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The nature and purpose of risk assessment

by Joseph V. Rodricks[*]

***Abstract**. Risk assessment is a widely used procedure for gaining understanding of the risks to health posed by the many threats that exist in the environment. For purposes of this paper, the risks of concern are the many forms of toxicity that can be caused by chemicals of all types. Risk assessment findings are typically used by regulatory and public health authorities to establish limits on human exposure to avoid toxicities. This paper is devoted to explaining the procedure, and demonstrating the proper interpretation of its results. Specifically, it will be shown why risk assessments of this nature are designed to apply only to generic populations, and not to any actual individuals in those populations. Thus, for example, claims by individuals that they have suffered harm as a result of incurring exposures in excess of limits established by applying risk assessment results cannot be justified scientifically. Certainly, exposures to a chemical known to cause toxicity can in some cases harm individuals, but the type of evidence and analysis needed to evaluate causation in such cases is substantially different from the risk assessment procedure used to establish protections for populations. This paper summarizes the bases for this conclusion.*

1. Introduction.

Risk assessment is a procedure used to provide support for decisions needed to protect human health from various threats that may arise in the environment. For purposes of this paper, the threats of interest are chemical substances that are known to display certain toxic properties, and to which humans may become exposed through air, water, food, soil, or consumer products. I shall explain the content of risk assessment, its scientific basis and limitations, and the use of

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risk assessment results to support decisions. The decisions for which risk assessments provide support are typically those of regulatory or public health agencies having the responsibility to establish or recommend limits on human exposures to chemicals in order to protect health.

One major purpose of this paper is to demonstrate and explain that risk assessment results cannot be used to determine whether any actual people who become exposed to a substance that is the subject of a risk assessment have been or will be harmed by that exposure. Risk assessments apply to hypothetical, generic populations, and can be used to establish limits on exposure that will protect the most sensitive (hypothetical) members of those populations. But, as we shall see in this paper, they provide no information regarding whether any specific (actual) people will suffer harm. Different and more purely scientific methods are available for the latter purpose, and these methods will be outlined below, in paragraph 6.

Risk assessment came into use in the United States in the 1970s, and has since become common practice around the world. The principles guiding the conduct and use of risk assessment were first made formal in a 1983 report of the United States National Academy of Sciences (NAS)[1]. NAS has published a large number of reports on risk assessment since 1983, and I have relied on these reports and other authoritative guidance documents in developing this paper (see references, n. 1-4).

The paper begins with a broad overview of the content and limitations of risk assessment, and a discussion of its appropriate uses and of its possible misuses (paragraph 2). In paragraph 3, there is a brief discussion of the science of toxicology, and of the scientific issues related to the critical subject of how and to what extent humans may become exposed to chemicals that display toxic properties. I shall show that methods currently available to identify the toxic properties of chemicals have significant limitations, and that the application of data on toxicity to humans exposed through the environment involves many significant uncertainties.

The need to use data on toxicity and human exposure, and to deal with the uncertainties in these data, gave rise to the risk assessment approach, and I describe the conduct of risk assessment in detail in paragraph 4.

In paragraph 5, I provide an interpretation of risk assessment results and discuss the lack of relevance to understanding harms in actual people. In paragraph 6, I present a brief outline of the scientific approaches that are necessary to evaluate the possibility of harm to actual people; I shall show that these approaches are based on empirical data and do not include the many assumptions necessary for the conduct of risk assessments. This section will also demonstrate the importance of understanding the nature and magnitude of exposures experienced by actual individuals in any evaluation of whether they have or could suffer harm.

Paragraph 7 provides background on various legal contexts in which risk assessments have been found useful and appropriate for decisions.

[1] The NAS is the foremost authoritative scientific body in the United States. It is now the National Academies of Science, Engineering, and Medicine (NASEM). It is not a government agency, but is relied upon by government agencies for scientific advice. It performs its work through assembling independent committees of experts to evaluate problems and to recommend approaches to dealing with those problems.

2. Broad overview of risk assessment.

Risk assessments of environmental chemicals have as their purpose an evaluation of the probability that the toxic effects of those chemicals will be expressed under various conditions of exposure to those chemicals. Policy makers, in what is called a risk management process, use these results to establish limits on human exposures to those chemicals. These limits are established at exposure levels at which the probability that toxic effects will be expressed is extremely small. These limits are typically referred to as "safe levels of exposure," and are used to develop regulatory standards or public health recommendations. Thus, a statement that exposure to a chemical at a certain level (concentration) in drinking water will be safe to consume is typically based on a risk assessment result demonstrating a very small probability of harm at that level[2]. There is substantial policy guidance from regulatory and public health agencies on the determination of such safe levels (see references, n. 1, 3).

The safe level is intended to apply to populations, and to be protective of the "most sensitive" individuals in those populations. Sensitivities to the toxic effects of chemicals vary widely among members of highly diverse human populations. If it is assumed that the "most sensitive" person is protected, then it is clear that everyone will be protected.

The populations that are typically the subjects of risk assessments are hypothetical, not actual people. That is, they are assumed to include individuals demonstrating a specific range of variabilities in sensitivity to the toxic effects of chemicals, and include no evidence related to the sensitivity of any actual individuals in the population.

Risk assessments thus cannot be used to determine whether or to what extent any actual individuals exposed to a chemical will be adversely affected by that exposure. In paragraphs 4 and 5, I elaborate further on this matter, and in paragraph 6, I discuss the type of scientific analysis, quite different from risk assessment, that is needed to evaluate possible harms to actual people.

The 1983 NAS report mentioned earlier and every additional NAS report on risk assessment, emphasizes that while risk assessments depend upon the availability of scientific information on toxicity and human exposures to chemicals, they cannot be completed without the use of various assumptions that are not fully validated scientifically. Some, in fact, have very poor validation. I shall elaborate on these various assumptions, and their influence on risk assessment results, in paragraphs 4 and 5, but one example at this point may illustrate this important issue.

I shall show in paragraph 3 that the toxic properties of chemicals are to a large extent identified from studies in experimental animals. These experiments typically involve exposing relatively small groups of rats or mice to a chemical at exposures greatly in excess of any known human exposure. Data from such experiments, assuming they are of high quality, are universally used for risk assessments that will be used to derive safe exposure levels for humans. There is some scientific basis for assuming findings in animals apply to humans, but it is by no means scientifically established. There is thus an inherent uncertainty involved in using animal data. Risk assessments typically involve the *assumption* that animal data apply to humans, but this assumption is in part policy-based, and rests upon a precautionary public health policy. Such assumptions have utility for the purposes of regulation, but the scientific bases for inferring from

[2] The actual probability in most cases may be zero, but there is no strictly scientific way to prove this statement. Science has no way to demonstrate the complete absence of risk.

animal data that the chemical may produce any specific adverse health effect in humans is uncertain, and, in many cases, highly uncertain (see references, n. 5).

Many other assumptions are involved in the risk assessment process (paragraphs 4 and 5) and their use supports the conclusion that risk assessment results cannot be used to understand risks or harms to actual individuals.

These types of assumptions are often referred to as "default assumptions" A "default" is a position taken when a number of different options are available, but it is decided that there is little basis for choosing among those options. For convenience, one option is selected for general application (the "default"). Many defaults are used in risk assessments, and, because of the public health contexts for risk assessments, defaults are typically chosen by invoking precautionary principles. Thus, defaults are chosen to avoid a significant chance of understating risk.

Because each individual default assumption is chosen to avoid underestimating risk, the cumulative effect of the several (sometimes many) defaults used in a risk assessment is likely an overestimation of risk to the hypothetical population. This precautionary approach used by regulatory and public health officials is appropriate (as long as it is not too extreme, and is grounded in generally accepted risk assessment practice norms) for their missions.

The NAS reports have strongly emphasized the need for guidance documents on the conduct of risk assessments. These documents are especially important for specifying the default assumptions used in risk assessment (see references, n. 1, 3, 6).

Because many different approaches to risk assessment, involving different assumptions, can be taken, regulatory officials in both the United States and in the European Union have specified in written guidelines the specific default assumptions they have adopted. Such guidelines are necessary if regulatory risk assessments are to be transparent and free of bias. Risk analysts are generally required to adhere to guidelines, and cannot introduce arbitrary assumptions that are intended to yield some predetermined or desired result (see references, n. 6).

3. Toxicology and exposure assessment for chemicals.

Risk assessment approaches for chemicals cannot be understood without some background in toxicology and human exposure assessments. These are very complex topics, but the points important for risk assessment can be readily summarized (see references, n. 5).

(i) All chemicals can cause some form of toxicity (any type of adverse effect on health) under certain conditions of exposure. Toxicities take many different forms and differ from chemical to chemical.

(ii)"Conditions of exposure" refers to the amount of chemical coming into contact with or entering the body, referred to as "dose". Conditions also refer to duration of exposure and the route of exposure (ingestion, inhalation, and skin contact are the routes for environmental chemicals).

(iii) The types of toxicity produced by a chemical (for example, damage to liver or kidney, harm to the nervous system, etc.) vary among chemicals and for a given chemical also may vary as the conditions of exposure change.

(iv) Chemicals cannot be tested for toxicity in humans, for obvious ethical reasons. But it is sometimes possible to identify some forms of toxicity for a chemical by studying certain human populations that are exposed to a chemical in their daily lives. Occupational exposures and certain environmental exposures are examples of such exposure situations. Such studies are called observational epidemiology studies: epidemiologists study past and sometimes ongoing exposures, making observations about the health of exposed groups of people. It is not possible to study most chemicals in this way and such studies are difficult to perform and (especially) to interpret. But with sufficient effort, the toxic properties of some chemicals can be identified through such studies.

(v) Because it is important to identify the toxic properties of chemicals to which people may be exposed, the most common way to achieve this goal is through experiments in animals. Such studies can be carefully controlled and many different forms of toxicity can be identified. As noted in paragraph 2, there are significant uncertainties regarding the applicability to humans of results from such studies, but for regulatory purposes, animal data are accepted as the basis for risk assessment unless there are convincing scientific reasons for not doing so.

(vi) A critical feature of the science of toxicology concerns the well-established fact that the risk of toxicity increases as the dose (or the dose and duration of exposure) increases. Thus, from animal and human studies comes information on the dose-response relationship (where "response" is "risk of toxicity").

(vii) For most forms of toxicity, a certain dose of the chemical must be exceeded before toxicity occurs. This is referred to as the threshold dose for toxicity[3]. This threshold dose is referred to as the "No-Observed Adverse Effect Level" (NOAEL), and it can be considered a safe dose for the specific population (human or animal) that has been studied. For reasons to be discussed in paragraph 4, the NOAEL is by no means to be considered the safe dose for other populations (risk assessment, as noted earlier, is used to identify the safe dose for populations to be protected).

(viii) The NOAEL is the highest point in the observed dose-response relationship at which no toxicity is seen[4].

(ix) As will be seen in paragraph 4, toxicity and dose-response data are the starting points for risk assessment. Deriving safe levels of exposure for large, diverse human populations requires the use of many assumptions having varying degrees of scientific support, and policy choices based on precautionary principles. These are the "defaults" discussed earlier.

(x) Safe levels, as we shall see, are typically only a tiny fraction of the NOAEL. The safe level is used to set limits on the amount of chemical that can be present in the medium of human exposure (air, water, food, soil, consumer products). The limit is established so that human exposure to the medium of exposure will not lead to doses exceeding the safe dose.

[3] Certain forms of toxicity may not exhibit such a threshold. See paragraph 4.
[4] All experiments have control (unexposed) groups. Sometimes adverse effects unrelated to a chemical are observed at low rates in control groups. To say that a chemical produces a certain form of toxicity, the toxicity has to be observed at a rate greater than its occurrence in control groups. Generally, the increased risk has to be statistically significant.

(xi) If it is found that certain exposures in populations exceed safe limits, risk management approaches are invoked to reduce those exposures so that safe levels are not exceeded.

We shall turn in paragraph 4 to the procedures followed in risk assessment to derive safe doses for human populations; we need to keep in mind that the populations are hypothetical, in that they are assumed to consist of people having many characteristics in common (body weight, for example), but who are assumed to vary in their sensitivities to the toxic effects of chemicals *in a specified way*. The actual variability occurring in populations of actual people is unknown, and thus cannot be used in risk assessments[5].

4. The conduct of risk assessment: data and assumptions used.

Risk assessments are undertaken to identify safe levels of exposure for populations that may become exposed to chemicals through the environment. Once those levels are identified, regulatory or public health agencies use them as guides to determine whether environmental media contain levels that exceed the safe levels, and actions are taken to reduce exposure to safe levels (by, for example, various treatments of the media). Thus, risk assessments are used to assess current exposures and to define exposure limits for the future. It is conceivable that risk assessments might be used to evaluate exposures that might have existed in the past, but this would require extensive quantitative data on what those past exposures were. Such data are typically unavailable or highly incomplete, and without them it is not possible to determine whether past exposures exceeded the safe level.

It should be kept in mind that this discussion is focused on regulatory limits or public health recommendations, based on the application of risk assessment. Knowledge regarding exposures occurring in different settings is useful for determining compliance with regulatory standards or public health recommendations. As has already been mentioned, and will be further discussed below, it cannot reveal whether or to what extent actual individuals have suffered or might suffer harm from those exposures.

4.1. Steps in the risk assessment process.

(i) Risk assessment begins with identifying the specific chemical(s) of interest, and the environmental media in which it is present and through which people become exposed. The route(s) of exposure are important, and so must be identified.

(ii) Investigations are undertaken to identify and retrieve for expert review all available data on the toxic properties of the chemical of interest. Both epidemiology and animal data are sought. In addition, any experimental studies on the way the chemical enters, is distributed within, and excreted from the body are retrieved, as are studies on the biological mechanisms by which the chemical produces its adverse effects.

[5] Total variability in responses (or sensitivities) to chemical toxicity is a function of many factors. Some aspects of variability are understood reasonably well, but others are not. In the absence of knowledge regarding total variability, default assumptions are used in risk assessment (paragraph 4).

(iii) Experts review the retrieved studies. Studies judged to be of low quality are usually rejected. Out of this review the critical toxic properties of the chemical are identified, usually those occurring at lowest dose – those having the lowest NOAEL values. Studies in which the route of exposure is the same as that by which people may become exposed, if available, are preferred to those involving other routes.

(iv) The amount of data and the numbers and types of studies are highly variable among chemicals. For a few chemicals there are extensive human epidemiology data, and when these are available they are usually selected as the starting point for risk assessment. In most cases, the epidemiology data will be limited or non-existent, and so data from animal studies are used[6].

(v) The NOAEL derived from these studies is a critical value, because it represents a threshold dose in the specific study chosen for risk assessment. But the NOAEL cannot be taken as the threshold dose for a large and highly diverse human population. There is no scientifically certain way to derive a threshold (safe) dose for a human population, and, as discussed earlier, default assumptions are used to deal with these uncertainties.

(vi) If the study selected for risk assessment is an animal study, the first consideration is the relative sensitivities of humans and animals to the chemical's toxic effects[7]. It takes very extensive research to estimate relative sensitivities for specific chemicals, and such research is rarely available. In the absence of such scientific information, it is generally assumed that the "average human" is 10 times more sensitive than the experimental animals. There are sound reasons to believe people will, on average, be more sensitive than animals, but the magnitude of that difference is generally unknown. Because the true value is unknowable, the default assumption of 10 is used as the magnitude of the difference in sensitivity to toxicity. The NOAEL is divided by 10 to estimate a threshold dose for the "average human". Of course, the actual "average human" is unknown, and is a purely hypothetical person, assumed to be 10-fold more sensitive than the experimental animals (see references, n. 6).

(vii) That there is variability in sensitivity across the human population is scientifically verified, but the magnitude of that variability is generally unknown in specific cases. A default assumption of 10 is used to derive a threshold dose for the hypothetical "most sensitive" human. The "most sensitive human" is thus assumed to be 10 times more sensitive than the average human. Another factor of 10 is thus applied. These factors of 10 are not known to be accurate in any empirical, scientifically verifiable sense, but there is some reason to believe that they are more cautious than they need to be to protect health – they are precautionary (see references, n. 4).

(viii) If the starting point for risk assessment involves data from human epidemiology studies, a judgment is made about whether the studied human population might represent the "average" human. Many epidemiology studies are of worker populations, which do not involve children and young people, and often include few women. Variable factors based on judgment are applied to estimate a threshold for the "most sensitive individual" when human data are used for risk assessment. There is no single default assumption.

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[6] It is especially difficult, based on observational epidemiology studies, that observed associations between chemical exposures and certain disease outcomes are actually *causal*. Determining causality usually requires consistent findings of associations from several studies, and compliance with other criteria (see references, n. 5).

[7] As used here, "sensitivity" refers to the extent of toxicity associated with a given dose. Highly sensitive individuals will experience a certain degree of toxic harm at *lower doses* than will less sensitive individuals.

(ix) These default assumptions, when expressed quantitatively, are called Uncertainty Factors (UFs). They are intended to deal with uncertainty.

(x) Additional UFs are often applied. They are used to account for limitations in the database. If, for example, there are no studies having exposures of lifetime duration, an additional UF is applied, typically in the range of 3-10.If no data exist pertaining to the possible effects of a chemical on reproductive and developmental processes, additional UFs may be applied. In some cases the data do not reveal a NOAEL, and if this is the case, an additional UF is applied. These defaults have nothing to do with risk, but rather with the absence of certain kinds of knowledge about toxicity.

(xi) Because of the introduction of these various UFs, the safe doses estimated by risk assessments are almost always a very small fraction of the minimum dose identified as toxic. The fractions will vary among different chemicals because they depend in part on the toxic characteristics of specific chemicals and on the type of data available concerning their toxic properties. Based on risk assessments conducted by the U.S. EPA, the observed toxic dose in animals for chloroform is more than 1,200 times greater than the safe dose. The minimum toxic dose for chromium is 800 times greater than the safe dose. The minimum toxic dose for perfluorooctanoic acid (PFOA) is 20,000 times greater than the safe dose. These values demonstrate the very large uncertainty factors that are used in risk assessments.

(xii) For some toxic effects there is a scientific debate regarding the existence of thresholds. In some cases, a NOAEL is not used as the starting point for risk assessment. Rather, efforts are made to "model" the risk of toxicity at very low doses, based on the observed dose-response relationship and the application of statistical models. Various models are available, and it is not at all certain which provides the most accurate answer about risk to health that may or may not exist at doses much smaller than those that have been studied. A single model now dominates this area of risk assessment (the so-called linear no-threshold model) and has become the usual default. Other models may well be more accurate, but there is no simple way to demonstrate this possibility. The default linear no-threshold model predicts greater risks at low doses than do other models. This precautionary feature of the default is one reason for its selection. Under this approach to risk assessment, safe doses are identified by specifying the dose associated with a very small level of risk. Decisions to use the linear no-threshold model and the specification or selection of safe doses are essentially policy choices; in other words, such decisions are not strictly scientific and data-driven, and are influenced by non-scientific factors (see references, n. 4, 5, 6).

The risk assessment procedures outlined above are widely used, and have general acceptance by regulatory and public health agencies in most countries. Some differences exist across countries, often because of differences in laws governing environmental and even product exposures. But the general principles demonstrated in the above outline can be said to be universally accepted.

5. Interpretation.

It should be clear from the above that the data used in risk assessment and the manner of their application are not intended to apply to any actual people. Rather, they apply to generic people, assumed to have certain characteristics, useful for application of risk assessment principles. It is not known how results from risk assessments apply to any actual living population

or to individuals within the population. Although some people in those populations no doubt have some characteristics of the hypothetical people considered in the risk assessment process, there is no way to determine who those people are. The picture becomes even less certain when risk assessments are based on animal data collected at very high doses. As noted earlier, there are precautionary public health reasons to use animal data for risk assessment, but assuming without a great deal of additional scientific study and evidence that toxic effects observed in animals at very high doses predict effects in specific humans exposed at very low doses is scientifically unsupportable. Risk assessment results are useful guides to decisions that regulatory officials need to make to protect the health of the public, but they do not reveal whether and to what extent, if at all, actual individuals will be harmed by chemical exposures.

6. Evaluating possible harms to actual people.

There are methods that can be used to assess the likelihood that actual people exposed to toxic chemicals have been harmed by that exposure or at significant risk of future harm, but those methods bear only weak resemblance to the risk assessment methods outlined above. A brief summary of this methodology is offered here, with an example involving the petroleum product known as benzene.

(i) Benzene has been the subject of numerous epidemiology studies, and under certain conditions of exposure has been shown with relatively high certainty to be a cause of leukemia in humans. The conditions of exposure involve inhalation of certain amounts of benzene over several years or more.

(ii) If actual individuals have experienced exposure to benzene (for example, because they live near a petroleum refinery emitting benzene to the air, or because they have experienced exposure in their work places where benzene was used as a solvent), it is possible they are at risk of developing leukemia. If one or more of these individuals has developed leukemia, it is possible benzene was the cause. As noted, benzene is considered a cause of human leukemia, under certain conditions of exposure.

(iii) As with most diseases, leukemia can be caused by other agents and by other unknown conditions. Diseases such as cancer are called multifactorial because there are many factors that can initiate and promote the disease process in humans.

(iv) Thus, because benzene causes leukemia in certain studied populations, it is not necessarily the case that it will be a significant causal factor in other people who become exposed.

(v) To determine the probability that an individual having leukemia acquired that disease by exposure to benzene, efforts have to be made to understand the magnitude and duration of the individual's exposure, and to determine whether it falls clearly in the range of exposures over which actual leukemia risk has been observed in epidemiology studies. This is a complex undertaking, and requires knowledge of past exposures to benzene that may be difficult to acquire. But there is no other scientifically supportable way to understand whether this individual has been harmed by benzene exposure. This same approach could be used to estimate the likelihood of harms in the future if leukemia has not already occurred.

This approach is purely empirical, and is entirely based on empirical data. It is completely unlike the risk assessment approach described earlier. A risk assessment for benzene might begin

with the same epidemiology data described here, but as illustrated in paragraph 4, many default assumptions are applied to these data to derive risk-based regulatory limits and public health advisories. Finding that actual individuals are exposed to benzene at levels greater than those derived from risk assessment provides no useful information about the probability of actual harms in actual people. Evaluating the likelihood of actual harm to actual people requires knowledge of the exposures those people have experienced and demonstration that those exposures are closely similar to the exposures at which disease has been shown to occur in human populations that have been the subject of epidemiological studies.

7. Legal applications.

Certain committees of the NAS have focused on legal cases in the United States that involve issues of disease causation in individuals and the use of risk assessment (see references, n. 4). There have been legal cases in which risk assessment issues and regulations based upon them have been important subjects, but these have involved debates over the quality and scientific appropriateness of risk assessments that have reached different conclusions. These cases have arisen in regulatory contexts, and do not concern actual harms to actual people. They concern possible violations of regulations.

I am, of course, not expert in legal matters. But I can say that if criminal legal actions are based on the assumption that risk assessments can be used to describe specific harms to actual people, then those actions are scientifically unsupportable, for the reasons set forth in this paper. Moreover, they are even less supportable – not supportable at all – if there is no evidence at all that actual humans have been exposed to the chemicals at issue. No one can be harmed, or put at risk of harm, if no exposure to a hazardous chemical has or could occur. As shown in paragraph 6, actual harm can be demonstrated only if there is clear evidence from epidemiology studies that the chemical at issue can cause human disease, and clear evidence that people have experienced exposures closely similar to those experienced by the individuals that were the subjects of those studies.

Risk assessment has important regulatory purposes, but it is not appropriate for understanding actual harms to actual people.

References, with commentary.

1. National Academy of Sciences (NAS), *Risk Assessment in the Federal Government: Managing the Process*, The National Academies Press, 1983.
The foundations for risk assessment principals, most especially the need for and use of default assumptions and the policy components governing its content and uses, are fully addressed in this important work.

2. National Academy of Sciences (NAS), *Science and Judgement in Risk Assessment*, The National Academies Press, 1994.
This volume contains a highly technical presentation of risk assessment, and reaffirms the principals set forth in the 1983 report (above).

3. National Academy of Sciences (NAS), *Science and Decisions: Advancing Risk Assessment*. Washington, The National Academies Press, 2009.

The most advanced report on both scientific and policy aspects of risk assessment. The report reaffirms and further elucidates both the need for default assumptions and improved approaches to identifying the appropriate assumptions.

4. National Academy of Sciences (NAS), *Reference Manual on Scientific Evidence: Third Edition*, The National Academies Press, 2011.

This volume contains 16 chapters on law, the use of science in legal settings, and guides to science and medicine intended to educate federal judges. It was produced as a joint effort of the U.S. Federal Judicial Center and the National Academy of Sciences. For purposes of my report, the most important chapter is called *Reference Guide in Epidemiology*, which focuses on evaluating disease causation and methods to evaluate whether exposures to hazardous substances can cause harm in actual people. There are also excellent chapter on *The Admissibility of Expert Testimony* and on *How Science Works*.

I served on the committee that produced the above four reports. I also have a chapter in the fourth report entitled *Reference Guide on Exposure Science*. Other experts prepared the other chapters in the report. All four of these reports can be acquired from (by download) the NASEM website.

5. My own text *Calculated Risks: The Toxicity and Human Health Risks of Chemicals in our Environment* (2nd Edition), Cambridge University Press, 2007, provides background on both toxicology and risk assessment. I also recently prepared a chapter on the science of toxicology for the Thomson Reuters volume *Modern Scientific Evidence: The Law and Science of Expert Testimony*, Vol. 3, Chapter 22.

6. Guidelines for risk assessment have been published by the U.S. Environmental Protection Agency (USEPA) and the European Chemicals Agency (ECHA) of the European Union (EU):

a. *USEPA Risk Assessment Guidelines*.
b. *USEPA. 1989-2009. Risk Assessment Guidance for Superfund*, Washington, DC.
c. *USEPA. 2011. Exposure Factors Handbook: 2011 Edition (Final Report)*, Washington, DC: EPA/600/R-09/052F.
d. *USEPA. 2005. Guidelines for Carcinogenic Risk Assessment*, Washington, DC: EPA/630/P-03/001F.
e. ECHA. 2011-2017. *Guidance on Information Requirements and Chemical Safety Assessment (Parts A – E)*, Helsinki, Finland.