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Great Lakes Water Quality Initiative Technical Support Document for Human Health Criteria and Values

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GREAT LAKES WATER QUALITY INITIATIVE TECHNICAL SUPPORT DOCUMENT FOR HUMAN HEALTH

I. INTRODUCTION

A. Goal

The goal of the human health criteria and values for the Great Lakes and their tributaries is the protection of humans from unacceptable exposure to toxicants from consumption of contaminated fish, drinking water and water related to recreational activities. Emphasis is on protection of the individual in evaluating toxicity information and its application in the derivation of criteria and values. Exposure assumptions follow trends and activities for the general population as a region and also attempt to protect sensitive subpopulations. Based on differences in behavior, there may be some individuals who receive a greater level of protection or a lesser level of protection via these procedures.

B. Level of Protection

Numeric criteria or interpretations of narrative criteria developed for human health generally restrict chemical carcinogen exposure in a target population to levels estimated to result in a lifetime incremental risk of no greater than 1 in 100,000 of developing cancer. The procedure generally used to estimate the risk level leads to the development of a plausible upper limit of the risk. This means that the actual risk is unknown, is unlikely to exceed 10^{-5}, and may even be as low as zero.

The selection of an "acceptable" target risk level does not turn on scientific analysis, but on more subjective "risk management" considerations. Differences in perception of risk, opinions as to benefit versus risk reduction costs, as well as distinctions between risks that are considered voluntary or involuntary, all could play a meaningful role in determining risk acceptability. For this initiative, a 10-5 cancer risk level has been selected as acceptable. This is consistent with the existing practice of the eight Great Lakes states, and therefore is consistent with existing risk management policy in these states. It is also a risk level that EPA has found acceptable in its review of state criteria in the past, and which EPA itself has used as a basis for certain of its regulations. EPA notes that States and Tribes are free to adopt a more stringent approach than that contained in the final Guidance. It is also instructive to note that this level of risk of developing cancer appears to be roughly comparable to that which exists for death due to natural phenomena. Table 1 represents data from a study of everyday risks of death from several naturally occurring incidents such as tornados, floods, lightning and animal bites or stings. When extrapolated to lifetime risks, we see that these risks range from 1.4 in 100,000 for animal bites or stings to 4 in 100,000 for floods and tornadoes. It is acknowledged that risk of death (as described in Table 1) is not equatable with

risk of cancer since many forms of cancer are now easily curable. The comparison is made only for the purpose of illustrating the potential background risk in the region.

For noncarcinogens, protection of human health is generally centered on determining a level of daily exposure that is likely to be without an appreciable risk of deleterious effects for a lifetime. The concept of acceptable exposure incorporates the potential for long term exposure of sensitive individuals in a population to an environmental contaminant without any anticipated adverse health effects.

TABLE 1. **EVERYDAY RISKS**

	Time to Accumulate a 1 in 100,000 Risk of Death	Average Annual Risk per Capita	Extrapolated to Risk/Lifetime*
********** **Living in the United States** **********			
Motor vehicle accident	15 days	2×10^{-4}	1.4×10^{-2}
Falls	60 days	6×10^{-5}	4.2×10^{-3}
Drowning	100 days	4×10^{-5}	2.8×10^{-3}
Fires	130 days	3×10^{-5}	2×10^{-3}
Firearms	360 days	1×10^{-5}	7×10^{-4}
Electrocution	20 months	5×10^{-6}	3.5×10^{-4}
Tornadoes	200 months	6×10^{-7}	4×10^{-5}
Floods	200 months	6×10^{-7}	4×10^{-5}
Lightning	20 years	5×10^{-7}	3.5×10^{-5}
Animal bite or sting	40 years	2×10^{-7}	1.4×10^{-5}
********** **Occupational Risks** **********			
GENERAL			
Manufacturing	45 days	8×10^{-5}	5.6×10^{-3}
Trade	70 days	5×10^{-5}	3.5×10^{-3}
Service and government	35 days	1×10^{-4}	7×10^{-3}
Transport and public utilities	10 days	4×10^{-4}	3×10^{-2}
Agriculture	150 hours	6×10^{-4}	4×10^{-2}
Construction	140 hours	6×10^{-4}	4×10^{-2}
Mining and quarrying	90 hours	1×10^{-3}	7×10^{-2}
SPECIFIC			
Coal mining (accidents)	140 hours	6×10^{-4}	3×10^{-2}
Police duty	15 days	2×10^{-4}	1.4×10^{-2}
Railroad employment	15 days	2×10^{-4}	1.4×10^{-2}
Fire fighting	110 hours	8×10^{-4}	5.4×10^{-2}

Some One in a Million Cancer Risks

Cosmic rays	one transcontinental round trip by air living 1.5 months in Colorado compared to New York camping at 15,000 feet for 6 days compared to sea level
Other radiation	20 days of sea level natural background radiation 2.5 months in masonry rather than wood building 1/7 of a chest x-ray using modern equipment
Eating and drinking	40 diet sodas (saccharin) 6 pounds of peanut butter (aflataxia) 180 pints of milk (aflataxia) 200 gallons of drinking water from Miami or New Orleans 90 pounds of broiled steak (cancer risk only)
Smoking	2 cigarettes

Adapted from Crouch and Wilson (1962)

* Risk/Lifetime = $1 - (1-s)^{70}$

C. Two Tiered Approach

A two tiered approach is used to derive ambient concentration levels protective of human health. Both tiers rely generally on the same standard procedure for data review and criteria derivation. The difference between the two focuses heavily on the certainty with which one can predict a level of risk or a level of safety for humans from the data available. The more adequate the database to estimate actual human risk or to establish no adverse effect levels, the greater the certainty in the appropriateness of the criterion or value. This level of certainty depends heavily on the weight of experimental evidence which includes factors such as: the quantity of studies or size of the experimental database available for review; the quality of study design, its conduct and range of effects evaluated; the potency or range and type of adverse effects observed and, the appropriateness of this data in predicting human effects, i.e. evaluation of effects in humans or in animal species biologically similar to human.

The greater the level of certainty in the database for noncancer effects, generally the lower the need for adjustment of the research findings to assure a level without appreciable risk. The greater the weight of evidence for carcinogenicity, the greater the strength in predicting cancer risk to humans. Chemicals with databases providing a high level of certainty in predicting a level of risk or safety for humans from adverse health effects are suitable for Tier I numeric criteria derivation. Tier I criteria are conceptionally those criteria where the probability of change is low.

Chemicals with less extensive data or where the weight of evidence toward predicting human health effects is less certain, are subject to Tier II values. Under Tier II, the probability of future change is greater than for Tier I as demonstrated by the extent, level of quality and/or weight of evidence or conclusiveness of effects demonstrated by the database. The values derived via Tier II are more likely to change based on new data and/or reinterpretation of effect or potency.

D. Technical Background

The process used to evaluate effects and in development of criteria shall be based on currently acceptable scientific methods and consider guidance offered by the various USEPA methods. Particular attention should be paid to RfD and cancer risk estimation development contained within the Integrated Risk Information System (IRIS).

To promote consistency with other USEPA guidance for chemical management, it is important to review and strongly consider the IRIS values for chemicals undergoing criteria or values development whenever available. Although consistency is important, it is also important that the most current and complete data should be used when generating criteria or values

whether IRIS has considered this data or not. Further, since IRIS values are developed under guidance and through the judgement of workgroups, the final values may not always be arrived at consistently, i.e., duration of studies, selected, uncertainty factors applied, basis for derivation of potency slopes, etc., may differ between decisions. If data used in deriving Tier I criteria or Tier II values have not been considered by the IRIS RfD or CRAVE workgroups, the appropriate workgroup should be advised of the data. In cases where IRIS RfDs or potency slopes have not been developed consistent with these procedures, it is suggested that the rationale for RfD or potency slope development be evaluated and determination made whether 1) justification is sufficient to support deviating from these procedures, or 2) justification exists to deviate from IRIS guidance. When deviations from IRIS are contemplated, EPA strongly urges States and Tribes to communicate these potential changes to EPA, either through a Regional EPA Office or directly to the EPA Reference Dose (RfD) and/or Cancer Risk Assessment Verification Endeavor (CRAVE) workgroups, as soon as possible. This will help foster consistency between EPA and the States and Tribes. Additionally, when deviating from IRIS, States and Tribes are encouraged to work with the Clearinghouse described in Section II of the SID, to ensure that other States and Tribes are aware of the deviations.

Specific references which should be reviewed and evaluated for greater details on the basic parameters of the criteria and values derivation methodology are as follows:

National Cancer Institute (NCI). 1976. Guidelines for Carcinogen Bioassay in Small Rodents, Technical Report Series No. 1, U.S. Department of Health, Education and Welfare, NCI-CG-TR-1.

Office of Science and Technology Policy (OSTP). 1985. Chemical Carcinogens; A Review of the Science and Its Associated Principles, Federal Register, Vol. 50, No. 50. March 14, 1985, 10371-10442.

Organization for Economic Cooperation and Development (OECD). 1987. Guidelines for Testing of Chemicals, Paris, France.

U.S. Environmental Protection Agency (EPA). 1989. Risk Assessment Guidance for Superfund, Volume 1, Human Health Evaluation Manual (Part A) - Interim Final, Office of Emergency and Remedial Response, Washington, D.C., EPA/540/1-89/002.

U.S. Environmental Protection Agency (EPA). 1980. Water Quality Criteria Availability, Appendix C Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Quality Criteria

Documents, Federal Register, Vol. 45, November 28, 1980, 79347-79357.

U.S. Environmental Protection Agency (EPA). 1985. Toxic Substances Control Act Test Guidelines; Final Rules, Federal Register, Vol. 50, NO. 188. September 27, 1985, 39421-39425.

U.S. Environmental Protection Agency (EPA). 1986. Guidelines for Carcinogen Risk Assessment. Federal Register, Vol. 51, No. 185. September 24, 1986, 33992-34002.

U.S. Environmental Protection Agency (EPA). 1986. Guidelines for the Health Assessment of Suspect Developmental Toxicants, Federal Register, No. 51, No. 185. September 24, 1986 34028-34040.

This is by no means a complete list. Other sources of information and guidance may also be considered as appropriate.

II. MINIMUM DATA REQUIREMENTS

A. Carcinogens

1. Weight of Evidence

Evidence of a chemical's possible carcinogenic effects in humans shall be categorized according to the existing EPA weight of evidence classification system, which is adapted from the International Agency for Research on Cancer (IARC). The five categories or groups are as follows:

Human Carcinogen (identified as Group A under existing classification scheme)
"sufficient" evidence from epidemiologic studies to support a causal association between exposure to the chemical and cancer;

Probable Human Carcinogen (identified as Group B)
"limited" evidence from epidemiologic studies with or without supporting animal data (Group B1); or, "sufficient" evidence of carcinogenicity based on animal studies, but for which there may be "inadequate evidence" or "no data" from epidemiologic studies (Group B2);

Possible Human Carcinogen (identified as Group C)
"limited" evidence of carcinogenicity in animals and the absence of data for humans;

Not Classifiable as to Human Carcinogenicity (identified as Group D)

"inadequate" evidence of carcinogenicity in humans and animals, or, for which no data are available; and

Evidence of Noncarcinogenicity for Humans (identified as Group E)
"no evidence" for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and
animal studies.

The definitions of the EPA weight of evidence classifications are as follows:

1. Humans
   a. **Sufficient evidence** - a causal association can be inferred between exposure to the chemical and human cancer.

   b. **Limited evidence** - a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding could not adequately be excluded.

   c. **Inadequate evidence** - there were few pertinent data, or, a causal interpretation is not credible from available studies since they did not exclude change, bias or confounding.

   d. **No evidence** - no association was found between exposure and an increased risk of cancer in well-designed and well-conducted independent analytical epidemiologic studies.

2. Animals
   a. **Sufficient evidence** - an increased incidence of malignant or combined malignant and benign tumors: 1) in multiple species or strains, 2) in multiple experiments using different dosage levels and possible different routes of exposure; or 3) in a single experiment with a high incidence, unusual site or type of tumor, or early onset.

   b. **Limited evidence** - data suggest a carcinogenic effect but are limited because: 1) the studies involve a single species, strain or experiment which does not demonstrate a high incidence, unusual site or type of tumor, or early onset; 2) the experiments used inadequate dosage levels, inadequate exposure duration, inadequate follow-up periods, poor survival, too few animals, or inadequate reporting; 3) an increase in benign tumor incidence only and no response in a variety of short-term tests for mutagenicity; or 4) tumor responses of marginal statistical significance

due to inadequate study design or reporting, or, in tissue known to have a high or variable background rate.

c. **Inadequate evidence** - because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.

d. **No evidence** - no increased tumor incidence in at least two well-designed and well conducted animal studies in different species.

Further detail regarding this classification system for categorizing weight of evidence for carcinogenicity may be found in the EPA Guidelines for Carcinogen Risk Assessment (EPA, 1986).

2. Appropriate Study Design and Data Development

The following discussion summarizes the process for evaluating evidence of carcinogenicity and outlines an approach study design by which one may measure the quality and adequacy of data development. When available, human epidemiologic data with quantifiable exposure levels are preferred for evaluating a chemical's carcinogenic potential over use of animal data alone. Epidemiological studies can provide direct evidence of a chemical's carcinogenicity in humans (OSTP, 1985). The type of epidemiologic study conducted indicates whether the study may be useful in assessing carcinogenic risk to exposed humans (analytical studies) or if it is merely hypothesis-generating and inherently incapable of proving a causal association. Case reports, descriptive studies and ecological (correlational) studies generally cannot establish whether risks are associated with particular exposures. Analytical studies can assess carcinogenic risks to exposed humans, and can infer a casual association (Mausner and Kramer, 1985; OSTP, 1985). The two general types of analytical studies are case-control and cohort. In case-control studies, a group of diseased "case" individuals is initially identified and matched with nondiseased "controls". Information on past exposure to reputed risk factors or causative agents is then collected for both groups. If the proportion of cases with a certain exposure is significantly different than that of controls, an association between exposure and disease may be indicated. A cohort study starts by identifying a group of individuals with a particular exposure and a similar group of unexposed persons and follows both groups over time to determine subsequent health outcomes. The rates of disease in the exposed and unexposed groups are then compared. Cohort studies may be based on current exposure and future health outcomes (prospective cohort study), or on past exposure information and disease occurrence (historical cohort study). As with case-control

studies, cohort studies that are well-designed, well-conducted, and well-evaluated can test hypotheses and provide the basis for causal inferences (OSTP, 1985; EPA, 1986). Factors such as proper selection and characterization of exposed and control groups, adequacy of duration and quality of follow-up, proper identification and characterization of confounding factors and bias, appropriate consideration of latency effects, valid ascertainment of causes of morbidity and mortality, and the ability to detect specific effects are all elements for determining the adequacy of epidemiologic studies (EPA, 1986). In interpreting a reported causal association, reference may be made to the following criteria, as described by IARC (1985), EPA (1986), and the Tripartite Working Group (1985):

- There is no identifiable positive bias which could explain the association.

- The possibility of positive confounding factors has been considered and ruled out as explaining the association.

- The association is unlikely to be due to chance alone.

Although the weight of evidence increases with the number of adequate studies, in some instances, a single epidemiologic study may be strongly indicative of a cause-effect relationship (IARC, 1985; EPA, 1986). Confidence to infer a causal association is increased by any of the following: when several independent studies are concordant in showing the association; when the association is strong; when there is a dose-response relationship when a reduction in exposure is followed by a reduction in the incidence of cancer; when the effect is biologically plausible; or when the effect is specific for a particular chemical. When epidemiological evidence based on analytical studies appears to be significantly flawed, the evidence may then be downgraded to being suggestive of an association based on scientific judgment. This may still provide evidence that a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded.

Epidemiological studies are inherently capable of detecting only comparatively large increases in the relative risk of cancer (EPA, 1986). Other limitations of epidemiological studies include the long latency of cancer, and the difficult task of exposure assessment, including multiple exposures. Therefore, negative results from such studies do not verify that a particular agent is noncarcinogenic in humans (IARC, 1985; EPA, 1986; OSTP, 1985).

Although epidemiologic studies are preferable for assessing carcinogenic potential for humans, the relative paucity of such data necessitates the use of animal data as a surrogate for humans in most situations. In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents

for which there is sufficient evidence of carcinogenicity in experimental animals as if they present a carcinogenic risk to humans (IARC, 1991). The weight of evidence that an agent is potentially carcinogenic in humans increases with: a) the increase in tissue sites affected; b) the increase in number of animal species, strains, sexes, doses and experiments showing a carcinogenic response; c) the occurrence of clear-cut dose-response relationships as well as a high level of statistical significance of the increased tumor incidence in treated groups as compared to controls; d) a dose related shortening of the time-to-tumor occurrence or time to death with tumor; and e) a dose-related increase in the proportion of tumors that are malignant (EPA, 1986).

The guidelines detailed by EPA (1985), OSTP (1985) and NCI (1976) for evaluating long-term carcinogenicity bioassays will be utilized to determine the adequacy of design and the strength of evidence provided by the study. Specific study design elements of these guidelines are synopsized as follows:

- Species used: The most widely used and accepted test species is the rat. NCI/NTP bioassays routinely use the Fischer inbred (F344) strain of rat and the B6C3F1 hybrid mouse. Hamsters have also been frequently used. Other animal species and strains may also be appropriate surrogates to demonstrate a chemical's carcinogenic potential.

- Number of animals: At least 100 rodents (50 of each sex) should be used at each dose level and concurrent control.

- Age at start: Dosing of rodents should begin as soon as possible after weaning to allow for the long latency of cancer. For rats, dosing ideally begins before the age of 6 weeks and should not begin after 8 weeks of age.

- Survival: All groups should have at least 50% survival at the time of termination.

- Concurrent control groups: These should be untreated, sham treated, or, if a vehicle is used in administering the test substance, vehicle control groups. The use of historical control data is desirable for assessing the significance of changes observed in exposed animals, but only if the strain of animals and laboratory conditions have not changed. For the evaluation of rare tumors, even small tumor responses may be significant compared to historical data. The review of tumor data at sites with high spontaneous background requires special consideration (OSTP, 1985). For instance, a response that is significant with respect to the experimental control group may become questionable if the historical control data indicate that the experimental

control group had an unusually low background incidence (NTP, 1984).

- Dose levels: At least 3 dose levels are recommended in addition to the concurrent control group, for the purpose of risk assessment (OSTP, 1985; EPA, 1985). For the purpose of hazard assessment, detection of a carcinogenic response is possible with one dose level, although 2 dose levels are preferred and are necessary to demonstrate a dose-response relationship. The highest dose level should target the maximum tolerated dose (MTD). The MTD is the dose which, when given for the duration of the chronic study, elicits signs of minimal toxicity (e.g., less than or equal to 10% weight gain decrement) without substantially altering the normal life span due to effects other than carcinogenicity. The MTD is intended to provide an adequate statistical power for the detection of carcinogenic activity. While not an ideal solution to the problem of low bioassay sensitivity, use of the MTD is appropriate if it is properly determined (OSTP, 1985; EPA, 1986).

- Dosing route: The test substance should be administered via the oral, dermal or inhalation route.

- Dosing schedule: The animals should ideally be dosed on a 7 day per week basis. However, based primarily on practical considerations, dosing on a 5 day per week basis is acceptable. Treatment preferably should be continued for the major portion of the animal's lifespan. This is at least 18 months for mice and hamsters, and 24 months for rats.

- Data collection: During the study, animals should be monitored for body weight and food intake, as well as for the onset and progression of all toxic effects. Clinical examinations, including hematology, biochemistry of blood, urinalysis, and ophthalmological examination, should be made. Gross necropsy and histopathology should be performed on all animals. Specific requirements are too numerous to list here, but may be reviewed via the EPA (1985) and NCI (1976) guidelines.

- All observed results should be evaluated by an appropriate and generally accepted statistical method. Evidence for carcinogenic action should be based on the observation of statistically significant tumor responses in specific organs or tissues. Appropriate statistical analysis should be performed on data from long-term studies to help determine whether the effects are treatment-related or possibly due to chance. These should at least include a statistical test for trend, including appropriate correction for differences in survival. The weight to be given to the level of

statistical significance (the p-value) and to other available pieces of information is a matter of overall scientific judgment. In a review of 25 NTP feeding studies as discussed by OSTP (1985), a simple statistical rule was derived by Haseman which appeared to mimic the scientific judgment process used in those experiments. "Regard as carcinogenic any chemical that produces a high dose increase in a common tumor that is statistically significant at the 0.01 level or a high-dose increase in an uncommon tumor that is statistically significant at the 0.05 level. The overall false positive rate associated with this rule was estimated to be no more than 7-8% for the NTP two-sex, two-species protocol". A statistically significant excess of tumors of all types in the aggregate, in the absence of a statistically significant increase of any individual tumor type, should be regarded as minimal evidence of carcinogenic action unless there are persuasive reasons to the contrary (OSTP, 1985).

These guidelines represent ideal parameters. Studies will not be expected to meet all of these desirable conditions in order to be further considered for use in the process. The adequacy and appropriateness of all animal carcinogenicity bioassays will be carefully considered. It is crucial that judgment of adequate testing be based on sound scientific principles. In general, it can be expected that most substances tested for carcinogenicity have been reviewed by NCI/NTP, IARC, and/or EPA. Historically the evaluations by these agencies have been sufficient for decision-making. A thorough assessment of the data should be performed regardless of the findings of those independent agencies since these reviews might be dated in that research data available subsequent to the date of review were not considered by the reviewing group. The overall assessment of a chemical's carcinogenic potential will depend on weight-of-evidence based upon full consideration of all the evidence. Also see Section III. Principles for Criteria Development for a discussion of Mechanism/Mode of Action and the use of mutagenicity studies in determining carcinogenicity.

3. Borderline Conditions

With regard to the overall database used in determining carcinogenicity, a variety of studies may be encountered which may be considered flawed or lacking in adequate design or reporting. Such studies may only be able to be utilized anecdotally and only considered suggestive evidence of carcinogenicity. Examples of conditions meeting such a criteria are:

1. Borderline conditions of:

a. Statistical significance. A general example would be a study in which the MTD was administered and the test for positive dose-related trend (e.g., Cochran-Armitage Test) determined that the slope of the dose-response curve was different from zero; however, comparisons of the tumor incidences in treated groups with that in the control group (e.g., Fisher-Irwin exact test) were not significant at $p = 0.05$.

b. Study design.

c. Study reporting. A general example would be a study reporting a tumorigenic response, but lacking statistical analyses to verify that an apparent increase in incidence was statistically significant.

d. A tumor response in a tissue known to have a high and variable background rate.

2. Tumor responses or lack of response which are more than likely attributable to excessive doses that compromise major organ systems. Positive studies at levels above the MTD should be carefully reviewed to ensure that the responses are not due to factors which do not operate at exposure levels at or below the MTD. Evidence indicating that high exposures alter tumor responses by indirect mechanisms that may be unrelated to effects at lower exposures should be dealt with on an individual basis. As noted by the OSTP (1985), "Normal metabolic activation of carcinogens may possibly also be altered and carcinogenic potential reduced as a consequence [of high-dose testing]." Negative long-term animal studies at exposure levels above the MTD may not be acceptable if animal survival is so impaired that the sensitivity of the study is significantly reduced below that of a conventional chronic animal study at the MTD.

   "The carcinogenic effects of an agent may be influenced by non-physiological responses (such as extensive organ damage, radical disruption of hormonal function, saturation of metabolic pathways, formation of stones in the urinary tract, saturation of DNA repair with a functional loss of the system) induced in the model systems. Testing regimes inducing these responses should be evaluated for their relevance to the human response to an agent and evidence from such a study, whether positive or negative, must be carefully reviewed." (OSTP, 1985).

3. Tumors at the site of oral, dermal or inhalation administration attributable to irritation or frank tissue damage.

4. Tumor responses following administration by a route other than oral, dermal or inhalation. Such tumors may be at the site of administration or removed from it. Some general examples are tumors induced following intraperitoneal, intravenous or subcutaneous injection, or bladder implantation.

Solid-state carcinogenesis is the occurrence of tumors around an inserted inert object. It is a phenomenon that is dependent primarily on the size and shape of the object, rather than the chemical composition of the implanted material (Williams and Weisburger, 1986). Therefore, induction of solid-state tumors generally will not be considered in the weight-of-evidence approach.

Data from all long-term animal studies should be considered in evaluating carcinogenicity. However, carcinogenic responses should be evaluated as to their relevance of predicting cancer risks to humans. Therefore, data from species that respond most like humans should be used preferentially when such information exists. Data on tumors in organs or as a result of effects on metabolic or biochemical pathways that don't exist in humans should be evaluated very carefully as to their inference of human cancer risk. Further, a positive carcinogenic response in one species/strain or sex is not generally negated by negative results in other species. Replicate negative studies, however, that are essentially identical in all other respects to a positive study may cast doubt on the validity or reproducibility of a positive study. A variety of other weight of evidence issues may make it difficult to interpret the significance of tumor data and therefore result in a lower classification of carcinogenicity. Examples of such issues include: increased incidence of tumors in the highest dose group only and/or only at the end of the study; no substantial dose-related increase in the proportion of tumors that are malignant; the occurrence of tumors that are predominantly benign; no close-related shortening of the time to the appearance of tumors; negative or inconclusive results from a spectrum of short-term tests for mutagenic activity; or, the occurrence of excess tumors only in a single sex (EPA, 1985).

B. Noncarcinogens

The full range of possible adverse health effects shall be evaluated when establishing an acceptable exposure to noncarcinogens. Acute/subacute, subchronic/chronic and reproductive/developmental effects shall be considered. The principles of data selection are similar to those for carcinogenic effects, a well-conducted epidemiologic study which

demonstrates a positive association between a quantifiable exposure to a chemical and human disease is generally preferred for evaluating adverse health effects. At present, however, human data adequate to serve as a basis for quantitative risk assessment are available for only a few chemicals. Frequently, inference of adverse health effects to humans must be drawn from toxicity information gained through animal experiments with human data serving qualitatively as supporting evidence. Under this condition, health effects data must be available from well conducted studies in animals relevant to humans based on a defensible biological rationale, i.e. similar metabolic pathways, etc.

The following provides guidance on appropriate study design for a variety of types of toxicity studies against which one may evaluate the quality and adequacy of data development. This evaluation of adequacy of data coupled with effects information forms the basis for selection of uncertainty factors and subsequent acceptable exposure levels.

1. Appropriate Study Design

a. Acute Toxicity

Acute Toxicity Determination of an LD50 or LC50 is often an initial step in experimental assessment and evaluation of a chemical's toxic characteristics. Such studies are used in establishing a dosage regimen in subchronic and other studies and may provide initial information on the mode of toxic action of a substance. Because LD50 or LC50 studies are of short duration, inexpensive and easy to conduct, they are commonly used in hazard classification systems. Acute lethality studies are of limited use in this process. However, the data from such studies do provide information on health hazards likely to arise from individual short-term exposures. Although this process should never allow exposures which approach such acute levels, such studies provide high dose effects data from which to evaluate potential effects from exposures which may temporarily exceed the acceptable chronic exposure level. An evaluation of the data should include the incidence and severity of all abnormalities, the reversibility of abnormalities observed other than lethality, gross lesions, body weight changes, effects on mortality, and any other toxic effects.

In recent years guidelines have been established to improve quality and provide uniformity in test conditions. Unfortunately, many published LD50 or LC50 tests were not conducted in accordance with current EPA or OECD guidelines since they were conducted prior to establishment of guidelines. For this reason, it becomes necessary to examine each test or study to determine if the study was conducted in an adequate manner.

The following is a list of ideal conditions compiled from various testing guidelines which may be used for determination of

adequacy. Unfortunately, many published studies do not report details of test conditions making such determinations difficult. However, test conditions guidelines that might be considered ideal may include:

- animal age and species identified;
- minimum of 5 animals per sex per dose group (Both sexes should be used.);
- 14 day or longer observation period following dosing;
- minimum of 3 dose levels appropriately spaced. (Most statistical methods require at least 3 dose levels.);
- identification of purity or grade of test material used (particularly important in older studies);
- if a vehicle used, the selected vehicle is known to be non-toxic;
- gross necropsy results for test animals; or
- acclimation period for test animals before initiating study.

Specific conditions for oral LD50:

- dosing by gavage or capsule;
- total volume of vehicle plus test material remain constant for all dose levels; and
- animals were fasted before dosing.

Specific conditions for dermal LD50:

- exposure on intact, clipped skin and involve approximately 10% of body surface; and
- animals prevented from oral access to test material by restraining or covering test site.

Specific conditions for inhalation LC50:

- duration of exposure at least 4 hours; and
- if an aerosol (mist or particulate) the particle size (median diameter and deviation) should be reported.

Although the above listed conditions would be included in an ideally conducted study, not all of these conditions need to be included in an adequately conducted study. Therefore, some discretion is required on the part of the individual reviewing these studies (EPA, 1985, OECD, 1987).

b. 14 Day or 28 Day Repeated Dose Toxicity

The following guidelines were derived using the OECD Guideline for Testing of Chemicals (1987), for determining the design and quality of a repeated dose short-term toxicity study. The similarity between the conduct of a 14-day and 28-day study is sufficient to consider them under the same guideline. The main difference is the time period over which the dosing takes place. These guidelines represent ideal conditions and studies will not be expected to meet all standards in order to be considered. For example, the National Toxicology Program's cancer bioassay program has generated a substantial database of

short-term repeated dose studies. The study periods for these range from 14 days to 20 days with 12 to 15 doses administered generally for 5 dose levels and a control. Since the quality of this data is good, it is desirable to consider these study results even though they do not always identically follow the protocol.

The purpose of short-term repeated dose studies is to promote information on possible adverse health effects from repeated exposures over a limited time period. Where subchronic or chronic data are lacking, short-term repeated dose studies of 28 days or longer, with the application of appropriate uncertainty factors, may be used by this initiative to estimate acceptable long-term exposure levels.

According to OECD Guidelines, short-term repeated dose studies should include the following:

- minimum of 3 dose levels administered and an adequate control group used;
- minimum of 10 animals per sex, per dose group (both sexes should be used);
- the highest dose level should ideally elicit some signs of toxicity without inducing excessive lethality and the lowest dose should ideally produce no signs of toxicity;
- ideal dosing regimes include 7 days per week for a period of 14 days or 28 days;
- all animals should be dosed by the same method during the entire experiment period;
- animals should be observed daily for signs of toxicity during the treatment period (i.e. 14 or 28 days). Animals which die during the study are necropsied and all survivors in the treatment groups are sacrificed and necropsied at the end of the study period;
- all observed results, quantitative and incidental, should be evaluated by an appropriate statistical method;
- clinical examinations should include hematology and clinical biochemistry, urinalysis may be required when expected to provide an indication of toxicity. Pathological examination should include gross necropsy and histopathology.

The findings of short-term repeated dose toxicity studies should be considered in terms of the observed toxic effects and the necropsy and histopathological findings. The evaluation will include the incidence and severity of abnormalities, gross lesions, identified target organs, body weight changes, effects on mortality and other general or specific toxic effects (OECD, 1987).

c. Subchronic and Chronic Toxicity

The following guidelines were derived using the EPA Health Effects Testing Guidelines (1985), for determining the quality of a subchronic or chronic (long term) study. Additional detailed guidance may be found in that document. These guidelines represent ideal conditions and studies will not be expected to meet all standards in order to be considered. The subchronic and chronic studies have been designed to permit determination of no-observed-effect levels (NOEL) and toxic effects associated with continuous or repeated exposure to a chemical. Subchronic studies provide information on health hazards likely to arise from repeated exposure over a limited period of time. They provide information on target organs, the possibilities of accumulation, and, with the appropriate uncertainty factors, may be used in establishing safety criteria for human exposure. Chronic studies provide information on potential effects following prolonged and repeated exposure. Such effects might require a long latency period or are cumulative in nature before manifesting disease. The design and conduct of such tests should allow for detection of general toxic effects including neurological, physiological, biochemical and hematological effects and exposure-related pathological effects.

According to the EPA Guidelines, high quality subchronic/chronic studies include the following:

- minimum of 3 dose levels administered and an adequate control group used;
- minimum of 10 animals for subchronic, 20 animals for chronic studies per sex, per dose group (both sexes should be used);
- the highest dose level should ideally elicit some signs of toxicity without inducing excessive lethality and the lowest dose should ideally produce no signs of toxicity;
- ideal dosing regimes include dosing for 5-7 days per week for 13 weeks or greater (90 days or greater) for subchronic and at least 12 months or greater for chronic studies in rodents. For other species, repeated dosing should ideally occur over 10% or greater of animals lifespan for subchronic studies and 50% or greater of the animal's lifespan for chronic studies;
- all animals should be dosed by the same method during the entire experimental period;
- animals should be observed daily during the treatment period (i.e., 90 days or greater);
- animals which die during the study are necropsied and, at the conclusion of the study, surviving animals are sacrificed and necropsied and appropriate histopathological examinations carried out;

- results should be evaluated by an appropriate statistical method selected during experimental design; and
- such toxicity tests should evaluate the relationship between the dose of the test substance and the presence, incidence and severity of abnormalities (including behavioral and clinical abnormalities), gross lesions, identified target organs, body weight changes, effects on mortality and any other toxic effects noted (EPA, 1985).

d. Reproductive and Developmental Toxicity

Studies considered here can be evaluated for quality by comparing the study protocol or methods section with accepted testing guidelines prepared by EPA, OECD or Interagency Regulatory Liaison Group (IRLG). The EPA Health Effects Testing Guidelines (1985) include guidelines for both reproduction and fertility studies and developmental studies. These EPA guidelines can serve as the ideal experimental situation with which to compare study quality. Studies being evaluated do not need to match precisely but rather should be similar enough that one can be assured that the chemical was adequately tested and that the results closely reflect the true reproductive or developmental toxicity of the chemical.

Developmental toxicity can be evaluated via a relatively short-term study in which the compound is administered during the period of organogenesis. Some of the specific guidelines for developmental studies are cited below.

- minimum of 20 young, adult, pregnant rats, mice or hamsters or 12 young, adult, pregnant rabbits recommended per dose group;
- minimum of 3 dose levels with an adequate control group used;
- the highest dose should induce some slight maternal toxicity but no more than 10% mortality. The lowest dose should not produce grossly observable effects in dams or fetuses. The middle dose level, in an ideal situation, will produce minimal observable toxic effects;
- dose period should cover the major period of organogenesis (days 6 to 15 gestation for rat and mouse, 6 to 14 for hamster, and 6 to 18 for rabbit);
- dams should be observed daily; weekly food consumption and body weight measurements should be taken;
- necropsy should include both gross and microscopic examination of the dams; the uterus should be examined so that the number of embryonic or fetal deaths and the number of viable fetuses can be counted; fetuses should be weighted; and

- one-third to one-half of each litter should be prepared and examined for skeletal anomalies and the remaining animals prepared and examined for soft tissue anomalies.

The EPA Health Effects Testing Guidelines (1985) recommend a two-generation reproduction study to provide information on the ability of a chemical to impact gonadal function, conception, parturition and the growth and development of the offspring. Additional information concerning the effects of a test compound on neonatal morbidity, mortality and developmental toxicity may also be provided. The recommendations for reproductive testing are lengthy and quite detailed and may be reviewed further in the Health Effects Testing Guidelines. In general, the test compound is administered to the parental (P) animals (at least 20 males and enough females to yield 20 pregnant females) at least 10 weeks before mating, through the resulting pregnancies and through weaning of their F1 offspring. The compound is then administered to the F1 generation similarly through the production of their F2 offspring until weaning. Recommendations for numbers of dose groups and dose levels are similar to those reported for developmental studies. Details are also provided on mating procedures, standardization of litter sizes (if possible, 4 males and 4 females from each litter are randomly selected), observation, gross necropsy and histopathology. Full histopathology is recommended on the following organs of all high dose and control P and F1 animals used in mating: vagina, uterus, testes, epididymides, seminal vesicles, prostate, pituitary gland and target organs. Organs of animals from other dose groups should be examined when pathology has been demonstrated in high dose animals (EPA, 1985).

As with any other type of study, the appropriate statistical analyses must be performed on the data for a study to qualify as a good quality study. In addition, developmental studies are unique in the sense that they yield two potential experimental units for statistical analysis, the litter and the individual fetus. The EPA testing guidelines do not provide any recommendation on which unit to use, but the Guidelines for the Health Assessment of Suspect Development Toxicants (EPA, 1986) states that "since the litter is generally considered the experimental unit in most developmental toxicity studies, the statistical analyses should be designed to analyze the relevant data based on incidence per litter or on the number of litters with a particular end point". Others (Palmer, 1981 and Madson et al., 1982) identify the litter as the preferred experimental unit as well.

Information on maternal toxicity is very important when evaluating developmental effects because it helps determine if differential susceptibility exists for the offspring and mothers. Since the conceptus relies on its mother for certain physiological processes, interruption of maternal homeostasis could result in abnormal prenatal development. Substances which

affect prenatal development without compromising the dam are considered to be a greater developmental hazard than chemicals which cause developmental effects at maternally toxic doses. Unfortunately, maternal toxicity information has not been routinely presented in earlier studies and has become a routine consideration in studies only recently. In an attempt to use whatever data are available, maternal toxicity information may not be required if developmental effects are serious enough to warrant consideration regardless of the presence of maternal toxicity.

C. Tier Designation

1. Carcinogens .

Adequate weight-of-evidence of potential human carcinogenic effects sufficient to calculate a Tier I Human Cancer Criterion (HCC) generally consists of data sufficient to meet the categorical definition of a Human Carcinogen and Probable Human Carcinogen. Certain Possible Human Carcinogens may also be suitable for Tier I criterion development. Designation of Possible Carcinogens should be done on a case-by-case basis. For example, where cancer bioassays have been well conducted, yet are limited because they only involve a single animal species, strain or experiment and do not demonstrate a high incidence, unusual site or type of tumor, or early onset of tumorigenesis, such data may be suitable for Tier I criterion development. In addition, mode of action, the potential for the compound to interact directly with DNA as discussed earlier, should be reviewed in making a Tier designation.

As discussed earlier, data used for developing Tier I criteria are expected to carry a high degree of certainty in their ability to predict an effect. In this case, the quality of data and the weight-of-evidence needs to be sufficient to ascertain that the chemical holds at least a good potential of producing carcinogenic effects in humans.

For chemicals where the weight-of-evidence and quality of data is not sufficient for Tier I numeric criteria the database may be adequate to develop Tier II values. In this case, the data needs to be sufficient to ascertain that the chemical is at least a possible human carcinogen, i.e. Group C. As discussed previously under Weight-of-Evidence and Appropriate Study Design, data on chemicals in this Group suggest only limited evidence of carcinogenicity. Studies may be flawed or lacking adequate design or reporting yet show strong enough evidence of carcinogenicity or the potential for carcinogenic effects such that the data should not be ignored. Examples of such data may be studies where statistical analysis may be lacking or tumor incidence may be only marginally significant; tumor responses or lack of response may be attributable to excessive dosing, or there may be high mortality in the exposed groups also due to

excessive dosing; increases exist for benign tumors only with no evidence of mutagenicity, etc. Further discussion as to how these data are treated in criteria derivation and what potential differences may exist in such treatment will be discussed further in the section on criteria development.

It is important to note that the Group C category may contain chemicals with databases of highly variable quality. Because of this, EPA has decided to allow States and Tribes to address Group C chemicals on a case-by-case basis. As the final GLWQI Guidance is written, States and Tribes have the discretion to develop Tier I criteria or Tier II values for Group C chemicals based on the overall toxicological database. The final Guidance directs that this case-by-case determination be made taking into account information on mode of action, including mutagenicity, genotoxicity, structure activity and metabolism. Those Group C chemicals (and all chemicals, in general) which act via a genotoxic mechanism, that is through direct interaction with DNA and in which a linear low-dose tumor incidence relationship is expected, may be most appropriately dealt with through use of a linearized multistage model (LMS) or other model which appropriately reflect this type of mechanism of action. The quality of data, as discussed above, would then determine the Tier designation. If the chemical does not interact with DNA and the dose response is considered nonlinear, it may be best dealt with as a noncancer agent and an RfD should be developed. See section on Mode of Action under Section III. Principles for Criteria Development, B. Carcinogens.

2. Noncarcinogens

All available toxicity data should be evaluated considering the full range of possible effects of a chemical. Unfortunately, expansive data exists for a limited number of chemicals. Although all data are evaluated, a line must be drawn below which data are not sufficient for criteria development. Adequate data necessary to develop a Human Noncancer Criterion (HNC) for noncancer effects should ideally incorporate at least one well conducted epidemiologic study which demonstrates a positive association between a quantifiable exposure to a chemical and human disease. Such data exist for only a few chemicals, therefore, reliance on animal data in establishing noncancer criteria and values is usually necessary. Although a more extensive effects database is desirable, for this initiative, the minimum database for a Tier I criterion must contain at least a well conducted subchronic mammalian study. The duration of the study must be at least 90 days in rodents or 10% of the lifespan of other appropriate species with exposure preferably via the oral route. Subchronic toxicity studies utilizing dosing periods of approximately 10% of the test animal's lifespan (approx. 90 days in rodents) are sufficient to provide information on target organ effects and can provide an estimate of a no effect level of

exposure which can be used to establish human health criteria and values (OECD, 1981).

It has been observed, with up to a 95% degree of certainty, that as little as a 6 fold difference may exist between chemical effect levels observed at 90 days exposure and at lifetime (7 years) in rodents. (Weil,et al.,1969.) Such a study (90-day or otherwise used to develop a HNV) should ideally establish a frank-effect-level (FEL), a lowest-observed-adverse-effect-level (LOAEL) and a no-observed-adverse-effect-level (NOAEL). The study must be conducted in an animal species relevant to humans (for example, birds, reptiles, and fish are not considered biologically relevant to humans due to incompatible pharmacokinetics, organ structure, toxicokinetics, etc.) based on a defensible biological rationale and generally follow the study protocol previously discussed. To further reduce uncertainty, data from longer studies approaching the lifetime of the test animal are preferable. In some cases, chronic studies of one year or longer in rodents or 50% of the lifespan or greater in other appropriate test species may be sufficient. Dose response must be demonstrated in these longer term studies, however a LOAEL involving relatively mild and reversible effects may be considered an acceptable data point for decision making. For example, there are many studies for which only one dose has been tested with resulting minimal, reversible effects such as minimal enzyme changes or slight body weight decreases. These minimal changes or effects, on their own, may not be thought of as adverse but may be indicators or precursors to more severe effects which result from extended exposure and or higher doses. In those cases, while it can be argued that such an effect may be a LOAEL, it may also be very close to the NOAEL and is therefore suitable for criteria derivation.

Reproductive/developmental effects data as well as evidence of effects seen in test animals consistent with human epidemiologic data are also highly desirable in order to evaluate the full range of potential adverse effects to humans. When data are not sufficient to meet the minimum requirements for deriving Tier I numeric criteria, such data may be considered for development of Tier II values. As with Tier I, all available data should be considered, however, a minimum database suitable for Tier II must contain at least a well conducted subacute mammalian study with an exposure period of at least 28 days, preferably via the oral route of exposure. The 28-day study was chosen as a minimally acceptable test that can yield sufficient information upon which to derive a Tier II value. Please refer to Appendix A for further discussion of the use of less than chronic data to predict chronic endpoints. The study should, ideally, establish a dose-response relationship including a frank-effect-level (FEL), a lowest-observed-adverse-effect-level (LOAEL), and a no-observed-adverse-effect-level (NOAEL). Acceptable protocol for conducting such 28 day studies may be found in the OECD Testing Guidelines (OECD, 1987) as discussed previously. Although the effects observed from short duration

studies are usually fewer than normally evaluated in longer duration studies., such effects should at least include mortality, clinical observations, body weight changes and necropsy of major organs with whatever histopathology that may be available. The minimum data point for decision making on such short term exposure data must be a NOAEL. A NOAEL was chosen over a LOAEL since it is believed the use of a LOAEL may result in underprotective Tier II values. A LOAEL from a 28-day study may not capture the most critical toxic endpoint or be predicting of chronic endpoints. Structure-activity relationship (SAR) review should also accompany the minimum data evaluation. SAR compares a chemical with substances that have structural similarities in order to predict whether the chemical might cause similar toxic effects. Such information may then be used in deciding what uncertainty factors may be appropriate to apply to such limited data in order to protect against potential similar effects.

Studies of longer duration than 28 days and with greater evaluation of effects are more desirable for use in Tier II and may allow the use of a LOAEL for decision making, depending on the quality and duration of the study. As with Tier I, reproductive/developmental effects data as well as any supportive epidemiologic evidence is highly desirable in order to evaluate the full range of potential adverse effects of the chemical. As with carcinogens, further discussion as to how these data will be applied in the derivation of acceptable exposure levels and what adjustments must be made to account for uncertainty will be discussed in further detail in the section on criteria development.

III. PRINCIPLES FOR CRITERIA DEVELOPMENT

A. General

The process to derive Tier I criteria or Tier II values is generally the same. The weight of evidence and level of certainty in the data available for calculating acceptable exposure levels establishes the major difference between the two. For risk assessment of noncarcinogenic effects, the minimum data requirements differ between tiers. Therefore, differences in adjustments to the data (i.e., uncertainty factors) may also occur between tiers. These differences reflect differing levels of certainty in the data base and an attempt to estimate a level without appreciable risk of deleterious effects over a lifetime. In the case of carcinogens, the same quantitative risk assessment approach generally followed for Tier I is used as well for Tier II when the data allow. When the bioassay data for Tier II carcinogens are not suitable for quantitative risk assessment and the chemical does not appear to interact with DNA, yet the weight-of-evidence supports concern for possible threshold carcinogenic effects, an additional uncertainty factor may be

applied to the LOAEL or NOAEL for the chemical in order to account for carcinogenicity.

All available appropriate human epidemiologic data and animal toxicologic data shall be considered. Data specific to an environmentally appropriate route of exposure shall be used for criteria and values development, i.e. oral, dermal or inhalation versus injection, implantation, etc. Findings from studies using less than appropriate routes of exposure may be considered supportive of data obtained through more appropriate routes. Although local effects are important, for the purposes of this initiative oral exposure should be considered preferential to dermal and inhalation data since ingestion is the primary route of exposure, i.e. water and fish consumption. Caution must be exercised in the use of dermal and inhalation data. Strong consideration must be given for pharmacokinetic information on absorption, distribution and metabolism in establishing equivalent doses with oral exposure. Effects produced through exposure via a non-oral route generally should be as a result of systemic distribution of a toxicant rather than as local effects to the skin or the respiratory tract.

- In general, study results shall be converted, as necessary, to the standard unit of milligrams of toxicant per kilogram of body weight per day (mg/kg/day).

- If a study does not specify water or food consumption rates, or body weight of the test animals, standard values may be used for the test species, such as may be obtained from the National Institute of Occupational Safety and Health, Registry of Toxic Effects of Chemical Substances (RTECS) or similar appropriate references.

- Study results from multiple exposures shall be adjusted, as necessary, to a daily dose exposure as if received daily for the duration of the exposure period. The exposure period shall be defined as the interval beginning with administration of the first dose through the last dose, inclusively.

B. Carcinogens

1. Mechanism/Mode of Action

The mechanism by which chemicals cause cancer is not completely known, and may involve a variety of mechanisms occurring at various stages in the carcinogenic process. A chemical may act at a single stage or more than one stage. Currently, the dominant theory regarding the process by which a chemical causes cancer is based on two stages: initiation and promotion (Borzsonyi, 1984; OSTP, 1985; Trosko, 1983; Williams, 1986). The concept of two-stage carcinogenesis has been

supported by investigations involving skin and liver systems (Argyris, 1985; Pitot and Sirica, 1980). This operational theory allows the classification of carcinogens according to their apparent biological activity. Some chemicals are capable, by a variety of genotoxic mechanisms, of triggering the carcinogenic process (initiation). Other chemicals may only alter the expression of the initiated genome and enhance tumor development by a variety of non-genetic mechanisms (promotion). Complete carcinogens operate by both processes. Initiators are capable of directly altering in an irreversible manner the native structure of the DNA. Promotion may be reversible in the early stages, appears to be highly dose-dependent, and apparently requires prolonged or repeated exposure (Pitot, 1981; Slaga, 1984; Thomas, 1986).

Calling an agent a promoter does not eliminate the carcinogenic hazard potential of a chemical. Indeed, data indicate that promoting phenomena are largely responsible for the expression of many human cancer types (Williams, 1986). However, it is very difficult both in principle and in practice to confirm the assertion that a given chemical acts by promotion alone (OSTP, 1985).

Currently, for most if not all chemicals, data are not available to determine the exact mechanism by which they cause cancer. As a result, significant controversy exists regarding the existence of thresholds for carcinogens. Therefore, for the purpose of routine cancer risk assessment, agents that are positive in long-term animal experiments should be considered as complete carcinogens unless there is evidence to the contrary because, at present, it is difficult to determine whether an agent is acting only as a promoting or cocarcinogenic agent (EPA, 1986). However, in making all judgements with regard to mechanism, all data related to mode of action should be considered

EPA, in revising its Guidelines for Carcinogenic Risk Assessment, is suggesting that mode of action information, reflecting the manner in which an agent causes cancer, be used more extensively in carcinogen assessments than has been done in the past. As a result, the final GLWQI Guidance now includes a requirement to review all possible evidence including available information on mode of action including mutagenicity/genotoxicity, structure activity, and metabolism. Mode of action should be used in the assessment and characterization of the potential human carcinogenicity of a substance, and in the selection of a model for quantifying its risks, especially at low doses. This change in emphasis, while still draft and in the formative stages, is being recommended so that all relevant scientific data can be used to carry out cancer risk assessments. Of particular importance, in determining mode of action, is distinguishing between carcinogens that are mutagenic (i.e., interact directly with DNA) and those that are non-mutagenic.

To distinguish between carcinogenic agents that are mutagenic and non-mutagenic, many test systems can be used. These include assays for changes in DNA base pairs of a gene such as gene mutation tests in bacteria or mammalian cells (see 40 CFR 798:5265, USEPA 1991) and chromosomal aberrations, such as in vivo cytogenetics tests. Initial consideration is usually given to mammalian bone marrow using either micronucleus assays to detect damage of chromosomes or mitotic apparatus by agents (See 40 CFR 798:5398, USEPA 1991; Dearfield et al. 1991) or metaphase chromosomal analysis for detection of structural aberrations (also see 40 CFR 798:5385, USEPA 1991). Mutagenicity assessment guidelines are provided in USEPA (1991). Other assays that do not measure gene mutations or chromosomal aberrations per se (e.g., tests for DNA adducts, unscheduled DNA synthesis, sister chromatid exchange, strand breaks, repair and recombination) are not sufficient in and of themselves to make a determination of mutagenicity; they only provide supportive evidence of mutagenicity.

For the purpose of this initiative, unless adequate mechanistic data demonstrate otherwise, a nonthreshold mechanism will be assumed for those chemicals classified as Group A, B and C carcinogens.

2. Data Review

If acceptable human epidemiologic data are available, a risk associated dose shall be set equal to the lifetime exposure which would produce an incremental increased cancer risk of 1 in 100,000. If more than one study is judged acceptable, the study resulting in the most protective risk associated dose is generally used to calculate the human cancer criterion.

In the absence of appropriate human studies, data from a species that responds most like humans should be used, if information to this effect exists. Where several studies are available, which may involve different animal species, strains, and sexes at several doses and by different routes of exposure, the following approach to selecting the data sets is used:

- The tumor incidence data are separated according to organ site and tumor type.

- All biologically and statistically acceptable data sets are presented.

- The range of the risk estimates is presented with due regard to biological relevance (particularly in the case of animal studies) and appropriateness of route of exposure.

- Because is it possible that human sensitivity is as high as the most sensitive responding animal species, in the absence of evidence to define the most relevant species to humans,

the biologically acceptable data set from long-term animal studies showing the greatest sensitivity should generally be given the greatest emphasis, again with due regard to biological and statistical consideration (EPA, 1986).

Exceptions to the above may exist as follows:

- If two or more studies exist which are identical with respect to species, strain, sex and tumor type and are of equal quality, the geometric mean of the potency from these studies may be used (EPA, 1980). In certain instances where there are several studies in various strains and even several species and where there is no indication of a single study or species judged most appropriate, the geometric mean estimates from all studies may be used to determine the potency. This ensures that all relevant data are included in the derivation (EPA, 1989d).

- Where two or more significantly elevated tumor sites or types are observed in the same study, extrapolations may be conducted on selected sites or types. These selections will be made on biological grounds. To obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation so long as double-counting of tumor-bearing animals is prevented. The pooled estimates will generally be used in preference to risk estimates based on single sites or types. Quantitative risk extrapolations will generally not be done on the basis of totals that include tumor sites without statistically significant elevations (EPA, 1986).

- Benign tumors should generally be combined with malignant tumors for risk estimates unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin. The contribution of the benign tumors, however, to the total risk should be indicated (EPA, 1986).

3. Model

a. Nonthreshold Approach

When acceptable human epidemiologic data are not available and a nonthreshold mechanism is assumed, carcinogenesis bioassay data, as appropriate, are fitted to a linearized multistage computer model. (Note: Other models, such as time-to-tumor, modifications or variations of the multistage model may be used which consider the data more appropriately under case-by-case circumstances.)

Since risks at low exposure levels cannot be measured directly either by animal experiments or by epidemiologic studies, a number of mathematical models have been developed to extrapolate from high to low dose. Different extrapolation models, however, may fit the observed data reasonably well but may lead to large differences in the projected risk at low doses (EPA, 1986).

"No single mathematical procedure is recognized as the most appropriate for low-dose extrapolation in carcinogenesis. When relevant biological evidence on mechanism of action exists (e.g., pharmacokinetics, target organ dose), the models or procedures employed should be consistent with the evidence. When data and information are limited, however, and when much uncertainty exists regarding the mechanism of carcinogenic action, models or procedures which incorporate low-dose linearity are preferred when compatible with the limited information." (OSTP, 1985)

In an attempt to characterize the underlying dose-response relationship, models which use the nonthreshold assumption of carcinogenicity are commonly used. The linearized multistage (LMS) model calculates an upper bound based on the theory that a developing tumor goes through several different stages which can be affected by a chemical carcinogen. The LMS model is forced to be linear in the low-dose region, regardless of the shape of the dose response curve, and therefore LMS-based risk estimates may be regarded as relatively conservative when used for public health protection.

In calculating upper bounds on potency from the LMS model, the bioassay data are fitted to the LMS model, e.g. Global 86 developed by Howe et al. (1986). The 95 percent upper bound estimate on the linear term, q_1^*, is used to calculate the upper confidence bound on risk for a given dose, or the lower confidence bound on dose for a given risk. The slope factor (q_1^*) is taken as an upper bound of the potency of the chemical in inducing cancer at low doses. When pharmacokinetic or metabolism data are available, or when other substantial evidence on the mechanistic aspects of the carcinogenesis process exists, a low-dose extrapolation model other than the linearized multistage procedure might be considered more appropriate on biological grounds. When a different model is chosen, the risk assessment should clearly discuss the nature and weight-of-evidence that led to the choice. Considerable uncertainty will remain concerning response at low doses; therefore, in most cases an upper-limit risk estimate using the linearized multistage procedure should also be presented for comparison (EPA, 1986).

b. Threshold Approach

Whenever appropriate human epidemiological data are not available, and the preponderance of data suggest that a chemical causes cancer via a threshold mechanism, the risk associated dose

may be calculated via a method other than a linearized multistage model on a case-by-case basis.

As a default, a safety factor approach may be pursued after thorough evaluation of the toxicologic and pharmacologic data on the compound including, but not limited to: mechanism of carcinogenesis, number and type of tumors induced, the spontaneous incidence of tumors, the number of animal species tested and affected, metabolic considerations, epidemiologic data, extent of data supporting a non-genotoxic mechanism of tumor induction, i.e. mutagenicity assay data, initiation/promotion assay data, etc.

4. Lifespan Adjustment

If the duration of the study (Le) is significantly less than the natural lifespan for the species (L), the slope factor, q_1^* can be adjusted to account for unobserved tumors due to the short study duration. The assumption is that if the duration of the study was increased, tumor incidence would continue to increase as a constant function of the background rate. EPA believes this adjustment should be made on a case-by-case basis taking into consideration factors such as mechanism of action, the type of tumor and the organ affected. One option for correcting for less than lifetime duration is to use the method described by EPA (1980). Based on the EPA (1980) method it is assumed that the cumulative tumor rate would increase at least by the 3rd power of age since age specific rates for humans increase at least by the 2nd power of age and often considerably higher.

For mice and rats, the natural lifespan (L) is defined as 90 weeks and 104 weeks, respectively. The slope factor adjustment may be conducted for mice and rat data if the study duration (Le) is significantly less than natural lifetime such as less than 78 weeks for mice or 90 weeks for rats, by multiplying the slope factor by the factor $(L/Le)^3$. For other species, this adjustment factor may also be used whenever appropriate, using species-specific values for L and the Le trigger level. The latter may be determined using the trigger levels for mice and rats as a guideline.

5. Species Scaling

Low-dose risk estimates derived from laboratory animal data extrapolated to humans are complicated by a variety of factors that differ among species and potentially affect the response to carcinogens. Included among these factors are differences between humans and experimental test animals with respect to life span, body size, genetic variability, population, homogeneity, existence of concurrent disease, pharmacokinetic effects such as metabolism and excretion patterns, and the exposure regimen.

The usual approach for making interspecies comparisons has been to use standardized scaling factors. Commonly employed standardized dosage scales include mg per kg body weight per day, ppm in the diet or water, mg per m^3 body surface area per day, and mg per kg body weight per lifetime. In the absence of comparative toxicological, physiological, metabolic and pharmacokinetic data for a given chemical, extrapolation on the basis of surface area is considered to be most appropriate because certain pharmacological effects commonly scale according to surface area (Dedrick, R.L., J. Pharmacokin. Biopharm. 1:435-461; Freireich et al., Cancer Chemother. Rep. 50:219-244 (1966); Pinkel, D., Cancer Res., 18:853-856 (1958)).

The species scaling factor is calculated by dividing the average weight of a human (Wh) by the weight of the test species (Wa) and taking the cube root of the resultant value. This is based on the premise that a close approximation of the surface area is 2/3 the power of weight, and that the exposure in mg-2/3 the power of body weight/day is similarly considered to be an equivalent exposure (EPA, 1980). The animal slope factor is multiplied by this factor to obtain the human slope factor.

$$q_1^*\ (human) = q_1^*\ (animal)\ X\ 3\sqrt{\frac{Wh\ kg}{Wa\ kg}}$$

The weight (Wa) of the test species should be the average adult weight from the particular bioassay if possible, or derived from available data tables or standard assumed weights.

EPA also believes other scaling factors may be used as long as there is justification on the basis of species-specific pharmacokinetic data.

C. Noncarcinogens

1. Mechanism

Noncarcinogens generally are assumed to have a threshold dose or level below which no adverse effects should be observed (NOAEL). For many noncarcinogenic effects, protective mechanisms are believed to exist that must be overcome before an adverse effect is manifested. For example, where a large number of cells perform the same or similar function, the cell population may have to be significantly depleted before the effect is seen. As a result, a range of exposures exists from zero to some finite value that can be tolerated by the organism with essentially no expression of adverse effects. In the development of an estimate without appreciable risk of deleterious effect from exposure to a chemical, the effort exists to find the upper bound of this tolerance range (i.e., the maximum subthreshold level). Because variability exists in the human population, attempts are made to

assure a subthreshold level which would not result in appreciable risk to sensitive individuals in the population. For most chemicals, this level can only be estimated and incorporates the use of uncertainty factors indicating the degree of extrapolation used to derive the estimated value (EPA, 1989d).

Exceptions to this principle exist. Noncarcinogenic chemicals may exist with no identifiable threshold. One example of this phenomenon appears to be nickel, for which there is no apparent threshold for subsequent dermal effects of the chemical. Another example is the effects of lead exposure, where no discernable threshold has been identified. Other examples of this exception may include genotoxic teratogens and germline mutagens. These agents have been specifically identified to differentiate between chemicals thought to produce reproductive and/or developmental effects via a genetically linked effect from those chemicals more routinely considered to act via a nongenetic mechanism. There are few chemicals, if any, which currently have sufficient mechanistic information about their mode of action to link teratogenic or developmental effects to mutational events during organogenesis, histogenesis or other stages of development. These chemicals may also interact with germ cells to produce mutations which may be transmitted to the zygote and also be expressed during one or more of these stages of development.

EPA has recognized this potential and discussed this issue in their 1989 Proposed Amendments to Agency Guidelines for Health Assessments of Suspect Developmental Toxicants (EPA, 1989c) and in their 1986 Guidelines for Mutagenicity Risk Assessment (EPA, 1986). Various statements within these guidelines should raise concern for the potential for future generations inheriting chemically induced germline mutations or suffering from mutational events occurring in utero:

- "It is estimated that at least 10% of all human disease is related to specific genetic abnormalities..."

- "Life in our technological society results in exposure to many natural and synthetic chemicals. Some have been shown to have mutagenic activity in mammalian and sub-mammalian test systems, and these may have the potential to increase genetic damage in the human population... The extent to which exposure to natural and synthetic environmental agents may have increased the frequency of genetic disorders in the present human population and contributed to the mutational "load" that will be transmitted to future generations is unknown at this time. However, for the reasons cited above, it seems prudent to limit exposure to potential mutagens."

- "Approximately 3% of newborn children are found to have one or more significant congenital malformation at birth, and by the end of the first postnatal year, about 3% more are found to have serious developmental defects. Of these, it is

estimated that 20% are of known genetic transmission, 10% are attributable to known exogenous factors (including drugs, infections, radiation and environmental agents) ..."

An awareness of the potential for such teratogenic/mutagenic effects should be established in order to deal with such data should it occur in the future. However, without adequate data to support a genetic or mutational basis for developmental or reproductive effects, the default becomes an uncertainty factor approach. This approach follows the procedure identified for noncarcinogens assumed to have a threshold. Genotoxic teratogens and germline mutagens should be considered an exception while the traditional uncertainty factor approach is the general rule for calculating criteria or values for chemicals demonstrating developmental/ reproductive effects.

A nonthreshold mechanism shall be assumed for genotoxic teratogens and germline mutagens. Since there is no well established mechanism for calculating criteria protective of human health from the effects of these agents, criteria will be established on a case-by-case basis. For more information on this phenomenon, it is recommended that the reader refer to the EPA Drinking Water Criteria Documents for Nickel and Lead.

2. Data Review .

All toxicity data on a chemical should be evaluated for criterion or level of concern development. Those studies representing the best quality and most appropriate data as discussed previously under appropriate study design should be selected for defining adverse effects and their level of occurrence. As previously discussed, adequate human epidemiologic data should be used in evaluating the adverse health effects of a chemical whenever available. When adequate human data are not available, animal data from species most relevant to humans should be used. In the absence of data on the "most relevant" species or the inability to identify the most relevant species, data from the most sensitive animal species tested, i.e., the species demonstrating an adverse health effect at the lowest administered dose via a relevant route of exposure, shall generally be used.

For guidance, adverse health effects are those deleterious effects which are or may become debilitating, harmful or toxic to the normal functions of an organism including reproductive and developmental effects. These do not include such effects as tissue discoloration without other noted effects, or the induction of enzymes involved in the metabolism of the substance. Guidelines for defining the severity of adverse effects have been suggested by Hartung and Durkin (1985) which proposes a ranking from slight to severe effects. Distinguishing slight effects such as reversible enzyme induction and reversible subcellular change from more severe effects is critical in distinguishing

between a no observed adverse effect level (NOAEL) and a low-observed-adverse-effect (LOAEL).

The experimental exposure level representing the highest dosage level tested at which no-adverse-effects were demonstrated (NOAEL) shall be used in the formula for criteria development. In the absence of such data, the dosage level at which the lowest-observed adverse-effect-level was demonstrated may be used in some circumstances for criteria development.

Preference should be given to studies involving exposure over a significant portion of the animal's lifespan since this is anticipated to reflect the most relevant environmental exposure. An exception to this is where reproductive and/or developmental effects may be demonstrated to have a lower NOAEL over a shorter exposure period.. When two or more studies of equal quality and relevance exist, the geometric means of the NOAEL or LOAEL may be used.

3. Uncertainty Factors

The choice of appropriate uncertainty and modifying factors reflects a case-by-case judgement by experts and should account for each of the applicable areas of uncertainty and any nuances in the available data that might change the magnitude of any factor. Several reports describe the underlying basis of uncertainty factors (Zielhuis et al., 1979; Dourson and Stara, 1983) and research into this area (Calabrese, 1985; Hattis et al., 1987; Hartley and Ohanian, 1988; Lewis et al., 1990; Dourson et al., 1992).

The following are examples of where uncertainty exists as a result of weakness either in the data base or the process which needs accommodation:

- using dose-response information from effects observed at high doses to predict the adverse health effects that may occur following exposure to the low levels expected from human contact with the agent in the environment;

- using dose-response information from short-term exposure studies to predict the effects of long-term exposures, and vice-versa;

- using dose-response information from animal studies to predict effects in humans; and

- using dose-response information from homogeneous animal populations or healthy human populations to predict the effects likely to be observed in the general population consisting of individuals with a wide range of sensitivities. (EPA, 1989d)

For this initiative, accommodation for these uncertainties will be handled in the following process. For further detail in the selection of these uncertainty factors, please see Appendix A.

a. Intraspecies uncertainty factor

An uncertainty factor of 10 shall generally be used when extrapolating from valid experimental results from studies on prolonged exposure to average healthy humans. This 10-fold factor is used to protect sensitive members of the human population.

b. Interspecies uncertainty factor

An uncertainty factor of 100 shall generally be used when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. In comparison to a, above, this represents an additional 10-fold uncertainty factor in extrapolating data from the average animal to the average human.

c. Subchronic to chronic uncertainty factor

An uncertainty factor of up to 1000 shall generally be used when extrapolating from animal studies for which the exposure duration is less than chronic (but greater than subchronic, e.g., 90 days or more in length) or when other significant deficiencies in study quality are present, and when useful long-term human data are not available. In comparison to b, above, this represents an additional uncertainty factor of up to 10-fold for less than chronic (but greater than subchronic) studies.

d. Less than subchronic duration uncertainty factor

An uncertainty factor of up to 3000 shall generally be used when extrapolating from animal studies for which the exposure duration is less than subchronic (<90 days, e.g., 28 days). In comparison to b, above, this represents an additional uncertainty factor of up to 30-fold for less than subchronic studies (<90 days, e.g., 28-day). The level of additional uncertainty applied for less than chronic exposures depends on the duration of the study used relative to the lifetime of the experimental animal.

e. LOAEL to NOAEL uncertainty factor

An additional uncertainty factor of between one and ten may be used when deriving a criterion from a lowest observable

adverse effect level (LOAEL). This uncertainty factor accounts for the lack of an identifiable no observable adverse effect level (NOAEL). The level of additional uncertainty applied may depend upon the severity and the incidence of the observed adverse effect.

f. Limited database uncertainty factor

An additional uncertainty factor of between one and ten may be applied when there are limited effects data or incomplete subacute or chronic toxicity data (e.g., reproductive/developmental data). The level of quality and quantity of the experimental data available as well as structure-activity relationships may be used to determine the factor selected.

When deriving an uncertainty factor in developing a Tier I criterion or Tier II value, the total uncertainty, as calculated following the guidance of a-f, cited above, shall not exceed 10,000 for Tier I criteria and 30,000 for Tier II values.

D. Exposure Assumptions

When dealing with site specific and individual specific exposure, it is more accurate to use actual available exposure information to estimate an individual's specific risk. Individual behaviors can be assessed and specific activity information compiled to address quantity, frequency and duration of exposure. When dealing with such diverse populations of individuals covering as large an area as the Great Lakes Basin, extreme ranges of behaviors and activities are likely. Therefore, deriving default assumptions that can estimate reasonable exposures which address the vast majority of the Basin population becomes necessary.

1. Body Weight

National body weight data has been compiled by the National Center for Health Statistics from a survey conducted from 1976 through 1980 entitled the second National Health and Nutrition Examination Survey (NHANES II). Approximately 28,000 people aged 6 months to 74 years were surveyed with other 20,000 individuals actually interviewed and examined. Weighted mean body weights have been determined from this data. Since body weights change so rapidly during childhood, it is reasonable to use mean adult body weight to reflect population body weights when assuming a long exposure duration. From national survey data, the mean adult body weight appears to be approximately 72 kg (EPA, 1989). If NHANES data are separated out by Great Lakes regional data, it appears that the mean may even be higher for the Great Lakes

Basin population. However, as a matter of convention, 70 kg has been used for many years in chemical regulatory programs and still appears appropriate for this initiative.

EPA believes 70 kg is an appropriate body weight because it represents a reasonable measurement for the entire population. If a State believes that use of a lower body weight is appropriate (which yields a more stringent criterion), the State or Tribe may adopt such an assumption in calculating their criteria and values under their authority to establish more stringent requirements pursuant to section 510 of the Act.

As to whether lower body weights should be used to protect women of childbearing age, children and fetuses, EPA believes that categorically adopting more conservative body weight assumptions may not be appropriate. Each chemical must be addressed separately since some chemicals may be generically toxic to both adult sexes, while others may be specifically toxic to one sex more than the other, or children, specifically. It therefore would not be appropriate to require generally that all criteria be based on conservative body weight assumptions. In the case of mercury, however, a fetotoxic chemical, to be protective of women of child bearing age, EPA has assumed a body weight of 65 kg (as opposed to 70 kg) which results in a Tier I mercury criterion of 1.8 ng/L, which is slightly less than the proposed criterion of 2 ng/L. EPA has set a final Tier I criterion for mercury at 1.8 ng/L.

Body Weights of Adults (kilograms)

Age		Men Mean	Men Std. Error of Mean	Women Mean	Women Std. Error of Mean	Men and Women Mean	Men and Women Std. Error of Mean
18	25	73.7	0.0035	60.6	0.0032	67.2	---
25	35	78.7	0.0034	64.2	0.0037	71.5	---
35	45	80.8	0.0040	67.1	0.0043	74.0	---
45	55	81.0	0.0041	67.9	0.0044	74.5	---
55	65	78.8	0.0041	67.9	0.0045	73.4	---
65	75	74.8	0.0051	66.6	0.0048	70.7	---
18	75	78.1	0.0016	65.4	0.0017	71.8	---

(USEPA, 1989a)

Body Weights of Children (kilograms)

Age		Boys Mean	Boys Std. Error of Mean	Girls Mean	Girls Std. Error of Mean	Boys and Girls Mean	Boys and Girls Std. Error of Mean
	3	11.9	0.0016	11.2	0.0011	11.6	---
3	6	17.6	0.0014	17.1	0.0015	17.4	---
6	9	25.3	0.0023	24.6	0.0024	25.0	---
9	12	35.7	0.0038	36.1	0.0043	36.0	---
12	15	50.5	0.0051	50.7	0.0049	50.6	---
15	18	64.9	0.0047	57.4	0.0042	61.2	---

(USEPA, 1989a)

2. Duration of Exposure

a. Population Mobility

The default assumptions for mobility is to consider that an individual remains in the same residence for a "lifetime". Movement of individuals from individual residences, communities, or even regions of the country may influence exposure duration to contaminants from sources such as drinking water and sport caught fish dramatically. If movement occurs within the same community, the influence by drinking water may not change. If movement is still within the region, the influence of contaminated sport fish may not change. Be that as it may, mobility may lower or increase exposure duration and intensity.

Based on a survey conducted by the Oxford Development Corporation, a property management company, the average residence time for an apartment dweller is estimated to range from 18 to 24 months. A survey conducted by the Bureau of the Census in 1983, determined that 93% of householders moved into their present home between 1950 and 1983. Using this information, the following time of residence ranges have been determined:

Years in Current Home	Total % of Householders
0 - 1	7.5
1 - 3	16.9
3 - 13	40.2
13 - 18	11.0
18 - 23	7.9
23 - 33	9.5
33	7.0

Based on these statistics, the 50th percentile of householders living in their current residence is 9.4 years and the 90th percentile is 29.8 years. This data does not, of course, indicate how far people move or whether they will increase or decrease their exposure by moving. Accordingly, it is only of limited relevance in determining exposure patterns.

b. Life Expectancy

Life Expectancy Statistical data on life expectancy is gathered annually by the U.S. Department of Commerce. Data presented by the Bureau of Census for 1985 show that life expectancy for the total U.S. population is 74.7 years. The breakdown of this average is as follows:

	Male	Female	Total
white	71.8	78.7	75.3
black and other	67.2	75.2	71.2
black	65.3	73.7	69.5

total average	71.2	78.2	74.7

(USEPA, 1989a)

Although the average life expectancy now is approximately 75 years, it is probable that over the course of a lifetime there should be periods of no exposure that add up to at least five years. Accordingly, the traditional default value for "lifetime" exposure of 70 years appears adequate for considering chronic "lifetime" exposure.

3. Incidental Exposure

The suggested 0.01 liter/day adjustment for recreational exposure is based on an assumption of 123 hours of recreational exposure equivalent to swimming, and consumption of an average mouthful (30 mL) of water per hour of such recreational exposure. Exposure potential, when averaged over a year, equals 0.01 liters/day. Such exposures could result from an average of one hour swimming per day during the four month warm weather period starting in mid May and ending in mid September (i.e., 123 days).

EPA has recently estimated a national average frequency of swimming to be 7 days/year with a 2.6 hour duration (EPA, 1989d). An earlier EPA publication estimated an average annual frequency of 9 days/year with a 2 hour duration of exposure. Other total body contact recreation such as water skiing was also identified as having approximately 20 million participants with a total exposure of 260 million hours per year or an average of 14 hours exposure per participant. Partial body contact was identified as 20% body exposure for fishing and 40% body exposure for boating. This earlier reference listed 68 million people involved nationally in boating with an average duration of 1600 million person hours per year and 54 million people involved nationally in fishing with 6600 million person hours duration per year. The resulting individual participant average exposure duration equals approximately 24 hours and 122 hours of participation, respectively (EPA, 1979). If each hour of total body contact equivalent for bathing, water skiing, boating and fishing were calculated (18, 14, 10 and 24 hours, respectively), the total equals 66 hours of average body contact exposure.

Various recreational surveys have been conducted in Michigan and may serve as a typical example of Great Lakes Basin activity. Estimations similar to EPA's for activities per participant and hours per participation may be calculated from this information. If we were to assume an individual were to participate in <u>all</u> activities for the number of days listed from the 1981 Michigan Travel and Recreation Survey and for the duration of hours per participation as identified in the 1976 Recreation survey, and the percentage adjustment made for total body contact exposure from the older EPA reference, the following calculations may be made:

	Activity Days per Participant	Hours per Participation	Body Contact Adjustment	Hours of Exposure
Swimming	13.3	2.1 (ave.)	1.0	27.9
Fishing	14.3	3.7 (ave.)	0.2	10.6
Power Boating	24.5 (total)	3.2	0.4	31.4
Water Skiing	9.6	1.5	1.0	14.4
Sailing	10.4 (total)	3.2	0.4	13.3
Canoeing	4.8	3.9	0.4	7.5
			TOTAL	105.1

(Wells, 1990)

Given these comparisons of water recreation activities, the suggested incidental exposure level appears appropriate, given the variability in individual behavior.

4. Drinking Water

Two liters of water has been the nationwide conventional estimate of adult human's daily water consumption. The 2 liters of water per day is a historical figure set by the U.S. Army in determining the amount of water needed for each person in the field. The National Academy of Sciences (NAS) estimates that daily water consumption may vary with physical exercise and fluctuations in temperature and humidity. It is reasonable to assume those living in a more arid, hot climate will consume higher levels of water. NAS has calculated the average per capita water consumption to be 1.64 liters per day. The National Cancer Institute (NCI) in a study, also known as the Cantor (1987) study, also has looked at this issue with an overall tap water consumption rate of 1.39 liters of water per day as their study average. The NCI study is of particular interest since data were compiled from Detroit, Iowa, New Jersey and Connecticut giving a database of over 3500 respondents with similar weather conditions to the Great Lakes Basin. The consumption rate of less than or equal to 1.96 liters per day is equated to the 100% cumulative frequency level as seen in the following table:

Frequency Distribution of Tap Water Consumption Rates*

Consumption Rate (L/day)	Cumulative Frequency (%)
0.80	19.2
0.81 - 1.12	39.6
1.13 - 1.33	59.7
1.45 - 1.95	79.9
1.96	100.0

*Represents consumption in a "typical" week. (Cantor et al., 1987)

Other researchers have discovered average levels both higher and lower than NCI. The Food and Drug Administration's (FDA) Total Diet Study estimated rates for water and water-based foods for two groups of adults to be 1.07 and 1.3 liters per day with an average of 1.2 liters per day. The U.S. Department of Agriculture (USDA) in the 1977-78 Nationwide Food Consumption Survey identified daily beverage intakes of from 1.24 to 1.73 liters per day. In a more recent study specifically characterizing tap water intake by Ershow and Cantor (1989), 2 liters/day represents approximately the 85th percentile value of drinking water consumption. After review of all these studies, EPA has judged the average adult drinking water consumption rate to be 1.4 liters per day with a reasonably conservative assumption of 2 liters per day as being the 90th percentile value (USEPA, 1989a). This compensates in part for parts of the population, such as manual or migrant laborers, who drink much more than 2 liters a day.

5. Fish Consumption

Much debate has occurred over the years as to the appropriate regionally caught fish consumption rate for the Great Lakes Basin. This is one area where extreme differences exist in the region's consumption behavior. A large segment of the population consumes little or no fish caught from the region, while a small segment of the population consumes a significant quantity of regionally caught fish.

Several studies of fish consumption and sport angler behavior have been evaluated to estimate an appropriate fish consumption value for the region. Three regional surveys; Michigan (West, 1989), Wisconsin (Fiore, 1989) and New York (Connelly, 1990); have been selected for consideration. In summary, the results of the Michigan survey suggest that approximately 65% of the licensed anglers consume less than one meal per week of all fish. This is consistent with Wisconsin data which estimates the mean annual total number of all fish meals consumed by anglers to be 41. This is also consistent with New York anglers who consume 45.2 meals statewide and approximately 41.6 total meals in the regions with

the greatest number of sport anglers and greatest sport fishing effort. Based on the Michigan and Wisconsin surveys, approximately 43% of the fish meals consumed are sport caught, or approximately 18-19 meals per year. Estimates of meal sizes range up to 8 ounces (0.5 pounds) or an approximate total of 9-9.5 pounds per year. This equates to a daily fish consumption rate of 11-12 g/day. The Michigan survey data indicate a mean annual total fish consumption rate of 17 gm/day or (at 43%) approximately 7 gm of sport caught fish. There is poor data on the proportion of the nonsport caught (commercial) fish consumed within the region which is actually caught within the region. Using the Michigan survey data, at least 22% of the fish consumed are species from outside the region. Thereby, the maximum proportion of regionally caught and consumed fish in Michigan may be estimated to be only 78% or 13 grams per day. All those contacted familiar with commercial fishing within the region estimated the major amount of regionally caught commercial fish are sold outside of the region and therefore, generally not available to regional anglers. If one assumes a conservative mean total of regionally caught meals to equal 24 meals per year at 8 ounces per meal or up to 48 meals per year at 4 ounces per meal, the mean daily consumption rate is 15 gm/day.

A second study conducted by West et al. (1993) for the State of Michigan provided results which were very supportive of the use of 15 grams/day. This study is a full year (February 1991 to February 1992) fish consumption survey of 7000 licensed Michigan anglers. The survey found that the average sport fish consumption rate, adjusted for non-response bias, was 14.5 grams/day. The average total fish (all fish, not just Great Lakes sport fish) consumption rate, adjusted for non-response bias, was 24.4 grams/day. This study indicated that fish consumption rates may differ according to race and income level. The lowest income group (< $14,999/year) averaged 21 grams/day sport fish consumption as compared to 14.7 grams/day for those making $40,000 or more/year. The average sport fish consumption rate for minorities was 23.2 grams/day as compared with 16.3 grams/day for non-minority individuals. Lower income ($24,999 or less) minorities averaged the highest consumption rate of all groups in the survey: 43.1 grams/day sport caught fish and 57.9 grams/day total fish; Non-minority individuals of lower income averaged 18.6 grams/day sport fish and 25.8 grams/day total fish. The study also indicated that minorities eat less fish from the Great Lakes and more fish from the inland tributaries than non-minority individuals. For greater detail on the West et al. (1993) study and a statistical analysis of the west study findings refer to U.S. EPA (1995).

For this initiative, the assumption of 15 g/day of regionally caught fish should adequately estimate the consumption rate of the mean angler population and their families for all sport caught fish. A much larger segment of the sport angler population is included if this consumption is attributed totally to species of fish more susceptible to persistent and bioaccumulative contaminants, i.e., the salmonids. Based on the Regional Survey data, including number of licenses bought and used, members per

family, and fish consumption rates for sport anglers, 15 g/day approximates at least the 90% consumption level of regionally caught fish for the regional population as a whole, i.e., fisherpersons as well as nonfisherpersons.

6. Relative Source Contribution

In the final GLWQI Guidance, the Agency assumes an 80 percent relative source contribution (RSC) from surface water pathways (water and fish) for all chemicals, bioaccumulative chemicals of concern (BCCs) and non-BCCs, in deriving noncancer criteria/values. A 100 percent RSC is assumed for all chemicals in deriving cancer criteria/values. EPA also recommends that actual data be used in developing an RSC when available. As stated in the 1980 National Guidelines, to account for exposures from other sources, actual exposure data can be subtracted from the RfD (ADI, as it was called in 1980) to account for contributions of the pollutant from diet and air (ADI - (DT + IN) where DT is the estimated non-fish dietary intake and IN is the estimated daily intake by inhalation (U.S. EPA, 1980). Therefore, where data are available, if States or Tribes want to use actual data in developing their RSC, they may do so, following the procedure outlined in the 1980 National Guidelines. It is important to note, however, that EPA's policy on how to use exposure data in developing an RSC is now under review. Once EPA has finalized its policy review on the RSC, EPA will address the application of the RSC during the triennial review of Water Quality Standards under section 303 of the Clean Water Act. Until such time, the Agency has decided to apply an RSC of 80% to all noncarcinogenic chemicals (both BCCs and non-BCCs).

With regard to using different RCSs for BCCs and non-BCCs which was presented in the Proposed Human Health TSD, EPA does not believe there is a clear difference in RSC development for BCCs as opposed to non-BCCs. While it may be true that surface water may be the major route of exposure for bioaccumulatives (through fish consumption), even though a pollutant is not bioaccumulative, it does not preclude the possibility that there may be other significant sources of exposure.

With regard to the use of a 80 percent default value, EPA believes that the assumption helps to provide some measure of protection against the possibility that exposures from other sources may contribute to the overall exposure of the public to a particular contaminant. Available data indicate that non-water sources contribute varying amounts to overall exposure to a particular chemical (U.S. EPA 1982, U.S. EPA 1983). Such exposures can occur through air and the diet. Since available data indicate that such exposures can and do occur, but these data are often limited in their ability to predict with precision the relative source contribution, EPA believes it is prudent not to assume that all exposure to a pollutant occurs from one medium. The 80 percent default was chosen because it reflects the approximate contribution from surface water pathways (fish consumption) to the

overall exposure to BCCs such as PCBs in the Basin. For PCBs, the FDA Total Diet Study estimates that consumption of pollutant-bearing fish represents the most significant exposure. The average adult's daily intake of PCBs via diet is estimated to be 560 ng, versus estimated inhalation levels of 100 ng per day. Based on these estimates, diet contributes approximately 85% of exposure (ATSDR, 1987). It appears likely that, for other highly bioaccumulative chemicals, a similar estimate may be made as well.

For nonbioaccumulatives, 80 percent was also chosen as a default value to account for the other possible non-water sources which may contribute to the overall exposure of the chemical. However, actual exposure data may also be used in the final Guidance by States and Tribes to calculate a relative source contribution. EPA recognizes that the choice of a default value of 80% in these cases is fundamentally a policy judgment that criteria development should reflect the fact that exposures to a pollutant occur through other media, rather than an empirically-based calculation of the precise proportion of exposure via water versus non-water sources, since such values vary on a case-by-case basis. EPA also acknowledges that use of a 80% default for non-BCCs is a conservative measure, however, if other significant exposures are not accounted for, the criteria could underestimate overall exposure to the chemical and thus could underestimate the risk of adverse health effects. In addition, in the absence of data, it is prudent and consistent with the health protection goals of the CWA to include a margin of safety in the event that there are exposures from other sources. The important fact, EPA believes, is to take <u>some</u> accounting of other possible exposure pathways.

With regard to the concern that point sources should not be expected to compensate for the failure to address other pollutant sources, EPA does not believe that the relative source contribution factor in the final methodology unduly burdens point source dischargers. It is common practice in EPA programs (e.g., in establishing maximum contaminant level goals under the SDWA) to take into account other routes of exposure to a chemical when establishing health-based standards for a particular route of exposure. If this step is not taken, and EPA were always to assume that no exposures occurred through other media (in spite of evidence to the contrary), then the totality of exposures could obviously result in adverse health effects, contrary to EPA's goal of establishing standards that insure that such effects do not occur. EPA agrees, however, that it is important to take steps to address <u>all</u> routes of exposure to pollutants in order to achieve the greatest overall public health protection at the least cost.

IV. CRITERIA CALCULATIONS

A. Standard Exposure Assumptions

BW = weight of an average human (BW = 70 kg).

WC = per capita water consumption for surface waters classified as public water supplies (WC_d = 2 liters/day)

-or-

average per capita incidental daily water exposure for surface waters not classified as drinking water supplies (WC_r = 0.01 liters/day)

FC = per capita daily consumption of regionally caught fish = 0.015 kg/day

BAF = bioaccumulation factor.

B. Carcinogens

When a linear, nonthreshold dose-response relationship is assumed, the human cancer value shall be calculated using the following equation:

$$HCV = \frac{RAD \times BW}{WC + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

Where:

HCV = Human Cancer Value in milligrams per liter (mg/L).

RAD = RAD in milligrams toxicant per kilogram body weight per day (mg/kg/day) that is associated with a lifetime incremental cancer risk equal to 1 in 100,000.

BW = Body weight of an average human (BW = 70kg).

WC = average per capita water consumption (both drinking and incidental exposure) for surface waters classified as public water supplies (WCd = 2 L/day) and average per capita incidental daily water exposure for surface waters not used as public water supplies (WCr = 0.01 liters/day)

FC_{TL3} = mean consumption of trophic level 3 fish by regional sport fishers = 0.0036 kg/day

FC_{TL4} = mean consumption of trophic level 4 fish by regional sport fishers = 0.0114 kg/day

BAF_{TL3} = BAF for trophic level 3 fish

BAF_{TL4} = BAF for trophic level 4 fish

C. Noncarcinogens

The human noncancer value shall be calculated as follows:

$$HNV = \frac{ADE \times BW \times RSC}{WC + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

Where:

HNV = HNV in milligrams per liter (mg/L).

ADE = ADE in milligrams toxicant per kilogram body weight per day (mg/kg/day).

RSC = RCS factor of 0.8 for all chemicals of concern. This is used to allow for potential exposure via sources other than consumption of contaminated water and fish recreational exposure. States may develop an RSC using actual exposure data following the procedures specified in the 1980 National Guidelines.

An ADE may be derived directly from the following example methods depending on the type and quality of the toxicity database:

1. a scientifically valid reference dose (RfD) as identified through best available information sources, such as IRIS; and

2. a scientifically valid acceptable daily intake (ADI) as identified from the U.S. Food and Drug Administration. Both sources should be updated with the most recent data available.

3. a chronic or subchronic NOAEL for humans exposed to the toxicant via contaminated drinking water as follows:

$$ADE = \frac{NOAEL\ (mg/l) \times WC_d}{U \times Wh}$$

Where:
U = Uncertainty factor of 10-100 depending on the quality of the data.

4. a chronic or subacute NOAEL from a mammalian test species exposed to toxicant contaminated drinking water as follows:

$$ADE = \frac{NOAEL\ (mg/l) \times \frac{Vw}{Wa}}{U}$$

Where:
Vw = Volume of water consumed per day by test animals (L/day).

Wa = Weight of test animal (kg).
U = Uncertainty factor of 100-1000 depending on quality of data. An additional uncertainty factor of up to 10 may be used to account for studies of very short term, e.g., 28 days.

5. a chronic or subacute NOAEL from a mammalian test species exposed to toxicant-contaminated food as follows:

$$ADE = \frac{NOAEL\ (mg/kg\ food) \times \frac{fc}{Wa}}{U}$$

Where:
fc = Daily food consumption by test animal (kg).
Wa = Weight of test animal (kg).
U = Uncertainty factor of 100-1000 depending on quality of data. An additional uncertainty factor of up to 10 may be used to account for studies of very short term, i.e., 28 days.

6. a chronic or subacute NOAEL from a mammalian test species exposed to a toxicant by gavage as follows:

$$ADE = \frac{NOAEL\ (mg/kg) \times Fw}{U}$$

Where:
Fw = Fraction of week dose.
U = Uncertainty factor of 100-1000 depending on quality of data. An additional uncertainty factor of up to 10 may be used to account for studies of very short term, i.e., 28 days.

7. A chronic or subacute NOAEL from a mammalian test species exposed to a toxicant by inhalation:

$$ADE = \frac{NOAEL\ (mg/m^3) \times I \times fw \times fd \times r}{U \times Wa}$$

Where:
I = Inhalation rate for test species (m^3/day).
fw = Fraction of week exposed.
fd = Fraction of day exposed.
r = Absorption coefficient.
Wa = Weight of test animal (kg).
U = Uncertainty factor of 100-1000 depending on quality of data.An additional uncertainty factor of up to 10 may be used to account for studies of very short term, i.e., 28 days.

8. Similar approaches shall be followed when data is limited to a LOAEL with an appropriate increase in uncertainty factor. For example, a subacute LOAEL from a mammalian test species exposed to toxicant contaminated drinking water would be calculated as follows:

$$ADE = \frac{LOAEL\ (mg/l) \times \frac{Vw}{Wa}}{U}$$

Where:
Vw = Volume of water consumed per day by test animal (L/day).
Wa = Weight of the test animal (kg).
U = Uncertainty factor of 1000-30,000 depending on quality of data and severity of effect.

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APPENDIX A
UNCERTAINTY FACTORS

A. INTRODUCTION

Uncertainty factors (also called safety factors) are intended for use in extrapolating toxic responses thought to have a threshold (i.e., noncarcinogenic effects). "Uncertainty factor" is defined as a number that reflects the degree or amount of uncertainty that must be considered when experimental data in animals are extrapolated to man (EPA, 1980). In addition, uncertainty factors are used when extrapolating from small populations of humans to the entire heterogeneous human population and when extrapolating from a single animal species to wildlife communities. The use of uncertainty factors in extrapolating animal toxicity data to acceptable exposure levels for humans has been the cornerstone of regulatory toxicology (National Academy of Sciences, 1980). This appendix will provide the risk assessor with additional guidelines, rationale and information concerning the selection of uncertainty factors.

Because of the high degree of judgment involved in the selection of uncertainty factors, the risk assessment justification should include a detailed discussion of the selection of the uncertainty factors along with the data to which they are applied.

This report is organized with the recommended uncertainty factors listed in Part B for quick reference, and a discussion of those factors and their support in Part C. Also included in Part C is a discussion of the exposure duration terms "subacute", "subchronic", and "chronic".

B. RECOMMENDED UNCERTAINTY FACTORS

1. An uncertainty factor of 10 shall generally be used when extrapolating from valid experimental results from studies on prolonged exposure to average healthy humans. This 10-fold factor is used to protect sensitive members of the human population.

2. An uncertainty factor of 100 shall generally be used when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. In comparison to 1, above, this represents an additional 10-fold uncertainty factor in extrapolating data from the average animal to the average human.

3. An uncertainty factor of up to 1000 shall generally be used when extrapolating from animal studies for which the exposure duration is less than chronic (but greater than subchronic, e.g., 90 days or more in length) or when other significant deficiencies in study quality are present, and when useful long-term human data are not available. In comparison to 2, above, this represents an additional uncertainty factor of up to 10-fold for less than chronic (but greater than subchronic) studies.

4. An additional uncertainty factor of between one and ten may be used when deriving a criterion from a lowest observable adverse effect level (LOAEL). This uncertainty factor accounts for the lack of an identifiable no observable adverse effect level (NOAEL). The level of additional uncertainty applied may depend upon the severity and the incidence of the observed adverse effect.

5. An uncertainty factor of up to 3000 shall generally be used when extrapolating from animal studies for which the exposure duration is less than subchronic (<90 days, e.g., 28 days). In comparison to 2, above, this represents an additional uncertainty factor of up to 30-fold for less than subchronic studies (<90 days, e.g., 28-day). The level of additional uncertainty applied for less than chronic exposures depends on the duration of the study used relative to the lifetime of the experimental animal.

6. An additional uncertainty factor of between one and ten may be applied when there are limited effects data or incomplete subacute or chronic toxicity data (e.g., reproductive/developmental data). The level of quality and quantity of the experimental data available as well as structure-activity relationships may be used to determine the factor selected.

When deriving an uncertainty factor in developing a Tier I criterion or Tier II value, the total uncertainty, as calculated following the guidance of 1-6, cited above, shall not exceed 10,000 for Tier I criteria and 30,000 for Tier II values.

The following discussion is generalized for categories of commonly applied uncertainty factors which are used in the developing the specific uncertainty factors used in GLWQI, described above..

C. DISCUSSION

Dourson and Stara (1983) reviewed available literature on uncertainty factors which are used to estimate acceptable daily intakes (ADIs) for toxicants. They found that the use and choice of these factors is supported by reasonable qualitative biological premises and specific biological data. Therefore, in the absence of adequate chemical-specific data, uncertainty factors for criteria derivation may be selected according to reasonable assumptions and approximations rather than total arbitrariness. They presented a set of guidelines for the use of uncertainty factors based on those utilized by the FDA, WHO, NAS, and EPA, indicating consistency and widespread acceptance among the scientific community. Those guidelines have been adapted herein for use in risk assessment under the Great Lakes Initiative. Their rationale and experimental support are discussed below. The guidelines should not be misconstrued as being unalterable and inflexible. They are intended to help ensure appropriateness and consistency of risk assessments. They should be regarded as general recommendations, with the realization that the data for a particular chemical may be such that a different uncertainty factor would be more appropriate.

A 10-fold factor is recommended when extrapolating from valid experimental results from human studies of prolonged exposure. People of all ages, states of health, and genetic predispositions may be exposed to environmental contaminants. The 10-fold factor is intended to offer protection for the sensitive subpopulations (the very young, the aged, medically indigent, genetically predisposed, etc.), since the observed no-effect level is generally based on average healthy individuals. Experimental support for this 10-fold factor is provided by log-probit analysis and the study of composite human sensitivity (Dourson and Stara, 1983).

However, Calabrese (1985) has presented data on human variability in several physiological parameters and in susceptibility to several diseases, and concluded that human variation may range up to two or three orders of magnitude. While human variation in the metabolism of various xenobiotics may have a 1000-fold range, Calabrese (1985) noted that the vast majority of the responses addressed fell clearly within a factor of 10. Another study on key human pharmacokinetic parameters indicates that the 10-fold factor to encompass human variability may only capture the variability among normal healthy adult humans. That report recommends further study to determine the degree of additional susceptibility among sensitive subpopulations (EPA, 1986).

Given the heterogeneous and highly outbred state of the human population, and the multifactorial nature of disease susceptibility, reliance on the adequacy of the 10-fold factor for extrapolation to "safe" levels appears somewhat precarious. But because of its history of use and current widespread acceptance, this factor may continue to be used until the availability of new data indicating quantitatively a more acceptable factor.

A 100-fold factor is recommended when extrapolating from valid results of long-term studies on experimental animals with results of studies of human exposure not available or scanty (e.g., acute exposure only). This represents the 10-fold factor for intraspecies extrapolation (see C.1) and an additional 10-fold uncertainty factor for extrapolating data from the average animal to the average man.

The 100-fold uncertainty factor has been justified for use with the risk extrapolation for food additives. That justification has been based on differences in body size, differences in food requirements varying with age, sex, muscular expenditure, and environmental conditions within a species, differences in water balance of exchange between the body and its environment among species, and differences among species in susceptibility to the toxic effect of a given contaminant (Bigwood, 1973). The use of the 100-fold uncertainty factor has also been substantiated by citing differences in susceptibility between animals and humans to toxicants, variations in sensitivities in the human population, the fact that the number of animals tested is small compared with the size of the human population that may be exposed, the difficulty in estimating human intake, and the possibility of synergistic action among chemicals (Vettorazzi, 1976).

On a dose per unit of body weight basis, large animals (e.g., man) are generally more sensitive to toxic effects than small animals (e.g., rats, mice). This principle is attributed to the relationship between animal size and pharmacokinetics, whereby the tissues of a large animal are exposed to a substance (mg/kg dose) for a much longer time than the tissues of a small animal. This principle has been demonstrated experimentally. The pharmacokinetic processes underlying this phenomenon include: in general, large animals metabolize compounds more slowly than do small animals; large animals have many more susceptible cells; in large animals, substances are distributed more slowly and tend to persist longer; the blood volume circulates much more rapidly in small animals. Thus, for the same mg/kg dose, human tissues are exposed to a substance for a much longer time than rodent tissues (National Academy of Sciences, 1977).

Experimental support for the additional 10-fold uncertainty factor when extrapolating from animal data to humans is provided by studies on body-surface area dose equivalence and toxicity comparisons between humans and different animal species (Dourson and Stara, 1983). On a dose per unit of body-surface area basis, the effects seen in man are generally in the same range as those seen in experimental animals. An interspecies adjustment factor accounts for differences in mg per kg body weight doses due to different body-surface areas between experimental animals and man. The factor may be calculated by dividing the average weight of a human (70 kg) by the weight of the test species (in kg) and taking the cube root of this value. Thus on a body weight basis, man is assumed to be more sensitive than the experimental animals by factors of approximately 5 and 13 for rats and mice, respectively. For most experimental animal species (i.e., all species larger than

mice), the 10-fold decrease in dose therefore appears to incorporate a margin of safety. For mice, the interspecies adjustment factor suggests that the additional 10-fold uncertainty factor for interspecies extrapolation to humans is not large enough (Dourson and Stara, 1983). Nevertheless, the additional 10-fold factor is considered adequate to adjust from mice to humans when chemical-specific data are not available.

A factor of up to 1000 is recommended when extrapolating from animal studies for which the exposure duration is less than chronic (i.e., less than 50% of the lifespan) or when other significant deficiencies in study quality are present, with no useful long-term or acute human data. This represents the 10-fold factors for intraspecies and interspecies extrapolation (see C.2), and an additional uncertainty factor of up to 10-fold for extrapolating from less than chronic to chronic animal exposures (or when the data are significantly flawed in some other way). Injury from chronic exposure may occur in at least three ways: by accumulation of the chemical to a critical concentration at sites of action sufficient to induce detectable injury; by accumulation of injury until physiological reserves can no longer compensate (i.e., repair is never complete); or after a long, latent period beginning with an exposure that has an unrecognized biological effect and precipitates the eventual appearance of injury (National Academy of Sciences, 1977). Obviously, sufficient duration of exposure is necessary in order for the effects seen in chronic toxicity to become manifest. Subchronic toxicology studies may not offer reliable means for assessment of long-term toxic effects in animals, let along extrapolation to chronic effects in man (National Academy of Sciences, 1977). However, it is often the case that a good quality, chronic exposure study for a particular chemical is unavailable. The intention of this additional uncertainty factor is to enable the use of subchronic or flawed studies to protect against the risk of adverse effects which might only appear with chronic dosing.

Experimental support for the additional uncertainty factor is given by literature reviews which compare subchronic NOAELs and chronic NOAELs for many compounds (McNamara, 1971; Weil and McCollister, 1963). The studies reviewed by those investigators employed a variety of rodent and non-rodent species. The duration of the subchronic exposures was usually 90 days, but ranged from 30 to 210 days. Wide variations in endpoints and criteria for adverse effects were encountered in these literature reviews. However, their findings do give a rough indication of the general subchronic and chronic NOAELs for other than carcinogenic or reproductive effects. For over 50% of the compounds tested, the chronic NOAEL was less than the 90-day NOAEL by a factor of 2 or less. There was some indication that chronic dosing may result in the development of tolerance toward certain chemicals, as the chronic NOAEL was larger than the 90-day NOAEL in a few cases. However, it was also found that the chronic NOAEL may be less than the 90-day NOAEL by a factor of 10 or more. The latter situation appeared to be uncommon. Therefore, these reviews report that the additional 10-

fold uncertainty factor appears to be adequate or incorporate a margin of safety in the majority of cases.

As the literature reviews by McNamara (1971) and Weil and McCollister (1963) are limited and the studies reviewed utilized a variety of toxicologic endpoints with questionable sensitivities, one must be cautious in interpreting their conclusions. But for lack of data to the contrary, it appears that application of the additional 10-fold uncertainty factor is appropriate and justified when extrapolating a NOAEL from a 90-day study to a chronic NOAEL estimate. This practice may underestimate the true chronic NOAEL far more often than overestimating it, thus adding a margin of safety to the risk calculations.

One remaining question regarding exposure duration is: At what point is the duration considered adequate, such that the additional uncertainty factor of up to 10 is unnecessary? In other words, how is "chronic" defined for the sake of this guideline?

At this point, further discussion of the terms "chronic" "subchronic", and "subacute", is necessary. The term "subacute" has been used to describe a duration less than subchronic, while it has also been used as a term analogous to subchronic. EPA (1980) describes "subacute" exposures (in this case, analogously to "subchronic") as often exceeding 10% of the lifespan, e.g., 90 days for the rat with an average lifespan of 30 months. However, as pointed out by the Organization for Economic Cooperation and Development (OECD, 1981), the term "subacute" is semantically incorrect. The OECD prefers to use the phrase "short-term repeated dose studies", referring to 14, 21 and 28 day studies, to distinguish from "subchronic" studies of greater duration.

"Subchronic" is generally defined as part of the lifespan of the test species, although opinions differ on the precise definition. Klaassen (1986) defines "subacute" as repeated exposure to a chemical for one month or less, and "subchronic" as repeated exposure for 1-3 months. Chan et al. (1982) describe "subchronic" exposure durations as generally ranging from 1 to 3 months in rodents and one year in longer-lived animals (dogs, monkeys), or for part (not exceeding 10%) of the lifespan. Stevens and Gallo (1982) define "long-term toxicity tests" (encompassing subchronic and chronic toxicity studies) as studies of longer than 3 months duration, i.e., greater than 10% of the lifespan in the laboratory rat. EPA (1985) describes "subchronic" toxicity testing as involving continuous or repeated exposure for a period of 90 days, or approximately 10% of the lifespan for rats.

The various definitions offered for "chronic" are generally inconsistent. Klaassen (1986) defines "chronic" as repeated exposure for more than 3 months. According to the National Academy of Sciences (1977), chronic exposure in animals is generally considered to be at least half the life span. In estimating chronic SNARLs, the National Academy of Sciences (1980) in most cases utilized data from studies lasting a "major portion of the lifetime of the experimental animal". According to the EPA's Health Effects Testing Guidelines (EPA, 1985), chronic toxicity tests should involve dosing over a period of at least 12 months.

The application of their guidelines, they add, should generate data on which to identify the majority of chronic effects and shall serve to define long-term dose-response relationships. The OECD (1981) states that the division between subchronic and chronic dosing regimes is sometimes taken as 10% of the test animal's life span. They also state that the duration of the exposure period for chronic toxicity studies should be at least 12 months. They describe "chronic" as prolonged and repeated exposure capable of identifying the majority of chronic effects and to determine dose-response relationships.

Others have investigated the delayed appearance of toxic effects which might be missed under shorter dosing regimes. Frederick (1986) conducted a pilot survey of new drug evaluators for incidences of delayed (greater than 12 month) drug-induced pathology. It was concluded that <u>new</u> toxic effects "not infrequently" arise after one year of dosing in rodents. It was further stated that those findings formed the basis for the conclusion of the Bureau of Human Prescription Drugs: the duration of the long-term toxicity tests of drugs that are likely to be used in man for more than a few days should be at least 18 months. Glocklin (1986) reviewed the issues regarding testing requirements for new drugs, and concluded that 12 month chronic toxicity studies seemed to be an appropriate requirement for characterization of the dose-response.

It is evident that there are discrepancies in the qualitative and quantitative characterization of "chronic" animals studies. An appropriate and reasonable working definition for "chronic" would appear to be at least half the life span (therefore, at least 52 weeks for rats and at least 45 weeks for mice). Qualitatively, "chronic" means that the exposure duration was sufficient to represent a full lifetime exposure, in terms of dose-response relationships. For example, a study providing an experimental NOAEL which approximates a lifetime NOAEL is considered a chronic study. It is recognized that the above quantitative definition (at least half the life span) does not demonstrate the flexibility inherent in the above qualitative description. That flexibility reflects the vast differences in the toxicology of various chemicals: demonstration of a lifetime NOAEL for some chemicals may require dosing for half the life span, while the toxicology of most chemicals may allow demonstration of a lifetime NOAEL under a much shorter dosing regime. It may be argued that the lifetime NOAEL for noncarcinogenic effects of many chemicals can be demonstrated in rodent studies of much less than one year. While the previously-discussed works of McNamara (1971) and Weil and McCollister (1963) support that view, they also demonstrate that the chronic NOAEL may be less than the 90-day NOAEL by a factor of 10 or more, for some chemicals.

This discussion is necessary in order to properly interpret the uncertainty factor guideline, which recommends that the additional uncertainty factor of up to 10 be applied when the exposure duration is less than "chronic". The intent of the uncertainty factor is to adjust the experimental NOAEL to a lifetime NOAEL in

those cases where the lifetime NOAEL was presumably not adequately demonstrated. The key issues are summarized in the following points and recommendations:

a. An acceptable quantitative definition of "chronic" is elusive. Due to differing toxicological properties, the necessary minimum exposure duration to demonstrate a lifetime NOAEL differs widely among chemicals. A qualitative, philosophical definition of chronic is: "Chronic" is when the exposure duration is sufficient for the identification of the majority of long-term effects and their dose-response relationships. Therefore, a "chronic" study reporting a NOAEL is one which can be reasonably presumed to predict the lifetime NOAEL.

b. The use of scientific judgment is predominant in the decision of when chronic exposure conditions exist, and hence, when the additional uncertainty factor is no longer appropriate.

c. That scientific judgment should be guided by a review of all available pertinent data, e.g., metabolism, pharmacokinetics, bioaccumulation, mechanism of action, target organ characteristics, potential for latent effects, etc.

d. Available reviews of rodent studies indicate that, for many chemicals, studies of much less than one year duration can provide reasonable estimates of lifetime NOAELs. However, it is also recognized that the toxicological characteristics of some chemicals will prevent the qualitative and quantitative demonstration of latent adverse effects and a lifetime NOAEL if the duration is less than one year. If the lack of additional data prevents scientific judgment in these cases, 50% of the lifespan (52 weeks for rats; 45 weeks for mice) may be considered the minimum necessary duration for a "chronic" exposure. Application of the additional uncertainty factor for these apparently "subchronic" studies may later provide to be excessively conservative in some cases. But, if the toxicologic database is inadequate, the additional uncertainty factor should be included, both as a matter of prudent public policy and as an incentive to others to generate the appropriate data.

e. Ordinarily, the additional 10-fold factor may be applied for all rodent studies of 90 days duration, unless there is chemical-specific data indicating that would be unnecessary and overly conservative.

f. For rodent studies of between 90 days and 12 months duration, the use of the additional 10-fold uncertainty

factor is best determined by professional judgment. As described above, if data are not available to sufficiently guide professional judgment, then such studies may be subject to part or all of the additional 10-fold factor. A "sliding scale" or between 1 and 10 is a reasonable means of selecting a lesser factor when 10 appears excessive. Under this concept, the additional uncertainty factor applied may vary on a scale of one to ten according to how closely the dosing duration approached 50% of the lifespan. Of course, consideration must be given of the study quality and the other pertinent data mentioned in 3.c above. A 90-day rodent study would be subject to a 10-fold additional factor, if study quality is otherwise nominal and other chemical-specific data are lacking. A nominal-quality study, with exposure over 50% of the lifespan, would be subject to a "1", i.e., no additional adjustment. Situations where the exposure duration is between 90 days and 50% of the lifespan, and/or study quality is flawed, must be handled on a case-by-case basis. This "sliding scale" concept may offer guidance to the scientific judgment that will be necessary.

Dosing duration is but one parameter upon which to assess the adequacy of a study. Other deficiencies in the study design may cause increased concern about the validity of the reported NOAEL or LOAEL. Therefore, risk assessors may utilize part or all of this additional 10-fold uncertainty factor to compensate for data which appears less-than-adequate. Factors which may affect the degree of confidence in the data include the number of animals per dose group, the sensitivity and appropriateness of the endpoints, the quality of the control group, the exposure route, the dosing schedule, the age and sex of the exposed animals, and the appropriateness of the surrogate species tested, among others. EPA's Health Effects Testing Guidelines (EPA, 1985) provide specific information on the desirable qualities of subchronic and chronic toxicity tests.

An additional uncertainty factor of between 1 and 10 is recommended depending on the severity and sensitivity of the adverse effect when extrapolating from a LOAEL rather than a NOAEL. This uncertainty factor reduces the LOAEL into the range of a NOAEL, according to comparisons of LOAELs and NOAELs for specific chemicals. There is evidence available which indicates, for a select set of chemicals, 96% have LOAEL/NOAEL ratios of 5 or less, and that all are 10 or less (Dourson and Stara, 1983). In practice the value for this variable uncertainty factor has been chosen by the U.S. EPA from values among 1 through 10 based on the severity and sensitivity of the adverse effect of the LOAEL. For example, if the LOAEL represents liver cell necrosis, a higher value is suggested for this uncertainty factor (perhaps 10). If the LOAEL is fatty infiltration of the liver (less severe than liver cell necrosis), then a lower value is suggested (perhaps 3; see the

following discussion). The hypothesized NOAEL should be closer to the LOAEL showing less severe effects (Dourson and Stara, 1983).

In some cases the data do not completely fulfill the conditions for one category of the above guidelines, and appear to be intermediate between two categories. Although one order of magnitude is generally the smallest unit of accuracy that is reasonable for uncertainty factors, an intermediate value may be used if felt necessary (Dourson, 1987). According to EPA (1980), such an intermediate uncertainty factor may be developed based on a logarithmic scale rather than a linear scale. Calculating the mean logarithmically may be the more appropriate option, because the precision of all uncertainty factor estimates is poor, and a logarithmic scale is the best way to estimate the mean of two imprecise estimates (Dourson, 1987). Halfway between 1 and 10 is approximately 3.16 on a logarithmic scale. However, so as not to imply excessive accuracy in the estimate, that mean value should be rounded-off to 3 (Dourson, 1987).

An additional uncertainty factor of up to 10 may be applied when there are limited or incomplete subacute or chronic toxicity data, such as with short-term repeated dose animal studies where the exposure regime involves a limited period that is markedly short-term relative to the lifespan of the test species (e.g., 28-day rodent NOAEL). As previously noted (see C.3) the OECD (1981) distinguishes between 14, 21 or 28 day studies and "subchronic" studies of greater duration, by referring to the former as "short-term repeated dose studies". The short-term studies are commonly conducted by the NTP to enable appropriate dose selection in subchronic studies (NCI, 1976). When a limited database exists, short-term animal studies of 28 days or longer may be of sufficient quality to support risk assessment of potential chronic exposure. Because the duration of exposure is substantially less than the 90-day period discussed under C.3, the risk assessment may require an additional uncertainty factor in conjunction with the 1000-fold factor recommended under C.3. As guidance, an additional factor of up to 10 is recommended when extrapolating from a short-term NOAEL (e.g., 28 days) to subchronic duration (e.g., 90 days).

Although the extrapolation from oral LD_{50}s to chronic oral NOAELs has been reported by several investigators (Venman and Flaga, 1985; Layton et al., 1987; McNamara, 1971), there has been relatively little investigation of the extrapolation from short-term NOAELs (much less than 90 days in rodents) to chronic NOAELs. EPA (1989) states that when experimental data are available only for shorter durations than desired for subchronic RfD derivation an additional uncertainty factor is applied. However, further details on the selection of an adequate and appropriate uncertainty factor for those "shorter durations" are not provided. Weil et al. (1969) evaluated the relationship between 7-day, 90-day and 2-year minimum effect levels (MiE) for 20 materials via feed exposure. They found that the median value for a 90-day MiE was obtained by dividing the 7-day MiE by a factor of 3. The 95th percentile for the 90-day MiE was obtained by dividing the 7-day MiE by 6.2. Also noteworthy is

the finding that the 95th percentile for the 2-year MiE was obtained by dividing the 7-day MiE by a factor of 35.3.

These data, albeit limited, support the general principle that as exposure duration decreases, the ability of the data to demonstrate chronic dose-response relationships also decreases. While an additional 10-fold uncertainty factor may reasonably and appropriately convert a 90-day NOAEL to a surrogate chronic NOAEL, an additional uncertainty factor may be necessary when extrapolating from short-term exposures. Applying an additional uncertainty factor of up to 10 will help ensure that the risk assessment for potential chronic exposures is adequately conservative, i.e., the true chronic NOAEL will generally not be overestimated.

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