Risk Assessment for Chemicals in the Environment

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In 1983, the National Academy of Sciences (NAS) published a seminal report, *Risk Assessment in the Federal Government: Managing the Process* [8], on the theory and practice of human health risk assessment for chemicals in the environment.

Even though dictionaries define risk in terms of the probability of injury, damage, or loss [19], and even though other professions have long since adopted probabilistic frameworks using the Monte Carlo method developed in 1946, most human health risk assessments for chemicals in the environment still use deterministic methods that use point values for all variables. Probabilistic methods have three key advantages over the deterministic ones that they replace. First, probabilistic methods use all the information available about the variability and the uncertainty inherent in the assessment, while deterministic assessments discard most of the information. Second, by using probability distributions to represent the range of exposure and/or toxicity, probabilistic methods reveal the compounded conservatisms inherent in deterministic methods. Third, probabilistic methods -- relying as they do on the full range of values that a variable may assume -- re-establish the now blurred boundary between risk assessment and risk management.

We note that risk assessment and epidemiology have some goals in common, but that risk assessment differs from epidemiology by its central focus on the prediction of future events.

Risk Assessment vs Risk Management

The NAS report defined two roles for individuals and stressed the need to keep these roles and associated activities well separated from each other:

- A <u>risk assessor</u> is an analyst -- perhaps an engineer or scientist -- who uses facts and quantitative reasoning to estimate or bound the exposures and health effects, if any, to a person exposed to chemicals in the environment. The risk assessor may also analyze different technical options for remediation of the property.

- A <u>risk manager</u> is a different person -- perhaps a legislator, judge, member of a jury, a regulator, or the public itself -- who then weighs the health risks in light of other social, political, and economic factors. The risk manager(s) then decide(s) the actions necessary or appropriate for a given situation. The actions may range from continuing the "do nothing" or "no action" alternative, to restrictions on land use, to complete excavation and removal. Risk management is the process of weighing policy alternatives and selecting the most appropriate regulatory action by integrating the results of risk assessment with engineering data and with social, economic, and political concerns to reach a decision.

Considering a contaminated property as an example, a risk assessor usually (i) performs a "baseline risk assessment," i.e., she or he analyzes the health risks to people who use the property under both the current and reasonable foreseeable use for reducing the risk and then (ii) estimates cleanup targets, as appropriate. A risk assessor may also complete a "verification risk assessment" *ex post* remediation. A risk assessor may perform the same general types of studies to assess or compare the effects of pesticide residues in foods, the operation of a proposed incinerator, new methods to disinfect public water supplies, the reliability of a manufacturing plant, or even the transportation of hazardous materials.

Risk Assessment: The 5-Step Process

Risk assessors usually follow a 5-step process when completing a risk assessment. Figure 1 shows the typical 5-step process used today.

In the next sections, we use the assessment of a contaminated property as an example.

1. Hazard Identification

In this first step the risk assessor reviews information about the property, such as location, land use, and abutting land use, and plans for future development. For a hazardous waste site, the risk assessor would review and analyze all of the monitoring data, including, for example, (i) chemical measurements in soils, ground water, sediments, surface water and/or air, and (ii) physical measurements, such as wind speed, temperature, hydraulic gradients, and turbulence. In the hazard identification step, the risk assessor must define the nature and extent of the problem, especially the lateral and vertical extent of the contamination. The resulting "study area" need not conform to property boundaries of ownership or even to state lines.

In hazard identification, the risk assessor must also select a list of "study chemicals" or "chemicals of concern," a subset of organic and/or inorganic compounds reported at the site that entails the highest exposure and the highest risk. The risk assessor usually selects the study chemicals for consideration according to these (sometimes competing) factors:

- high average and/or maximum concentrations,

- long persistence in the environment,

- high toxicity, especially carcinogenicity, teratogenicity, or reproductive toxicity,

- high frequency of detection,

- great mobility in the environment, and/or

- high public concern or awareness.

The risk assessor may also consider other factors as well, including whether the chemical is related to human activities or naturally occurring, whether the chemical is reported in concentrations above either natural or anthropogenic background concentrations, and whether the chemical is an essential nutrient for plants or animals.

2.   Dose-Response Assessment

The risk assessor assembles information on the acute, subchronic, and chronic toxicities of the study chemicals selected in the previous step. Toxicologists distinguish between (i) potential carcinogens, which are chemicals that may initiate or promote the development of cancer, and (ii) noncarcinogens, which are chemicals that cause damage other than cancer to cells, tissues, organs, or organ systems in the exposed individual. More often now, toxicologists also identify neurotoxins, mutagens (agents that may cause somatic or genetic mutations), and teratogens (agents that may cause birth defects in newborns). Of course, some chemicals may cause multiple effects at different times and doses. For example, in high doses, a particular dioxin called 2,3,7,8-TCDD may cause immediate tissue damage and a skin disease (effects of acute exposure); in lower doses, and over time, it may increase the probability that a few different types of cancer will develop (an effect of low-dose chronic exposure). (For general references, see: [7] and [9]).

Developing Reference Doses (RfDs)

Studies have shown that many people incorrectly believe "No dose of a chemical is safe." In fact, for any chemical, there is a dose low enough that it does not cause significant clinical effects and a dose high enough that it probably does. We safely eat small amounts of cyanide in almonds, accidentally swallowed apple seeds, and other foods; on the other hand, ingestion of less than a half pound of salt all at once will likely kill an adult. Mammals (including humans) have evolved to eat safely a multitude of naturally occurring toxic chemicals in foods, and, as a result, mammals have excellent defenses against many types of chemicals (including many industrial chemicals) and can readily detoxify and excrete them.

Identifying a dose of a chemical that is unlikely to cause effects is challenging. Experience has taught us that humans do not respond the same way as any particular experimental animal species. Sometimes humans are more sensitive to a certain chemical than rats are but less sensitive than, say, guinea pigs. Different animals (including humans) sometimes even respond to a chemical or drug exposure with different types of responses altogether. For example, some tranquilizer drugs used with dogs and horses will make cats more excited instead of depressing them. And humans

themselves vary from person to person in their response: one person can drink alcohol seemingly all evening, while another is quite drunk after one glass of wine. Given a new chemical, a toxicologist cannot predict whether humans are more or less sensitive than the test animal, or whether they will respond with the same toxic effect, or how much variability different people will exhibit in their response. If this were not trouble enough, most animal toxicity tests last for 6 months to two years, while a human exposure might occur over 30 or 40 years or more.

The solution to these questions has been to apply limits on the uncertainty. Experience over many years with thousands of chemicals has allowed toxicologists to develop rules for estimating a "safe" dose. The US EPA has developed a standardized method for developing "reference doses" (RfDs) for several hundred of the solvents, pesticides, metals, and other chemicals most commonly encountered in the environment. The method does not identify the highest dose of a chemical that is safe, but it does identify a dose unlikely to cause effects; that is, the highest safe dose is probably not lower than the RfD.

The current US EPA method has three main steps (although changes are proposed for the future). First, test animal studies and human observations (if available) are reviewed for study quality and to find the lowest dose where adverse effects were observed (the "LOAEL" or lowest adverse effect level), and the next lower dose where these effects are not seen (the "NOAEL," or no observed adverse effect level). Second, depending on the quality and findings of the experimental data, several uncertainty factors are applied to the LOAEL (or the NOAEL, if it is available) to estimate the RfD. If good dose information is available from accidental human exposures (as for mercury) one can use a NOAEL directly as an RfD or one can divide it by a factor of 1 to 10 to account for variations among humans. For most chemicals we must use animal studies. If we have available only a LOAEL from an animal study, we divide by a factor of 10 to estimate a NOAEL. The factor of 10 accounts for potential differences between humans and experimental animals. The result may be divided by a factor between 1 and 10 if the experiment lasted less than the animals' lifetime (rats and mice live about 2 yr) to estimate a safe dose for a human lifetime. We can use an additional modifying factor if we have reason for additional concern, such as the only effects observed in the test are very serious ones. Sometimes we make other modifications in the dose estimate to represent more closely the dose that we expect that humans will receive. This process

has been used both for ingested and inhaled doses of chemicals. There is no comparable approach developed for dermal exposure to chemicals; generally we use the oral RfD to evaluate a dermally absorbed dose, in spite of the obvious uncertainties.

The final step in the derivation of an RfD is to identify qualitatively the scientific confidence in it. Good, plentiful, studies with consistent findings result in high confidence, while if the available studies are poor or few, confidence is low. Note that low confidence usually results in a lower RfD because the greater uncertainty is reflected in higher uncertainty factors. So the RfD is no less "safe" if confidence is low; in fact, the true highest safe dose may be 1,000 or more times higher.

Most scientists recognize that this approach is not optimal; it may result in overprotection at unnecessary expense. The current approach produces some odd results, such as an RfD for phenol that is below the dose received when one uses a common over-the-counter sore throat medication as directed (phenol is its active ingredient). The US EPA and other groups are working on more effective approaches, using pharmacokinetics, modeling, sophisticated statistics, quantitative analysis of variability and uncertainty, and other methods. One such approach is used for lead and is being developed for other metals such as arsenic and mercury. The approach is to use a model to evaluate several sources of exposure to lead and to predict the expected values in a population of a particular biomarker, in this case blood concentrations. (This approach has had only limited success so far.) Meanwhile, risk managers need to be mindful of how RfDs are developed and understand that if a risk assessment shows that a certain chemical concentration "exceeds a level of concern," that this does not mean we shall see toxic effects in exposed people. For most chemicals, there is a large margin of safety built into the toxicity value used in the risk calculation. Also, the target concentrations of concern are so low that the effects cannot be detected in small or medium sized populations.

Developing Cancer Slope Factors (CSFs)

Toxicologists agree that there is a safe dose with respect to toxic effects other than cancer. The US EPA has assumed that there is not a safe dose for carcinogens; there is, however, a dose that poses an acceptably low risk. Cancer is considered a dose-related stochastic process; that is, there is always a chance to acquire cancer from

exposure to a carcinogen, no matter how small the dose; however, the smaller the dose, the smaller the chance. For some cancer causing agents, such as radiation, this appears to be true. Cancer (really a group of diseases) differs fundamentally from other toxic effects such as liver damage, in which a certain threshold of damage is necessary before the damage makes any practical difference, since the body can live with or replace many damaged cells. It is thought that cancer can result from a single mutation in DNA. This mutation can theoretically be caused by a single molecule of a carcinogenic chemical [1]. Therefore, there is theoretically always a possibility that a single molecule could cause the damage that leads to cancer. In reality, this is probably not true for most chemicals, but the US EPA currently regulates carcinogens on this basis.

There are only about 30 known chemicals or industrial processes that cause cancer in humans. All other chemicals considered carcinogenic are only suspected to cause cancer in humans, perhaps because of weak evidence from human studies, or because the chemical tested positive in an animal test system. Groups of test animals (usually rats, mice, or dogs) receive the highest dose or half the highest dose of the test chemical that one expects they can tolerate for their lifetime without significant toxic effects other than cancer, and at the end of that time (about two years for rats and mice) the test animals are necropsied and examined for tumors. If the test groups have more tumors than the control group, then one can employ tumor data in a model to predict possible cancer rates in humans exposed over a much longer lifetime to much lower doses. The model most commonly used by the US EPA produces a "Cancer Slope Factor" (CSF), that one can use to estimate cancer risk in exposed humans. The CSF assumes a linear relationship between exposure dose and carcinogenic response. For example, with a person exposed to 0.02 mg alachlor /kg body weight every day for a lifetime and where the CSF is 0.08 (kg•d)/mg, an estimate of the cancer risk is (0.02 • 0.08) = 0.0016 = 1.6 in 1,000.

Often, results from the animal studies fail to show a clear effect. In any case, toxicologists must evaluate all available evidence for a chemical, including studies among different animal species, and epidemiologic studies in humans, to determine whether the weight of evidence indicates whether a chemical may be a human carcinogen. Under the pre-1996 guidelines [10], the US EPA classified carcinogens according to the weight of evidence into one of five groups that ranged from "Known

human carcinogen" to "No evidence of carcinogenicity." All but perhaps 35 or 40 chemicals ever studied fall somewhere between these two categories; their carcinogenicity in humans is uncertain. Guidelines published for review in 1996 replace the five groups with three categories and a narrative to describe the weight of evidence [18].

Much of this uncertainty concerning carcinogenicity comes from the process of identifying and evaluating potential carcinogens. Toxicologists know that these are serious questions about the validity of animal carcinogenicity studies. Some scientists believe cancer in test animals is actually a byproduct of the cell damage and subsequent cell reproduction and tissue repair induced in the experimental animals due to the toxic dose levels typically used in the tests. With humans exposed to extremely low doses of the same chemical in the environment, the cell damage is too minor to induce tissue repair, and the chemical probably does not cause cancer. On this basis, many people believe that the true risk from such low exposures may be as low as zero. A second argument applies to chemicals that only cause tumors in specific situations. For example, many chemicals appear to cause tumors only in mice, not other experimental animals, and only in the livers of those mice, not in other organs. Chlordane is such a chemical. We would not expect these chemicals to cause cancer in humans: experts disagree, however, so the cancer risk is uncertain. The same issues discussed for non-cancer reference doses apply here, as well; toxicologists must extrapolate from high doses to low, short term experiments to long term environmental exposure, and animals to humans. Finally, uncertainty about the models used to develop the CSF is large. While the true cancer slope factor is not likely higher than the published CSF, it may be much lower, and perhaps as low as zero.

Sources of Chemical Toxicity Information

The US EPA has already established and published the physical, chemical, and toxicological properties of many chemicals found at hazardous waste sites. These evaluations, based on the results from studies conducted by the National Cancer Institute (NCI) and from articles in refereed journals, are often reduced to either "chemical profiles" or simply a handful of numbers that represent toxic potencies. Published by the US EPA, the findings and opinions on these chemicals are usually listed in two widely available resources: (i) the Integrated Risk Information System

(known as IRIS; [17]), a database updated monthly and available over several wide-area computer networks and (ii) the Health Effects Assessment Summary Tables (known as HEAST; [16]), a database updated quarterly or semi-annually and available in print from the National Technical Information Service (NTIS) in Springfield, VA. These two databases typically give several toxicity values for a single chemical, depending whether the exposure occurs via ingestion (e.g., via food or water) or via inhalation (e.g., via gases or particulates). Neither of these databases currently includes toxicity values for dermal exposures.

For use in a numerical example later in this essay, we note that US EPA's IRIS database recently listed the CSF for the ingestion of benzene as $2.9 \bullet 10^{-2}$ (kg•d)/mg.

3. Exposure Assessment

The risk assessor first determines if complete "exposure pathways" exist and then estimates the doses delivered along those pathways [11].

Exposure Pathways

An exposure pathway is any route that a chemical may travel from an environmental source (e.g., an abandoned dry sludge lagoon) to a receptor (also called the exposed individual), such as a child living nearby. An exposure pathway has five main parts:

- a chemical source,

- a release mechanism (e.g., leaking, leaching, wind erosion),

- a transport and/or exposure medium (e.g., air, water, soil, sediment, food),

- an exposure point with receptors present or potentially present (actual location where exposure is possible), and

- a route of entry (inhalation, ingestion, dermal contact).

A complete exposure pathway is one that has no functional barrier that prevents an exposure. The pathway may be completed (i) by the chemical moving from the source to the receptor or (ii) by the receptor moving to the source. In this example, fugitive dust

that carries the chemicals may blow from the lagoon to the child's house, or the child may play in or near the old lagoon. Either way, with a completed pathway, the receptor comes into contact with some of the chemical from the source. If no exposure pathway is complete, there is no exposure and subsequently no risk.

In exposure assessment, the risk assessor usually considers three different exposure routes into the body: inhalation, ingestion, and dermal contact. With ingestion, the risk assessor considers whether a person may deliberately or inadvertently swallow some liquid or solid, including food, beverages, or soils (say, by hand to mouth movement). With inhalation, the risk assessor considers whether a person breathes toxic materials as gases, vapors, aerosols, or particles. With dermal contact, a risk assessor considers whether a person may touch gases, liquids, or solids that contain toxic materials and possibly absorb the chemical through the skin. Of course, in some situations, all three exposure routes may convey meaningful amounts of a chemical.

Exposure pathways are often categorized as "direct" or "indirect" pathways. Although no strict definitions exist, a direct pathway exists when the exposed person experiences the chemical in the same medium as it is present in the source. In our example, the child may inadvertently ingest contaminated soil near the abandoned lagoon and thus experience a direct pathway. Alternatively, an indirect pathway exists when the exposed person experiences the contaminants in a different medium, often at a distance from the source. In a different example, the child may drink cow's milk containing dioxin that traveled from an incinerator via this complicated route: formation in the incinerator, emission into the atmosphere as a gas, adsorption onto a particle in the atmosphere, wet or dry deposition onto grass in a pasture, ingestion by the cow, secretion in the cow's milk, and ingestion by the child drinking milk. For some types of facilities, e.g., some incinerators, risk assessments show that these indirect pathways, although challenging and difficult to measure or analyze, may cause greater exposures than do direct exposures for some chemicals. In some areas of the US and in many other countries, homegrown vegetables may be an important part of the diet, and transfer of chemicals from soil, water, or air to vegetables may be highly important. In other cases, high exposure estimates for indirect pathways may result from compounding many conservative assumptions.

Estimation of Dose

When reading a risk assessment or a research publication, one should always check the definition of dose used by the authors, because different concepts and different units of measurement are common in the literature [1].

Here we distinguish three primary concepts of dose, noting that the first is most commonly used in risk assessments at hazardous waste sites.

- <u>Exposure dose</u> is the mass of chemical that enters a person's body via ingestion, inhalation or dermal contact. No allowance is made for excretion or exhalation of the chemical before absorption or metabolism. The conventional measure of exposure dose in units of milligrams of chemical per kilogram of body weight per day, mg/(kg•d), explicitly scales by body weight because a larger person needs greater exposure than does a smaller person to have a comparable effect. A milligram of chemical theoretically causes more harm to a child than to an adult.

- <u>Absorbed dose</u> is the mass of chemical absorbed or metabolized by the receptor's body. Although measured in the same units, mg/(kg•d), absorbed dose is always smaller than exposure dose because some of the chemical is excreted or exhaled from the body before absorption from the lungs or gastrointestinal tract. On scientific merit, absorbed dose is always preferable to exposure dose, but it is also more difficult to measure or estimate because the (relative) absorption of the chemical may depend on many factors, including the age, health, and health status of the exposed person. With some chemicals, such as lead and other metals found in soils, identification of the absorbed dose may be very important in estimating risk. It may also be used in extrapolating from one exposure route to another, such as from an ingestion to a dermal dose.

- The third concept of dose -- <u>biologically effective dose</u> (BED) -- is rarely used today directly in practical risk assessments for hazardous waste sites. BED is the mass of chemical (or sometimes the concentration of chemical) that reaches the target organ or tissue and causes the physiological or genetic damage. Of central importance in laboratory studies, BED is rarely used in practical risk assessments, because it is so difficult to determine even the identity of the chemical or the metabolite that causes the damage at the molecular level in the

body. Usually, laboratory scientists study BED using radio-labeled compounds or other chemical measurement and pharmacokinetic models of absorption, metabolism, and excretion. This type of information can be helpful in extrapolating from animal studies to predicted human effects, or from one exposure situation to another. The toxicity values used in risk assessments may be refined as a result of such studies.

The duration of exposure clearly plays a central role in toxicology. Sometimes a brief, relatively large dose may cause less damage to an organism than does a much lower total dose sustained over a longer period of time, and sometimes the opposite is true. While occupational hygienists, police, or fire officials focus on exposures that occur over minutes or hours, risk assessors usually focus on exposures that range in duration from a year or so to a full lifetime (usually assumed to be 70 yr). Thus, risk assessors rarely consider acute health effects (from exposures of a few seconds to a few weeks) and instead tend to focus on subchronic, chronic, or lifetime exposures (here taken to mean, respectively, a few months, a few to many years, or a full lifetime). The exception to this is if very high exposures over a short time are possible, such as during site remediation. When reading an article or report, it is important to understand what time frames are included and what are excluded from the analyses.

We estimate exposure dose from the measurements or models of the exposure point concentration (e.g., the concentration in soil in a residential yard) and the contact rate (e.g.,, the amount of soil ingested from the yard). The exposure point concentration is the steady or time-varying concentration of the chemical in the medium to which a person has been exposed. In a particular situation, a single exposed person may have several exposures to a single compound. For example, at work, a person may breathe air that contains a chlorinated solvent, while at home the person may ingest water that contains the same compound. If the contaminant comes from a single source, the analysis is usually much easier than if the compound comes from multiple sources. A risk assessor may rely upon measurements or models to estimate the exposure point concentration. In most instances, concentration measurements are more reliable than modeled concentrations. However, models are frequently used if there are no cost-effective or realistic ways to measure the exposure point concentrations directly. Also, models are often used to predict the fate and transport of chemicals in air or ground water.

When using a model to estimate the exposure point concentrations of a chemical, especially a multi-media model, a risk assessor should remember the words of George Box, "All Models Are Wrong But Some Are Useful" [2]. Although originally penned for another purpose, these words suggest the need for great caution in using models to estimate exposure point concentrations and movement of chemicals in the environment. Before one can rely upon any concentrations modeled by oneself or others, we urge that one attempts to understand all of the limitations of the model(s) and to make a reality check for the values before proceeding.

When estimating the contact rate, a risk assessor is really estimating intensity, frequency, and duration of exposure. A typical adult may drink daily ~1 to ~3 liters of water, some at home and some at work. Those exposures may last 5, 20, or more years, depending on changes in residence, employment or occupation. The same person may have other exposures also via ingestion, inhalation, or dermal contact. Some exposures happen intermittently in time or space, e.g., recreational use of a park.

The US EPA has published numerous guidance manuals on the selection of the exposure factors needed to estimate contact rate [15]. For example, the Agency's *Exposure Factors Handbook* [12] lists point values for many physiological or behavioral variables for children and adults. The Agency's *Exposure Factors Handbook* does contain many of the standard values widely quoted and mandated in risk assessments. According to the US EPA, each adult is assumed to weigh 70 kg, to ingest 2 l/d of drinking water, to breath 20 to 24 m^3/d of air, and to live in the same residence 30 yr. The Agency chose some of the values as "conservative" or upperbound values (e.g., 2 l/d of drinking water for each adult) and chose others as typical or average values (e.g., 70 kg as the average weight of an adult).

While these numbers are simple to memorize and easy to apply, it is important to realize that they misrepresent conditions that most people experience. People vary in many attributes. Not everyone weighs the same amount, or has the same diet, or lives in a home as long as 30 yr. Furthermore, the actual values for some assumptions such as soil ingestion rates are simply unknown. Each of these exposure factors is better represented by a range or distribution of values -- a topic discussed later.

As a practical matter, we recommend that risk assessors first estimate the exposure dose to a person on a day during which exposure is known to occur. For example, if a child has exposure to a toxic chemical when trespassing on an industrial property, the risk assessor should first estimate the dose on that particular day of trespass. If the behavior occurs every day of a year, then the average daily dose on a day of exposure equals the average daily dose during that year of exposure. However, if the exposure does not happen every day, then the average daily dose for the year is less than the average daily dose on the day of exposure. All doses need evaluation against an appropriate measure of toxicity. For example, an adult could drink one martini every night for two weeks without serious adverse effect, but drinking 14 martinis in one night would have dangerous health effects even though the average daily dose over two weeks is the same. The risk assessor must account for high-dose, short term exposure potential, even during one year or less.

As a numerical example, we estimate the Average Daily Dose averaged over a lifetime of exposure for an adult who (unwittingly) drank water from a contaminated well at a vacation home. To make the calculation, we estimate the exposure dose to this person who weighed 70 kg, drank 2 l/d of water, and visited the vacation home 2 d/wk (the weekend) for 10 wk/yr (the summer). This person owned the house for 20 yr. The well water contained 115 μg/l of benzene (a known human carcinogen). We use this formula:

$$\langle ADD \rangle_{life} \;=\; \frac{Conc \bullet IngR \bullet CF}{BW} \bullet \frac{D}{7} \bullet \frac{W}{52} \bullet \frac{Y}{70}$$

where:

$\langle ADD \rangle_{life}$	=	average daily dose, averaged over a lifetime, mg/(kg•d)
Conc	=	concentration in drinking water (μg/l)
IngR	=	ingestion rate (l/d)
CF	=	conversion factor (mg/μg)
BW	=	body weight (kg)
D	=	number of days of exposure per week
W	=	number of weeks of exposure per year
Y	=	number of years of exposure in lifetime of 70 yr

Substituting the values with CF = 10^{-3}, we find $\langle ADD \rangle_{life} \sim 5.16 \bullet 10^{-5}$ mg/(kg•d)

While doses of carcinogens may be averaged over a lifetime, doses of noncarcinogens are averaged over a shorter time (usually the duration of exposure). In the example above, it is appropriate to average exposure to a noncarcinogen over 20 yr.

4.   Risk Characterization

The risk assessor combines all the information gathered in the preceding three steps to estimate quantitatively the health risk. In practice, this step usually culminates (i) in a numerical estimate of noncarcinogenic health effects as measured by a summary statistic called the total hazard index and also (ii) in a numerical estimate of the carcinogenic potential as measured by a summary statistic called the total incremental lifetime cancer risk. (See, for example, [13]).

For exposure to a single noncarcinogenic chemical via a single exposure pathway, the hazard index is usually defined as the average daily dose averaged over one year of exposure divided by the reference dose for that chemical via that exposure pathway.

$$HQ_{ij} \quad = \quad <ADD>_{year} \; / \; RfD$$

where:

HQ_{ij} denotes the hazard quotient for that combination of chemical and exposure pathway. As a ratio, it has no units;

$<ADD>_{year}$ denotes the average daily dose averaged over one year, expressed in mg of chemical per kg of body weight per day, and

RfD denotes the reference dose for that chemical and route of exposure (e.g., inhalation), also expressed in mg of chemical per kg of body weight per day.

In a full study, the risk assessor estimates the Hazard Index (HI) by summing the hazard quotients over all chemicals and exposure pathways [14]:

$$HI = \sum_i \sum_j HQ_{ij} .$$

Given its definition as a ratio of positive numbers, the HI may range from zero to infinity. If the HI > 1, then the risk assessor may disaggregate it into those components that act on a common organ system or by a single molecular mechanism. The reasoning behind this is that the body can handle multiple chemical stresses through multiple defenses. For example, at a mining site, people may be exposed to lead, zinc, arsenic, manganese, and copper. For practical purposes, at low doses, these metals act independently on different organ systems, and regulatory agencies often treat the risks from these metals separately instead of adding them together. The risk manager may become increasingly concerned as the HI disaggregated by organ system or molecular mechanism exceeds 1.

For exposure to a single carcinogenic chemical via a single exposure pathway, the incremental lifetime cancer risk is usually defined as the average daily dose averaged over a lifetime multiplied by the cancer slope factor [10]:

$$ILCR_{ij} = <ADD>_{life} \bullet CSF$$

where:

$ILCR_{ij}$ denotes the incremental lifetime cancer risk for that combination of chemical and exposure pathway. As a probability, it has no units;

$<ADD>_{life}$ denotes the average daily dose averaged over a full life, usually taken as 70 yr, expressed in mg of chemical per kg of body weight per day, and

CSF denotes the cancer slope factor for that chemical and route of exposure, expressed in the inverse of [mg of chemical per kg of body weight per day].

Continuing the numerical example from above, the adult who drank the water contaminated with benzene (CSF = $2.9 \bullet 10^{-2}$ (kg•d)/mg) while staying at a vacation home has an estimated ILCR ~ $1.5 \bullet 10^{-6}$.

In a full study, the risk assessor estimates the total incremental lifetime cancer risk by summing over all chemicals and exposure pathways [13]:

$$\text{Total ILCR} \quad = \quad \sum_i \sum_j \text{ILCR}_{ij} .$$

Before estimating the total incremental lifetime cancer risk, the risk assessor may estimate subtotals by chemical source and by route of exposure to help clarify which exposure pathways cause the greatest risk. Of course, for a contaminated site, the risk assessor must take care to add risks from exposures related to the site.

Because the incremental lifetime cancer risk is formulated and interpreted as a probability of developing cancer sometime during a lifetime, the value (in theory) ranges from zero to one. As a practical matter, the probability of developing cancer is not linear at high doses (as the CSF implies). Even very heavy cigarette smokers are not guaranteed to develop lung cancer. Probabilities that exceed 1 in 100 are usually highly inaccurate.

5. Analysis of Variability and Uncertainty

The risk assessor names the sources, magnitudes, and likely effects of variability and the uncertainty in the analysis. We define variability and uncertainty as:

- Variability represents diversity or heterogeneity in a well characterized population of plants, animals, or people. Fundamentally a property of the Nature, variability is usually not reducible through further measurement or study. For example, different adults drink different volumes of tap water each day no matter how carefully or how often we measure their diets.

- Uncertainty represents partial ignorance or lack of perfect information about poorly-characterized phenomena or models. Fundamentally a property of the risk analyst, uncertainty is sometimes reducible through further measurement or study. For example, a risk assessor may not now know how much soil each adult ingests per day, but she or he may be able to design experiments to gain additional (but still imperfect) information.

Few risk assessments contain more than a few paragraphs of text acknowledging the variabilities and uncertainties in the methods and results. Some risk assessments go further and include some sensitivity analyses. For example, a risk assessment may include several calculations of the same result, but each one predicated on a different set of input values chosen within the range of the variability or the uncertainty inherent in the analysis. A sensitivity analysis might indicate that the risk estimate is sensitive to the rate of fish ingestion and may suggest that a survey of the affected population might tighten the upper and lower bounds on the risk estimate.

Risk assessments may include information on model uncertainty, i.e., the uncertainty inherent in the mathematical formulation of the models used in exposure assessment, dose-response assessment, or risk characterization.

New Directions in Human Health Risk Assessment

The practice of human health risk assessment for exposure to chemicals in the environment is shifting from a deterministic to a probabilistic paradigm. Two features distinguish the two paradigms. In the probabilistic paradigm we consider, (i) all variables as random variables instead of point values, and (ii) quantitative analyses of variability and uncertainty now become an integral part of the risk characterization in step 4.

Most people understand intuitively that exposure variables such as body weight, the daily ingestion rate of drinking water, and the number of days a person visits a park are random variables. Similarly, most people understand intuitively that toxicity values, such as the RfD or the CSF, are also random variables (by exhibiting inter-individual variability). However, some people are uncomfortable with the logical consequence from these facts -- namely, if all of the input variables in a risk assessment are random variables, then the output variable -- the estimated incremental lifetime cancer risk -- is also a random variable. In other words, the estimated risk for a situation is not a point value but a range of values (see, for example, [6] and [3]).

When establishing the probability distributions for the input variables for a risk assessment, it is instructive to distinguish two driving forces behind the need for

probability distributions -- variability and uncertainty -- as defined earlier. For example, with body weight, the random variable captures mostly the known and well measured inter-individual variability in a population. As a second example, for the number of days a person swims in a local pond, the random variable may capture mostly the unknown or poorly measured inter-individual behavior in a population. So in a risk assessment, the random variables inevitably capture different combinations of variability and uncertainty for each different input variable [4].

For the probabilistic risk assessment paradigm, in any given situation, the risk assessor should focus on choice of (i) accurate input distributions and (ii) accurate exposure, toxicity, and risk characterization formulas. In probabilistic risk assessment, the analyst has to select input distributions based on the facts of the situation.

In the probabilistic paradigm, the risk manager receives more information than in the deterministic paradigm, namely, she or he receives distributions for exposure and risk instead of merely point values. While risk management in the deterministic paradigm consists of comparison of point values for estimated and acceptable risks as a so-called "bright line test," risk management in the probabilistic paradigm consists of comparison of estimated and acceptable distributions of risk.

To continue the numerical example from above, we learn that the fixed values used earlier over-simplified the history. After discussion with the exposed individual and with further field testing, we find that we can better represent some of the variables in the equations as probability distributions than as point values, precisely because variability was an intrinsic part of the person's behavior and also of the aquifer from which the person consumed ground water. With this new information, we find that these probability distributions better describe the situation than do the point values that they replace:

- the variability in Conc (concentration) is well described by a Triangular probability distribution with a minimum of 80, a mode of 85, and a maximum of 120, in units of µg/l;

- the variability in IngR (ingestion rate) is well described by a Normal or Gaussian probability distribution with a mean of 1.60 and a standard deviation of 0.20, in units of l/d;

- the variability in BW (body weight) is well described by a Normal or Gaussian probability distribution with a mean of 70 and a standard deviation of 10 in units of kg;

- the variability in D (days per week) is well described by a Uniform probability distribution with a minimum of 1.0 and a maximum of 2.5; and

- the variability of W (weeks per year) is well described by a Uniform probability distribution with a minimum of 7 and a maximum of 11.

All the other variables and conversions in the equation have the same point values as before.

With this new information, we use a commercial software package named Crystal Ball® [5] to convolve (an operation analogous to ordinary multiplication) the probability distributions and the point values in the equations for estimating $<ADD>_{life}$ and ILCR. Figure 3 shows the results of the convolution (as done by 5,000 repetitions of a Monte Carlo simulation in the software package). The graph in Figure 2 now more fully expresses the variability inherent in the situation as a range of values from ~$5.0 \bullet 10^{-7}$ to ~$2.0 \bullet 10^{-6}$. The point estimate calculated earlier (~$1.5 \bullet 10^{-6}$) occurs well above the 95th percentile of the estimated distribution. This graph conveys considerably more information than did the point value calculated earlier in this article.

Given an estimated distribution for risk, the risk manager might use decision rules along these lines to render an opinion on the acceptability of the estimated risk: (i) is the median of the risk distribution less than 1 in a million?, (ii) is the average of the distribution less than 1 in 100,000?, AND (iii) is the 95th percentile of the risk distribution less than 1 in 10,000? If yes is the answer to all three questions, the risk manager might decide the risk is acceptable. In other words, the risk manager may only look at selected percentiles or summary statistics when deciding if a risk is acceptable for a population.

The new paradigm does require more effort to specify the input variables and more computation to estimate the distribution of the output variable, namely risk.
The probabilistic paradigm still contains unquantified uncertainty. Entire exposure pathways may have been overlooked. Laboratory analyses may have been biased. Statistical data analysis may have been inappropriate. Conservative assumptions may

have been incorporated in the risk assessment unnoticed. The risk paradigm itself may over- or under- estimate risk due to the averaging of exposure, the interactions of chemicals, or other reasons. Overall, the uncertainties for some exposure variables such as soil ingestion rates or toxicity values may have been underestimated in the past due to a focus on specific studies without consideration of fundamental biological principles or other information. One should acknowledge these and other uncertainties to allow for proper interpretation of the distribution of risk. Even considering these remaining uncertainties, the output distribution conveys much more fully the full range and probabilities of plausible health risks -- and provides enormous benefit over the simple point estimates that result from a deterministic calculation.

The probabilistic paradigm builds on the fundamental definition of risk as the probability of adverse outcome. It reestablishes the now blurred lines between risk management and risk assessment.

Glossary

ADD	Average Daily Dose
ARAR	Applicable, or Relevant and Appropriate Requirements
CSF	Cancer Slope Factor
HEAST	Health Effects Assessment Summary Tables
HI	Hazard Index
HQ	Hazard Quotient
ILCR	Incremental Lifetime Cancer Risk
IRIS	Integrated Risk Information System
LOAEL	Lowest Observed Adverse Effect Level
OSWER	Office of Solid Waste and Emergency Response
NAS	National Academy of Sciences
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
NTIS	National Technical Information Service
RfD	Reference Dose
SDWA	Safe Drinking Water Act
US EPA	US Environmental Protection Agency

Trademarks

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Acknowledgments

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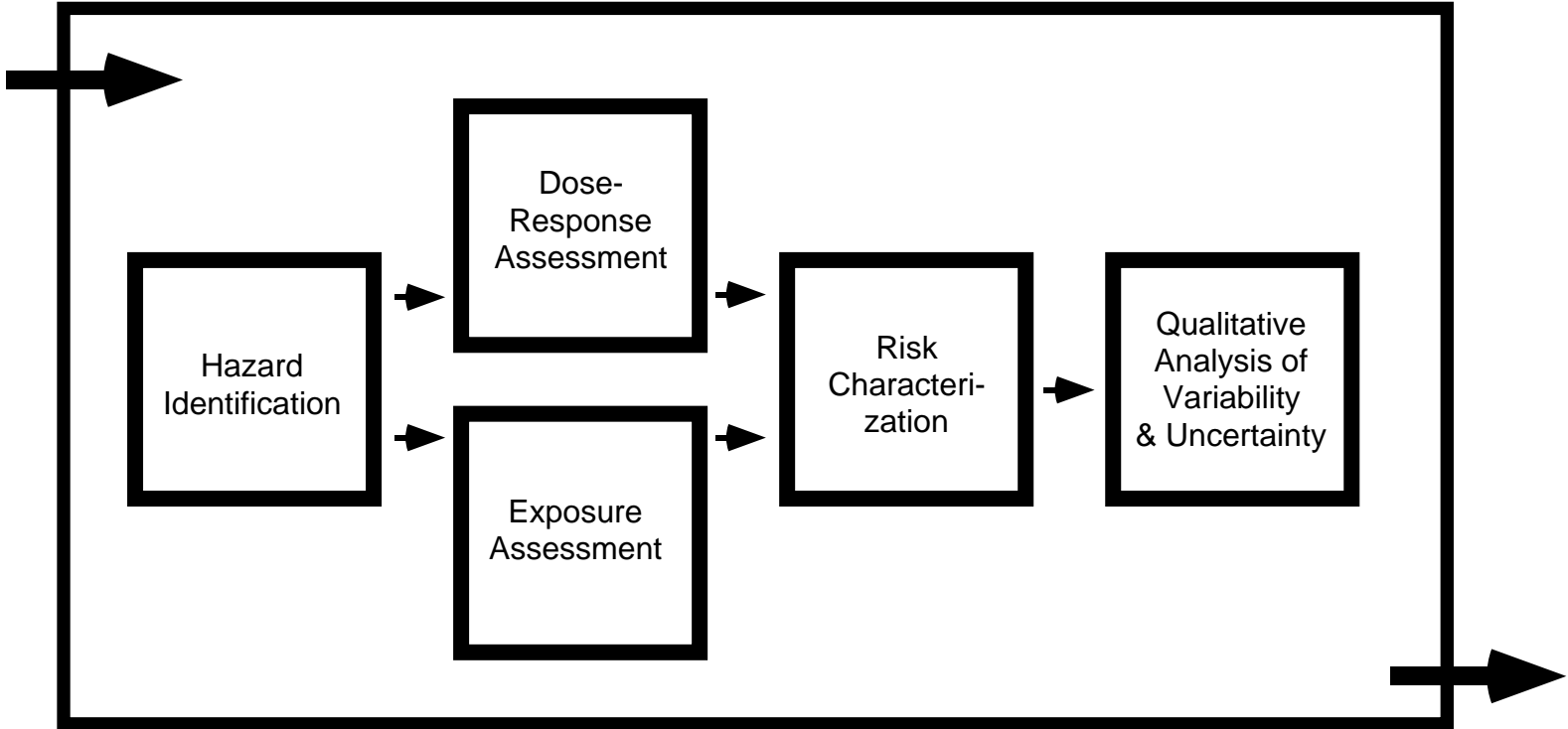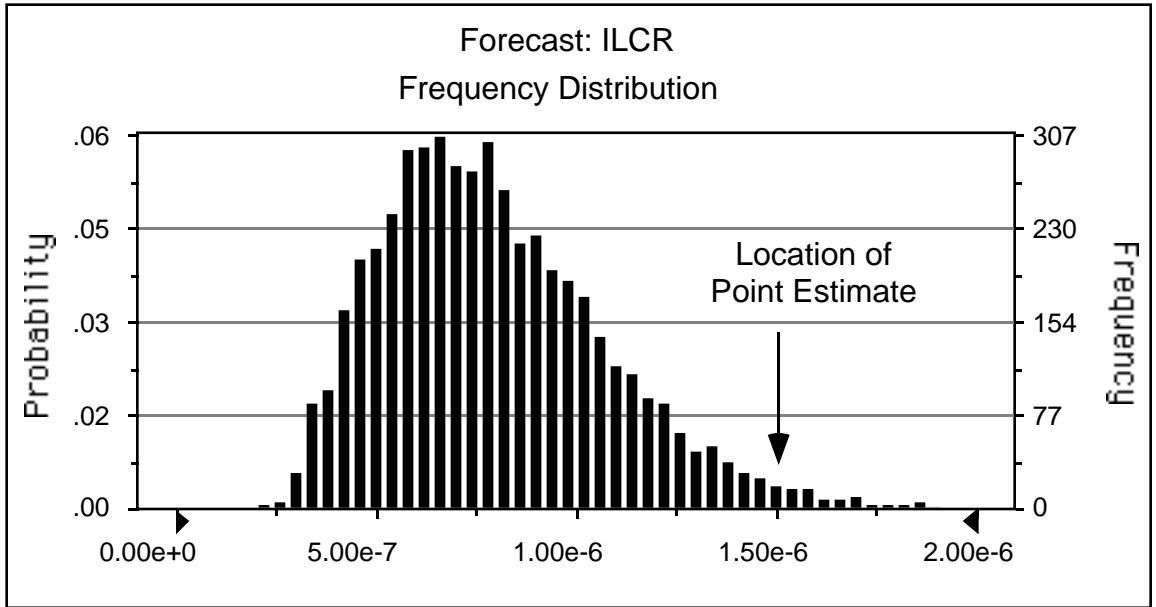
Figure 1: The 5-Step Process for a Risk Assessment

Figure 2
Estimated Distribution of Risk
based on
Estimated Distribution of Exposure