NOTE: This not formal guidance but is provided for informative purposes only, to assist in understanding and performing risk assessments

Introduction to Air Toxics Risk Assessment

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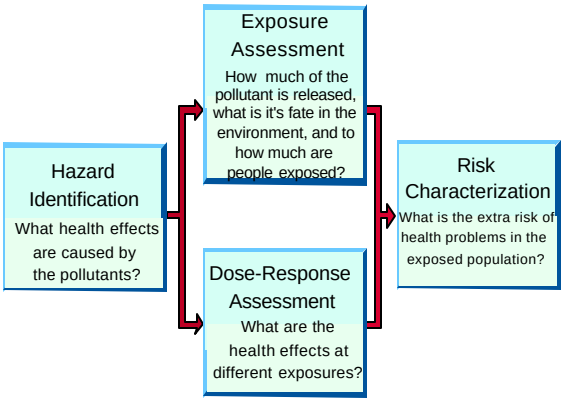
1.0 What is Risk Assessment?

To evaluate the potential for various levels of air toxics to cause disease or to damage the environment, scientists and government officials use a tool called "risk assessment". Using these risk assessments and other factors, we can set regulatory standards to reduce exposures to toxic air pollutants and reduce the risks of experiencing health problems or environmental damage. This report attempts to give a broad overview of risk assessment and how it applies to assessing risks associated with air toxics. More detailed technical discussions of risk assessment methods are also available (e.g., EPA, 1993).

1.1 Human Health Risk

A human health risk assessment combines three types of information: (1) the type and severity of adverse effects that can be caused by the pollutant, (2) the exposure ("dose") of a pollutant estimated to cause adverse effects in laboratory animals or humans, and (3) the level of exposure people are estimated to receive from the source of the pollutant. From this information, we estimate the risk of health problems posed by the pollutant exposure (i.e. additional to other contributors to the risk of that problem). Although there is a large amount of uncertainty associated with the estimates provided by these risk assessments, they often represent the best tool available to help scientists evaluate the risks associated with emissions of toxic air pollutants (USEPA, 1991).

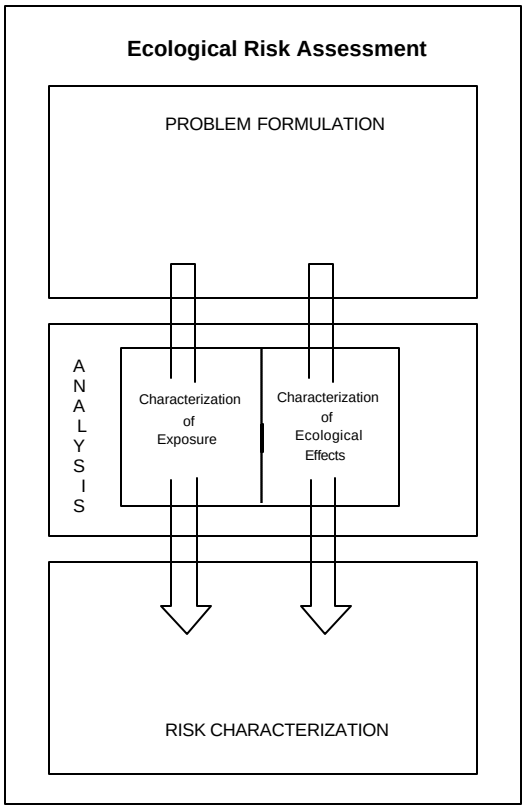


The 4-Step Risk Assessment Process is a tool to evaluate the potential for observed levels of toxics to cause disease

1.2 Ecological Risk

Ecological risk assessment is a process that evaluates the likelihood that adverse ecological effects may occur or are occurring as a result of exposure to one or more chemicals or other stressors. The ecological risk assessment framework (as shown in figure below) consists of three major elements, problem formulation, analysis and risk characterization.

The distinctive nature of the ecological risk framework results from three differences in emphasis relative to previous risk assessment approaches. First, ecological risk assessment can consider effects beyond those on individuals of a single species and may examine population, community, or ecosystem impacts. Second, there is no one set of assessment endpoints (environmental values to be protected) that can be generally applied but are selected form a large number of possibilities based on both scientific and policy considerations. Finally, a comprehensive approach may go beyond the traditional emphasis on chemical effects to consider the effects of nonchemical stressors.



FRAMEWORK FOR ECOLOGICAL RISK ASSESSMENT

Source: EPA, 1992a

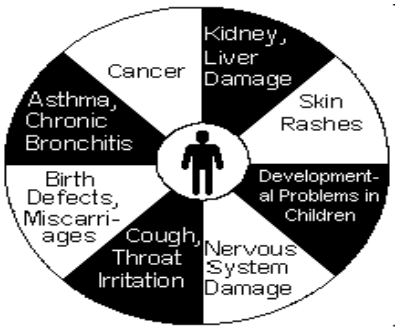
Ecological risk assessment may evaluate one or many stressors and ecological components. As with human health risk assessment, an ecological risk does not exist unless (1) the stressor has the inherent ability to cause one or more adverse effects and (2) it co-occurs with or contacts an ecological component (i.e., organisms, populations, communities, or ecosystems) long enough and at sufficient intensity to elicit the identified adverse effect (USEPA, 1992a).

Ecological risk may be expressed in a variety of ways. While some ecological risk assessments may provide true probabilistic estimates of both adverse effects and exposure elements, others may be deterministic or even qualitative in nature. In these cases, the likelihood of adverse effects is expressed through a semi-quantitative or qualitative comparison of effects and exposure.

2.0 Hazard Identification
- What health problems or adverse environmental effects are caused by HAPs?

There are two key parts to hazard identification: (1) identifying potential hazards, and (2) weighing the evidence of whether or not a particular hazard is likely to be of practical significance in terms of public health or the well being of the environment. Both elements require a combination of knowledge and judgement. The spectrum of undesired effects of pollutants is broad and can cause numerous types of health effects of varying severity depending on the exposure route and level of exposure or dose (Klaasen et al., 1986). A single pollutant may cause mutliple effects. In the hazard identification process, we judge the likelihood of a pollutant causing various health effects in humans by considering what is known about how the pollutant will behave when it enters the body and what harm it can cause. In the next step (called dose-response) we describe the characteristics of the exposure which may lead to harm, including the route of exposure, the size of exposure and the duration of the exposure (e.g. ingestion of 500 milligrams of the pollutant over 2 weeks).

A wide range of effects are possible from exposure to toxicants -- the type and degree of effects depends on the potency, exposure concentration and dose, and time of exposure



Environmental effects are discussed in section 2.5. Most of the discussion in the other subsections of this section 2, while having some application to hazard identification for ecological species, is specific to human hazard identification.

2.1 What types of information are considered in assessing potential hazards of a chemical?

In determining a chemical's potential to do harm, scientists rely on several different types of information. These data include (1) epidemiological studies of health effects occurring in human populations (*e.g.,* the general population, or workers exposed in the workplace), (2) case reports that document human exposure incidents (*e.g.,* accidental releases or poisonings), (3) responses of volunteer human subjects in carefully-controlled laboratory exposures, (4) results of laboratory studies on animals, (5) results of "test-tube" studies using cell cultures or fragmented cells, and (6) predictions by computer models or professional judgment based on knowledge of similar substances.

This information, generally obtained from reports published in highly regarded scientific journals, varies widely in the types of effects reported and in the time scale of the exposure. Reported effects include death or life-threatening diseases such as cancer, serious chronic diseases such as kidney disease, and less immediately serious, reversible effects such as eye irritation. Exposures may include periods ranging from a few minutes to an entire human or animal lifetime.

Human studies, considered the most useful for predicting health effects, often suffer from undocumented exposure levels and uncontrolled confounding factors (factors that play a role in

producing the same response as the chemical being studied)[1]. Toxicity studies with laboratory animals avoid these limitations by using precise doses (exposures) and eliminating confounding factors. However, it is not possible to be fully certain that humans will react in the same way as test species (usually rodents). Also, as the objective in animal studies is to evaluate a chemical's hazard potential, higher exposures than those that humans get from the environment are often deliberately used in order to (1) see what type of health effects a particular chemical can cause when it exhibits its toxicity and (2) to increase the likelihood of observing effects which might be rare in a much larger population. These high-dose results must then be extrapolated to estimate potential effects at lower exposures.

"Test tube" studies have the dual advantages of taking little time to perform and of producing specific information on how substances interact with cells and even molecules, to cause damage. When relying on this type of data to infer what effects these interactions will have on whole organisms, accompanying information on the response of the whole organism is also needed in order to judge its relevance to an adverse effect on that organism and to humans.

2.2 How do HAPs behave in the body?

Once a pollutant enters the body via the lungs, digestive system or skin, it may stay where it entered, be exhaled or eliminated, or move into the blood. Although each HAP may do some of each, the chemical characteristics of the HAP determine which is the principal behavior. For example, when asbestos is inhaled, its tendency is to remain in the lungs. Benzene, however, exists primarily as a gas and, when inhaled, is easily absorbed into the lung (and some benzene will also be exhaled). As it moves around the body, a pollutant can undergo chemical changes, especially as it passes through the liver, sometimes becoming less toxic and sometimes becoming more toxic. Once in the body, some HAPs are transported to and stored in bone, or fat. HAPs stored in fat may, in persons experiencing rapid weight losses, be released back into the body's circulation where they may pose harm. These stored HAPs may also be released into the breast milk of nursing mothers.

Pollutants enter the body through point of contact with contaminated environmental media (e.g., breathing air)

Once a pollutant enters the body it can move throughout the body to specific target organs

2.3 Many HAPs May Cause Cancer

[1]For example, a study may draw conclusions about a chemical exposure's contribution to lung cancer risk without having adequate information about the levels of the chemical in the air or without separating the study population into smokers and non-smokers).

A major determination made during the hazard identification step concerns a substance's potential to cause cancer in humans. This determination, which involves considering (or weighing) all the available evidence, is called the "weight of evidence". This determination is complicated by possible inadequacies of the published studies as well as differences in body processes between people and laboratory animals. EPA follows detailed guidelines describing how evidence for carcinogenicity should be evaluated, and substances placed in one of five broad categories: known carcinogen, probable carcinogen, possible carcinogen, no evidence for carcinogenicity, and evidence for non-carcinogenicity (EPA. 1986). Draft revisions to these guidelines (EPA, 1996a) specify the need to consider the evidence more comprehensively and to more completely describe the context of a chemical's carcinogenic potential (e.g. likely carcinogenic by inhalation and not likely carcinogenic by oral exposure).

About half of the HAPs have been classified by EPA as "known", "probable" or "possible" human carcinogens. Known human carcinogens are those which have been demonstrated to cause cancer in humans. Examples of these include benzene, which has been shown to cause leukemia in workers exposed over several years to certain amounts in their workplace air, and arsenic which has been associated with lung cancer in workers at metal smelters. "Probable" human carcinogens are those chemicals for which testing in two animal species indicates cancer causing potential yet human cancer data are sparse or lacking. "Possible" human carcinogens include chemicals about which we are less certain as to their potential to cause cancer in people, yet for which laboratory animal testing demonstrated some type of cancer response. It is important to realize that the weight-of-evidence determination concerns only the strength of the supporting database for carcinogenicity. In the dose-response analysis the data are evaluated and the chemical's cancer-causing potency is estimated (see section 3.2). In that step, it is possible for a substance considered only a possible carcinogen to be assigned, based on the data available, a higher carcinogenic potency value than a known carcinogen. The two pieces of information must both be considered when assessing potential health risks of the chemical.

The International Agency for Research on Cancer (part of the World Health Organization) makes similar determinations on a chemical's carcinogenic potential that EPA often uses in risk assessments involving substances that EPA has not yet evaluated.

2.4 HAPs also Cause Health Effects Other Than Cancer

There are different health effects which under certain circumstances may be caused by HAPs. These include cancer, neurological, cardiovascular, and respiratory effects, effects on the immune system and reproductive system and effects on fetal and child development. HAPs differ in the health effects which may occur, as well as the circumstances under which these various health effects may occur. Additionally, the severity of effect may vary among HAPs and with the exposure circumstances.

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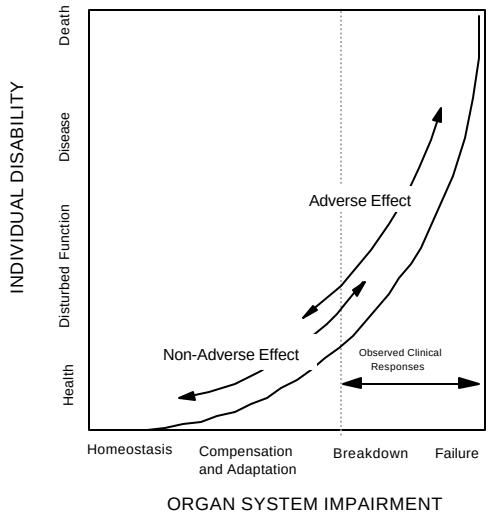
Exposures to toxicants can result in a number of different effects of varying severity where impairment of organs or biological systems may or may not affect the overall health of the organism (as shown in the figure to the right). Individuals may not show any signs of toxicity at low exposures because the body has the ability to detoxify or compensate for exposures to pollutants, or because multiple cells perform the same function. However, at a certain level the body can no longer accommodate or compensate for the exposure to pollutants and physiological changes can be observed. Initially these physiological changes (e.g., changes in enzyme levels or lung function) may not affect the overall health of the organism. However, a large change may be considered adverse to health. As dose or exposure further increases, the body's protective mechanisms continue to break down, and clinical or pathological changes can be observed (e.g., damage to tissues, decreases in function, and severe irritation). As exposure further increases, individuals begin to exhibit obvious clinical effects which includes obvious illness, requirement for medicine or need for hospitalization.

Whether an efffect is adverse or not is dependent on the continuum of severity of noncancer effects



Source: EPA, 1993

Some health problems occur very soon after a person inhales a toxic air pollutant. These immediate effects may be serious, such as life-threatening lung damage, or they may be minor, such as watery eyes. Minor effects can, under some circumstances, contribute to more serious risk of harm (e.g. experiencing eye irritation while driving a car may increase one's risk of an automobile accident). Health problems which are usually associated with long-term exposures may develop slowly over time or may not appear until many months or years after a person's first exposure to the toxic air pollutant (e.g. cancer).

Some HAPs pose particular hazards to people of a certain age or stage in life (e.g. as a developing fetus, young child, adolescent, adult, or elderly person). For example, some HAPs (e.g. mercury) are developmentally toxic. Exposure to certain amounts of these chemicals during the development of a fetus or young child can prevent normal development into a health adult. Other HAPs are reproductive toxicants, i.e. they may have the potential to affect the ability of adults to conceive or give birth. One example of this is ethylene oxide, occupational exposure to which has been associated with increased miscarriages in exposed workers, and which has been shown to affect both male and female reproductive abilities in laboratory animal exposures. Additionally, there are certain segments of the population such as the elderly or asthmatics, which due to differences from the general population in how their body's biological processes react to chemical exposures, may be more sensitive or susceptible to health effects from HAP exposure.

2.5 Environmental Effects of HAPs

Toxic pollutants in the air, or deposited on soils, vegetation or surface waters, can also pose harm to plants, wildlife and aquatic animals. The effects on a population of wildlife species may be direct or, because of the interrelationships among species in an ecosystem, may be indirect. Both direct and indirect effects may occur within the same time frame of exposure, but indirect effect tend to be long lasting and can persist well after the direct effects have been eliminated.

Direct effects are those involving a chemical exerting toxicity on individual members of a certain population or populations. As with people, direct effects to animals can include death, cancer, reproductive effects, immunological effects, metabolic/enzyme effects, impaired growth and development, and neurological/behavioral effects, etc. An extreme example of a direct effect might be deaths of waterfowl caused by an accidental release of an extremely toxic chemical. HAPs which accumulate in plant and animal tissue provide a well known example of a direct harmful effect on wildlife. During the 1950s and 1960s, DDT built up in the wild food chain such that it caused thinning of eggshells of top predators such as bald eagles and brown pelicans, which dramatically reduced the birds' hatching success. The national populations of these birds plummeted, driving them to the brink of extinction.

Indirect effects can move along any of the pathways connecting the directly affected population with the other populations in an ecosystem. These indirect effects occur through biological interaction of one or more species' populations with individuals or populations which have been directly exposed. For example, exposure to a toxic air pollutant may cause adverse effects on one or more species of microscopic algae, bacteria, or fungus can adversely affect an ecosystem's nutrient cycling and primary production. This can lead to an alteration in the abundance, distribution, and age structure of a species or population dependent on these microscopic organisms which can then lead to changes in competition and food web interactions in other species. These ecosystem effects can be propagated to still other populations, affecting their presence or representation within the ecosystem. An example of indirect effects involves the aerial application of pesticides in Canada which dramatically reduced the population of an aquatic insect. This impact to the insect population indirectly affected wild ducklings in the ecosystem which depend on the insects as a food supply (Sheehan et.al, 1987).

2.6 Selection of Hazardous Air Pollutants (HAPs)

Section 112(b)(1) of the Clean Air Act Amendments of 1990 (the Act) established an initial list of 189 specific toxic substances to be subject to potential emission regulations described under other parts of Section 112. This list of substances of concern, being written into law, is similar to a hazard identification step for the air toxics program. EPA worked closely with Congress to develop a list of chemicals that were targeted by one or more Federal statutes or already subject to state or local regulations. Of the HAPs initially listed, 172 were individual chemicals and 17 were groups of chemicals (*i.e.*, compounds of 11 different metals, cyanide compounds, glycol ether compounds, polycyclic organic matter (POM) compounds, fine mineral fibers, radionuclides and coke oven

emissions).

The Act provided for revisions to this list by both addition and deletion. A HAP can be added upon a showing that it is "known to cause or may reasonably be anticipated to cause adverse effects to human health or adverse environmental effects". To remove a HAP from the list it is necessary to show that the HAP "may not reasonably be anticipated to cause any adverse effects to human health or adverse environmental effects." Since the passage of the Act in 1990 only one HAP (caprolactam) has been removed from the list, and none have been added. There are currently 188 HAPs listed

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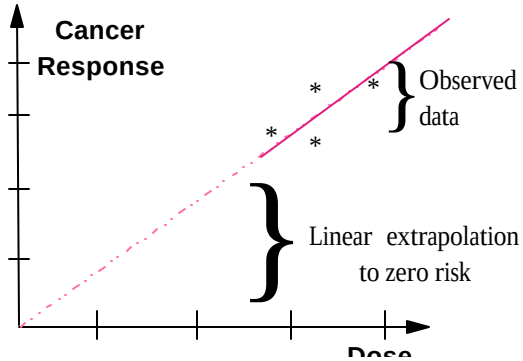
3.0 What is Dose-Response Assessment?
- What type and how much exposure may be harmful?

As an integral part of the risk assessment process, dose-response assessment provides a numerical basis for translating exposure information (described in section 4) into an evaluation of risk. The dose-response assessment answers two questions about a substance's potential to cause adverse health effects. First, what is the adverse effect (*i.e.*, "response") that occurs at the lowest exposure (or dose) at which an effect is observed? This response is called the "critical" effect. Second, what is the quantitative relationship between exposure and adverse effects? This association is termed the "dose-response" relationship. It is often expressed as a graph that shows exposure (*i.e.*, "dose"), on the horizontal axis and proportion of individuals (either humans or laboratory animals) showing the critical effect on the vertical axis. With increasing dose more individuals will show the effect and the rate of this increased response with increased dose is the slope of the "dose-response". Alternatively, we may graph the different levels of effect such that increasing dose results in increasingly more severe effects. Toxicologists often fit a mathematical model to the dose-response graph in order to make predictions of

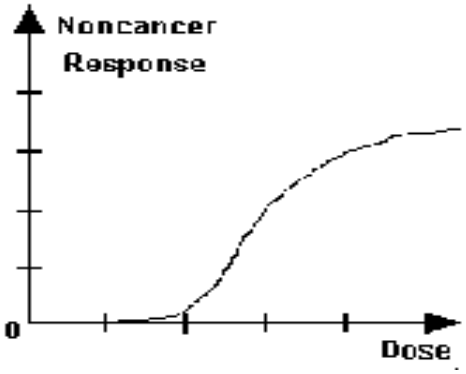
The Analysis is Different for Cancer and Health Effects Other than Cancer

The type of dose-response assessment developed for a substance depends on whether it has been determined to cause cancer or a policy decision on its mechanism of action. Substances which cause cancer are treated differently than those causing health effects other than cancer. In assessments performed to date, EPA has treated nearly every non-carcinogenic substance as having a threshold for adverse effects, and nearly every carcinogenic substance as having no threshold.

Dose-response relationship for cancer. [graph to right] In the absence of clear evidence to the contrary, EPA assumes that there are no exposures that have "zero risk" -- even a very low exposure to a cancer-causing pollutant can increase the risk of cancer (albeit a small amount) -- and that the relationship between dose and response is a straight line -- for each unit of increase in exposure (dose), there is an increase in cancer response.



Dose-response relationship for noncancer effects. [graph to right] A dose may exist below the minimum health effect level for which no adverse effects occur. EPA typically assumes that at low doses the body's natural protective mechanisms repair any damage caused by the pollutant, so there is no ill effect at low doses. Even long-term ("chronic") exposures below the threshold are not expected to have adverse effects. However, for some substances noncancer effects may occur at low doses. The dose-response relationship (the response occurring with increasing dose) varies with pollutant, individual sensitivity, and type of health effect.



effects for doses that have not been tested. For risk assessment, we use the dose-response for the "critical" effect to estimate the exposure level at which adverse effects would not be expected to occur in people.

As some HAPs are chemical groups (e.g. cadmium compounds), this analysis must be performed for all members of the group. When evaluating exposures to these HAPs, it is important to ascertain which group members are present so that the potential risks of the relevant chemicals are assessed.

3.1 Dose-Response Assessment for Carcinogens

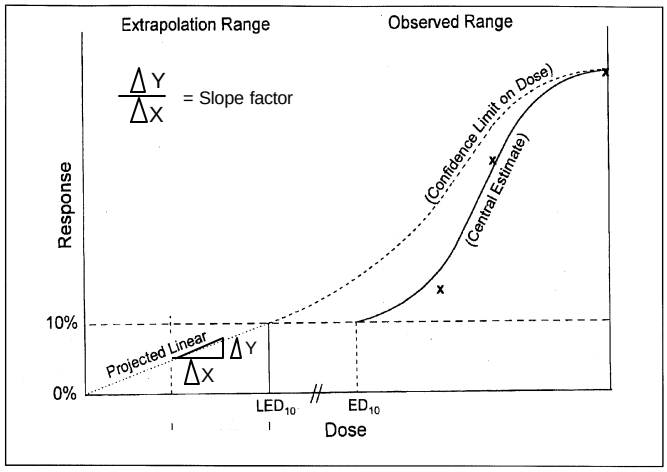
In order to compare relative risks of possible, probable and known carcinogens, EPA and other agencies assign numeric estimates of carcinogenic potency or unit risk using the available dose-response information. In identifying the most appropriate study on which to base calculation of these values, we identify the most representative results (*e*.g., human or primate studies, if available) or the most sensitive results (*e.g.*, studies showing an increase in tumors at the lowest exposure levels). We then give preference to long-term studies over short-term ones, to studies using an appropriate exposure route (*e.g.*, inhalation exposure for developing an inhalation potency value), and to studies showing a clear pattern of increasing tumor formation with increasing dose or exposure level.

When we rely on a laboratory animal study in this analysis, the exposure levels must be translated to human equivalent levels. For inhalation exposures, this step, in addition to accommodating any relevant differences in physiology between animals and humans, involves translating the exposure concentration used in the study from the conditions of the lab animal or human occupational study (e.g. 8 hrs a day, 5 days a week, over 2 years) to the corresponding concentration for a continuous exposure over a human lifetime. For ingestion exposures, the dose must also be translated to account for physiological differences between humans and animals. When the requisite data are available, "physiologically-based pharmacokinetic" (PBPK) modeling may be used to assist in the conversion of animal exposure to human exposure. Once translated to human doses or exposure concentrations, the dose response relationship is examined using a mathematical model.

In fitting a dose-response model, we assume (unless there is evidence to the contrary) that no threshold exposure exists for cancer. This means that, in the absence of other evidence, there is assumed to be no level of exposure that does not carry a risk of cancer development. This assumption is based on a science policy decision that arises from what we currently know about the processes by which chemicals cause cancer. Many carcinogens (or their breakdown products) work by interacting directly with DNA to cause genetic mutations that eventually lead to tumor formation. By this theory, the somewhat simple implication is that, a single mutation can begin a process that eventually results in cancer. Because of the body's DNA repair mechanisms and other protective processes, as well as the body's own spontaneous DNA mutation rate, the development of cancer is actually much more complex and not all carcinogens act through DNA interaction. However, the default assumption (i.e. when there are no data indicating otherwise) is that there is a linear relationship between exposure and cancer.

Some chemical carcinogens have a "nonlinear mode of action". One type of nonlinear action is when cancer development is dependent on the chemical first causing another health effect, which is associated with a threshold exposure. Thus, for these chemicals, there are threshold exposures below which cancer does not occur. If there is adequate supporting evidence, a carcinogen may be assessed as having a nonlinear mode of action. This assessment method is only recently being used and adequate evidence for this assessment is not available for most carcinogenic substances . Consequently, few if any of EPA's cancer assessments are currently based upon a threshold assumption. Rather, a straight line relationship was usually assumed from the lowest dose that produced tumors in a study to a dose of zero.

After fitting the model to the dose-response data, the cancer potency value (or slope factor) for the chemical is determined, i.e. the rate at which it is predicted that the probability of tumors increases with increasing amount of chemical. The slope factor is mathematically the slope of the line drawn in extrapolating from the observed data to zero (see figure). If animal data (or human data of limited quality) are relied upon for the dose response analysis, the statistical 95 percent upper confidence limit on that slope (rather than the slope itself) is used. EPA does this to minimize the risk of underestimating the potency of the substance. In other words, there is only a 5 percent chance that the actual slope factor could be greater than that derived based on the animal data and model used. In cases where good human epidemiologic data are available, the slope factor may be based on the statistically best fitting line of extrapolation rather than the upper 95 percent confidence limit. When data support a different approach, a nonlinear method may be used.



The slope factor from the linear approach is translated into a "unit risk". The unit risk is the upper bound of the likelihood that an individual will contract cancer from a constant dose of one "unit" of the substance. Unit risks for inhalation are based on one microgram of the carcinogen per cubic meter of air ($\mu g/m^3$) (*i.e.*, upper bound cancer risk per $\mu g/m^3$ of air concentration). Unit risks for oral exposure are based on one milligram of the carcinogen ingested per kilogram of body mass per day (mg/kg/d)(*i.e.*, upper bound cancer risk per mg/kg/d of exposure). "Risk" is an estimate of probability of experiencing an effect (cancer), with one equaling a certainty and zero an impossibility. Risk estimates for environmental exposures are typically very small fractions, often expressed in scientific notation. For example, an upper bound lifetime cancer risk estimate of one in ten thousand would be given as 1×10^{-4}; one in one million would be 1×10^{-6}.

To understand the proper context of unit risks, it is crucial to remember the uncertainties involved in their development, and the protective assumptions that EPA applies as a way of addressing these uncertainties. First, assessments are often based on the most sensitive species, which, in order that we are using a sensitive tool to identify carcinogens, may have been selected because of its susceptibility to cancer. Second, because we are lacking information about the carcinogenic activity of chemicals at low dose, in nearly every case results are extrapolated from high to low doses using a conservative model that may not be appropriate for all carcinogens. Third, the upper bound of the modeled line of best fit is used usually used as the slope factor, rather than the best fit, to avoid underestimating potency. Fourth, results may be extrapolated from animal species to humans based on a conversion that may not fit all carcinogens.

It is important to think of unit risks, and the cancer risk estimates that derive from them, as upper bound estimates. True risks are likely to be lower, and may be zero. Such upper bound estimates must not be confused with actuarial risks (e.g., the likelihood that a 45-year-old male will die during the next year, as used to set life insurance rates) which are best estimates based on actual observations of that event and consequently, have a high degree of accuracy.

3.2 Dose-Response Assessment for Chronic Effects Other Than Cancer

It is an axiom among toxicologists that all substances are poisons, if the dose is high enough. Substances that do not cause cancer may cause a wide variety of other damage, including impairment of the nervous, cardiovascular, pulmonary, immune, and reproductive systems, and adverse effects on fetal and child development. As already described, EPA nearly always assumes that a substance has a threshold dose below which non-cancer effects will not occur. The purpose of the dose-response assessment for these effects is to predict or estimate a dose that is below that threshold for humans. Factors that must be considered in this evaluation are the severity of the effect, differences in sensitivity between humans and laboratory animals, possible heightened sensitivity of some individuals (e.g., children or people with respiratory disease), and the length of the exposure needed to produce the effect.

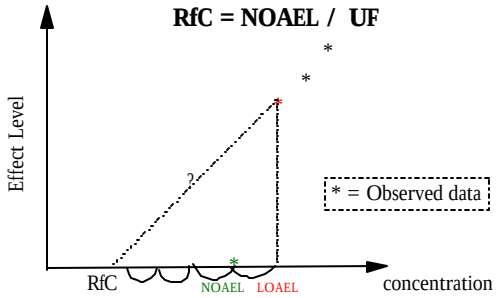
In developing a dose-response assessment for non-cancer effects, toxicologists evaluate the available data for a substance in much the same way as for a cancer assessment. Studies of high-quality are selected, and the assessment is focused on the most appropriate studies. As with carcinogens, preference is given to long-term studies over short-term ones, to studies using an appropriate exposure route (*e.g.*, inhalation exposure for developing an inhalation reference level), and to studies showing a clear pattern of increasing frequency or severity of response with increasing dose. The toxicologists use the information to select the most sensitive species (when human data are not adequate), and the "critical effect" (i.e., the adverse effect that appears at the lowest dose at which an adverse effect is observed).

Using the dose-response relationship for the critical effect, toxicologists identify the highest exposure that did not result in an effect (the "no observable adverse effect level" or NOAEL) in the studied population (either test animals or humans). If the data are of very high quality, a dose-response

model may be employed to more precisely estimate that exposure. This estimate of the NOAEL is calculated as the statistical 5 percent lower confidence limit of the dose at which a low percentage (usually 5 percent) of individuals showed a toxic response. The selection of percentage showing toxic response is intended to coincide with the sensitivity limit of the experimental design (EPA 1995).

Next, as described earlier in the assessment for carcinogens, this exposure must be converted into an equivalent lifetime exposure for humans. This equivalent lifetime exposure level is then divided by a series of applicable "uncertainty factors" (usually 3 or 10) to account for uncertainties in extrapolating from the type of study serving as the basis for the RfC to the situation of interest for the risk assessment (EPA, 1991a). Division by additional uncertainty factors (of 10 or 3) may be performed to account for:

Reference Concentration (RfC) for inhalation exposures, is based on applying uncertainty factors to effect levels from experimental studies



(1) the lack of information on the difference between humans and lab animals in how the chemical behaves in the body. If the requisite data are available and PBPK modeling is used, this interspecies uncertainty factor may be reduced.

(2) the possibility of the most sensitive subpopulation being more sensitive than the general population (i.e., intraspecies variability);

(3) use of a study which did not include an exposure level at which no effect was observed (a NOAEL);

(4) use of a sub-chronic study (much shorter than lifetime) in place of a chronic (lifetime) study; and

(5) use of an incomplete data base.

Before obtaining the final value, there may be an additional division by 3 or 10 ("modifying factors") to account for inadequacies of the critical study. Because of this procedure to address our lack of information on the translation from experimental data to a human scenario (USEPA, 1994), the resultant Reference Concentration (RfC)[2] is for many HAPs on the order of 100 to 300 times lower than the lowest concentration at which an effect was observed in the tested species. This reflects our need to identify a reference value that is protective of humans. For those HAPs that have had their

[2]EPA's inhalation reference exposure for noncancer effects from a chemical is called a Reference Concentration (RfC) which is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime" (USEPA, 1994).

effects well documented in human studies, the RfC may be much closer to the concentration at which an effect was observed (e.g. within a factor of 3 to 10).

The concentrations or doses that emerge from this process are called "reference concentrations" (RfCs) or, for dietary exposures, "reference doses" (RfDs). The reference concentration (or dose) is defined as 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 appreciable risk of deleterious effects during a lifetime". EPA includes with each RfC and RfD a statement of high, medium, or low confidence based on the completeness of the database for that substance. High confidence RfCs are considered less likely to change substantially with the collection of additional information, while low confidence RfCs may be especially vulnerable to change (USEPA, 1994).

It is important to realize that RfCs and RfDs are not estimates of the threshold dose for noncancer effects in humans. Rather, they are doses that, given the limitations of the database, are considered to have no significant risk of adverse noncancer effects under lifetime exposure conditions. There is substantial uncertainty surrounding the needed extrapolations from animal to human effects, from high to low doses, from short- to long-term exposures, from effect- to no-effect-levels, and from average to sensitive individuals. In each case the process by which EPA develops RfCs and RfDs has intentionally given the benefit of this doubt to the exposed public.

This means that while EPA believes that doses equal to or below the RfC or RfD are likely safe from noncancer effects, it does not automatically follow that doses above this level are not safe. That is, no adverse health effects are expected below these exposures. We cannot predict, especially in degrees of severity, what might occur above these exposure points.

3.3 Availability of Reference Levels and Unit Risks for Chronic Exposure

EPA's various programs have responsibility for regulating many hundreds of toxic chemicals, and it has not been possible to develop high-quality dose-response assessments for all of them. Some substances lack the basic toxicity database needed for an assessment, while others, for which data are adequate, have not yet been assessed by EPA due to resource limitations.

For substances that EPA has not yet assessed, the Agency often considers assessments developed by agencies of other countries, other federal agencies, and states. Although some details of cancer and non-cancer dose-response assessments may vary among these agencies (resulting in somewhat different values), there is a general consistency among the methods. The following paragraphs describe some common sources for reference levels and unit risks (or cancer slope factors).

EPA: EPA produces dose-response assessment information in several forms, based on the level of internal review received. EPA publishes dose-response assessments which have achieved full intra-agency consensus on its Integrated Risk Information System (IRIS), available on EPA's Internet website (USEPA, 1998a). Assessments prepared by the EPA Office of

Research and Development (ORD) that have not been approved by all EPA program offices are often published as individual Agency health effects assessment documents. The results of many such assessments have been assembled, and are updated and circulated regularly, in EPA's Health Effects Assessment Summary Tables (HEAST - EPA, 1997a). Interim assessments that ORD prepares under short deadline pressure in support of specific regulatory decisions are usually sent only to the requesting program office (e.g the Superfund program), and not published. This type of interim assessment information is sometimes used to fill critical data gaps.

The Agency for Toxic Substances and Disease Registry (ATSDR): ATSDR, which is part of the US Centers for Disease Control, regularly publishes Health Guidelines Comparison Values (CVs) for many toxic substances. ATSDR describes CVs as media-specific concentrations to be used by health assessors in selecting environmental contaminants for further evaluation. CVs are concentrations below which it is considered unlikely that contaminants pose a health threat. Concentrations above a CV do not necessarily represent a threat, and CVs are thus not intended for use as predictors of adverse health effects or for setting cleanup levels.

ATSDR's chronic duration minimum risk level (MRL) is the CV that most closely approximates EPA's RfD and RfC. An MRL is an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (other than cancer) over a specified duration of exposure. ATSDR develops MRLs for acute, intermediate, and chronic duration exposures by the inhalation and oral routes. The concept, definition, and derivation of MRLs are consistent with those of EPA's RfC and RfD. ATSDR publishes MRLs as part of its toxicological profile documents for each substance (ATSDR 1998).

Air Resources Board of the California Environmental Protection Agency (CalEPA): CalEPA has developed dose-response assessments for many HAPs that have not been evaluated by either EPA or ATSDR. These assessments contain information on carcinogenicity, and health effects other than cancer resulting from chronic and acute exposure. The non-cancer information includes available inhalation health risk guidance values developed by EPA or CalEPA, expressed as acute or chronic reference exposure levels (RELs). CalEPA defines the REL as a concentration level or dose at (or below) which no health effects are anticipated. Because this concept is substantially similar to EPA's non-cancer dose-response values, RELs are useful tools for substances that EPA has not assessed. CalEPA's quantitative dose-response information on carcinogenicity by inhalation exposure is expressed in terms of the unit risk, defined similarly to EPA's unit risk. CalEPA assessments tend to be somewhat more protective than EPA's but are often used by EPA where other unit risks are not available. CalEPA's methodology and values were subjected to an external peer review process in 1995-1996, and although some individual values were judged in need of improvement, the methodology was considered generally similar to that of the EPA (CalEPA 1996). Since then Cal EPA has updated many of their values (CalEPA 1997a, 1997b) to further improve consistency with the EPA and reflect current knowledge.

International Agency for Research on Cancer (IARC): IARC was established in 1965 by the World Health Organization, to coordinate and conduct research on the causes of human cancer and to develop scientific strategies for cancer control. IARC performs epidemiological and laboratory research, and disseminates scientific information through meetings, publications, courses and fellowships. As part of its mission, the IARC assembles evidence that substances cause cancer in humans and issues judgments on the strength of evidence. IARC's weight-of-evidence categories are Group 1 (carcinogenic in humans), Group 2A (probably carcinogenic), Group 2B (possibly carcinogenic), Group 3 (not classifiable), and Group 4 (probably not carcinogenic). The rankings may be applied to either single chemicals or mixtures (IARC 1998). EPA often relies on IARC weight-of-evidence determinations for substances that EPA itself has not assessed.

3.4 Dose-Response Assessment for Acute Effects

It has long been known that brief exposures to small amounts of some chemicals (*e.g.*, cyanide), can cause dramatic harm. Society has responded to this knowledge by eliminating exposure to those chemicals where possible, and by otherwise limiting exposure levels and times of exposure as much as possible. Various regulatory agencies have developed short-term (acute) exposure guideline levels to assist in protecting people from potentially extreme health effects.

Although episodes of short-term environmental exposures causing drastic health effects to the public are relatively rare, they are notorious when they do occur, as with the 1984 incident in Bhopal, India. EPA (and other government agencies) have historically responded to the threat of acutely toxic hazards through first, prevention (via proper storage precautions, etc.) and second, response planning requirements. In the late 1980s, EPA recommended "levels of concern"(LOCs) to assist in response planning for those chemicals identified as posing greatest threat in an accidental release situation. Since then, EPA, in its development of quantitative risk assessment methods, has focused on chronic (lifetime) exposures to much lower levels of chemicals. Recently, however, EPA is engaging in several activities to insure that our tools (including exposure guideline values) for assessing potential hazard from short-term exposures are adequate.

Levels of concern (LOCs) for chemicals listed as "extremely hazardous substances" under Section 302 in the Superfund Amendments and Reauthorization Act (SARA) were recommended by EPA in 1987 (EPA 1987). The LOCs were derived by dividing by 10 the Immediately Dangerous to Life and Health (IDLH) values set by the National Institute for Occupational Safety and Health as 30 minute levels to guide the need for a respirator. EPA's division of IDLH values by 10 was intended to recognize that the IDLH values were set for the healthy worker population rather than the general population, that the 30 minute exposure period may not be realistic for accidental releases for which LOCs were needed and that LOCs needed to protect against serious, yet reversible injury for which IDLH values may not be protective (EPA, 1987).

Unlike the one-time development of LOCs in 1987, the American Industrial Hygiene Association routinely develops and updates short-term exposure (1-hour) exposure levels called

Emergency Response Planning Concentrations (ERPGs), which along with LOCs are utilized in the response planning for accidental releases required by the Clean Air Act (EPA, 1996b). Recently, USEPA's Office of Prevention, Pesticides and Toxic Substances convened a National Advisory Committee (NAC) to develop Acute Exposure Guideline Levels (AEGLs). The NAC/AEGL Committee is a discretionary Federal advisory committee that combines the efforts of stakeholders from the public and private sectors to promote efficiency and utilize sound science. AEGLs for a substance take the form of a matrix, with separate ambient levels for discomfort, serious effect, and lethality. Each of these three effect levels are provided for four different exposure periods, typically 30 minutes, and one, four, and 24 hours. The NAC published an initial priority list of 85 chemicals for AEGL development in May 1997, and has thus far proposed AEGLs for approximately 20 HAPs. AEGLs for 8 HAPs were published in the Federal Register in October 1997 (USEPA 1997b) and await final approval by the National Academy of Sciences. These new guideline levels, as they are finalized, are to be used in place of LOCs and ERPGs by federal, state, and local agencies and organizations in the private sector in emergency planning, prevention, and response activities (USEPA 1996b).

EPA's Office of Research and Development is currently developing an acute exposure methodology intended to be directly comparable to that used for RfCs (USEPA, 1998b).

3.5 Screening Values for HAPs

Many EPA decisions concern the selection of those specific substances, and releases or environmental levels of those substances, on which to focus increased attention and analysis. The EPA Office of Air and Radiation bases decisions about what HAPs or HAP sources to study in depth on screening-level analyses of health risk that incorporate a simplified version of EPA's risk assessment procedures. These simplified risk assessments often use "risk based concentrations" (RBCs) or "health based benchmarks," expressed as concentrations in air (for inhalation risks) or dose per body mass (for risks via food or drinking water) as the screening values (Smith 1996).

RBCs are simply the concentration (or dose) of a HAP that, when assumed to be inhaled (or ingested) over a lifetime, translates to a fixed level of inhalation (or oral) risk to an average person. Any fixed level of risk can be used. For example, RBCs may be set at an exposure that, when lifetime exposure is assumed, equal a one in a million upper bound excess lifetime cancer risk or the RfC or RfD. The use of RBCs provides advantages for the risk assessor. First, it places all HAPs on the same scale, and, for cancer based RBCs, provides concentrations translating to the same level of risk. By comparing ambient levels of HAPs with these concentrations, the risk assessor can quickly determine which HAPs may be most likely to create the greatest hazard. RBCs can also be used with HAP emission rates to adjust for the vastly different toxic potentials of different substances, enabling more meaningful comparison of different HAP emissions. Additionally, RBCs place cancer and non-cancer endpoints on the same measurement scale (e.g. ug/m^3, air concentration), enabling development of a single set of priorities for both. As the risk level (inherent in setting cancer based RBCs) is a risk management decision, its selection needs to be carefully considered when using RBCs in this way.

As already discussed, EPA has not developed dose-response assessments for many HAPs,

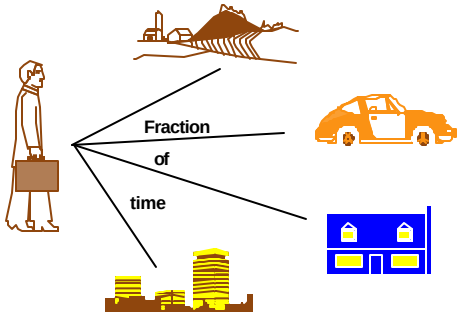
and therefore, may, for screening level evaluations, also use assessments developed by certain other regulatory agencies. We recognize that these various reference values and unit risks were created at different times, based on similar but not identical protocols, sometimes intended for different purposes, and subjected to varying types of review. Nevertheless, we consider their use defensible for screening-level analyses involving many HAPs because the alternative is, for some HAPs to use no information at all, a *de facto* assumption of negligible toxic potential. Such a practice could create false negatives (i.e., an incorrect conclusion that a HAP poses negligible risk) that may be unacceptable at the screening level. While using values of varying background, conversely, has the potential to create false positives (i.e., identifying a HAP as a priority when it poses negligible risk), these are preferable to false negatives in screening analyses. False positives, if they occur, can be addressed in the subsequent more detailed analysis of the smaller HAP group.

Recent EPA screening-level analyses for air toxics, such as the Cumulative Exposure Project (Woodruff, 1998) and the identification of HAPs for proposal under the urban air toxics program (USEPA, 1998c), have used RBCs (or health based benchmarks) based on dose-response assessments from a variety of sources. In each case the sources were prioritized according to applicability, conceptual consistency with EPA risk assessment guidance, and level of review received. Even when we relied on multiple sources for assessments, a lack of toxicity information prevented us from evaluating a substantial number of HAPs.

4.0 Exposure Assessment
- How are we exposed to HAPs?

Exposure to environmental pollutants is determined by the concentration of that pollutant in various environmental media (i.e., air, soil, water, food), and the contact of an individual with that media. Since concentrations in the environment vary from place to place and over time, it is important to know where and how long people spend their time. Through modeling and monitoring, the ambient concentrations of the pollutants can be estimated geographically and temporally. Exposure and risk to human populations via the inhalation route and through secondary exposure routes (such as food and water contaminated by deposited pollutants) involves combining pollutant concentration information with information on the geographic distribution of people in the study area. Actual exposure (or dose) is principally defined by the concentration to which the individual is exposed; time spent in various micro environments[3], exposure duration, and an individual's activity pattern which may influence such things as inhalation rate.

A person's *exposure* depends on the concentration within a location (*microenvironment*) and how long a person spends in each microenvironment



4.1 Monitoring (Exposure Measurement)

The most accurate way to determine a person's exposure is to measure the concentrations of a pollutant in the environmental media which a person comes in contact with, either through ambient air monitoring or personal exposure monitoring.

Personal Exposure Monitoring: Personal exposure to toxic pollutants may be determined through direct measurement techniques. In direct measurement, chemical concentrations contacting a person's body are measured, sampling the air the person breathes (where the collection medium is positioned in or as near has possible to the breathing zone for the most accurate results), the food and water the person consumes, and by using patch or other techniques to estimate dermal exposure. These concentrations are measured as a function of time to obtain an individual exposure profile. A set of these individual profiles can be pooled or grouped together to paint a picture about the exposure profiles of the population as a whole, provided the individuals sampled are representative of the entire population (U. S. EPA, 1988). Personal monitoring is not usually feasible for large study areas or populations because of the significant expense and technical difficulties in measuring all individuals, or to select individuals for monitoring who are representative of the general population (U.S. EPA, 1992b). Furthermore, personal monitoring cannot attribute the contribution of specific sources to overall exposure.

Ambient Monitoring: Ambient monitoring is useful because the data can be applied to a larger

[3]A microenvironment is a place where the pollutant concentration is considered uniform.

population. Outdoor fixed-location monitoring identifies the general concentrations and trends in concentrations at that location over time. As the distance from that location increases, the certainty of how that data applies to other locations decreases (U.S. EPA, 1992b) . However, this method, referred to as ambient air monitoring, can evaluate the overall quality of outdoor air in a relatively large area by using a network of fixed site monitors. Monitoring networks may be designed to characterize the ambient concentrations resulting from the emissions of a particular source, or may be designed to characterize the overall background concentration in an area. Practical considerations, such as site accessibility, availability of electric power, and security are also considered. Because ambient concentrations can vary widely within a study area, the location of monitors is critical in properly characterizing exposures. Sampling to isolate a particular facility's contribution to the ambient composition of air toxics will require simultaneous sampling of meteorological variables (notably wind direction) to determine when the air sampled by the monitor is representative (i.e., coming from the direction of the facility). The number of stations required to obtain representative characterization will depend on the local meteorology and terrain and the size of the area to be characterized, as well as other factors.

Ambient air monitoring results are used in conjunction with data on sources, environmental processes, target organisms, and activity patterns to estimate exposures. Monitoring may also be carried out in specific micro environments which affect people's exposures. Examples would be an automobile in heavy traffic, or a kitchen while cooking.

4.2 Modeling (Exposure Assessment)

There is considerable expense and technical difficulties in conducting detailed exposure assessments using ambient air and personal exposure monitoring. Due to differences in chemical properties, a fixed site monitor can not often measure all pollutants. As a result, even when monitoring occurs, we typically do not have coverage across all HAPs. Therefore, modeling (often called Exposure Assessment) is the most common approach to estimate exposures within a population. Exposure assessment has four major components: emissions or source characterization, environmental fate and transport, characterization of the study population, and exposure calculation.

4.2.1 Emissions or Source Characterization

Pollutant emissions are characterized in the early stages of a risk assessment to identify and quantify the amount of each specific chemical released to the environment. Once the quantity of emissions has been estimated, potential exposure of the study population can be assessed. Pollutants may be released in indoor and outdoor environments from a wide variety of sources and activities. OAQPS regulatory standards for HAPs typically focus on stationary sources of emissions released into an outdoor atmosphere. For use in human exposure models, a full emissions characterization requires addressing three different types of data: rate of emissions, source release parameters, and chemical speciation.

Emissions Estimates: Chemical emissions are typically defined in terms of the mass released to the atmosphere over time. Emissions rates may be expressed on an annual basis to assess chronic exposure, or on a short-term basis to estimate more acute exposures. The most accurate information can be obtained from a carefully planned and conducted emissions test; however, it may not be feasible to test all the sources for which estimates are desired. If adequate test data are not available, emissions estimates may be derived from reliable and representative emission factors (quantity of pollutant typically released to the atmosphere with a particular source operation) or mass-balance (unaccounted-for mass after tallying the quantity entering and leaving a facility) data.

Source Release Parameters: Knowledge of the release characteristics are needed in addition to emission rate in order for the pollutant fate and transport to be estimated. Modeling of emissions released from a stack requires knowledge of the stack height, inner stack diameter, gas exit velocity or flow rate, and gas exit temperature. For facility area sources (e.g., storage pile fugitives or emissions from ponds), the dimensions of the area source should be identified. While point source emission rates are expressed in terms of mass per unit time, area source emission rates are more typically modeled in terms of mass per unit time per unit area. Another important consideration in specifying the source emission rates is whether the rates should reflect short-term or annual operating conditions. This will depend on whether the focus of the assessment is on acute or chronic exposure.

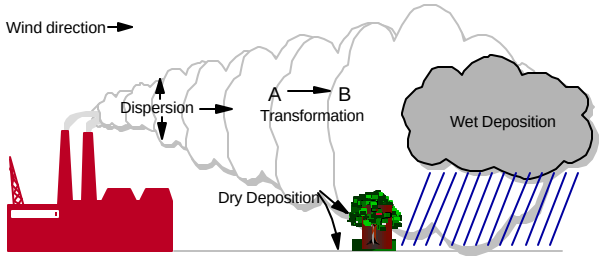
Chemical Properties and Speciation: Chemical properties and speciation are important for several reasons and can influence the overall risks attributable to HAP releases. Chemical speciation may affect how a released chemical may be subject to various chemical transformation and removal processes which would influence the potential for estimated exposure, or differ in their relative toxicity and influence the potential for adverse health effects.

4.2.2 Environmental Dispersion and Fate and Transport Modeling

Once the pollutants of interest and their rates and sources of emission are defined, the process of conducting a risk assessment continues with estimation of the pollutant fate and transport. Pollutant emissions are translated into concentrations to which the study population is ultimately exposed. The concentration of a pollutant usually decreases as it travels from the location of the release because it spreads or is diluted by clean air and influenced by atmospheric transport and dispersion, and chemical transformation and deposition processes.

Atmospheric Transport and Dispersion: After air pollutants are released to the atmosphere, their transport and dispersion are governed by fundamental meteorological principles, as well as source-related characteristics. Initially, the diffusion of pollution is largely determined by the source release characteristics, particularly the effective height of release. This effective height is

a combination of the physical release height and any additional rise which may be due to buoyancy or momentum effects (in the case of stationary point sources). Buoyant rise is driven by the temperature difference between the stack gas and the ambient air and the gas volume flow rate. Momentum rise is directly proportional to the stack exit velocity and stack diameter and is significant when little temperature difference exists between the stack gas and ambient air. Wind and turbulence are important meteorological factors affecting pollutant dispersion. Pollutants are naturally transported with the wind and are diluted with increasing wind speed. (An increase in wind speed can also lead to suppression of plume height, augmenting plume impact at ground level.) Dispersion by circular motions (eddies) of varying sizes in the atmosphere is the principal means of turbulent mixing. A widely used mathematical models to describe the transport and fate of pollutants released to the atmosphere is the Gaussian plume model, where pollutant concentrations in the Gaussian model are assumed to be directly proportional to the pollutant emission rate and are diluted at a rate inversely proportional to the wind speed at the height of release. Concentrations within the plume are assumed to exhibit a normal or Gaussian distribution in the horizontal and vertical directions and are, thus, a function of the receptor height and crosswind distance from plume centerline.



Air toxics, once released to the environment, are influenced by numerous physical and chemical processes which affect their concentration.

Pollutant Transformation and Deposition: A pollutant's degree of chemical reactivity may be an important consideration; atmospheric chemical reactions may lessen the pollutant concentration, through its transformation to other products, or conversely its concentration may be increased through its formation from other compounds. Pollutant emissions are also subject to other removal processes, particularly dry deposition and scavenging by rain and clouds. These removal processes may significantly affect the fate of hazardous pollutants released to the atmosphere. Dry deposition involves pollutant transport to the earth's surface and subsequent physical and chemical interactions between the surface (including plants) and the pollutant. Precipitation scavenging or wet deposition, is a function of the intensity and size of the raindrops and the solubility and reactivity of the chemical. For nonreactive gases, solubility is the most important physical property to consider.

4.2.3 General Population Characteristics

In order to estimate aggregate population exposure, one must identify how people are distributed within the area of interest. Depending on the scope of the assessment and the extent to

which health effects data are known for the pollutant(s) of interest, information about age, sex and activity patterns may be needed. Determining how to characterize the study population will depend on the scope of the assessment and the level of available information on the population of interest. Information may be needed on the demographics of the population (such as that found in the US Census), time-activity patterns to determine time spent in various micro environments (i.e., population mobility), and land use data which may influence mobility and indirect exposures.

U.S. Census Bureau Data: The U.S. Bureau of the Census is the major source of demographic and geographic information. U.S. Census data, collected and revised every decade, provide a complete population count of the entire United States population and more detailed population and socio-economic characteristics for a subset of the entire population. Census data are organized according to geographical area. Data collected by the Census Bureau provides population counts down to the most detailed categorization at the *block* level (essentially city blocks), to larger units which are less detailed including the *block group* level and the *Census tract* level (containing about 5000 persons on average).

Population Mobility: Exposure over a given time period is a function of the amount of time the population is estimated to be in various micro environments and, therefore, depends on the movement of people from one place to another. In a general sense, population migration may be categorized as indoor-outdoor, within the study area, and out of the study area. Population movement may be achieved through the assignment of population cohorts (total population or specific subgroup) to various micro environments based on a prescribed activity pattern.

Land Use Data: Land use data are typically presented in map format and can be used to identify where people are located. Population density can be determined by correlating people with land use type (e.g., residential, commercial). Land use maps obtained from county planning commissions will generally delineate various residential, public, commercial and industrial areas.

4.2.4 Exposure Calculations

In exposure calculation, the pollutant fate and transport elements are combined with the population characterization elements to estimate human exposure. The predicted pollution concentrations from dispersion models are combined with population data. Risk assessments for routine air emissions from stationary sources typically focus on cancer and noncancer health effects resulting from chronic exposures. The average lifetime exposure is the measure of interest in such studies. Various units can be used to express average lifetime exposure. The units selected partially depend on the form of the dose-response model output, since the exposure assessment and dose-response assessment must be combined in the risk characterization step. When the dose-response assessment is expressed in the form of a Unit risk Estimate (URE) (i.e., risk per $\mu g/m^3$ or ppm ambient concentration), then the lifetime exposure should be expressed in units of ambient air concentration (average $\mu g/m^3$ or ppm). The general equation for lifetime exposure would be (U.S. EPA, 1989):

$$\text{Lifetime Exposure} = \frac{\sum[(\text{Ambient air conc}) \times (\text{duration})]}{\text{Lifetime (70 years)}}$$

Inhalation exposure can also be expressed in units of lifetime average mg of pollutant inhaled per kg of body weight per day. The general equation for expressing inhalation exposures in these units is:

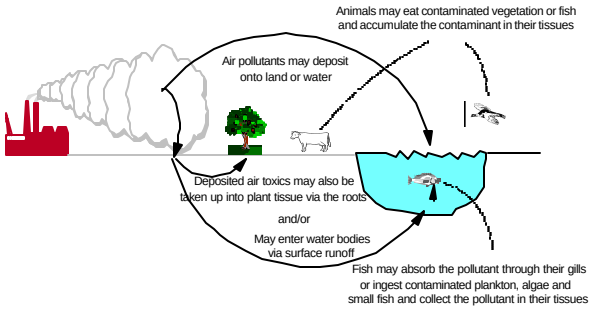
$$\text{Lifetime Average Inhalation Exposure} = \frac{\sum[(\text{Ambient air conc}) \times (\text{duration}) \times (\text{inhalation rate})]}{\text{Body Weight} \times \text{Lifetime (70 years)}}$$

Inhalation rates vary depending upon exertion level, sex, and age. Ranges of measured values are presented in the literature (U.S. EPA, 1985). Common default values (which are inherent in the URE approach) are 70 kg average adult body weight and 20 m^3/day inhalation rate.

4.2.5 Indirect Exposure Assessment

Several of the HAPs (e.g., mercury, dioxins) are known to be persistent and bioaccumulate in the environment and are known to be toxic via oral or dermal routes of exposure. As a result, risks from HAP air emissions may not be limited to direct inhalation exposures but may also include risk associated with indirect exposures to other contaminated media. HAPs originally released into the air may deposit on water or soil. Risk may then be associated with exposure (ingestion) of these contaminated media. Furthermore, these pollutants may also bioaccumulate in the tissues of plants and animals of the food stock and ingestion of these would also result in risk. For some pollutants (e.g., mercury), these indirect exposures have been shown to dominate risks associated with direct inhalation. Therefore, multimedia, multipathway modeling of these indirect exposures are essential to obtain an accurate estimate of risks associated with HAP air emissions. To estimate exposures, modeling is often required in each of the environmental media which may become contaminated and to which people may be exposed. As a result, modeling is often needed to account for pollutant transport in soil and water, as well as through the food chain. Once this is accomplished, estimates can be made of exposure via ingestion of contaminated media.

Transport in Water and Soil Media: In water bodies the pollutant movement may be the result of flow (transport out of the area of initial deposition) such as down a river or stream, or may deposit in slow moving water to the bottom of the water body or sediment. The sediment bed underlying the water body acts as both a source and sink of dissolved and particulate pollutants. Many organic chemicals and heavy metals partition to the organic and clay fraction of the sediment bed. Estuaries, lakes, and reservoirs tend to deposit pollutants in sediment, whereas rivers or streams tend to reentrain



Some HAPs are known to be persistent and bioaccumulate in the environment

previously deposited material. In surface water models, deposited pollutants generally enter a water system from runoff, precipitation, and groundwater discharge and exit by evaporation or downstream flow. Models are used to simulate the transport and fate of organic chemicals in surface water environments. These models account for external loadings, transport processes that distribute the chemicals and export them to other water bodies or study areas, and transformation processes (such as photolysis, hydrolysis, biolysis and oxidation) that convert the chemicals into daughter products (U.S. EPA, 1990).

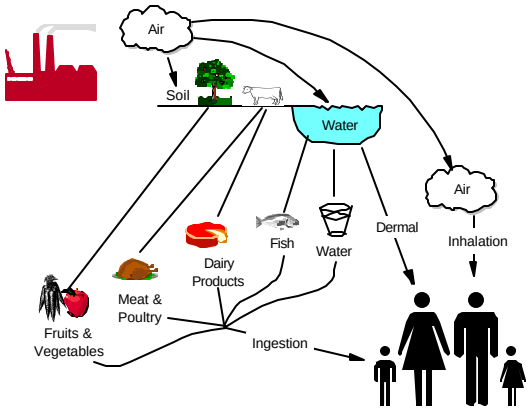
Soil compartment models commonly stratify the soil column into two or more layers. The upper soil layer typically contains the most decomposed plant matter. The lower soil layer is often defined as the unsaturated zone between the upper soil layer and the water table. The depths of these layers can vary dramatically in various locations. Some models assume no unsaturated zone as a worst-case scenario; in this case, the pollutant goes from the upper layer directly into the water. The soil layers are characterized by parameters, such as depth, bulk density (dry soil mass per unit volume), porosity, water content, and organic carbon fraction. Pollutants introduced into the upper layer are removed by chemical transformation, volatilization, runoff, uptake by plants, and downward leaching. Chemical transport to a lower soil layer is estimated by the product of the recharge rate (liters/year) and the pollutant concentration (mg/liter) in soil water (McKone and Layton, 1986).

Uptake of Pollutants in the Food Chain: Calculation of the concentrations of contaminants in food is a complex process requiring the integration of physical, chemical, and biological factors. For example, plants accumulate pollutants via root uptake, direct deposition onto plant parts, and air-to-plant transfer of vapor-phase pollutants. Many factors affect the relative importance of each of these, including:

- plant type (leafy vegetables, exposed produce, such as fruits, protected produce such as root crops, grains, and forage);
- pollutant type (organics or metals); and,
- duration of plant exposure (usually defined as the growing season at the affected site).

Pollutants also enter the food chain through animals. For example, cattle accumulate pollutants by ingesting contaminated food and soil. To estimate the amount of pollutants in beef, the amount of pollutant in the forage, grain, and soil consumed by cattle and the biotransfer factor for each type of animal tissue must be calculated. Fish from polluted water are also consumed by humans. The daily intake from fish ingestion is calculated as the product of water concentration of pollutant, bioconcentration factor (BCF), and fish ingestion rate (U.S. EPA, 1990). The BCF is the ratio of the contaminant concentration in an aquatic organism to the contaminant concentration in the water body.

Exposure Due to Ingestion Pathway: The methodology for assessing exposure due to the ingestion pathway is less well-established than that for inhalation. This is due to the complexity of even



People may be exposed to air toxics in ways other than direct inhalation

the simplest model that adequately describes the ingestion pathway as it relates to a specific contaminated media. Direct ingestion exposure may result from the ingestion of contaminated grains, fruits, and vegetables. Pollutants may accumulate in the tissues of animals who eat contaminated vegetation or in fish from polluted surface waters. Human consumption of this contaminated meat, milk, or fish represents other sources of exposure. This ingestion exposure can occur in the vicinity of the pollutant source or some distance away should contaminated food be transported to other locations or markets. After contaminant concentrations in food have been calculated, the lifetime consumption of each food type must be calculated. It is necessary to determine the proportion of the diet that is locally grown on commercial farms or in backyard gardens as compared to imported foods, as well as the consumption patterns and locations of locally grown foods. In addition to foods, the ingestion of water and soil is included in a food chain analysis. Soil ingestion is generally higher for very young children (ages 1 through 6) than for adults, and includes inadvertent ingestion as well as abnormal soil consumption (pica). The target population may be evaluated with respect to age, diet, and activities to determine the exposure to pollutants through various ingestion pathways. Generally, at least two populations are considered: the average adult and the average child. The definition of these "average" individuals typically includes their body weight, life span (or duration of childhood) and the length of time spent in the target area. However, highly exposed and highly susceptible subgroups such as the sick, the elderly, pregnant women, and nursing mothers should also be considered.

5.0 Risk Characterization
- What is the extra risk of health or environmental problems from HAPs?

Risk characterization, the final step in risk assessment, is primarily used to integrate the information from the other three components and describes the nature and magnitude of human or nonhuman risk and the attending uncertainties. Risk characterization describes why risk was assessed the way it was in terms of choices made. Every risk assessment involves a multiplicity of choices and options. In the risk characterization, the key strengths and weaknesses of the assessment are described.

Two elements are required for full characterization of risk. First, the characterization must address qualitative and quantitative features of the assessment. That is, along with quantitative estimates of risk, full risk characterization must clearly identify all assumptions, their rationale and the effect of reasonable alternative assumptions on the conclusions and estimates. Second, it must identify any important uncertainties in the assessment as part of a discussion on confidence in the assessment. This statement on the confidence of the assessment must identify all major uncertainties and comment on their influence on the assessment. Risk characterization often serves as the link with risk management and the uncertainty statement is important for several reasons.

- Information from different sources carries different kinds of uncertainty and knowledge of these differences is important when uncertainties are combined for characterizing risk.

- Decisions must be made about expending resources to acquire additional information to reduce the uncertainties.

- A clear and explicit statement of the implications and limitations of a risk assessment requires a clear and explicit statement of related uncertainties.

- Uncertainty analysis gives the decision-maker a better understanding of the implications and limitations of the assessments.

5.1 Characterization of Risks to Human Health

Risk assessments are intended to address or provide descriptions of risk to (1) individuals among the majority of the population and those in the high end portions of the risk distribution, (2) important subgroups of the populations such as highly exposed or highly susceptible groups or individuals, if known, and (3) the exposed population as a whole.

Individual Risk. Individual risk predictions are intended to estimate the risk borne by individuals within a specified population or subpopulation. These predictions are used to answer questions

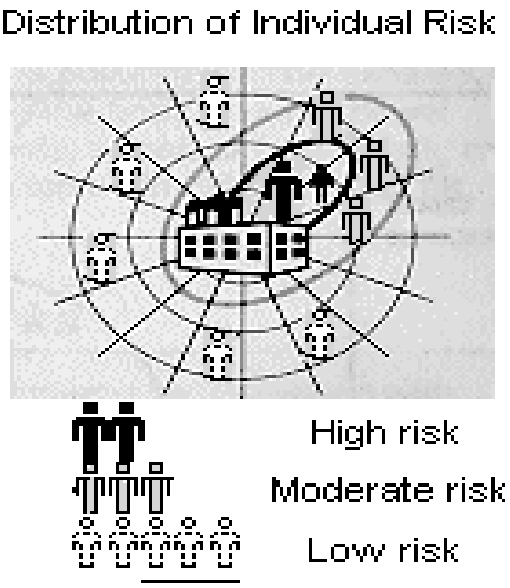
concerning the affected population, the risk levels of various groups within the population, and the average or maximum risk for individuals within the populations of interest.

Central Tendency Estimates of Risk are intended to give a characterization of risk for the typical situation in which an individual is likely to be exposed. This may be either the arithmetic mean risk (average estimate) or the median risk (median estimate), either of which should be clearly labeled (EPA, 1992c).

High-end Estimates of Risk are intended to estimate the risk that is expected to occur in a small but definable segment of the population. The intent is to "convey an estimate of risk in the upper range of the distribution, but to avoid estimates which are beyond the true distribution. Conceptually, high end risk means risk above about the 90% percentile of the population distribution, but not higher than the individual in the population who has the highest risk." (EPA, 1992c)

Population Risk. Population risk predictions are intended to estimate the extent of risk for the population as a whole. This typically represents the sum total of individual risks within the exposed population.

Exposure and risk may vary among an exposed population



Sensitive or Susceptible Subpopulations. Risk predictions for sensitive subpopulations are a subset of population risks. Sensitive subpopulations consist of a specific set of individuals who are particularly susceptible to adverse health effects because of physiological (e.g., age, gender, pre-existing conditions), socioeconomic (e.g, nutrition), other demographic variables, or significantly greater levels of exposure (EPA, 1992c). Subpopulations can be defined using age, race, sex, and other factors. If enough information is available, a quantitative risk estimate for a subpopulation can be developed. If not, then any qualitative information about subpopulations gathered during hazard identification should be summarized as part of the risk characterization.

Because cancer and noncancer dose response assessment are dramatically different, risk characterizations also differ and will be discussed separately.

5.1.1 Quantification of Cancer Risks

Risks for cancer are generally expressed as either individual risks or population risk. The distribution of exposures and individual risks within a given population can also be presented, providing an estimate of the number of people exposed to various predicted levels of risk. For air toxics emissions, individual or population cancer risks can be calculated by multiplying the exposure estimate by the unit risk estimate (URE). Cancer risk is defined as the predicted probability of contracting cancer following exposure to a pollutant at the estimated concentration over a 70-year (lifetime). This estimated risk focuses on the additional risk of cancer predicted from the exposure being analyzed, beyond that due to any other factors. Estimates of risk are usually expressed as a probability represented in scientific notation as a negative exponent of 10. For example, an additional risk of contracting cancer of 1 chance in 10,000 (or one additional person in 10,000) is written as $1x10^{-4}$.

Population risk is an estimate that applies to the entire population within the given area of analysis. The population risk is often expressed as a predicted annual cancer incidence, which is the annual number of excess cancer cases predicted in the exposed population. Each estimated exposure level is multiplied by the number of people exposed to that level and by the URE. This provides a prediction of risk for that group after a 70-year exposure (assumed human lifespan) to that level. The risks for each exposure group are summed to provide the excess cancer cases predicted in the entire exposed population. This 70-year risk estimate is sometimes divided by 70 to estimate the predicted annual incidence in units of cancer cases per year.

Before calculating individual or population risk, it is necessary to check the consistency and validity of key assumptions such as:

- the averaging period for exposure,
- the exposure route,
- absorption adjustments, and
- spatial consistency.

People are often exposed to multiple chemicals rather than a single chemicals. In those few cases where cancer potency values and IURs are available for the chemical mixture of concern or for a similar mixture, risk characterization can be conducted on the mixture using the same procedures used for a single compound. However, cancer dose response assessments are usually available only for individual compounds within a mixture. In such cases, the cancer risks predicted for individual chemicals are sometimes added to estimate total risk. This approach is based on the assumption that the risks associated with the individual chemicals in the mixture are additive. That assumption may not hold true for all carcinogens. The following equation estimates the predicted incremental individual cancer risk for simultaneous exposures to several carcinogens:

$$Risk_T = Risk_1 + Risk_2 + ... + Risk_i \quad (5\text{-}1)$$

where:

R_T = the total cancer risk (expressed as a probability of contracting cancer over a lifetime)

R_i = the risk estimate for the i^{th} substance.

5.1.2 Quantification of Noncancer Risks

As in the calculation of individual cancer risk, risks of effects other than cancer can be characterized for the individual(s) near central tendency and those at the high end of the risk distribution. A distribution of exposures and risks for the study population can also be presented. Unlike cancer risk characterization, noncancer risks typically are not expressed as a probability of an individual suffering an adverse effect. Instead, the potential for noncancer effects is evaluated by comparing an exposure level over a specified period of time (e.g., lifetime) with a reference level such as an RfC (described in Sections 3.2 and 3.5).

"Risk" for noncancer effects is quantified by comparing the exposure to the reference level as a ration. The resultant Hazard Quotient (HQ) is expressed as an equation: HQ=Exposure/Benchmark. Exposures or doses below the benchmark (HQ<1) are not likely to be associated with adverse health effects. With exposures increasingly greater than the reference level (i.e. Hqs increasingly greater than 1), the potential for adverse effects increases. The HQ, however, should not be interpreted as a probability. Comparisons of Hqs across substances may not be valid, and the level of concern does not increase linearly as exposures approach or cross the reference level. This is because of the differences among reference levels in their derivation and the fact that the slope of the dose-response curve above the benchmark can vary widely depending on the substance.

While some potential environmental hazards may involve significant exposure to only a single compound, exposure to a mixture of compounds that may produce similar or dissimilar noncancer health effects is more common. In a few cases, reference levels may be available for a chemical mixture of concern or for a similar mixture. In such cases, risk characterization can be conducted on the mixture using the same procedures used for a single compound. However, noncancer health effects data are usually available only for individual compounds within a mixture. In screening level assessments for such cases, a hazard index (HI) approach is sometimes used. This approach is based on the assumption that even when individual pollutant levels are lower than the corresponding reference levels, some pollutants may work together such that their potential for harm is additive and the combined exposure to the group of chemicals poses harm. The assumption of dose additivity is most appropriate to compounds that induce the same effect by similar modes of action (EPA, 1986).

The HI (for a mixture of *i* compounds) is calculated as: $HI = HQ_1 + HQ_2 = ... + HQ_i$

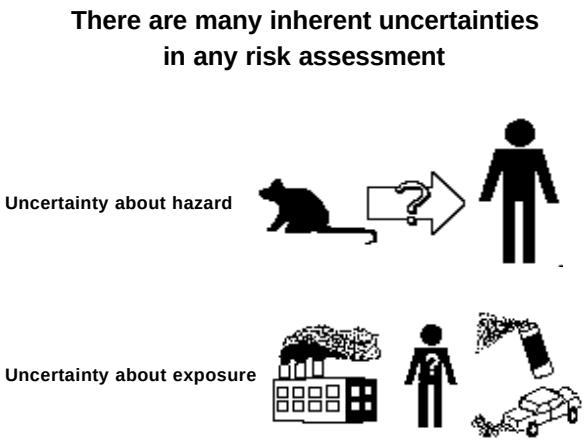
The HI should not be interpreted as a probability of risk, nor as strict delineation of "safe" and "unsafe" levels (EPA, 1986; EPA/OSW, 1989). Rather the HI is a rough measure of potential for risk and needs to be interpreted carefully. Although the HI approach may be appropriate for a screening-level study (EPA/OSW, 1989), it is important to note that application of the HI equation to compounds that may produce different effects, or that act by different mechanisms, could overestimate the potential for effects. Calculating a separate hazard index for each noncancer endpoint of concern when

mechanisms of action are known to be the same is scientifically more appropriate (EPA, 1986).

5.1.3 Characterization of Uncertainty

Uncertainty can be introduced into a health risk assessment at every step in the process. It occurs because risk assessment is a complex process, requiring the integration of:

- the fate and transport of pollutants in a variable environment by processes that are often poorly understood or too complex to quantify accurately;
- the potential for adverse health effects in humans as extrapolated from animal bioassays; and
- the probability of adverse effects in a human population that is highly variable genetically, in age, in activity level, and in life styles.



Even using the most accurate data with the most sophisticated models, uncertainty is inherent in the process. There are several different types of uncertainty. One is the fact that variables cannot be measured precisely (either because of equipment limitations or because the quantity being measured varies). A second type of uncertainty is associated with a variety of models used in all phases of a risk assessment. These include the animal models used as surrogates for testing human carcinogenicity as well as the computer models used to predict the fate and transport of chemicals in the environment. The use of rodents as surrogates for humans introduces uncertainty into the risk factor since different species do not respond to toxins in exactly the same way. Computer models are simplifications of reality and some variables are excluded.

Variability is another type of uncertainty, which is often used interchangeably with the term "uncertainty," although this is not strictly correct. The variability of a characteristic may be known with absolute certainty. For example, the age distribution of a population may be known and represented by the mean age and its standard deviation. The fact that ages do vary introduces uncertainty into characterizing risk for that population. On the other hand, the age distribution may not be known; then the variability associated with the population's age is in itself an uncertainty.

The degree to which all types of uncertainty need to be quantified and the amount of uncertainty that is acceptable varies. For a screening level analysis, a high degree of uncertainty is often

acceptable, provided that conservative assumptions are used to bias potential error toward protecting human health. Similarly, a region-wide or nation-wide study will be more uncertain than a site-specific one. In general, the more detailed or accurate the risk characterization, the more carefully uncertainty needs to be considered.

A complete risk assessment requires much of the data and information outlined in this document. Although risk assessments have been performed for air toxics in certain parts of the country, there has not yet been a complete risk assessment performed on the air toxics problem nationwide. There are, however, several analyses which have been performed on a broader scale. These broader analyses, although not complete risk analyses, provide us with preliminary information about the HAPs and geographic areas where air toxics risks are of most concern.

5.2 Ecological Assessment

Given that our first priority has been protection of public health, our methods for evaluating risk posed by HAPs to wildlife or ecosystems are less well established than those for human health. However, as a first step in addressing environmental risks, EPA has developed a decision framework which detailed a systematic iterative approach to the issue (USEPA, 1998d).

A specific application of this framework is planned under the CAA mandated OAQPS residual risk program. The OAQPS framework provides for a tiered approach, the first of which prioritizes HAPs based on their environmental behavior, e.g. ability to persist, bio-accumulate, or exhibit acute toxicity. HAPs meeting these criteria (i.e., exhibit a tendency to persist, bio-accumulate, and/or be acutely toxic) would undergo closer scrutiny in the second tier. Tier Two contains a more intensive evaluation that employs multi-pathway analysis to estimate if, and to what extent, ecological receptors (e.g. an oyster fishery, a wild duck population or a unique wetland community) may be exposed to HAPs. The exposure and potential impact is characterized and evaluated against predetermined risk management goals (i.e. edibility of oysters, sustainability of the duck population, maintainance of the integrity of the wetland community). For those HAPs that are determined to pose a potentially significant concern to one of the ecological receptors, a more detailed tier consisting of a site specific multi-pathway risk assessment, or similar analyses, is performed. From this last stage a detailed characterization of the environmental risks is developed.

6.0 References

AIHA.1998. Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook. American Industrial Hygiene Association.302-EA-98. Fairfax, VA.

ATSDR. 1998. Minimal Risk Levels for Hazardous Substances. Agency for Toxic Substances and Disease Registry. http://atsdr1.atsdr.cdc.gov:8080/mrls.html

CalEPA. 1996. A Review of the California Environmental Protection Agency's Risk Assessment Practices, Policies, and Guidelines, Report of the Risk Assessment Advisory Committee. California Environmental Protection Agency.

CalEPA. 1997a. Technical Support Document for Describing Available Cancer Potency Factors, public and scientific review panel draft. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.

CalEPA. 1997b. Technical Support Document for the Determination of noncancer chronic Reference Exposure Levels. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.

Finkel, A.M. 1990. Confronting Uncertainty in Risk Management. A Guide for Decision Makers. Center for Risk Management, Resources for the Future, Washington, D. C.

IARC. 1998. IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer. http://193.51.164.11/default.html

Klaasen, C.D., M.O. Amdur, J. Doull. [eds] 1986. Casarett and Doull's Toxicology, The Basic Science of Poisons. 3rd ed. Macmillan Publishing Company, New York. 974 pp.

McKone TE and DW Layton, 1986. Screening the Potential Risks of Toxic Substances Using a Multimedia Compartment Model: Estimation of Human Exposure, Reg Toxicol Pharm 6:359-380.

Sheehan PJ, Baril A, Mineau P, Smith DK, Harfenist A, Marshal WK. 1987. The impact of pesticides on the ecology of prairie-nesting ducks. Technical Report Series, No. 19. Ottwaw:Canadian Wildlife Service.

Smith RL. 1996. Risk-based concentrations: Prioritizing environmental problems using limited data. Toxicol 106:243-266.

USEPA. 1985. Methods for Assessing Exposure to Chemical Substances. Volume 4: Methods for Enumerating and Characterizing Populations Exposed to Chemical Substances. U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances, Exposure Evaluation Division, Washington DC. EPA 560/5-85-004.

USEPA. 1986. Guidelines for Carcinogen Risk Assessment. 51 Federal Register 33992-34003. September 24, 1986.

USEPA. 1987. Technical Guidance for Hazards Analysis. Emergency Planning for Extremely Hazardous Substances. U.S. Environmental Protection Agency, FEMA, USDOT. EPA-OSWER-88-001.

USEPA. 1989. Risk Assessment Guidance for Superfund Volume I - Human Health Evaluation Manual (Part A). USEPA, Office of Emergency and Remedial Response, Washington, DC. EPA 540/1-90-002.

USEPA. 1990. Methodology for Assessing Health Risks Associated with Indirect Exposure to Combustor Emissions. Office of Health and Environment Assessment, Cincinnati, OH. EPA 600/6-90-003.

USEPA. 1991. Risk Assessment for Toxic Air Pollutants: A Citizen's Guide. EPA 450/3-90-024.

USEPA, 1991a. General Quantitative Risk Assessment guidelines for Naoncancer health effects, External Review Draft, Office of Research and Development, ECAO-CIN-538.

USEPA. 1992a. Framework for Ecological Risk Assessment. Risk Assessment Forum, Office of Research and Development, U.S. Environmental Agency, Washington, D.C. EPA-630/R-92-001.

USEPA. 1992b. Guidelines of exposure assessment. Federal register publication on May 29, 1992 (57 FR 22888). EPA/600-Z-92/001

USEPA, 1992c. Office of the Administrator, Guidance on Risk Characterization for Risk Managers and Risk Assessors, 1992, memorandum from F. Henry Habicht, II, Deputy Administrator.

USEPA, 1993. A Descriptive Guide to Risk Assessment Methodologies for Toxic Air Pollutants, U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, EPA-453/R-93-038.

USEPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. U.S. Environmental Protection Agency, Office of Research and Development. EPA/600/8-90/066F.

USEPA. 1994. Ecological Risk Assessment Issue Papers. EPA/630/R-94/009. U.S. Environmental Protection Agency, Washington, DC..

USEPA. 1995. The Use of the Benchmark Dose Approach in Health Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum. EPA/630/R-94/007.

USEPA. 1996a. Proposed Guidelines for Cancer Risk Assessment. 61 Federal Register 179610-18011. (4/23/96)

USEPA. 1996b. Accidental Release Prevention Requirements: Risk Management Programs under Clean Air Act Section 112(4)(7). 61 Federal Register 31667-31730. (6/20/96)

USEPA. 1997a. Health Effects Assessment Summary Tables. U.S. Environmental Protection Agency, Solid Waste and Emergency Response, Washington, DC. EPA-540-R-97-036.

USEPA. 1997b. National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances. 62 Federal Register 58840-58850. (10/30/97)

USEPA. 1998a. Integrated Risk Information System. U.S. Environmental Protection Agency. [http://www.epa.gov/ngispgm3/iris/index.html]

USEPA. 1998b. Science Advisory Board, Environmental Health Committee, Notification of Public Meeting, June 9-10, 1998.

USEPA. 1998c. Draft Integrated Urban Air Toxics Strategy to Comply with Section 112(k), 112(c)(3) and Section 202(l) of the Clean Air Act. Federal Register, September , 1998.

USEPA. 1998d. Final Guidelines for Ecological Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC.

Woodruff TJ, Axelrad DA, Caldwell J, Morello-Frosch R, and A Rosenbaum. 1998. Public Health Implications of Air Toxics Across the United States. Environ Health Persp 106:245-251.