DNC CASE STUDY

Johns Hopkins Bloomberg School of Public Health
Risk Sciences and Public Policy Institute

Introduction to the Risk Sciences and Public Policy
317.600.81
Third Term, 2019-2020
Purpose of the Case Study

New information on the toxic properties of a widely used chemical, dinitrochickenwire (DNC) has just been published in a major scientific journal. Because DNC is manufactured and widely used in the State of Anxiety, the State's senior health and environmental policymaker must decide whether the new information justifies regulatory action. As a first step, the policy-maker must determine whether and to what extent current uses of DNC endanger the public’s health. The senior policy-maker thus assembled a group of top Department of Health and Environmental Protection (DHEP) scientists from various disciplines -- epidemiology, toxicology, biochemistry, pathology, statistics, chemistry -- and posed the following questions:

1. What types of health hazards might be associated with DNC, and how well are these known?
2. What is the magnitude of human exposure to DNC in the State of Anxiety, and how is the exposure distributed in various population groups?
3. What is the nature and magnitude of human risk associated with the various sources of exposure?

The group of scientists collected data to conduct a risk assessment. In particular, they developed information to estimate the likelihood that DNC will exhibit one or more of its hazardous properties under actual conditions of human exposure. At this stage, the senior policy-maker is concerned only with understanding the risks of DNC and the ways in which that risk can be characterized. The senior policy-maker is not presently concerned with what has been referred to as risk management (i.e., the issue of how to regulate DNC if a significant risk has been identified). Hence, the senior policy-maker is not considering the commercial importance of DNC and the possible regulatory consequences of reporting a significant health risk.

The senior policy-maker believes strongly that information must be assembled to allow a decision to be made. It would not be satisfactory to conclude that "no risk assessment would or could be performed," or that "more research" had to be conducted before any conclusions could be reached. Rather, the senior policy-maker feels it is essential that as definitive a statement as currently possible be made about the health risks of DNC and that the uncertainties in the assessment be identified. The senior policy-maker knows he/she will eventually have to make a decision about how to handle the scientific uncertainties in the risk management decision, but for now the need is to understand and characterize the current scientific knowledge of the risks of DNC.

Homework Assignments

Your homework assignments have been derived from the material presented in this case study. There will be 5 homework assignments in total, one for each step of the risk assessment process. This packet contains all the homework assignments for this course. Please note the separate due dates for each section of this packet, as listed in the syllabus. Late assignments will be penalized. Written responses for each assignment must be submitted electronically to the corresponding Drop Boxes on CoursePlus as Microsoft Word documents no more than 2 pages in length (single space, 12-point Times New Roman or Arial font, 1-inch margins).

Assignments 4 and 5 include mathematical calculations. Calculations, related assumptions/justification and references need not be within the 2-page limit (i.e., only the written responses to questions must be within 2 pages). For assignments 4 and 5, there are two Drop Boxes. Students may choose to scan, upload and submit a separate file for hand-written calculations or submit calculations in a Microsoft Excel or PDF file. However, using the second Drop Box is not required. If students choose to use Microsoft Word for calculations, they should be merged into a single file.
Students are expected to reference appropriately for all assignments (any referencing format will be accepted). Assignments may be uploaded to individual Drop Boxes more than once, but the most recent version uploaded will automatically replace the previously uploaded file.
DATA AND ANALYSIS TO BE REVIEWED

The attached report contains five sections. The homework is worth a total of 120 points.

Section I: Background: Problem Formulation (10 points)
- The first section is a discussion of the nature and uses of DNC and some general information about human exposure to it. You will summarize this information to present an overview of the problem to be addressed in the risk assessment.

Section II: Hazard Identification (20 points)
- This section presents the available toxicological and epidemiological data for DNC. You will examine several issues and reach conclusions regarding the data.

Section III: Dose-Response Assessment (25 points)
- This section provides detailed information from which to evaluate the quantitative relationship between the dose and a toxic health endpoint (e.g. death). In this section you will evaluate the conditions under which the toxic properties of DNC might be evidenced in people who are exposed to it. There may be several scientifically plausible options for describing this relationship in the region of likely human exposure, and you will be asked to judge the relative merits of these various options. That is, you will be asked to choose among them, or formulate a better one.

Section IV. Exposure Assessment (30 points)
- This section contains the monitoring data for DNC. You will use this information to characterize exposure to DNC for various groups of population based on limited monitoring data. Again, several issues arise concerning the interpretation and use of this information, and it will be necessary for the senior policy-maker to formulate appropriate conclusions.

Section V. Risk Characterization (35 points)
- In the final step, you will estimate the human health risks posed by DNC. This portion of the evaluation requires you to present the uncertainties associated with the risk estimates as part of your conclusions.
I. BACKGROUND INFORMATION ON DNC

USES OF DNC

• Chemical intermediate in the synthesis of several important dyes and pharmaceutical agents. There are no readily identifiable substitutes for these uses.

• Solvent for various resins, gums, and waxes. Several substitutes are available, but all are considerably more expensive.

• Fumigant for fruits and grains. Very effective at preventing insect damage. Substitutes are available, most of which are more expensive and less effective. The health risks of these substitutes are not well known.

CHEMICAL AND PHYSICAL PROPERTIES OF DNC

• Impurities: Commercial product contains trace amounts of dinitrochickenwire.

• Physical state: Liquid, moderate to high volatility.

• Stability: Degrades very slowly in aqueous environments.

• Solubility: Slightly soluble in water.

PRODUCTION (U.S.A.)

1940: 6.6 million pounds
1950: 70 million pounds
1960: 169 million pounds
1970: 180 million pounds
1980: 195 million pounds
1990: 230 million pounds

• Four major manufacturers, all in State of Anxiety.
• More than 200 commercial user companies; at least 50 are in State of Anxiety.

HUMAN EXPOSURE TO DNC

• General Population. Most members of the population are exposed to residues of DNC in bread, other goods derived from grains, and certain fruits. Some people living in the vicinity of manufacturing and use are also exposed. Fumigant use and waste disposal have led to contamination of groundwater used for drinking, showering, etc.

• Worker Population. Workers are exposed during manufacture and at fumigation areas.

BACKGROUND ON DNC TOXICITY

The toxic properties of DNC were first investigated in the 1940s and 1950s. In most of these tests, small groups of experimental animals were fed very high amounts of DNC to identify the intake conditions that would cause death. Animals received either a single dose, or repeated doses covering only a small fraction of their lifetimes.

During the 1950s and 1960s, more extensive animal toxicity tests were conducted, although none involved dosing the animals for more than about one-sixth of a lifetime. These tests revealed the "range" of doses that produced toxicity
(the principal site of toxic action was the liver), and also the dose below which no form of toxicity was identified in the experiments as conducted.

Information available in 1970 showed that the most highly exposed humans received a daily intake of DNC that is several hundred times lower than the "no-observed adverse effect level" (NOAEL) identified in the animal tests. For these reasons, the use of DNC was assumed to present no risk to the public.

No data had been published on the effects of DNC on exposed humans until after the results of the 1985 chronic toxicity study (below) became available. As will be discussed later, this toxicity study spurred collection of information on exposed humans.

THE FRANKENSTEIN STUDY

In late 1985, an article entitled "Chronic Toxicity of Dinitrochickenwire in Rats and Mice" appeared in a respected scientific journal (Frankenstein, V. J. Environmental Toxicology). The Frankenstein paper presented data on the effects in two species of rodents of lifetime exposure to DNC. These data revealed a form of toxicity -- carcinogenicity -- which had not previously been seen.
Problem Formulation (10 points):

Briefly summarize the problem of interest that you will address in the later steps of the risk assessment. In particular, discuss the following topics:

- Provide a brief summary of the public health problem to be investigated.
- What potential population health impacts (i.e. diseases or health endpoints) are of concern?
- Define the population of interest, including any sensitive populations that warrant additional considerations.
- What are two potential risk management options that might be considered at this stage? I.e., if you were a decision-maker, based on the information you have so far, what are some options you might consider taking to protect the public? This is not to say you would take immediate action based on the information you have so far, but just to have some options available for consideration?

Note: Although you are allocated two single-spaced, 12 point, 1 inch margin pages, ideally this assignment should be no longer than a couple of paragraphs.
II. HAZARD IDENTIFICATION

SOME GENERAL PRINCIPLES FOR HAZARD IDENTIFICATION

- The purpose of hazard identification is to identify the types of adverse health effects that may be associated with exposure to DNC and to characterize the quality and strength of evidence supporting this identification.

- The specific hazard of concern in this review is cancer.

- Well-conducted epidemiological studies in exposed human populations are generally considered the best source of information for hazard identification. Unfortunately, they are not available for most substances. Moreover, establishing firm causal links between exposure and chronic human disease (such as cancer) is very difficult.

- Studies in experimental animals also provide useful information for hazard identification. Such studies can be controlled, and thus can more easily establish causality. Results from such studies suffer from the obvious limitation that experimental animals are not the species of ultimate interest.

- With one possible exception (arsenic), all known human carcinogens are also carcinogenic in one or more experimental animal species. Most animal carcinogens have not been established as human carcinogens. In most cases, the lack of adequate epidemiological data means that no definitive decision about human carcinogenicity can be made. Nonetheless, the absence of epidemiologic data should not stop policy makers from making policy decisions on potential cancer risks.

- There are biological data supporting the proposition that responses in experimental animals should be mimicked in humans. However, for some agents, differences in response between species can be substantial.

- It is known that the specific site(s) of tumor formation in humans may be different from the observed in experimental animals.

- Data obtained by administering a substance by the same route of exposure that is experienced by humans are considered more predictive than data obtained by a different route. But, if tumors form at internal body sites, the route of exposure may not be important.

- In general, experimental results that show tumor formation in several species, both sexes, at several different exposure levels with increasing response at increasing exposure, and at multiple body sites provide more convincing evidence of potential human carcinogenicity than does a response that is limited to a single species or sex, or to a single common site of tumor formation.
THE FRANKENSTEIN STUDY

The design of the Frankenstein experiment, discussed in the previous section, and the major findings are presented in Tables I and II.

Table I: DESIGN OF THE FRANKENSTEIN STUDY

<table>
<thead>
<tr>
<th>Species and Route of Exposure</th>
<th>Groups Receiving DNC</th>
<th>Number of Animals</th>
<th>Amount of DNC Received (mg/kgBW-day)</th>
<th>Duration of Exposure (in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Rat, Inhalation</td>
<td>Control</td>
<td>60</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Low Dose</td>
<td>60</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>High Dose</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Rat, Gavage</td>
<td>Control</td>
<td>60</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Low Dose</td>
<td>60</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>High Dose</td>
<td>60</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Mouse, Gavage</td>
<td>Control</td>
<td>60</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Low Dose</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>High Dose</td>
<td>60</td>
<td>60</td>
<td>120</td>
</tr>
</tbody>
</table>

Note: Gavage is administration of a substance by means of a stomach tube.

Table II: SIGNIFICANT FINDINGS FROM THE FRANKENSTEIN STUDY

This study included all of the above species/sex/route of exposure combination, but the following are the only groups in which a statistically significant excess of tumors was found. Nearly 40 possible sites of tumor formation were examined in each sex of both species.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Sex</th>
<th>Tumors Found</th>
<th>Control (Percentage)</th>
<th>Low Dose (Percentage)</th>
<th>High Dose (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Inhalation</td>
<td>Male</td>
<td>Lung</td>
<td>3</td>
<td>5</td>
<td>25&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Spleen</td>
<td>0</td>
<td>2</td>
<td>25&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Liver</td>
<td>3</td>
<td>6</td>
<td>12&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rat, Gavage</td>
<td>Male</td>
<td>Stomach</td>
<td>0</td>
<td>6</td>
<td>40&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Stomach</td>
<td>0</td>
<td>0</td>
<td>30&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Liver</td>
<td>3</td>
<td>7</td>
<td>15&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Spleen</td>
<td>0</td>
<td>10&lt;sup&gt;iii&lt;/sup&gt;</td>
<td>33&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mouse, Gavage</td>
<td>Male</td>
<td>Liver</td>
<td>5</td>
<td>30&lt;sup&gt;iii&lt;/sup&gt;</td>
<td>50&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Stomach</td>
<td>0</td>
<td>0</td>
<td>10&lt;sup&gt;iii&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>i</sup> The units of "amount received" are milligrams of DNC per kilogram of the animal's body weight per day (mg/kgBW-day). The concentration of DNC in the air in the inhalation experiment has been converted to a unit of weight so that it can be compared to the units in the gavage study.

<sup>ii</sup> Approximate lifespan of the animals under laboratory conditions.

<sup>iii</sup> A statistically significant excess of tumors relative to untreated control animals. This means that the difference in tumor incidence between the treated and control animals is not likely due to chance. Because the only difference between the control and treated animals was the presence of DNC, it is likely that the excess tumor incidence is due to this compound. Tumors were found at other sites in both control and treated animals, but no others occurred in statistically significant excess.
REMARKS ON THE FRANKENSTEIN STUDY

- As far as can be determined from the published Frankenstein article, this study was carefully conducted and there is no reason to doubt the accuracy of the reported data.

- DNC increased the incidence or risk of tumors (percentage or proportion of animals with tumors) in certain groups of animals. Not all animals in a group receiving DNC develop tumors. Data in Table II can be interpreted as in the following example: the lifetime risk of stomach cancer in male rats exposed by gavage to the high dose of DNC daily, for their full lifetimes, is 40 percent (see Table II).

- Rats developed spleen and liver tumors following both inhalation and gavage exposures. Lung tumors were produced only by inhalation and stomach tumors only by gavage. Females of both species showed fewer tumors than males, and mice fewer tumors than rats.

- The stomach tumors appeared at the point at which DNC contacted the stomach when it was introduced by stomach tube. This point is in the rodent forestomach, an anatomical feature not present in humans.

NEW HAZARD INFORMATION ON DNC

EPIDEMIOLOGY DATA

After hearing about the Frankenstein report, three manufacturers of DNC decided to submit reports to the Department of Health and Environmental Protection regarding their investigations into employee health. The data from these three reports are summarized below.

Manufacturer A

A mortality study was conducted on the experience of 161 employees. Although Manufacturer A had been producing DNC for 45 years, none of the employees in the study had been exposed for more than 20 years; most were exposed for 10 to 15 years. Although employee exposure data were not extensive, they suggested that past exposures were relatively high, sometimes approaching the inhalation levels that produced excess tumors in animals. (Although the concentrations of air in the workplace approached those used in the animal experiment, the workers were exposed to these high levels for only fractions of their lifetimes.)

By January 1979, 35 of the 161 workers had died. No increase in cancers of all types was noted among these workers (3 cases observed, 3.8 expected in a population of the same size, sex, and age). Malignant neoplasms of the digestive system were elevated (2 cases observed, 0.7 expected), but this elevation was not statistically significant (i.e., it is not possible to say the observed difference is not due simply to chance). The workers were also exposed to several other chemicals, at least two of which are known animal carcinogens.

Manufacturers B and C

Reports from Manufacturers B and C are similar to that of Manufacturer A. No cases of malignant neoplasms of the stomach were reported by either manufacturer. Both manufacturers reported slight elevations in lung cancer, neither of which was statistically significant. No data on worker smoking habits were available. Manufacturer B studied 95 employees with 33 deaths.
Frankenstein's article reported that untreated male mice experienced a 5% incidence of liver tumors, the low dose group experienced 30% incidence, and the high dose group experienced a 50% incidence (Table II). However, Dr. Frankenstein's article did not point out that untreated, 78-week old male mice of the particular strain used to test DNC had, on several occasions, exhibited a 52% incidence of liver tumors, and, on average, exhibited a 21% incidence.

The pathologist consulting to DHEP also noted that the scientific community has debated the reliability of mouse liver tumor responses as a predictor of human carcinogenicity. The pathologist emphasized, however, that although the interpretation of the mouse liver tumor data may be controversial, most pathologists incorporate such findings in assessing human hazards -- especially when tumors occur at other sites.

**BENIGN AND MALIGNANT TUMORS**

Upon further inquiry, it was learned that Dr. Frankenstein had not reported that of the 15 lung tumors developed in the high dose group (Table II), only 6 were malignant. The other 9 animals developed benign lung tumors.

If only malignant tumors are considered, then there is not a statistically significant elevation in the incidence of lung tumors in male rats, compared to untreated animals (of whom 2 had malignant tumors).

**TOXICITY AT THE HIGH DOSE**

Finally, Dr. Frankenstein noted that she observed severe irritation in the areas of the rodents' stomachs that were exposed directly to the DNC delivered by stomach tube. This irritation was observed in all animals that had stomach tumors, and in several others that did not have tumors, but that showed early signs of a tumorigenic process. No signs of irritation were observed in low dose or control animals.

Dr. Frankenstein believes that the stomach tumors arose as a result of the severe toxic insult experienced by the direct high-dose stomach exposure. Moreover, she believes that these tumors would not have arisen at exposure levels that did not produce severe toxic irritation.

Based on Dr. Frankenstein's view, it appears highly unlikely that a finite risk of stomach tumors would exist at all finite DNC exposures; instead, a risk would exist only at or above the exposure level needed to cause strong irritation. That level of exposure is almost certain not to be expected in any exposed human population.
Hazard Identification Questions (20 points):

**Question 1)**
In light of the EPA Cancer Guidelines and the principles presented in this section, provide a brief overview of the strengths and weaknesses of the data. Please include **at least one strength** and **at least one weakness** from the animal data and likewise for the epidemiology data.

**Question 2)**
Based on your conclusions from the previous question, is there sufficient evidence to conclude that DNC is carcinogenic:

A) In rats? In mice? Is one animal more of a concern than the other? Why?
B) In male animals? In female animals? Is one sex more of a concern than the other? Why?

Please explain your answer.

**Question 3)**
Should the data obtained by gavage treatments be considered relevant to human exposure? Why or why not?

**Question 4)**
Should the information from DNC manufacturers A, B, and C alter earlier conclusions regarding the inferences drawn from animal data? If so, how? If not, why not?

**Question 5)**
Which of the following conclusions best characterize the evidence you have seen (see below)? Please **justify your answer**.

Possible Conclusions Regarding DNC Carcinogenicity:

A. DNC is a human carcinogen.

B. DNC is a probable human carcinogen.

C. DNC is a carcinogen at several sites in rats of both sexes, by both inhalation and oral routes of administration. It is also carcinogenic in male mice by the oral route of administration. DNC is thus a human carcinogen and is expected to increase the incidence of lung, spleen, liver, and stomach tumors in the exposed human population.

D. DNC is a carcinogen at several sites in rats of both sexes and in male mice. DNC is thus a probable human carcinogen, although only humans exposed by inhalation are likely to be at risk. Data obtained when DNC was administered by stomach tube are not relevant to any route of human exposure. Thus, exposure through contaminated food or water has no identifiable risk for humans.

E. Although DNC is carcinogenic in rats and mice, no data suggest that it is carcinogenic in humans. The animal data provide only weak evidence that DNC may be a human carcinogen.

F. Because of the extreme conditions under which tumors were produced in these animal experiments, there is no reason to believe DNC is a possible human carcinogen.

G. Other (formulate your own conclusion).
III. DOSE-RESPONSE ASSESSMENT

The General Problem and Guiding Principles to Its Solution

Recall that animal data showing that DNC is carcinogenic were obtained in the high dose region of the dose-response curve. Animal doses were in the 30 to 120 mg/kgBW-day ranges (Table I), and these produced measurable risks in the range of 10 to 50 percent (Table II). It is important to note that human doses are typically well below the dosages given to animal species in an experimental setting.

Various experts have proposed at least three general approaches to this problem of how to go from experimental results (high dose animal data) to the relatively lower doses experienced under typical human conditions. These approaches are discussed below.

Approach 1: Those who follow Approach I apply the following line of reasoning:

Based on general theories of how carcinogens act to produce cancer (largely derived from experimental studies and epidemiological data), all finite exposure levels will produce a finite probability of a response (i.e., no threshold is assumed). The magnitude of the risk will decline as the magnitude of the dose declines (this is even clear in the animal data).

If the quantitative relationship between the exposure (dose) and the risk were known for all exposures (doses), risks to rodents exposed at very low levels could be predicted from the measured exposure-response data. The probability of a response in humans could be predicted at these very low levels if the relationship between rodent and human susceptibilities were known. Although these relationships cannot be known with accuracy, a plausible Upper limit on risk can be predicted with sufficient accuracy to be used as a guide to making risk decisions. The actual human risk is not likely to exceed the upper limit, and it may be less.

A model is a mathematical formula that describes the relationships between various measures. If Approach 1 is used, then two models are needed to predict low exposure risk:

1. A high-to-low dose extrapolation model is needed to predict risks to rodents. Application of the model to the rodent dose-response (gavage) or exposure-response (inhalation) data produces an estimate of the excess lifetime cancer risk for each unit of exposure in the low exposure region. This is called the unit cancer risk. Other terms, such as "slope factor" (or q*) are more commonly used with the oral route of exposure.

2. An interspecies extrapolation model is used to extrapolate from rodent unit risks to human unit risks. Interspecies extrapolation models are commonly called "scaling factors" because they are used to scale doses between species. Historically, EPA assumes that rodents and humans are at equal risk at the same exposure measured in milligrams of carcinogen per square meter of body surface area per day. This scaling has been done for you and the results are presented in Table III.

Approach 2: Those who follow Approach 2 reject the reasoning in Approach 1, applying the line of reasoning presented here:

The quantitative relationships between the probability of responses at high dose versus at low dose in rodents (i.e., high to low dose extrapolation) and between rodent and human responses (i.e., interspecies extrapolation) are not known with sufficient reliability to be used in risk assessment. Moreover, there is no reliable theory on which it can be concluded with assurance that low-level human exposure (i.e., exposure below the range producing detectable responses) poses any risk. As with other toxic effects, carcinogenicity will not be initiated within an individual until a minimum amount of

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iv These two sentences are the proper formulation of the "no threshold" concept. The "no threshold" concept does not mean that all finite exposure will cause cancer; instead, it means that all finite exposures will increase the probability (i.e., risk) that cancer will occur.
exposure is exceeded (i.e., a threshold is assumed). In such circumstances, the only reasonable course is to report the magnitudes of the margin of exposure (MOE) by which humans are protected. MOE is the maximum amount of exposure producing no measurable tumorigenic response in animals (i.e., the NOAEL) divided by the actual amount of human exposure. MOE gives the risk manager information on which to decide whether exposures must be reduced or eliminated to provide human protection. A relatively large MOE is desirable because it is likely that the threshold for the entire human population is lower than the observed in small groups of experimental animals.

**Approach 3:** Those who follow Approach 3 agree with the underlying assumptions regarding the dose-response relationship in Approach 1, but not how the human dose response should be expressed. They follow the argument here:

Although there is adequate theory and some evidence to permit the conclusion that humans have a finite risk at all finite exposure levels, there is insufficient knowledge to allow prediction of the risk in quantitative terms. The risk assessor should simply attempt to describe risks qualitatively, perhaps coupling this description with some information on the potency of the compound and the magnitude of human exposure. This type of presentation is adequate for the risk manager, who should not be concerned with the quantitative magnitude of risk in any case.

Each of these views, and perhaps others as well, has some merit. Most federal public health and regulatory agencies now use the first approach (this does not mean that you have to accept it as the best approach). These agencies emphasize that the predicted numerical risks based on Approach 1 are not known to be accurate, but, because of the nature of the models used to predict them, they are likely to be upper bound estimates of human risk. An upper bound estimate is one that is not likely to be lower than the true risk, and that is likely to exceed the true risk (which could be zero).

### Dose-Response Evaluation Involving Formal Extrapolation

Following Approach 1, it is important to identify the Unit Cancer Risk (UCR) (or Q*). Calculation of a UCR gives us information about the excess lifetime cancer risk for each unit of exposure. Calculation of the UCR is often performed when the information provided by the study indicates that a carcinogenic process might be occurring, but it is not definitive proof of carcinogenicity.

#### Table III

**UPPER BOUNDS ON LIFETIME UNIT CANCER RISKS PREDICTED FROM APPLICATION OF LMS MODELS TO TUMOR DATA TABLE II**

<table>
<thead>
<tr>
<th>Species, Sex</th>
<th>Route of Exposure</th>
<th>Tumor Site</th>
<th>Unit Cancer Risk’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Male</td>
<td>Inhalation</td>
<td>Lung</td>
<td>0.0081</td>
</tr>
<tr>
<td>Rat, Male</td>
<td>Inhalation</td>
<td>Spleen</td>
<td>0.0059</td>
</tr>
<tr>
<td>Rat, Male</td>
<td>Inhalation</td>
<td>Liver</td>
<td>0.0029</td>
</tr>
<tr>
<td>Rat, Male</td>
<td>Gavage</td>
<td>Stomach</td>
<td>0.0110</td>
</tr>
<tr>
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<td>Gavage</td>
<td>Stomach</td>
<td>0.0069</td>
</tr>
<tr>
<td>Rat, Male</td>
<td>Gavage</td>
<td>Liver</td>
<td>0.0020</td>
</tr>
<tr>
<td>Rat, Male</td>
<td>Gavage</td>
<td>Spleen</td>
<td>0.0058</td>
</tr>
<tr>
<td>Mouse, Male</td>
<td>Gavage</td>
<td>Liver</td>
<td>0.0122</td>
</tr>
<tr>
<td>Mouse, Male</td>
<td>Gavage</td>
<td>Stomach</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

### Dose-Response Evaluation not Involving Formal Extrapolation

It is important to identify the exposures at which DNC produces tumors and those at which no tumor excess is found (the "no observed adverse effect level" or NOAEL). Table IV identifies NOAEL’s from data in Table II. Remember, NOAEL’s allow us to determine, with certain limitations, if a threshold exists for a particular chemical or

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*This is the scaled human unit cancer risk, which is the risk associated with each unit dose, in this case "lifetime average daily dose" (i.e. risk per mg/kgBW-day). This is also known as the cancer slope factor or q*.  

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14
compound. In other words, if a NOAEL exists, it is likely that there is a threshold effect where there is a dose below which adverse effects are not found.

Table IV
NO-OBSERVED ADVERSE EFFECT LEVELS (NOAELS) FOR CHRONIC EXPOSURE TO DNC

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Sex</th>
<th>Tumor</th>
<th>NOAEL (mg/kgBW-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Inhalation</td>
<td>Male</td>
<td>Lung</td>
<td>30</td>
</tr>
<tr>
<td>Rat, Inhalation</td>
<td>Male</td>
<td>Spleen</td>
<td>30</td>
</tr>
<tr>
<td>Rat, Inhalation</td>
<td>Male</td>
<td>Liver</td>
<td>30</td>
</tr>
<tr>
<td>Rat, Gavage</td>
<td>Male</td>
<td>Stomach</td>
<td>50</td>
</tr>
<tr>
<td>Rat, Gavage</td>
<td>Female</td>
<td>Stomach</td>
<td>50</td>
</tr>
<tr>
<td>Rat, Gavage</td>
<td>Male</td>
<td>Liver</td>
<td>50</td>
</tr>
<tr>
<td>Rat, Gavage</td>
<td>Male</td>
<td>Spleen</td>
<td>None Found*vi</td>
</tr>
<tr>
<td>Mouse, Gavage</td>
<td>Male</td>
<td>Liver</td>
<td>None Found</td>
</tr>
<tr>
<td>Mouse, Gavage</td>
<td>Male</td>
<td>Stomach</td>
<td>60</td>
</tr>
</tbody>
</table>

*vi "None Found" means that a measurable excess of tumors was found at both levels of exposure used in the experiment.
**Dose-Response Questions (25 points):**

**Question 1)**
Based upon the dose response data, is there evidence of a threshold level for DNC? Please justify your answer.

**Question 2)**
Are the observed NOAEL's true "no-effect" levels? Could they simply reflect the fact that in experiments with relatively small numbers of animals, the failure to observe a statistically significant increase of tumors is an artifact of the experimental design, and not a true absence of biological effect? Is it appropriate for a unit cancer risk to be used when the experimental data provides a NOAEL? Why or why not?

**Question 3)**
Which unit cancer risk value would you select to assess population risk, based on the information provided in Table III? List two (2) limitations to using this unit cancer risk in your estimates. Which would provide the highest estimate of risk? Which would provide the lowest estimate of risk?

**Question 4A)**
Which of the following approaches do you feel is the most appropriate, based on the dose response data? Please justify your answer.

A) A linear, no-threshold approach using unit cancer risks
B) A threshold based upon the NOAEL
C) A qualitative synthesis of both A and B

**Question 4B)**
Based on your answer to question 4A, which of the following best characterizes the information you have seen? Please justify your answer.

**Possible Conclusions Regarding DNC Carcinogenicity:**

A. The unit cancer risks listed in Table III are true upper bound estimates. The true unit risk is not likely to exceed those listed, they may be lower and could even be zero.

B. The same as the first conclusion, but add: The use of alternative, plausible models yields unit risks about 10 to 100 times lower than those in Table III.

C. Unit risks should be reported for all plausible models, and the full range of estimates should be reported without bias.

D. There is no justification for calculating and reporting unit risks. What is critical for understanding the public health importance of low level exposure to DNC is the margin of exposure (MOE). Estimation of the MOE is based on the NOAEL's for its carcinogenic effects; these figures are reported in Table IV.

E. Neither unit cancer risks nor NOAEL’s are reliable indicators of human risk, and neither should be considered for risk assessment. Dose-response relations for the human population are not known for DNC risk and should be described in qualitative terms only.
IV. HUMAN EXPOSURE ASSESSMENT

(Note: The terms 'exposure' and 'dose' are often used interchangeably even though they are distinct from one another. For a quick review of these terms refer to the review box at the end of the glossary and to the definitions of these terms in the glossary.)

PRINCIPLES FOR EXPOSURE ASSESSMENT

- The purpose of the exposure assessment is to identify the magnitude of human exposure to DNC, the frequency and duration of that exposure, and the routes by which humans are exposed. The number of exposed people also must be identified, along with other characteristics of the exposed population (e.g., age and sex).

- Exposure may be based on measurement of the amount of DNC in various media (air, water, food), and knowledge of the amount of human intake of these media per unit of time (usually per day) under different conditions of activity.

- Some individuals may be exposed by contact with several media. It is important to consider total intake from all media in such situations.

- Because only a limited number of samples of various media can be taken for measurement, the representative-ness of measured values of environmental contaminants is always uncertain. If sampling is adequately planned, the degree to which data for a given medium are representative of that medium can usually be known.

- Sometimes air levels of pollutants can be estimated by the use of mathematical models. Although some of these models are known to be predictive in many cases, they are not thought to be reliable in all cases. Models are not always validated and even when they are, there is uncertainty surrounding their adequacy for use in situations that are unlike those used for the validation process.

- Standard average values and ranges for human intake of various media (i.e. defaults) are available and are generally used unless data on specific agents indicate such values are inappropriate.

AVAILABLE DATA ON DNC:

Table V-A summarizes available data on DNC

1. Exposure through consumption of contaminated bread: DNC residue data for bread consumption were obtained from a single nationwide survey conducted by FDA in 1980. Approximately 2,000 bread samples were taken from all regions of the country. No information is available for other years, although there is no reason to believe that yearly variation would be substantial. Geometric mean of residue concentration is given in Table V-A. Bread intake rates determined by EPA’s Exposure Factor Handbook working group, and also given in Table V-A.

2. Exposure through drinking water: DNC concentrations in drinking water were based on analytical data developed by the State DHEP. Samples were taken from a few wells in the State during the summer of 1985. No attempt was made to obtain a representative sample. Analytical methods appear to have been carefully applied. Geometric mean concentration of DNC in drinking water is given in Table V-A.

3. Exposure through inhalation: Estimates for DNC concentration in ambient air were based on a mathematical model. DNC emission rates were estimated from manufacturing data and air concentrations predicted from a model that has been extensively used by EPA. No analytical data are available. Estimated air concentration is provided in Table V-A.

4. Occupational Exposure: Fumigators are exposed to relatively high levels, but for only 20 to 30 days per year. Air concentrations to which fumigators are exposed are assumed to be the OSHA permissible exposure limit (PEL); no
monitoring data are available. For chronic cancer effect, worker exposures are usually adjusted to a lifetime average by assuming that cumulative exposure (exposure conc. x time) is the determinant of risk. Thus, for example, the risk is assumed to be the same for a worker exposed to 10 units each day for 2 years and a worker exposed to 2 units for 10 years.

**TABLE V-A**

AVAILABLE DATA FOR DNC

<table>
<thead>
<tr>
<th>Source</th>
<th>Concentration</th>
<th>Frequency of Exposure</th>
<th>Adult Intake/Inhalation Rate</th>
<th>Child Intake/Inhalation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread</td>
<td>0.17 ppm (1980 sampling)</td>
<td>Daily</td>
<td>.062 kg/day</td>
<td>.03425 kg/day</td>
</tr>
<tr>
<td>Drinking Water</td>
<td>0.06 ppm (1985 sampling)</td>
<td>Daily</td>
<td>2 L/day</td>
<td>1 L/day</td>
</tr>
<tr>
<td>Air</td>
<td>0.021 mg/m3 (Model)</td>
<td>Daily</td>
<td>22 m³/day</td>
<td>15 m³/day</td>
</tr>
<tr>
<td>Fumigation</td>
<td>2.1 mg/m3 (OSHA-PEL)</td>
<td>20-30 days/year</td>
<td>22 m³/day</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Exposure Assessment Questions (30 points):

Part 1 (calculations worth 10 points)
Using Table V-A, calculate human lifetime average daily doses (LADDs) of DNC for the 4 exposure scenarios listed below (bread, water, air, fumigation) for adults, and calculate average daily doses (ADDs) of DNC for the 3 exposure scenarios listed below (bread, water, air) for children. Use Table V-B (1 & 2) to enter your answers.

Please include your calculations. You must show your work in order to receive full credit. Points will be deducted if you provide only the answer, even if it is correct. Written/typed calculations and assumptions do not count against the page limit for this assignment; use as much space as needed to display your calculations. The 2-page limit applies only to the written responses to questions. Be careful when completing your calculations to always include units, and to double-check that you have cancelled all units appropriately. Final answers must include correct units.

State and justify your assumptions. Standard/default values (e.g., weights, averaging times) are considered assumptions of the calculations, since government and non-government organizations use their own preferred defaults. It will be evident to you that a small change in default value can significantly alter the estimate of risk. Any reference format will be accepted but you must cite where you obtained the default values you elected to use (e.g., course lecture, EPA Exposure Factors Handbook or other source).

Table V-B (1): Adult Estimates of Human Exposure to DNC in the State of Anxiety

<table>
<thead>
<tr>
<th>Source</th>
<th>Lifetime Average Daily Dose (LADD)</th>
<th>Population Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread</td>
<td></td>
<td>Almost the entire general population of 5,000,000</td>
</tr>
<tr>
<td>Drinking Water</td>
<td></td>
<td>About 300,000 people because of ground water contamination</td>
</tr>
<tr>
<td>Air</td>
<td></td>
<td>1,500 to 2,000 people living in the vicinity of the four major manufacturing facilities</td>
</tr>
<tr>
<td>Fumigation</td>
<td></td>
<td>1,000 to 2,000 fumigation workers. Most would be exposed on only 20 to 30 days per year at levels much higher than the average daily lifetime exposure.</td>
</tr>
</tbody>
</table>

Table V-B (2): Child Estimates of Human Exposure to DNC in the State of Anxiety
(Hint: Default weight for a child given in class is 10 kg)

<table>
<thead>
<tr>
<th>Source</th>
<th>Average Daily Dose (ADD)</th>
<th>Population Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread</td>
<td></td>
<td>Almost the entire general population of 5,000,000</td>
</tr>
<tr>
<td>Drinking Water</td>
<td></td>
<td>About 300,000 people because of ground water contamination</td>
</tr>
<tr>
<td>Air</td>
<td></td>
<td>1,500 to 2,000 people living in the vicinity of the four major manufacturing facilities</td>
</tr>
</tbody>
</table>
Part 2 (each question worth 5 points):

Question 1)
The DNC concentrations for the various media (air, water, bread) were calculated in different ways: by sampling water, modeling air concentrations, and a market basket survey of bread consumption. Do you think that these LADDs provide an accurate assessment of population LADDs? Why or why not? Please list at least two (2) major uncertainties in your answer.

Question 2)
Is there any reason to believe that animal data obtained from continuous, lifetime exposures should NOT be used to characterize the risk to workers exposed intermittently, for a relatively small fraction of their lifetimes? Please justify your answer.

Question 3)
Estimations of exposure for fumigation workers are not based on actual sampling data. Do you think it is appropriate to use the PEL to calculate LADDs? Why or why not? Please make sure to justify your answer.

Question 4)
Which of the following best characterizes the data you have seen thus far? Please justify your answer.

Possible Conclusions Regarding DNC Carcinogenicity:

A) Exposure estimates that you have calculated based on monitoring data presented in Table V-A for bread are reliable and can be used for risk assessment. The other estimates are too speculative, and no risks should be assessed until appropriate data are obtained.

B) Although your estimates of exposure are based on different data and assumptions, they are all adequate for assessing DNC risks. The risk manager should be made aware of the uncertainties in each of the data sets.

C) In addition to Conclusion B, it should be noted that all of the exposures that you have estimated should be added together because some people will be exposed to all sources of DNC.

D) None of the exposure estimates is adequate for use in risk assessment. The risk assessment should describe exposure in qualitative terms only (e.g. most of the population is exposed continuously to relatively low levels, while some relatively small segments are exposed either continuously or intermittently to high levels). Such a qualitative description is appropriate and adequate for characterizing risk, which also can be done in qualitative terms only.

E) Other (formulate and explain your own conclusion).
V. RISK CHARACTERIZATION

PURPOSE:

In the last step of risk assessment the information collected and analyzed in the first three steps is integrated to characterize the excess risk to humans. In line with the alternative approaches for describing dose-response relation, at least three approaches can be taken to this step.

1. Provide an explicit numerical estimate of excess lifetime risk for each population group by multiplying the unit risk times the number of units of exposure experienced by each group.

   (Unit cancer risk) x (units of exposure) = excess lifetime risk

   In this equation, excess risk is unit less -- it is a probability.

2. Provide an estimate of the margin of exposure (MOE) for each group by dividing the NOAEL by the group’s exposure estimate.

3. Describe risks qualitatively for each of the population groups.

Risk characterization might also include some combination of all three approaches, along with a description of their relative merits. It is also essential that the statistical and biological uncertainties in estimating the extent of health effects be described in this step.
Risk Characterization Questions (35 points)

Part 1 (calculations worth 10 points):
Using unit cancer risks from Table III (from DNC Case Study) and the LADDS you calculated for adults in Table V-B (1) (from Assignment #4), calculate excess cancer risks for each population group. Present both the upper and lower estimates of excess risks. A good characterization of risk should include both the most conservative, upper estimate of excess risk (public health protective) from the data and the least conservative (lower estimate) excess risk estimate. Also, calculate the MOE for each group. Remember, the MOE is not an expression of risk, but reflects the difference between actual human exposure and the exposure level at and below which no observable carcinogenic effect was seen in the most sensitive animal species.

Please include your calculations in your submission. You must show your work in order to receive full credit. Points will be deducted if you provide only the answer, even if it is correct. Remember to be careful when completing your calculations to always include units, and to double-check that you have cancelled all units appropriately. Final answers must include correct units. Calculations and assumptions do not count against the page limit for this assignment; use as much space as needed to display your calculations and document your assumptions. The 2-page limit applies only to the written responses to questions.

State and justify your assumptions. You do not need to repeat assumptions made during Assignment #4. Why did you select the values you selected? Give justification.

Please insert your answers into Table VI below.

Table VI
ESTIMATES OF UPPER BOUND ON EXCESS LIFETIME HUMAN RISK AND MARGINS OF EXPOSURE FROM DNC EXPOSURE IN STATE OF ANXIETY

<table>
<thead>
<tr>
<th>Source</th>
<th>Upper Estimate Excess Risk</th>
<th>Lower Estimate Excess Risks</th>
<th>MOE</th>
<th>Size of Population Group</th>
<th>Upper Estimate on Number of Cancer Cases over Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread</td>
<td></td>
<td></td>
<td></td>
<td>5,000,000</td>
<td></td>
</tr>
<tr>
<td>Drinking Water</td>
<td></td>
<td></td>
<td></td>
<td>300,000</td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td></td>
<td></td>
<td></td>
<td>2,000</td>
<td></td>
</tr>
<tr>
<td>Fumigation</td>
<td></td>
<td></td>
<td></td>
<td>1,200</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Part II:

Question 1)
If you were presenting this data to a policymaker, what two (2) caveats would you make sure to include in your presentation?

Question 2)
Considering the health end-points of concern here and possible intervention options, is it important to distinguish routes of exposure? Should unit risks obtained from the inhalation data be used for population groups exposed by inhalation? Should gavage data be used to characterize risk by ingestion? Please justify your answer.

Question 3)
After reviewing the available animal and human data, there are still many uncertainties regarding the carcinogenicity of DNC in humans and the existence of a threshold. How does reporting both the MOE and excess risk estimates improve the characterization of risk? Please justify your answer.

Question 4)
Which pathway of exposure presents the highest risk to individuals? Which pathway presents the highest risk to the population? From a policy perspective, which of these (individual or population) would be your first priority for risk management?

Question 5)
Which of the following best characterized the information you have seen? Please make sure to justify your answer.

Possible Conclusions Regarding DNC Carcinogenicity:
A. DNC cancer risks calculated based on the highest unit risks are considered an upper estimate (most conservative) excess risks (check your answer in table VI). Although risks obtained from the use of other models are lower, the risks could be as high as those that you reported in Table VI. There is no evidence that a threshold dose exists for DNC so that the MOE estimates have little meaning.

B. Same as Conclusion 1, except restrict your estimates of excess risks for inhalation exposure to unit risks estimated from inhalation data, and restrict risks for ingestion to gavage data.

C. The excess risks that you have reported in Table VI, as well as those obtained from use of all other plausible models and all of the various tumor site data should be reported, and all estimates should be given equal weight. Such a presentation affords the decision-maker a view of the uncertainty in the estimated risks.

D. DNC is a probable human carcinogen, based on observations of carcinogenicity in two animal species. Exposures needed to produce animal carcinogenicity are many thousands of times higher than those to which humans are exposed. The margins of exposure by which humans are protected are reported (based on your calculations) in Table VI. Because of the concern about carcinogenic endpoints, a greater than usual MOE should be employed to protect human beings.

E. DNC is probable human carcinogen, based on observations of carcinogenicity in two species of experimental animals. Humans are exposed through food, air, water, and during employment. In general, large numbers of people are exposed continuously to very low levels
of DNC and a few groups are exposed to relatively high levels, some continuously, others intermittently. The individual risk in the general population risk is probably low to moderate, but this translates to a relatively large number of cancer cases because of the large population size, etc.

F. Other? Some combination of the others? Formulate and explain your own conclusion.
GLOSSARY

Acceptable daily intake (ADI). An estimate of the daily exposure dose that is likely to be without deleterious effect even if continued exposure occurs over a lifetime.

Attributable risk. The difference between risk of exhibiting a certain adverse effect in the presence of a toxic substance and that risk in the absence of the substance.

Carcinogen. An agent capable of inducing a cancer response.

Control animals. Animals that receive identical treatment as test animals except exposure to DNC for the purpose of observing the natural or background rate of cancer in that type of animal.

Dose. The amount of a contaminant that is absorbed or deposited in the body of an exposed organism (whether animal or human) for an increment of time. Units of dose are often presented in the form of mass per unit volume of physiologic fluid or mass per mass of tissue (i.e., blood levels in ug/DL).

Dose-response evaluation. A component of risk assessment that describes the quantitative relationship between the amount of exposure to a substance and the extent of toxic injury or disease.

Dose-response relationship. The quantitative relationship between the amount of exposure to a substance and the extent of toxic injury produced.

Epidemiological study. Study of human populations to identify causes of disease. Such studies often compare the health status of a group of persons who have been exposed to a suspect agent with that of a comparable non-exposed group.

Exposure. An event consisting of contact at a boundary between an organism and the environment at a specific environmental contaminant concentration for a specified interval of time. Exposure = concentration x time. In other words, exposure captures the contact with the contaminant and incorporates concentration and duration of exposure.

Extrapolation. The estimation of a value beyond the known range on the basis of certain variables within the known range, from which the estimated value is assumed to follow.

Gavage. Type of exposure in which a substance is administered to an animal thorough a stomach tube.

Hazard evaluation. A component of risk assessment that involves gathering and evaluating data on the types of health injury or disease (e.g., cancer) that may be produced by a chemical and on the conditions of exposure under which injury or disease is produced.

High-to-low-dose extrapolation. The process of prediction of low exposure risks to rodents from the measured high exposure-high risk data.

Human Exposure evaluation. A component of risk assessment that involves describing the nature and size of the population exposed to a substance and the magnitude and duration of their
exposure. The evaluation could concern past exposures, current exposures, or anticipated exposures.

**Human health risk.** The likelihood (or probability) that a given exposure or series of exposure may have or will damage the health of individuals experiencing the exposures.

**Incidence of tumors.** Percentage of animals with tumors.

**Interspecies Extrapolation model.** Model used to extrapolate from results observed in laboratory animals to humans.

**Linearized multistage (LMS) model.** Derivation of the multistage cancer model, where the data are assumed to be linear at low doses.

**Lowest-observed-effect-level (LOAEL).** The lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

**Margin of exposure (MOE).** The ratio of the no observed adverse effect level (NOAEL) to the estimated exposure dose (MOE = NOAEL ÷ Exposure dose).

**Model.** A mathematical function with parameters which can be adjusted so that the function closely describes a set of empirical data. A "mathematical" or "mechanistic" model is usually based on biological or physical mechanisms, and has model parameters that have real-world interpretation. In contrast, "statistical" or "empirical" models are curve-fitted to data where the math function used is selected for its numerical properties. Extrapolation from mechanistic models (e.g., pharmacokinetic equations) usually carries higher confidence than extrapolation using empirical models (e.g., logit).

**Multistage model.** Mathematical model based on the multistage theory of the carcinogenic process, which yields risk estimates either equal to or less than the one-hit model.

**Neoplasm.** An abnormal growth of tissue, as a tumor.

**No observed adverse effect level (NOAEL).** Dose level at which no adverse effects are noted.

**One-hit model.** Mathematical model based on the biological theory that a single "hit" of some minimum critical amount of a carcinogen at a cellular target -- namely DNA -- can initiate an irreversible series of events, eventually leading to a tumor.

**Potency.** A level of adverse effect produced by a unit amount of material. Often used in reference to the Cancer Potency Factor.

**ppb.** Parts per billion.

**ppm.** Parts per million (equivalent to mg/kg or mg/m³ or mg/L).

**q*.** Upper bound on the slope of the low-dose linearized multistage procedure.
Reference Dose (RfD). An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Risk. Probability of injury, disease, or death under specific circumstances.

Risk assessment. The multi-step process of applying scientific data to evaluate the toxic properties of a chemical and the conditions of human exposure to it both to ascertain the likelihood that exposed humans will be adversely affected, and to characterize the nature of the effects they may experience.

Risk characterization. Final component of risk assessment that involves integration of the data and analysis involved in hazard evaluation, dose-response evaluation, and human exposure evaluation to determine the likelihood that humans will experience any of the various forms of toxicity associated with a substance.

Risk management. Decisions about whether an assessed risk is sufficiently high to present a public health concern and about the appropriate means for control of a risk judged to be significant.

Route of exposure. Method by which the chemical is introduced into the biological organism.

Scientifically plausible. An approach or concept having substantial scientific support but that is without complete empirical verification.

Statistically significant. The difference in tumor incidence between the treated and controls animals that is probably not due to chance.

Systemic effects. Effects observed at sites distant from the entry point of a chemical due to its absorption and distribution into the body.

Threshold dose. The dose that has to be exceeded to produce a toxic response.

Total dose. Sum of doses received by all routes of exposure.

Uncertainty factor (UF). One of several, generally 10-fold factors, used in operationally deriving the Reference Dose (RfD) from experimental data. UF's are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure, and (3) the uncertainty in using LOAEL data rather than NOAEL data.

Unit cancer risk. Estimate of the lifetime risk caused by each unit of exposure in the low exposure region.

Unit risk. The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 ug/L in water, or 1 ug/cu.m in air.

Upper bound estimate. Estimate not likely to be lower than the true risk.

Weight of evidence (WOE). The extent to which the available biomedical data support the hypothesis that a substance causes cancer in humans.