk formula. This is shown below in **Figure 4** (an analogous chart could be drawn for benefits):

Figure 4: The Relationship between Key Concepts in this Primer and the Risk Formula



The risk formula bears an important lesson that echoes Paracelsus' insight: the hazard of a substance or product by itself says little about the risk because risk depends also on exposure. This in itself explains why the same substance or product may be treated differently in different regulatory contexts. Such discrepancy is not caused because scientists cannot agree; it is caused by the need to tailor assessments to real-world contexts.

However, it is possible that different risk assessment teams could describe the basic physical, chemical or biological features of the products differently, perhaps by relying on different original data. Risk assessment is *based* on science but it does not usually involve scientific research originating within Health Canada. Instead, it often relies on data provided by the proponents of products and other sources. Risk assessors have to make a series of *judgments* such as the decision if a particular scientific study is valid or not, or if the argument provided by the proponent of a product is acceptable or not. These judgments, together with the variability in the results of scientific research, introduce a measure of variation into risk assessments. While the fundamental approaches remain constant, it is a *basic feature* of *science* that results often vary in complex experiments, including the ones required in the risk assessment context.

After all relevant risks and benefits have been assessed, approaches to risk mitigation can be discussed and an overall regulatory decision can be made during the **risk management** step. The 2000 *Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks* describes these broader picture issues and we will only touch on a couple of salient points here. It is important to realize that a risk assessment is just one input into the decision-making process. Different risks may be considered concurrently and, most importantly, benefits assessments may be added to the overall balance. For example, a relatively hazardous drug can be judged acceptable at the risk management step because of the benefits it may provide to an AIDS patient. Similarly, many cancer drugs can damage DNA but they are made available to hospitals because they can save lives. The risk management step requires judgment and an understanding of the context of use, including the cultural or professional setting, and the somewhat subjective **risk tolerance** of the users. One can think of risk tolerance as the factor that mediates between risk assessment and **safety**. Managing risks toward acceptable "safety" (that is to say, the best balance of benefits and side effects in some contexts) is the ultimate goal of a risk system. It requires that risk managers develop a clear understanding of the precise scope and applicability

of the risk assessment data, integrate and balance all sources of evidence, consider the practical reality of how the decision will be implemented and arrive at a defensible judgment in light of the risk tolerance of the users (and all others affected).

The **precautionary principle** has gained importance in the risk management context. It is included in the latest versions of the *Canadian Environmental Protection Act, 1999* (CEPA) and the *Pest Control Products Act, 2002* (PCPA), both of which are at least in part administered by Health Canada. The texts in the two Acts are similar. Here is the version from the more recent PCPA: "Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent adverse health impact or environmental degradation."

In practice, precaution is now used to label an array of traditional risk assessment practices. Examples include that the absence of evidence is not proof of the absence of an effect; in some contexts, the sole focus of risk rather than the balance between risk and benefits; and that product registration is withheld until regulatory requirements are satisfied.

It is of interest to note, however, that the precautionary principle originated long after these traditional practices became established. The precautionary principle has its roots in the environmental domain and became internationally recognized when it was included in the 1992 *Rio Declaration on Environment and Development*. It is an extension of the traditional risk management practices in the specific context of a potentially catastrophic hazard at planetary scale. An example would be the destruction of much of Earth's biodiversity or ozone layer. Rapid action can be justified in these cases *even* given the risk that this action will be shown to be unnecessary as the scientific understanding advances. In other words, we do not want to gamble with the planet. The precautionary principle may have been a useful addition to risk management in the environmental context as it serves to emphasize the importance of these relatively new environmental risks. It is less clear that the introduction of precaution to the human health context has *substantially* changed the way risk assessment and management practices are carried out because the system was "precautionary" all along. It does provide, however, a new tool for decision makers to label, justify and communicate issues that require special attention.

This concludes the survey of the key concepts used in scientific risk assessment at Health Canada. Looking at these pages collectively, the reader should recognize that scientific risk assessment is very complex with respect to the richness of concepts used, yet almost banal in the underlying fundamental logic. We are all competent assessor of our personal risks (and thus familiar with the underlying logic) but only few have the professional training to implement the concepts shown here into the complex world of regulations and to provide the evidence needed for decisions that are in our collective best interest.

Further Reading

Health Canada Guides

- *Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks*. Ottawa (ON): Health Canada; 2000 Aug 1. Available from: http://www.hc-sc.gc.ca/ahc-asc/alt_formats/hpfb-dgpsa/pdf/pubs/risk-risques-eng.pdf
- *Science Policy Notice: Technical Paper—A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency*. SPN2001-01. Ottawa (ON): Health Canada, Pest Management Regulatory Agency; 2000 Dec 22. Summary of Technical Paper available from: http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/spn2000-01/index-eng.php
- *Health Products and Food Branch's Guide for Conducting Health Risk Assessments in Humans*. Ottawa (ON): Health Canada, Health Products and Food Branch; 2008 Nov. Draft: Version 4.1.

General Interest Books on Risk

- Beck U. *Risk Society: Towards a New Modernity*. London: Sage Publications Ltd.; 1992. (Originally published in German in 1986.)
- Bernstein PL. *Against the Gods: The Remarkable Story of Risk*. New York: John Wiley & Sons, Inc.; 1998.
- Doern GB, Reed T (editors). *Risky Business: Canada's Changing Science-Based Policy and Regulatory Regime*. Toronto (ON): University of Toronto Press; 2000.
- Gardner D. *Risk: The Science and Politics of Fear*. Toronto (ON): McClelland & Stewart Ltd.; 2008.
- Sparrow MK. *The Character of Harms: Operational Challenges in Control*. Cambridge (UK): Cambridge University Press; 2008.