United States
Environmental Protection
Agency

Office of Water (WH-586)
Office of Science and Technology
Washington, DC 20460

EPA-822-R-93-006
July 1993

EPA

Wildlife Criteria Portions of the Proposed Water Quality Guidance for the Great Lakes System

EPA-822-R-93-006
July 1993

Wildlife Criteria Portions of the Proposed Water Quality Guidance for the Great Lakes System

Office of Science and Technology
Office of Water
United States Environmental Protection Agency
Washington, D.C. 20460

DISCLAIMER

This document has been reviewed by the Health and Ecological Criteria Division, Office of Science and Technology, U.S. Environmental Protection Agency, and was published in the Federal Register, Friday, April 16, 1993 as part of the "Water Quality Guidance for the Great Lakes System and Correction; Proposed Rules." Publication does not signify that the contents necessarily reflect the views and policies of the U.S. Environmental Protection Agency or of any other organization or agency represented by the authors of, or contributors to, this document. Mention of trade names and commercial products does not constitute endorsement of their use.

AVAILABILITY NOTICE

Limited copies of this document, *Wildlife Criteria portions of the Proposed Water Quality Guidance for the Great Lakes System*, are available upon request from:

U.S. EPA
Water Resource Center (RC-4100)
401 M. Street, S.W.
Washington, D.C. 20460
202/260-7786

The contents of this document make up a portion of the document listed here: *40 CFR parts 122 et al. Water Quality Guidance for the Great Lakes System and Correction; Proposed Rule*. For individuals interested in the entire Great Lakes Water Quality Initiative, we suggest ordering the document listed in this paragraph. This document is available for a fee upon written request or telephone call to:

National Technical Information Service (NTIS)
U.S. Department of Commerce
5285 Port Royal Road
Springfield, VA 22161
(800) 553-6847
(703) 487-4650
NTIS Document Numbers:
Diskette Set: PB-93-504-504
Paper Copy: PB-93-164-515

or

Education Resources Information Center/Clearinghouse for Science, Mathematics, and Environmental Education (ERIC/CSMEE)
1200 Chambers Road, Room 310
Columbus, OH 43212
(614) 292-6717
ERIC Number:
Diskette Set: 526D
Paper Copy: 527D

PREFACE

Wildlife criteria are unique among the criteria proposed within the Great Lakes Water Quality Initiative (GLWQI) Guidance because the U.S. Environmental Protection Agency has not yet issued any nationally applicable criteria focused specifically at the protection of wildlife. This document was produced to facilitate review of and comment on the proposed wildlife criteria approach by persons who may not keep abreast of *Federal Register* notices, including the larger scientific community. Because there is not an established national approach, national guidance may eventually be modeled on the proposed GLWQI Guidance.

The U.S. Environmental Protection Agency will accept public comments on the proposed GLWQI Guidance until September 13, 1993 (see Appendix A for details). The Preamble to the proposed rule (Chapter 1 of this document) specifically invites comments on the modification of this approach for development of a national wildlife criteria procedure. Since these comments would be used for an effort outside the scope of the GLWQI, commenters need not feel constrained by the deadline within that proposal. Comments on the modification of the GLWQI approach for development of a national wildlife criteria can be sent at any time to: Wildlife Program (WH-586)/U.S. Environmental Protection Agency/401 M. St., S.W./Washington, D.C. 20460.

This document is composed of five chapters and two appendices. Chapter 1 describes the development of the proposed wildlife criteria procedure; Chapter 2 presents the proposed wildlife criteria methodology; Chapter 3 presents the Technical Support Document for the development of wildlife criteria; Chapters 4 and 5 present sections from the implementation procedures which may impact the wildlife criteria. Appendix A is introductory material from the *Federal Register* notice and includes the address where comments should be sent; Appendix B is an appendix to a separate document, *Great Lakes Water Quality Criteria Initiative Technical Support Document for Human Health Criteria and Values*, and is included because it is frequently cited in the main text of this document. Chapters 1 and 4 are excerpted from the Preamble to the GLWQI, Chapters 2 and 5 are excerpted from Appendices to the GLWQI proposed rule, and Chapter 3 is published as an Appendix to the Preamble in the *Federal Register* notice.

There is a companion document to this one entitled *Great Lakes Water Quality Initiative Criteria Documents for the Protection of Wildlife (PROPOSED): DDT; Mercury; 2,3,7,8-TCDD; PCBs*. The criteria document contains the derivation of the actual wildlife criteria values proposed in the GLWQI and may be obtained from National Technical Information Service (NTIS Document Number: PB93-154722) or the Education Resources Information Center/Clearinghouse for Science, Mathematics, and Environmental Education (ERIC/CSMEE Document Number 397D).

Contents

We recognize there are inconsistencies in the outline format among the chapters in this document. This is because we maintained the outlines used in the *Federal Register* to facilitate comparisons between this document and the *Federal Register* notice.

CHAPTER 3 (Continued)

CHAPTER 4
Portions of Section VIII of Preamble to Great Lakes Water Quality Guidance: General Implementation procedures

CHAPTER 5
Portions of Appendix F to Part 132--Great Lakes Water Quality Initiative Implementation Procedures

APPENDICES

CHAPTER 1
Section VI of Preamble to Great Lakes Water Quality Guidance: Wildlife

A. *Introduction*

For the purposes of the proposed Great Lakes Water Quality Criteria Guidance, "wildlife" is defined as species in both Taxonomic Classes, Aves and Mammalia (birds and mammals). The proposed Guidance for deriving wildlife criteria and values is included in appendix D of the proposed Guidance. The Technical Support Document for Wildlife Criteria is an appendix to this preamble. The actual criteria documents which provide the data and the derivation of the individual criteria are available in the administrative record for this rulemaking. EPA's expectations for determining whether a State's water quality standards are consistent with the Guidance are set forth in § 132.6 of the proposed Guidance.

In the case of toxic chemicals, terminal predators such as otter, mink, gulls, terns, eagles, ospreys and kingfishers are at risk from contaminants in Great Lakes waters. In addition to direct exposure via drinking the water, species at higher trophic levels are exposed to toxic substances through the food web as the chemicals proceed upward via biomagnification. Contaminants which are almost undetectable in lake water may be magnified hundreds of thousands of times within the flesh of fish and magnified still further in a carnivorous bird or mammal which consumes contaminated fish out of the Great Lakes.

Because wildlife species are at the top of the food web, current criteria derived to protect fish, which live in the water, may be inadequate to protect high-level wildlife consumers of contaminated fish. Wildlife are especially at risk from chemicals which biomagnify because they are frequently exposed to very high levels of the contaminants since they reside at the apices of aquatic food webs. For this reason, emphasis was placed on selecting piscivorous wildlife species (i.e., those which eat fish) for the derivation of wildlife criteria as representative of species likely to experience significant contamination through an aquatic food web. Wildlife species may also have unique metabolic pathways which make them more susceptible to the toxicity of a chemical than aquatic species.

Research on wildlife species resident in the Great Lakes indicates that wildlife populations are threatened in areas of high contamination by toxic chemicals. In the Great Lakes, reproductive impairment of numerous wildlife species has been correlated with the presence of PCBs, DDT and its metabolites, and other contaminants. In the 1960s, mink fed a diet of Great Lakes fish suffered complete reproductive failure. Detailed laboratory investigation revealed that the causative agent was PCBs in Great Lakes fish. The overall reproductive success of bald eagles is much lower along lake shore areas of the Great Lakes than in inland nesting territories.

There is additional discussion located in the section I (Background) of this preamble on the impacts of toxic chemicals on wildlife in the Great Lakes. Numerous studies confirm the adverse effects of pollution on Great Lakes wildlife and support the need for water

quality criteria formulated for their protection. It is because of the numerous impacts of toxic chemicals observed in wildlife in the Great Lakes and the inconsistencies among the Great Lakes States and Tribes in addressing wildlife impacts, that the Steering Committee, Technical Work Group, and EPA agreed there was a need for generation of separate wildlife criteria as a part of the Great Lakes Water Quality Initiative (GLWQI). This provides the rationale for proposing specific wildlife standards in this Guidance.

EPA has ample authority to develop criteria and methods specifically directed at protecting wildlife from threats originating in Great Lakes waters. Section 118(c)(2)(A) of the Clean Water Act requires EPA to develop numerical limits on pollutants in Great Lakes waters to protect wildlife as well as human health and aquatic life. Similarly, provisions of the Great Lakes Water Quality Agreement of 1978 require the United States and Canada to protect wildlife. For example, Article III of the Agreement established a "General Objective" of freeing the Great Lakes System from substances resulting from human activity that will adversely affect waterfowl.

Moreover, several of the "Specific Objectives" for individual pollutants set out in Annex I of the Agreement also set limits which should not be exceeded in order to protect fish-consuming birds and animals. These are presented as fish tissue concentrations or water concentrations as follows: DDT and its metabolites in whole fish should not exceed 0.3 micrograms per gram (wet weight basis), the concentration of total PCBs in whole fish should not exceed 0.1 micrograms per gram (wet weight basis), and the concentration of total mercury in whole fish should not exceed 0.5 micrograms per gram (wet weight basis). The "Specific Objectives" which present water concentrations which should not be exceeded for the protection of fish-consuming birds and animals are: the total concentration of DDT and its metabolites should not exceed 0.003 micrograms per liter; and mirex and its degradation products should be less than detection levels as determined by the best scientific methodology available.

Section 304(a)(1) of the Clean Water Act also authorizes EPA to develop criteria that protect wildlife for all waters of the United States. As explained in more detail later in this section of the preamble to this rule, EPA has not yet issued any nationally applicable criteria targeted solely at the protection of wildlife. Rather, EPA incorporated consideration of wildlife impacts into the 1985 methodology for developing criteria for aquatic life (Stephan, et. al., 1985).

The proposed Guidance relating to wildlife criteria was developed as part of the GLWQI. The Technical Work Group and the Steering Committee are collectively referred to within this portion of the preamble as the Committees of the Initiative. The Committees of the Initiative assigned the lead in developing an initial proposal for deriving criteria to protect wildlife for the Great Lakes Guidance to the State of Wisconsin. The procedure proposed by the Wisconsin Department of Natural Resources was modified through discussions in the Committees of the Initiative and modified and approved by EPA.

In developing the methodology for deriving wildlife criteria for the GLWQI, the Wisconsin Department of Natural Resources, Bureau of Water Resources Management,

obtained scientific guidance from participants in a one-day workshop (the Workshop) held in Madison, Wisconsin, November 8, 1990. Wildlife research toxicologists and biologists representing academia, State governments, the U.S. Fish and Wildlife Service and EPA were invited to participate in the Workshop. Representatives of the regulated community were also present at the Workshop.

B. *Wildlife Criteria Methodology*

Like the aquatic life and human health criteria methodologies described above, EPA is proposing a two-tiered approach for the Great Lakes Water Quality Guidance for Wildlife, which will hereinafter be referred to as Tiers I and II. EPA is proposing to require all Great Lakes States and Tribes to apply the methodology to derive Tier I criteria and Tier II values, as well as the Tier I numeric criteria proposed, to discharges into the Great Lakes System. The Committees of the Initiative developed, and EPA is proposing, a Tier II method that is very similar to the proposed Tier I method. However, because Tier II values are based on a less extensive data base than are Tier I criteria, the uncertainty factor which accounts for interspecies toxicological differences (the Species Sensitivity Factor) may be smaller than that used in deriving a Tier I criteria. In deriving Tier II values, the Species Sensitivity Factor may also account for interspecies toxicological differences across taxonomic classes. This uncertainty factor is intended to address any uncertainties stemming from the use of a less inclusive database and its use is meant to produce Tier II values that are conservative.

Tier II values are intended to be conservative to encourage data generation so a Tier I criteria can be calculated. Although States and Tribes have the authority at their discretion to do so, EPA does not intend that Tier II values will be adopted into State standards, but, rather, will serve as a translator mechanism for interpretation of the State's narrative criteria (e.g., no toxic pollutants in toxic amounts) and as a basis for developing control measures such as effluent limitations in NPDES permits. In the future, EPA may replace Tier II values with Tier I criteria as more data are generated.

1. Wisconsin State Wild and Domestic Animal Criteria

The Committees of the Initiative chose, as the starting point for the development of the wildlife criteria methodology, the Wild and Domestic Animal Criteria (WDAC) approach developed by the State of Wisconsin (Wisconsin Administrative Code NR 105.07, 1989; Technical Support Document for NR 105, 1988), which is available in the administrative record for this rulemaking. A WDAC is the lowest species wild and domestic animal value (WDAV) calculated using the equation presented below. The equation used to derive the WDAV portrays a "model animal" as follows:

$$WDAV = \frac{NOAEL \times Wt_A \times SSF}{W_A + (F_A \times BAF)}$$

where: WDAV is the wild and domestic animal value in milligrams per liter (mg/L); NOAEL is the no observable adverse effect level in milligrams of substance per kilogram of body weight per day as derived from mammalian or avian studies (mg/kg-d); Wt_A is the

average weight in kilograms (kg) of the test animals; W_A is the average daily volume of water in liters consumed per day (L/d) by the test animals; SSF is the species sensitivity factor which is an uncertainty factor ranging between 0.01 and 1 to account for differences in species sensitivity; F_A is the average daily amount of food consumed by the test animals in kilograms (kg/d); and BAF is the aquatic life bioaccumulation factor with units of liter per kilogram (L/kg).

2. Modifications to Wisconsin's WDAC Procedure

As mentioned, the proposed Guidance on a water quality criteria methodology for wildlife is based on the State of Wisconsin's wildlife criteria procedure. However, the Initiative Committees and EPA developed several modifications of this State procedure which EPA is proposing to incorporate into the proposed Guidance. They include: a requirement that States and Tribes use specific Great Lakes species identified by EPA as representatives of regional wildlife species likely to experience significant exposure from the aquatic food web rather than using a "model animal"; provisions that more clearly define and make more stringent toxicity data requirements (i.e., a dose-response study is required); provisions which allow a subchronic to chronic uncertainty factor to be applied to the NOAEL to extrapolate from subchronic to chronic exposure lengths; and provisions for two tiers of criteria rather than one as under the Wisconsin approach. A fifth modification to the approach submitted by Wisconsin is proposed in procedure 1 of appendix F to part 132 of this proposed Guidance (the site-specific modification portion of Great Lakes Water Quality Guidance Implementation Procedures). Procedure 1 allows for the incorporation of an additional uncertainty factor into the equation to account for intraspecies variability in the derivation of a species-specific wildlife criterion or value for a species other than the representative species proposed for general use. See section VIII.A of this preamble for a discussion of the additional uncertainty factor in the proposed procedure 1 of appendix F, as well as alternative text, upon which EPA invites comment, that provides additional guidance to States and Tribes.

3. The Great Lakes Water Quality Initiative Wildlife Criteria Methodology

The approach used in the aquatic life criteria methodology, where the aquatic life criterion is determined from a statistically valid distribution of toxicity values for a number of aquatic species, is not currently feasible for the derivation of wildlife criteria. This is because there is a less extensive and representative wildlife toxicity database and limited information on species-specific exposure parameters. The wildlife criteria methodology is more similar to that employed in the calculation of noncancer human health criteria.

The general procedure as well as the requirements for developing wildlife criteria and values are provided in appendix D to part 132. The Technical Support Document (TSD) provides additional background as well as guidance on the selection of values for uncertainty factors which may be used in the derivation of wildlife criteria. EPA believes that the States, the Tribes and the public would benefit from easy access to the background material provided in the TSD because the wildlife criteria are so new. EPA, however, acknowledges that the TSD repeats some of the material that appears in the Method. EPA also is

concerned that the States, the Tribes and the public may become confused and mistakenly believe that the TSD also sets out binding requirements. Consequently, EPA is considering either (1) combining the TSD with the Method for publication in the CFR, or (2) publishing only the Method in the CFR and distributing the TSD widely. EPA invites comment on this issue. If option (1) is pursued, EPA invites comments on whether there are any components of the TSD which should not become binding requirements.

As with the human health methodology, the wildlife methodology has both a hazard and an exposure component. The hazard component is determined from the toxicity data for a given pollutant and the exposure component is determined from species-specific exposure parameters.

a. *Parameters of the Hazard Component of the GLWQI Wildlife Criteria Methodology.* The Committees of the Initiative discussed various aspects of the hazard component of the final wildlife criteria methodology. EPA is proposing to adopt the ideas they developed on several aspects of the hazard component of the wildlife method which are presented below.

i. *LOAEL to NOAEL Extrapolations.* In some studies when a range of doses are used, an effect is observed at the lowest chemical concentration used in the study. The proposed Guidance proposes to allow use of an uncertainty factor that would permit a NOAEL to be estimated from the LOAEL determined in such a study. Experimental support for this concept is referenced in the Technical Support Document for Wildlife Criteria (the appendix to this preamble), as well as appendix A to the Great Lakes Water Quality Initiative (GLWQI) Technical Support Document for Human Health Criteria and Values, which is available in the administrative record for this rulemaking. Copies are also available upon written request to the address listed in section XIII of this preamble. EPA notes that use of such an adjustment factor is permitted within the existing human health water quality criteria process (45 FR 79353-79354, November 28, 1980; and 50 FR 46944-46946, November, 13, 1985). EPA is proposing to allow this adjusted NOAEL value to be used in the derivation of both Tier I wildlife criteria and Tier II wildlife values. EPA requests comment on this approach.

ii. *Subchronic to Chronic Extrapolations.* The wildlife criteria methodology allows for application of an uncertainty factor to adjust the NOAEL from a subchronic study to estimate a chronic NOAEL. Because of toxicokinetic considerations, bioassays that are of insufficient duration to encompass a significant portion of an organism's life span or a sensitive life stage may underestimate hazards. EPA proposes providing the option of considering exposure length by extrapolating from subchronic studies to estimate chronic impacts. As presented in the Technical Support Document for Wildlife Criteria (the appendix to this preamble), the value of this term must be based on the bioaccumulative potential of the chemical, toxicokinetic considerations, test length and available test data. The value applied can range from 1.0 to 10, adopting the 10-fold uncertainty factor value applied in the derivation of human health criteria as the upper limit for the value. Endorsement of this approach by EPA is referenced in the Technical Support Document for Wildlife Criteria (the appendix to this preamble), and experimental support for this approach

is referenced in appendix A to the GLWQI Technical Support Document for Human Health Criteria and Values. EPA requests comments on the provisions to allow for such adjustments to the NOAEL in the derivation of wildlife criteria.

iii. *Species Sensitivity Factor.* In the derivation of noncancer human health criteria, an uncertainty factor is applied when extrapolating from results of long-term studies on experimental animals to humans. EPA is proposing to allow use of a species sensitivity factor (SSF) which adjusts for the same type of uncertainty--differences in toxicological sensitivity--among wildlife species. Specifically, it adjusts only for differences in toxicological sensitivity between the test species (the species from which the NOAEL is derived) and the representative wildlife species identified for protection or the species identified as requiring greater protection. (The SSF is not intended to adjust for differences with regard to body weight and food and water consumption rates between the test species and representative species or the species requiring greater protection.)

Guidance in the selection of a SSF value is provided in appendix D to part 132 and the Technical Support Document for Wildlife Criteria. The discussion of an interspecies uncertainty factor located in section C of appendix A to the GLWQI Technical Support Document for Human Health Criteria and Values may also be useful in determining the value of a SSF.

In its December 16, 1992, report, "Evaluation of the Guidance for the Great Lakes Water Quality Initiative," (U.S. EPA, 1992), EPA's Science Advisory Board (SAB) recommended that the methodology for deriving wildlife criteria incorporate procedures that address a measure of the variability of species sensitivities observed in substance-specific studies. The guidance provided in the Technical Support Document for Wildlife Criteria for determining an appropriate SSF has been revised following submission to the SAB for review. The current guidance attempts to address the SAB's concerns and requires consideration of the amount and quality of available studies; the diversity of species for which data is available; known physicochemical, toxicokinetic and toxicodynamic properties of the chemical; and similar data for chemicals that operate by the same mode of action. EPA requests comment on the guidance provided in determining the value of a SSF.

For Tier I criteria, the Agency proposes that the SSF may be used to extrapolate toxicity data across species within each of the two taxonomic classes of Aves and Mammalia. An interclass SSF may be used for a given chemical for a Tier I criteria only if it can be supported by a validated biologically-based dose-response model or by an analysis of interclass toxicological data, incorporating the endpoints in question, for a chemical analog that acts under the same mode of toxic action.

Participants at the Workshop discussed the range of values for SSFs. The Workshop concluded that, in nearly all cases, the available toxicological data for the determination of a SSF to be applied in the derivation of a Tier I criteria, or any value calculated using the Tier I approach, would result in a SSF within the range of 1.0 to 0.01. EPA is proposing to require that a SSF outside of this range for a Tier I criteria, or any value calculated using the Tier I approach, must be based on sound scientific and technical reasons and must be

accompanied by a written justification presenting this reasoning. This justification should be provided to EPA by inclusion in the State's or Tribe's submission under § 132.5 of this proposed rule. Use of a SSF outside of this range is prohibited unless approved by EPA based on its consideration of the justification provided.

For Tier II wildlife values, EPA proposes that the SSF may be used to extrapolate toxicity data across the two taxonomic classes without the strict requirements presented above for use in deriving Tier I criteria. Because of the uncertainties associated with performing interclass extrapolations, and because Tier II values are intended to be conservative to encourage data generation, the SSF applied may not be greater than 1.0 but may be lower than 0.01. A written justification is not required when a SSF less than 0.01 is used in the derivation of Tier II values.

iv. *Intraspecies Variability.* Procedure 1 in appendix F to this Guidance discusses site-specific modifications to criteria/values and suggests the use of an additional uncertainty factor in the equation used to calculate Wildlife Values. Section VIII.A of this preamble presents a method for the use of this additional uncertainty factor, called an intraspecies uncertainty factor (ISF), to adjust for intraspecies variability in the development of site-specific criteria. The use of this additional uncertainty factor provides an additional level of protection when protection of all individuals in a given population is desired. The method presented in section VIII.A of this preamble proposes incorporation of an intraspecies sensitivity factor (ISF) into the hazard portion of the wildlife value equation. The following discussion provides more detail on the ISF proposed in appendix F and section VIII.A of this preamble.

The ISF is an uncertainty factor to adjust for intraspecies toxicological differences to protect sensitive individuals in a population. The National Academy of Sciences endorses the use of a 10-fold factor to account for differential sensitivities within the human population (NAS, 1980). A discussion of the experimental support for the application of an intraspecies uncertainty factor is provided in appendix A to the GLWQI Technical Support Document for Human Health Criteria and Values. Although chronic toxicological data for wildlife species are relatively scarce, EPA believes that the factor of 10 that EPA has developed to protect sensitive members of the human population will also protect sensitive members of wildlife species. EPA is proposing to allow the use of an ISF value of 10 without requiring the development of specific justification. EPA is proposing to require users who wish to use factors greater than 10 to develop specific and detailed scientific rationale for the factors they propose to use. The rationale must be submitted to EPA on request. EPA anticipates that users who have actual toxicological data from wildlife studies may be able to justify the use of greater ISFs. EPA is not proposing to permit the use of ISFs for wildlife that are less than 10.

In the December, 1992 Science Advisory Board (SAB) report (U.S. EPA, 1992), the EPA's SAB identified the need for wildlife criteria to be constructed so that, in special cases, they are able to protect the individual rather than the population. EPA believes incorporation of the ISF into the wildlife criteria methodology, as proposed in section VIII.A. of this preamble, adequately addresses this concern. EPA invites comment on the ISF.

v. *Alternative Formula for Hazard Component of Equation.* In appendix D to part 132, the hazard component is represented by:

[NOAEL x SSF].

The NOAEL applied in the equation may be: a NOAEL determined by applying a LOAEL to NOAEL uncertainty factor to a LOAEL; or a NOAEL adjusted to account for subchronic to chronic exposure durations by application of a subchronic to chronic uncertainty factor. In the equation, the NOAEL may be further adjusted to account for interspecies toxicological differences multiplication by of a SSF and/or intraspecies toxicological differences by division by an ISF. Because of these potential adjustments to the NOAEL which may be carried out in the calculation of a wildlife value, in this preamble EPA proposes a modification to the hazard component of the wildlife criteria calculation equation presented in appendix D to part 132. Rather than using the equation presented in appendix D to part 132, EPA requests comment on the replacement of the hazard portion of the equation (presented at the beginning of this section) with the formula presented below:

$$\frac{ED}{UF_S \times UF_C \times UF_E \times UF_I}$$

Where:

ED = the Effect Dose in mg/kg-d for the test species. This could be either a NOAEL or a LOAEL.

UF_S = Uncertainty Factor for extrapolating toxicity data across species. Because it appears in the denominator, the value of this term would be the inverse of the SSF described and defined in appendix D to part 132 and the appendix to this preamble.

UF_C = Uncertainty Factor for subchronic to chronic exposures. The value of this term would be the subchronic to chronic uncertainty factor previously described and discussed in appendix D to part 132 and the appendix to this preamble.

UF_E = Uncertainty Factor for LOAEL to NOAEL extrapolations. The value of this term would be the LOAEL to NOAEL uncertainty factor discussed in appendix D to part 132 and the appendix to this preamble.

UF_I = Uncertainty Factor for intraspecies toxicological differences to protect sensitive individuals in a population. Because it appears in the denominator above, this term would be the inverse of the ISF proposed in section VIII.A of this preamble, and discussed above in this section of the preamble.

In many cases, the value for these uncertainty factors may be one. That is, values other than 1.0 would rarely if ever be used for all uncertainty factors simultaneously. However, EPA believes that the alternative formula has the advantage that it more clearly presents the uncertainty factors employed. The equation used to derive wildlife criteria and values would be:

$$WV = \frac{\frac{ED}{UF_S \times UF_C \times UF_E \times UF_I} \times Wt_A}{W_A + (F_A \times BAF)}$$

The terms are defined above and in appendix D to part 132. This formula appears more similar to that used in the derivation of noncancer human health criteria. EPA requests comment on the adoption of the alternative formula in the final Guidance.

b. *Parameters of the Exposure Component of the GLWQI Wildlife Criteria Methodology.* In deriving human health criteria, the exposure estimates employed are for one species, *Homo sapiens.* The Committees of the Initiative and EPA, however, wanted to develop a wildlife method that would protect a broad range of wildlife species. There are two possible ways to accomplish this: estimate exposure parameters for a hypothetical "model animal," (the approach implicit in the Wisconsin methodology); or select an actual wildlife species as a representative wildlife species. The Committees and EPA agreed to select representative species for the two taxonomic classes, Aves and Mammalia, in order to provide a basis for determining an appropriate SSF and incorporating empirical exposure parameters where available for specific species in each taxonomic class. Selection of representative species which are then used to derive criteria to protect wildlife is a significant issue. The criterion and selection process used to select the representative species is presented in section V of the Technical Support Document for Wildlife Criteria (the appendix to this preamble). The species selected are representative of Great Lakes basin wildlife which are likely to experience significant exposure to contaminants from aquatic food webs. EPA requests comment on the selection process and the results employed in the derivation of wildlife criteria.

i. *Approach Used to Select Representative Species Identified for Protection.* To select representative avian and mammalian species, an analysis of wildlife species that inhabit the Great Lakes basin was undertaken to identify those most likely to be exposed to environmental contaminants from aquatic ecosystems (these representative species are not necessarily the most toxicologically sensitive species). This analysis is presented in the Technical Support Document for Wildlife Criteria. With regard to mammalian species, results of this assessment suggested that, in general, piscivorous species are at greatest risk from the chemicals identified for wildlife criteria development (see section iii, below). Two mammalian species were chosen to represent the range of body weights and food habits of piscivorous mammals. Representative avian species were categorized based on three species-specific parameters: body weight, food habits (e.g., food source and prey size) and foraging styles. Based on available data, the results of this assessment suggested that, with the precision of available data, ingestion rates for birds were generally proportional to animal mass and not influenced by foraging style. Therefore, EPA is proposing to select representative avian and mammalian species which represent a range of body weights and food habits appropriate for the Great Lakes basin and which are likely to experience significant exposure from the aquatic food web.

EPA requests submission of peer-reviewed empirical exposure information for wildlife species residing in the Great Lakes basin which were not referenced in the analysis presented in the Technical Support Document for Wildlife Criteria and which the commenter feels should be considered in the selection of representative avian and mammalian species.

As a result of applying this approach, the representative species proposed to represent avian and mammalian species of the Great Lakes basin which are likely to experience significant exposure to contaminants in aquatic ecosystems through the food chain are the mink *(Mustela vison)* and river otter *(Lutra canadensis)* and the belted kingfisher *(Ceryle alcyon)*, osprey *(Pandion haliatus)* and bald eagle *(Haliaeetus leucocephalus)*. EPA specifically invites comment on the choice of representative species identified for protection, and requests that the public document the basis for considering other species.

The SAB, in their December 1992 report (U.S. EPA, 1992), recommended that the approach to protect wildlife be expanded to consider ecologically representative species. EPA acknowledges that the approach used to select representative species does not consider potential impacts on wildlife species due to changes in communities or the ecosystems in which they reside and recognizes the need for research to better understand the large uncertainties which currently exist in this area. EPA welcomes suggestions on how to select ecologically representative species given the current state of knowledge.

ii. *Bioaccumulation Factors.* The procedure for determining the appropriate bioaccumulation factor (BAF) for calculation of Tier I wildlife criteria and Tier II wildlife values is presented in appendix B to part 132. Based on the food habits of the representative wildlife species, BAFs calculated for trophic levels 3 or 4 may be used. BAFs for invertebrates, aquatic plants or other trophic levels may also be used on a case-by-case basis based on their proportion in the total diet consumed by the wildlife species requiring greater protection.

iii. *Exposure Routes Considered.* The derivation of the equation used to calculate wildlife values, which are in turn used to calculate a wildlife criterion, considers oral exposure (i.e. food and water ingestion). EPA considers oral ingestion the most significant route of exposure for bioaccumulative pollutants and these pollutants represent the greatest risk to wildlife species. EPA requests comments on this assumption.

In its December 16, 1992 report, "Evaluation of the Guidance for the Great Lakes Water Quality Initiative" (U.S. EPA, 1992), EPA's SAB expressed concern that the wildlife exposure assessments in the proposed guidance do not consider exposures via inhalation or dermal contact which may be important for chemicals with significant vapor pressure and intermediate molecular weights. EPA solicits modifications of the proposed approach which would address these concerns and consider other significant routes of exposure for non-bioaccumulative chemicals.

C. *Additional Issues*

The sections below highlight some of the issues and discussions which occurred during the development of the wildlife criteria methodology proposed. EPA solicits comments on each of these issues.

1. Use of Human Health Paradigm

The December, 1992, SAB report (U.S. EPA, 1992) states that the wildlife criteria concepts were formulated around the perceived requirements of the human health paradigm and they are inadequate for wildlife. Adjustments made to the human health paradigm include: (1) defining database requirements such as preferred test species, test length, and toxicological endpoints; (2) selection of species representative of wildlife species likely to experience significant exposure from aquatic food webs and for which empirical dietary exposure information was available; and (3) options for the use of various uncertainty factors to ensure protection of the distribution of wildlife species. Given the extent of current exposure and toxicological data available for wildlife species, EPA believes the methodology (presented in appendix D to part 132, and clarified in the appendix to this preamble and the criteria derived based on this methodology, are scientifically defensible. EPA requests comments on additional modifications to the proposed methodology which would improve its scientific defensibility.

2. Minimum Database for Wildlife Criteria Derivation

There was a considerable amount of discussion in the Committees of the Initiative and at the Workshop on the minimum toxicological database requirements for both Tier I criteria and Tier II values. Due to the uncertainties in extrapolating data across taxonomic classes, EPA is proposing to require that the minimum toxicity database for Tier I criteria must provide enough data to generate a subchronic or chronic dose-response curve for both birds and mammals. For Tier II values, the minimum toxicity database need only provide enough data to generate a subchronic or chronic dose-response curve for one taxonomic class (Aves or Mammalia). In all cases, any study used in the derivation of wildlife criteria or values should be peer-reviewed.

Additionally, if available, field studies of wildlife species shall take precedence over studies using traditional laboratory species in the development of wildlife criteria and values because uncertainties in extrapolating from laboratory to field impacts are reduced. Any laboratory studies used must use avian or mammalian species.

The oral exposure route is the primary route of exposure to be considered in selecting toxicity studies. EPA proposes that studies involving other exposure routes (e.g., dermal or inhalation) should be considered in the derivation of a Tier I criteria or Tier II value only when an equivalent oral dose can be estimated. Such an estimation should be supported by toxicokinetic and in vivo metabolism data. Without this supporting data, the mechanism of toxicity and/or the dosimetry for these routes of exposure cannot be assumed to be the same

as for the oral route of exposure, and the criteria and value calculations are based on an oral route of exposure.

If laboratory studies are used to derive a Tier I criteria, EPA is proposing a 90-day requirement for any mammalian study and a 28-day requirement for any avian study. This is to ensure that the toxicity data on which a wildlife criterion is based does not underestimate effects associated with repeated exposures to a chemical.

If laboratory studies are used to derive a Tier II value, EPA is proposing the same requirements for Tier I except a 28-day mammalian study which meets the other requirements presented in appendix to part 132 may also be used.

3. Acceptable Endpoints for Toxicity Studies

The acceptable endpoints on which the NOAEL determined from the toxicity study must be based are defined in the wildlife methodology presented in appendix D to part 132. These endpoints were selected because they are parameters most likely to influence population dynamics. When more than one study is available which assessed different endpoints, EPA recommends that preference be given to studies which assess endpoints which best reflect potential impacts to wildlife populations.

EPA's SAB, in their December 16, 1992 report (U.S. EPA, 1992), recommended that EPA develop guidance for the selection of NOAELs appropriate for the protection of wildlife populations as distinct from the protection of individuals. EPA proposes that the restrictions and clarifications provided in the methodology adequately address this concern given the current extent of knowledge regarding population dynamics. EPA requests comments on other approaches which may address the recommendation received from EPA's SAB.

4. Use of an Acute to Chronic Conversion Ratio

Participants at the Workshop and the Committees of the Initiative discussed the application of acute to chronic conversion ratios in the derivation of Tier I criteria. An acute/chronic ratio is applied to acute toxicity data (typically mortality) to estimate chronic effect levels. Workshop participants concluded that more data analysis of existing mammalian and avian acute and chronic toxicity data, possibly broken down by class of compound or mode of action, was needed to adequately define the empirical relationship between acute endpoints (e.g., LD50, the lethal dosage causing death in 50 percent of the exposed animals) and chronic endpoints (e.g., NOAEL, the highest tested dosage causing no observed adverse effect). Workshop participants recognized that before the use of acute/chronic ratios could be scientifically defensible, additional toxicity data might be needed. Given the current limited database, there was concern that the factor for extrapolating from acute data to chronic data would have to be so large that it would result in criteria or values which could be overly conservative. Therefore, EPA is proposing not to incorporate the use of an acute-to-chronic conversion factor in the Tier I methodology. EPA is also proposing that Tier II values not be based solely on acute toxicity data, instead

requiring the use of subchronic or chronic data to derive an effect value. EPA invites comments on these proposed decisions.

D. *Chemical Selection for Wildlife Criteria Derivation*

The types of chemicals for which wildlife criteria should be developed under the GLWQI were addressed by the Workshop. These are: those which bioaccumulate (because wildlife species occupy higher levels in the trophic structure of a food web and, therefore, have a higher exposure); and those which have a unique metabolic pathway or mode of action which may make birds or mammals more sensitive toxicologically. The Committees of the Initiative agreed with the proposals of the Workshop that chemicals BAF greater than 250 should receive top priority for derivation of wildlife criteria. In addition, chemicals with BAFs less than 250 where wildlife impacts are suspected (e.g., lead) were included in the top priority list.

The Initiative Committees also identified non-persistent, multiple application biocides (such as triazine herbicides and carbamates) are another group of chemicals for which wildlife criteria may be derived. These chemicals, although they are highly degradable and, therefore, have low bioaccumulation factors, are known to have detrimental effects on wildlife.

EPA agrees that the chemicals described above are those that most warrant the development of wildlife criteria and values. EPA is not requiring the Great Lakes States or Tribes to develop values for all of these chemicals, nor is EPA prohibiting any State or Tribe from addressing other chemicals if it believes that those other chemicals are causing adverse impacts on wildlife. EPA merely recommends that States or Tribes place a high priority on developing wildlife values for the chemicals identified by the Committees. EPA also intends to focus any future efforts to develop additional Tier I criteria for wildlife on these same chemicals of concern.

E. *Tier I Wildlife Criteria and Tier II Wildlife Values*

In the proposed Guidance, there are four chemicals for which Tier I wildlife criteria are proposed. These are mercury, PCBs, 2,3,7,8-TCDD, and DDT and metabolites. Only four wildlife criteria are being proposed for two major reasons: field studies from the Great Lakes indicate that the four pollutants for which wildlife criteria are proposed have had the most severe impacts on wildlife within the Great Lakes; and the criteria proposed are the first set of criteria for wildlife that EPA has ever developed. EPA cannot take advantage of an established and peer-reviewed National methodology to develop National wildlife criteria as it can for both human health and aquatic life criteria. The Initiative Committees and EPA lacked time and resources to develop additional numeric criteria for wildlife prior to this proposal. The State of Wisconsin had already identified these four chemicals as chemicals of concern for wildlife impacts in their State and completed literature reviews for these four chemicals. These literature reviews were updated as part of the GLWQI effort. The proposed numerical criteria are presented in Table VI-1. For additional information, EPA refers readers to the proposed methodology in appendix D to part 132, the Technical Support

Document located in the appendix to this preamble, and the individual criteria documents available in the 2 administrative record for this rulemaking. No Tier II wildlife values were calculated for inclusion in the proposed Guidance.

Table VI-1. Great Lakes Tier I Wildlife Criteria

Chemical	Criteria (pg/L)
p,p'-dichlorodiphenyltrichloroethane (DDT) and Metabolites	0.87
Mercury (including Methylmercury)	180
Polychlorinated biphenyls (PCBs)	17
2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)	0.0096

F. *Comparison With the CWA and Relationship to National Guidance*

The observed effects on wildlife species in the Great Lakes basin are clear evidence that the Clean Water Act (CWA) goals of protecting the biological integrity of the Nation's waters and attaining water quality which provides for the protection of wildlife are not being met in the Great Lakes (see 33 U.S.C. 1251(a)).

1. Relationship to Existing National Guidance

Currently, there exists no National guidance for wildlife protection comparable to the proposed Guidance. However, there is a mechanism for consideration of wildlife impacts within the 1985 National aquatic life criteria guidelines (Stephan, et. al., 1985). In those guidelines, if a maximum permissible tissue concentration is available from a maximum acceptable dietary intake based on observations on survival, growth, or reproduction in: a chronic wildlife feeding study; or a long-term wildlife field study, or from an FDA Action Level, a Final Residue Value can be calculated. This Final Residue Value is calculated by dividing maximum permissible tissue concentrations by appropriate lipid-normalized bioconcentration or bioaccumulation factors.

This methodology provides a mechanism to protect against bioaccumulation of a compound within a food web. However, it also has limitations. A Final Residue Value derived using an FDA Action Level does not ensure protection of wildlife species which may consume contaminated aquatic organisms as a larger portion of their diet or exhibit a

greater sensitivity than the human which the FDA Action Level is derived to protect. If no maximum permissible tissue concentration is available, no Final Residue Value is calculated and, therefore, biomagnification of a chemical into the higher trophic levels of a food web, and potential impacts on these wildlife species, is not considered in the derivation of the Aquatic Life Criterion.

EPA's current National aquatic life criteria for DDT and PCBs are based on wildlife toxicity information (U.S. EPA, 1980a and b, respectively). Wildlife toxicity data was also considered in the derivation of the current aquatic life criterion for mercury (U.S. EPA, 1984). For both DDT and PCBs, a bioconcentration factor (BCF) rather than a bioaccumulation factor was used in the derivation of these aquatic life criteria. In both cases, the BCF was known to underestimate the bioaccumulative potential of the compound, and in the PCB Aquatic Life Criteria document (U.S. EPA, 1980c), underestimating the bioaccumulative potential was identified as leading to a criterion which may be underprotective of wildlife species at risk.

EPA has begun a separate effort to derive National wildlife criteria. Following the release of the 1987 General Accounting Office report entitled "National Refuge Contamination is Difficult to Confirm and Clean Up," (GAO, 1987), EPA began to work cooperatively with U.S. Fish and Wildlife Service to develop methods for deriving National wildlife criteria. The wildlife criteria efforts carried out within the Great Lakes Water Quality Initiative have been coordinated with the on-going National efforts. However, within the development of National wildlife criteria, wildlife are defined as mammals, birds, reptiles and amphibians. This broader definition of wildlife was considered in the early stages of wildlife criteria development for the GLWQI. However, the decision was made to move forward with wildlife criteria considerate of impacts on mammals and birds at this time because of the lack of chronic or sub-chronic toxicological data for reptiles and amphibians. The incorporation of effects on reptiles and amphibians is also complicated by the significance of, and lack of data for, the dermal route of exposure to reptiles and amphibians. EPA requests recommendations on how reptiles and amphibians can be incorporated into the proposed GLWQI methodology or suggestions for an alternative wildlife criteria methodology considerate of impacts on reptiles and amphibians.

2. Relationship to Current Efforts to Provide National Guidance for the Development of Wildlife Criteria

There are efforts underway within EPA to develop guidance for National wildlife criteria. The proposed Guidance is being considered as one alternative which might be modified for nationwide use. The Great Lakes Guidance has as its focus the protection of wildlife populations inhabiting the Great Lakes basin. Although National guidance may eventually be modeled on the proposed Guidance, it should not be expected that the National guidance would result in identical criteria. EPA invites comments on the modification of this approach for development of a National wildlife criteria procedure.

G. *Comparison of Wildlife Criteria and Methods to National Program and to Great Lakes Water Quality Agreement*

1. "No Less Restrictive" than the CWA and National Guidance

Since the current National guidance contains no method for calculating criteria for the sole protection of wildlife and no values based solely on the protection of wildlife, a direct comparison is difficult. The National guidance allows some consideration of wildlife impacts in the calculation of criteria for aquatic life. Current National criteria for aquatic life can be compared with the proposed criteria for wildlife, although the comparison may not be especially meaningful. All four of the Tier I criteria for wildlife proposed are, in fact, more restrictive than the existing aquatic life standards for the same pollutants. Since the new wildlife criteria will apply in almost all Great Lakes waters, they will in a rough sense provide more protection than the National guidance.

As explained in section B above, in the discussion of aquatic life criteria, Tier II values will almost always be more restrictive than both new Great Lakes Tier I criteria and existing National criteria. Hence, EPA believes that future Tier II wildlife values generally will not be less restrictive than the National program.

2. Conformance with the Great Lakes Water Quality Agreement

As explained above in the discussion of aquatic life criteria, EPA does not believe that Congress intended to require EPA to adopt criteria identical to the specific numerical limits set out as "Specific Objectives" in Annex 1 of the Great Lakes Water Quality Agreement (GLWQA). In addition, only five of these "Objectives" focus on the protection of wildlife. EPA notes that the proposed wildlife criterion that can be most readily compared to a wildlife limit in the GLWQA is more restrictive than the GLWQA's limit. EPA is proposing a wildlife criteria for DDT of 0.87 pg/L. The GLWQA's Annex 1 limit for DDT is 3.0 pg/L.

Finally, as discussed above, EPA intends to try to revise the GLWQA to replace existing Annex 1 limits with the new criteria proposed.

H. *Bibliography*

Great Lakes Water Quality Criteria Initiative. Appendix A: Uncertainty Factors in Great Lakes Water Quality Criteria Initiative Technical Support Document for Human Health Criteria and Values. NTIS #PB93-15468. ERIC: 3940.

National Academy of Sciences. 1980. Problems of Risk Estimation, pp. 25-65 in Drinking Water and Health, Volume 3. National Academy Press, 2101 Constitution Avenue, NW, Washington, D.C. 20418.

Stephan, C.E., D. I. Mount, D. J. Hansen, J.H. Gentile, G.A. Chapman, and W.A. Brungs. 1985. Guidelines for deriving numerical national Water Quality Criteria for the Protection of Aquatic Organisms and their uses. PB85-227049. National Technical Information Service. Springfield, VA.

U.S. EPA. 1980a. Ambient Water Quality Criteria for DDT. Office of Water Regulations and Standards, Criteria and Standards Division. U.S. EPA. Washington, D.C. EPA 440/5-80-038.

U.S. EPA. 1984. Ambient Water Quality Criteria for Mercury. Office of Water Regulations and Standards, Criteria and Standards Division. U.S. EPA. Washington, D.C. EPA 440/5-80-058.

U.S. EPA. 1980b. Ambient Water Quality Criteria for Polychlorinated Biphenyls. Office of Water Regulations and Standards, Criteria and Standards Division. U.S. EPA. Washington, D.C. EPA 440/5-80-068.

U.S. EPA. 1980c. Appendix C. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. pp. 79347-79357 in Water Quality Criteria Documents; Availability. Federal Register. 45:79318-79378. Friday, November 28, 1980.

U.S. EPA. 1992. An SAB Report: Evaluation of the Guidance for the Great Lakes Water Quality Initiative. Science Advisory Board, U.S. EPA, Washington, D.C. EPA-SAB-EPEC/DWC-93-005.

U.S. EPA. 1985. Section V.C. Evaluation of Health Effects and Determination of RMCLs pp. 46944-46950 in National Primary Drinking Water Regulations; Synthetic Organic Chemicals; Inorganic Chemicals and Microorganisms. 50 FR 46936-47022. Wednesday, November 13, 1985.

U.S. General Accounting Office. 1987. Wildlife Management National Refuge Contamination is Difficult to Confirm and Clean Up. Gaithersburg, MD. GAO/RCED-87-128.

Wisconsin Administrative Code, Chapter NR 105. Surface Water Quality Criteria for Toxic Substances. Register, February, 1989, No. 398.

Technical Support Document for Chapter NR 105 of the Wisconsin Administrative Code. May 1988.

CHAPTER 2

Appendix D to Part 132--Great Lakes Water Quality Initiative Methodology for the Development of Wildlife Criteria and Values

I. *Introduction*

A Great Lakes Water Quality Wildlife Criterion (GLWC) is the concentration of a substance which, if not exceeded, protects avian and mammalian wildlife populations inhabiting the Great Lakes basin from adverse effects resulting from the ingestion of surface waters and aquatic prey taken from surface waters of the Great Lakes System. These criteria are numeric or narrative in nature and are based on existing toxicological studies of the substance of concern and quantitative information about the exposure of wildlife species to the substance (i.e., food and water consumption rates). Since toxicological and exposure data for individual wildlife species is limited, a GLWC is derived using a methodology similar to that used to derive noncancer human health criteria (Barnes and Dourson, 1988; NAS, 1977; NAS, 1980; U.S. EPA. 1980). Separate avian and mammalian values are developed using taxonomic class-specific toxicity data and exposure data for five representative Great Lakes basin wildlife species. The representative wildlife species selected are representative of avian and mammalian species resident in the Great Lakes basin which are likely to experience significant exposure to contaminants through the aquatic food web; they are the bald eagle, osprey, belted kingfisher, mink, and river otter. Taxonomic class-specific avian and mammalian Wildlife Values (WVs)--concentrations of a substance which if not exceeded should protect the wildlife species--are calculated using the geometric means of the species' WVs and the lower of the mammalian and avian WVs is selected as the GLWC.

This appendix establishes a two-tiered approach to the protection of avian and mammalian communities in the Great Lakes basin. This appendix sets forth the method for deriving both Tier I criteria and Tier II values.

II. *Calculation of Wildlife Values for Tier I Criteria and Tier II Value Development*

Table 4 of part 132 and Table D-1 of this appendix to part 132 contain the proposed Tier I criteria calculated by EPA pursuant to the provisions below. No Tier II values have been calculated.

A. Equation for Avian Mammalian Wildlife Values

The Tier I GLWC is the lower of the two taxonomic class-specific wildlife values. A Tier II value may be based on the wildlife value derived from a single taxonomic class. These wildlife values are calculated using the equation presented below.

$$WV = \frac{[NOAEL \times SSF] \times Wt_A}{W_A + [F_A \times BAF]}$$

Where:
WV = Wildlife value in milligrams of substance per liter (mg/L).

NOAEL = No observed adverse effect level in milligrams of substance per kilogram of body weight per day (mg/kg-d) as derived from mammalian or avian studies as described in section II.E of this document.

Wt_A = Average weight in kilograms (kg) for the representative species identified for protection or the species identified as requiring greater protection.

W_A = Average daily volume of water consumed in liters per day (L/d) by the representative species identified for protection or the species identified as requiring greater protection.

SSF = Species sensitivity factor. An extrapolation factor to account for differences in toxicity between species. Further information is provided in section III.I of this document.

F_A = Average daily amount of food consumed in kilograms per day (kg/d) by the representative species identified for protection or the species identified as requiring greater protection.

BAF = Aquatic life bioaccumulation factor for wildlife in liters per kilogram (L/kg). Chosen using guidelines for wildlife presented in appendix B to part 132, Methodology for Development of Bioaccumulation Factors.

The term "wildlife value" is used to denote any value which results from each application of the equation presented above or any averaging of such numbers. It can refer to values derived using either the Tier I or Tier II database requirements. Wildlife values calculated for the representative species are used to calculate taxonomic class-specific wildlife values. "Tier II wildlife value," or "Tier II value," is used to denote any final number derived from data meeting only the Tier II requirements and using the procedure presented in this document. "Tier I wildlife value," or Tier I value," is used to denote any final number derived from data meeting the Tier I database requirements calculated using the procedure presented in this document. "Tier I criteria" are the four wildlife criteria presented in Table 4 of part 132 and in Table D-1 of this appendix to part 132.

B. Identification of Representative Species for Protection

Piscivorous species are identified as the focus of concern for wildlife criteria development in the Great Lakes. An analysis of known or estimated exposure components for avian and mammalian wildlife species is presented in the Technical Support Document for Wildlife Criteria (U.S. EPA, 1993a). This analysis identifies three avian species and two mammalian species as representative species for protection. The NOAEL obtained from

toxicity data for each taxonomic class is used to calculate Wildlife Values (WVs) for each of the five representative species identified for protection.

Because of the lack of empirical species-specific exposure information for all wildlife species in each taxonomic class, the geometric means of wildlife values for the representative species within each taxonomic class are used to determine the taxonomic class-specific wildlife value.

C. Identification of Species Requiring Greater Protection

Identification of Species Requiring Greater Protection. If exposure and/or hazard data identifies a Great Lakes basin avian or mammalian wildlife species which is at risk, for which the wildlife criteria or Tier II value based on the representative species may not be adequately protective, the final avian or mammalian WV will be calculated specifically for that species. A class-specific WV for a species determined to require greater protection is calculated using the equation presented above, but using exposure information for the species determined to require greater protection. Toxicity information specific for that species is also used if it is available. This provision can be invoked in the derivation of site-specific criteria where a wildlife species has been determined to require greater protection.

D. Calculation of Avian and Mammalian Wildlife Values

The taxonomic class-specific Wildlife Values (WV) can be determined in two ways, both of which use the equation presented above. The avian WV is the geometric mean of the WVs calculated for the three representative avian species identified for protection or it is the WV calculated for an avian species determined to require greater protection. The mammalian WV is the geometric mean of the WVs calculated for the two representative mammalian species or it is the WV calculated for a mammalian species determined to require greater protection. When a WV is calculated for a species determined to require greater protection, the taxonomic class-specific WV for use in the determination of a GLWC is the lower of the WVs calculated for the given taxonomic class (the geometric mean of the WVs calculated for the representative species or the WV calculated for the species determined to require greater protection.) The Tier I GLWC is set equivalent to the lower of the avian or mammalian WVs determined.

III. *Parameters of the Hazard Component of the Criteria Methodology*

A. Definitions

The following definitions provide additional specificity and guidance in the evaluation of toxicity data and the application of this methodology. These definitions are applicable to both Tier I criteria and Tier II value development.

Acceptable endpoints. For the purpose of wildlife criteria derivation, acceptable subchronic and chronic endpoints are those which affect organismal growth or viability, or

reproductive or developmental success or any other endpoint which is, or is directly related to, parameters that influence population dynamics.

Chronic effect. An adverse effect, measured by assessing an acceptable endpoint, resulting from continual exposure over several generations, or at least over a significant part of the test species projected life span or life stage.

Lowest-observed-adverse-effect-level (LOAEL). The lowest tested dose or concentration of a substance which resulted in an observed adverse effect in exposed test organisms when all higher doses or concentrations resulted in the same or more severe effects.

No-observed-adverse-effect-level(NOAEL). The highest tested dose or concentration of a substance which did not result in an observed adverse effect in exposed test organisms.

Subchronic effect. An adverse effect, measured by assessing an acceptable endpoint, resulting from continual exposure for a period of time less than that deemed necessary for a chronic test.

B. Minimum Toxicity Database for Tier I Criteria Development

A NOAEL or LOAEL value is required for criterion calculation. To derive a Tier I criterion for wildlife, the minimum toxicity database required must provide enough data to generate a subchronic or chronic dose-response curve for any given substance for both mammalian and avian species.

In reviewing the toxicity data available which meets the minimum data requirements for each taxonomic class, the following order of preference shall be applied to select the appropriate NOAEL or LOAEL to be used for calculation of individual wildlife values. Data from peer-reviewed field studies of wildlife species takes precedence over other types of studies. An acceptable field study must be of subchronic or chronic duration, provide a defensible, chemical-specific dose-response curve in which cause and effect are clearly established, and assess acceptable endpoints as defined in this document. When acceptable wildlife field studies are not available, the needed toxicity information may come from peer-reviewed laboratory studies. When laboratory studies are used, preference shall be given to laboratory studies with wildlife species over traditional laboratory animals to reduce uncertainties in making interspecies extrapolations. Whenever possible, all available laboratory data and field studies shall be reviewed to corroborate the final GLWC, to assess the reasonableness of the toxicity value used, and to assess the appropriateness of any uncertainty factors which are applied.

When laboratory data are used, the following requirements must be met:

1. The mammalian data must come from at least one well-conducted study of 90 days or greater designed to observe subchronic or chronic effects as defined in this document.

2. The avian data must come from at least one well-conducted study of 28 days or greater designed to observe subchronic or chronic effects as defined in this document.

In reviewing the studies from which a NOAEL is derived for use in calculating a wildlife value, studies involving exposure routes other than oral may be considered only when an equivalent oral daily dose can be estimated and technically justified. This is because the mechanism of toxicity and/or issues of dosimetry (e.g. delivered dose to target organs, extent of xenobiotic metabolism, etc.) for other routes of exposure (e.g., dermal or inhalation) may differ; and the criteria and value calculations are based on an oral route of exposure.

In assessing the studies which meet the minimum data requirements, preference should be given to studies which assess effects on developmental or reproductive endpoints because, in general, these are more important endpoints in ensuring that a population's productivity is maintained.

C. Minimum Toxicity Database for Tier II Wildlife Value Development

For those substances for which Tier I criteria cannot be derived, all data from avian and mammalian species may be considered in the development of Tier II values. To derive a Tier II value for wildlife, the minimum toxicity database required must provide enough data to generate a subchronic or chronic dose-response curve for any given substance for either a mammalian or avian species. Subchronic or chronic toxicity data shall be used to derive NOAELs for Tier II values. When laboratory data for avian species is used to calculate a Tier II wildlife value, it must meet the same requirements presented above for Tier I criteria derivation. When laboratory data for mammals is used to calculate a Tier II wildlife value, a 28-day subchronic study which assessed acceptable endpoints may be used in addition to studies which meet the requirements presented above for Tier I criteria derivation. Relevant LD50 or eight-day LC50 values from avian and mammalian studies may be used in support of subchronic and chronic toxicity data; however, a Tier II value shall not be calculated solely on the basis of LD50 or eight-day LC50 data.

D. Selection of NOAEL or LOAEL Data

In selecting data to be used in the derivation of wildlife values, the nature of the observed endpoints will be the primary selection criterion. All data not part of the selected subset may be used to assess the reasonableness of the toxicity value and the appropriateness of any uncertainty factor which is applied.

1. If more than one NOAEL is available within a taxonomic class, based on different endpoints of toxicity, that NOAEL which likely best reflects potential impacts to wildlife populations through resultant changes in mortality and/or fecundity rates shall be used for the calculation of wildlife values.

2. If more than one NOAEL is available within a taxonomic class based on the same endpoint of toxicity, the NOAEL from the most sensitive species is used.

3. If more than one NOAEL based on the same endpoint of toxicity is available for a given species, the NOAEL for that species shall be calculated using the geometric mean of those NOAELs.

E. Determination of the NOAEL in Proper Units

In those cases in which a NOAEL is available in units other than mg/kg-d, the following procedures shall be used to convert the NOAEL to appropriate units prior to calculating a wildlife value.

If the NOAEL is given in milligrams of toxicant per liter of water consumed by the test animals (mg/L), the NOAEL shall be multiplied by the daily average volume of water consumed by the test animals in liters per day (L/d) and divided by the average weight of the test animals in kilograms (kg).

If the NOAEL is given in milligrams of toxicant per kilogram of food consumed by the test animals (mg/kg), the NOAEL shall be multiplied by the average amount of food in kilograms consumed daily by the test animals (kg/d) and divided by the average weight of the test animals in kilograms (kg).

F. Drinking and Feeding Rates

When drinking and feeding rates and body weight are needed to express the NOAEL in mg/kg-d, they should be obtained from the study from which the NOAEL was derived. If not already determined, body weight, and drinking and feeding rates are to be converted to a wet weight basis.

If the study does not provide the needed values, they shall be determined from appropriate data tables for the particular study species. For studies done with domestic laboratory animals, the following reference should be consulted: Registry of Toxic Effects of Chemical Substances (National Institute for Occupational Safety and Health, the latest edition, Cincinnati, OH.). When insufficient data exist for other mammalian or avian species, the allometric equations from Calder and Braun (1983) and Nagy (1987) which are presented below shall be applied to approximate the needed feeding or drinking rates.

For mammalian species the allometric equations are:

1. $F_A = 0.0687 \times (Wt_A)^{0.82}$

Where:

F_A = Feeding rate of mammalian species in kilograms per day (kg/d) dry weight.

Wt_A = Average weight in kilograms (kg) of the test animals.

2. $W_A=0.099 \times (Wt_A)^{0.90}$
Where:
W_A = Drinking rate of mammalian species in liters per day (L/d).
Wt_A = Average weight in kilograms (kg) of the test animals.

For avian species the allometric equations are:
3. $F_A=0.0582 (Wt_A)^{0.65}$
Where:
F_A = Feeding rate of avian species in kilograms per day(kg/d) dry weight.
Wt_A = Average weight in kilograms (kg) of the test animals.

4. $W_A=0.059 \times (Wt_A)^{0.67}$
Where:
W_A = Drinking rate of avian species in liters per day (L/d).
Wt_A = Average weight in kilograms (kg) of the test animals.

G. LOAEL to NOAEL Extrapolations

In those cases in which a NOAEL is unavailable and a LOAEL is available, the LOAEL may be adjusted to estimate the NOAEL. Typically, the LOAEL is divided by an uncertainty factor to estimate a NOAEL for use in deriving wildlife values. The value of the uncertainty factor is typically within the range of 1.0 and 10, depending on the dose-response curve. Additional references which support this concept and are useful in choosing an appropriate LOAEL to NOAEL uncertainty factor are provided in the Technical Support Document for Wildlife Criteria (U.S. EPA, 1993a). Assistance in choosing an appropriate LOAEL to NOAEL uncertainty factor is also provided in appendix A to the Great Lakes Water Quality Initiative (GLWQI) Technical Support Document for Human Health Criteria and Values (U.S. EPA, 1993b).

H. Subchronic to Chronic Extrapolations

In certain instances where only subchronic data are available, the NOAEL may be divided by an uncertainty factor to extrapolate from subchronic to chronic levels. Typically the value of the uncertainty factor is within the range of 1.0 and 10. This factor may be used when assessing highly bioaccumulative substances where toxicokinetic considerations suggest that a bioassay of limited length underestimates chronic hazard. Assistance in choosing an appropriate subchronic to chronic uncertainty factor is provided in appendix A to the GLWQI Technical Support Document for Human Health Criteria and Values (U.S. EPA, 1993b).

I. Species Sensitivity Factor

The selection of the species sensitivity factor (SSF) shall be based on the available toxicological data and on available data concerning the physicochemical, toxicokinetic and toxicodynamic properties of the substance in question and the amount and quality of available data. This value is an uncertainty factor that is intended to account for differences in toxicological sensitivity among species. Guidance for choosing the SSF is provided in the Technical Support Document for Wildlife Criteria (U.S. EPA, 1993a). The discussion of an interspecies uncertainty factor located in appendix A to the GLWQI Technical Support Document for Human Health Criteria and Values (U.S. EPA, 1993b) may also be useful in determining the appropriate value for a SSF.

For the derivation of Tier I criteria, a SSF within the range of 0.01 to 1.0 may be applied. If a SSF outside this range is used, it must be based on sound scientific and technical reasons and must be accompanied by a written justification presenting this reasoning. This justification shall be provided to EPA as part of the State's or Tribe's submission as required under § 132.5. Use of a SSF outside this range is prohibited unless approved by EPA based on its consideration of the justification provided. For Tier I wildlife criteria, the SSF shall be used for extrapolating toxicity data across species within a taxonomic class. The Tier I SSF is not intended for interclass extrapolations because of the poorly defined comparative toxicokinetic and toxicodynamic parameters between mammals and birds. However, an interclass extrapolation employing a SSF may be used for a given chemical if it can be supported by a validated biologically-based dose-response model or by an analysis of interclass toxicological data, considerate of acceptable endpoints, for a chemical analog that acts under the same mode of toxic action.

For the derivation of Tier II wildlife values, a SSF may not be greater than 1.0 but may be lower than 0.01 without requiring a written justification. For Tier II wildlife values, the SSF may be used to extrapolate toxicity data across the two taxonomic classes.

IV. *Parameters of the Exposure Component of the Wildlife Criteria Methodology*

A. Drinking and Feeding Rates of Representative Species or Species Requiring Greater Protection.

The body weights (Wt_A), feeding rates (F_A), and drinking rates (W_A) for each of the five representative species are presented in Table D-2 of this appendix. Trophic level dietary composition for these species are also presented in Table D-2 of this appendix for use in selecting the correct bioaccumulation factor for use in the WV equation.

If the feeding rate (F_A) or drinking rate (W_A) for the species requiring greater protection are not known, they can be estimated using the allometric equations presented above in section III.F of this appendix.

B. Bioaccumulation Factors

The Methodology for Development of Bioaccumulation Factors is presented in appendix B to part 132. This Guidance document specifies that, in general, trophic level three or four BAFs are to be used in the derivation of wildlife values, depending on the species identified for protection. Trophic level three and four BAFs are used because these are the trophic levels at which the representative species identified for protection feed. Options to use plant and or other trophic level BAFs are permitted based on the identification of a species requiring greater protection which may feed, in part or whole, at other trophic levels.

V. *References*

Barnes D. G. and M. Dourson. 1988. Reference Dose (RfD): Description and Use in Health Risk Assessments. Regul. Toxicol. Pharmacol. 8:471-486. Academic Press, Inc. 1250 6th Avenue, San Diego, CA 92101-4312.

Calder III, W. A. and E. J. Braun. 1983. Scaling of Osmotic Regulation in Mammals and Birds. American Journal of Physiology. 244:601-606. Williams and Wilkins, 1316 East 16th Street, Brooklyn, NY 11230-6003.

Nagy, K. A. 1987. Field Metabolic Rate and Food Requirement Scaling in Mammals and Birds. Ecological Monographs. 57(2):111-128. Ecological Society of America, Arizona State University, Tempe, AZ 85287-0001.

National Academy of Sciences. 1977. Chemical Contaminants: Safety and Risk Assessment, pp. 19-62 in Drinking Water and Health, Volume 1. National Academy Press, 2101 Constitution Avenue, NW, Washington, D.C. 20418.

National Academy of Sciences. 1980. Problems of Risk Estimation, pp. 25-65 in Drinking Water and Health, Volume 3. National Academy Press, 2101 Constitution Avenue, NW, Washington, D.C. 20418.

National Institute for Occupational Safety and Health. Latest edition. Registry of Toxic Effects of Chemical Substances (available only on microfiche or as an electronic database). Division of Standards Development and Technology Transfer, 4676 Columbia Parkway, Cincinnati, OH 45226.

U.S. EPA. 1980. Appendix C. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. pp. 79347-79357 in Water Quality Criteria Documents; Availability. Available from U.S. Environmental Protection Agency, Office of Water Resource Center (WH-550A), 401 M. St., SW, Washington, DC 20460.

U.S. EPA. 1985. Section V.C. Evaluation of Health Effects and Determination of RMCLs pp. 46944-46950 in National Primary Drinking Water Regulations; Synthetic Organic Chemicals; Inorganic Chemicals and Microorganisms. Available from U.S. Environmental Protection Agency, Office of Water Resource Center (WH-550A), 401 M. St., SW, Washington, DC 20460.

U.S. EPA. 1993a. Great Lakes Water Quality Initiative Technical Support Document for Wildlife Criteria. Available from U.S. Environmental Protection Agency, Office of Water Resource Center (WH-550A), 401 M. St., SW, Washington, DC 20460.

U.S. EPA. 1993b. Great Lakes Water Quality Criteria Initiative. Appendix A: Uncertainty Factors in Great Lakes Water Quality Criteria Initiative Technical Support Document for Human Health Criteria and Values. NTIS #PB93-15468. ERIC: 3940.

Tables to Appendix D to Part 132

TABLE D-1. Tier I Great Lakes Wildlife Criteria.

Substance	Criterion
DDT & Metabolites	0.87 pg/L
Mercury	180 pg/L
PCBs (total)	17 pg/L
2,3,7,8-TCDD	0.0096 pg/L

TABLE D-2. Exposure parameters for the five representative species identified for protection.

Species	Body Wt. (Wt_A) (Kg)	Ingestion Rate (F_A) (Kg/d)	Drinking Rate (W_A) (L/d)	Trophic Level of Wildlife Food Source	%Diet at each trophic Level
Mink	1.0	0.15	0.099	3	100
Otter	8.0	0.9	0.64	3 4	50 50
Kingfisher	0.15	0.075	0.017	3	100
Osprey	1.5	0.3	0.077	3	100
Eagle	4.5	0.5	0.16	4	100

CHAPTER 3

Appendix to the Preamble--Great Lakes Water Quality Initiative Technical Support Document for Wildlife Criteria

Note: This appendix to part 132 contains background material and material intended to clarify portions of the regulation. It does not establish any additional regulatory requirements.

I. Introduction

The waters of the Great Lakes System provide vital resources not only to support numerous critical human activities and habitat for aquatic organisms, but also to sustain viable mammalian and avian wildlife communities. In order to assure that the quality of the waters in the System are adequate to support these uses, specific water quality criteria need to be set.

The purpose of establishing water quality criteria for wildlife is to determine surface water concentrations of toxicants that will remain protective of avian and mammalian wildlife populations that utilize waters of the Great Lakes System as a drinking and/or foraging source. Specifically, each criterion is the highest calculated aqueous concentration of a toxicant which causes no significant reduction in the viability or usefulness (in a commercial or recreational sense) of a population of exposed animals over several generations. For the purpose of these regulations, this concentration is called the Great Lakes Wildlife Criterion (GLWC).

Ideally, a safe concentration of a given pollutant would be calculated for every species and the GLWC would be determined based on the distribution of these values across all species (an approach similar to that used in deriving criteria to protect aquatic life, Stephan et al., 1985). Therefore, an approach similar to that proposed to derive a noncancer human health criterion (section III.C.3 of appendix C to part 132 of this rule, Methodologies for Development of Human Health Criteria and Values) was used in which representative wildlife species were selected to establish the basis for employing interspecies uncertainty factors for extrapolation of toxicity data and to define specific exposure parameters. Five Great Lakes basin wildlife species representative of avian and mammalian species resident in the Great Lakes basin which are likely to experience significant exposure to contaminants through the aquatic food web were identified. These species are the bald eagle, osprey, belted kingfisher, mink, and river otter. A Wildlife Value (WV) is calculated for each representative species (which is a safe concentration of a given pollutant) and then the geometric mean of these values within each taxonomic class is determined. The GLWC is the lower of two class-specific means.

To derive the WVs from which the GLWC is determined, scientific literature for the toxicant of concern is reviewed for mammalian and avian toxicity studies that meet the minimum toxicity database requirements. A tiered approach is used in the derivation of these criteria. Tier I values are developed for chemicals with databases providing a high level of

certainty in quantifying concentrations at which adverse effects may be experienced by the avian and mammalian wildlife communities. EPA is proposing four specific Tier I criteria that will be applicable across the Great Lakes System. States and Tribes will be expected to adopt into regulation these criteria (or more stringent values). They will also be expected to adopt the procedure for developing Tier I values for additional substances. EPA encourages States and Tribes to adopt these Tier I values as criteria.

Chemicals with less extensive data, or where the level of certainty is less, are subject to Tier II values. States and Tribes will be expected to adopt, by regulation, the procedure for developing Tier II values, rather than the numeric values the procedure generates.

II. Calculation of Wildlife Values for Tier I Criteria and Tier II Value Development

A. Derivation of Equation

The equation used to calculate Wildlife Values (WV), and ultimately the GLWC, has both a hazard and exposure component. The hazard component contains the NOAEL--the highest tested dose of a substance which does not result in an observed adverse effect. The exposure routes considered in this derivation are food and water ingestion. The intake level is dependent on organism size and therefore it is scaled to body weight. The total toxicant intake through these exposure routes is determined and then set equal to the NOAEL as follows:

Toxicant intake through drinking water = $(WV \times W_A)/Wt_A$ (Equation 1)

Toxicant intake through food = $(WV \times F_A \times BAF)/Wt_A$ (Equation 2)

Where:

WV = Wildlife value in milligrams of substance per liter (mg/L).

W_A = Average daily volume of water consumed in liters per day (L/d) by the representative species identified for protection or the species identified as requiring greater protection.

F_A = Average daily amount of food consumed in kilograms per day (kg/d) by the representative species identified for protection or the species identified as requiring greater protection.

BAF = Aquatic life bioaccumulation factor for wildlife in liters per kilogram (L/kg). Chosen using guidelines for wildlife presented in appendix B to part 132 of this rule, the Methodology for Development of Bioaccumulation Factors.

Wt_A = Average weight in kilograms (kg) for the representative species identified for protection or the species identified as requiring greater protection.

Equations one and two are combined to yield Equation three.

$$NOAEL > (WV \times W_A)/Wt_A + (WV \times F_A \times BAF)/Wt_A \quad \text{(Equation 3)}$$

Where:

NOAEL = No observed adverse effect level in milligrams of substance per kilogram of body weight per day (mg/kg-d) as derived from mammalian or avian toxicity studies.

Factoring and rearranging produces:

$$WV < \frac{NOAEL \times Wt_A}{W_A + [F_A \times BAF]} \quad \text{(Equation 4)}$$

To account for differences in toxicity among species, the NOAEL is multiplied by the species sensitivity factor, SSF. The final equation for the WV is:

$$WV = \frac{[NOAEL \times SSF] \times Wt_A}{W_A + [F_A \times BAF]} \quad \text{(Equation 5)}$$

B. *Weight of the Test Animal, Representative Species, or Species Requiring Greater Protection*

The weight of the test animal may be needed to convert the NOAEL determined in the study to the correct units for use in the equation to derive a wildlife value. If a species is identified as requiring greater protection and is not one of the representative species, its weight is needed for calculation of the GLWC. If this information is not given in the chosen study, the average weight of the test species shall be determined from available literature, including, if necessary, metabolic rate models, such as those presented by Nagy (1987), and discussed further, below.

C. *Drinking and Feeding Rates for the Test Animal or Species Requiring Greater Protection*

A feeding and drinking rate for a species identified as requiring greater protection and which is not one of the representative species identified for protection may also be needed for calculation of the GLWC. These rates are needed to accurately predict exposure. When consumption rates are given in the study of choice, they may be substituted directly into the equation. If this information is not available from the chosen toxicity study, it shall be obtained from other appropriate literature concerning the species. In some instances, however, this information is not available directly and needs to be estimated. The following reference may be consulted for studies done with domestic laboratory animals: Registry of Toxic Effects of Chemical Substances (National Institute for Occupational Safety and Health, the latest edition).

When insufficient data exist for other mammalian or avian species, the allometric equations presented in appendix D to part 132 should be used to approximate the needed feeding or drinking rates. These equations were adopted from Calder and Braun (1983), and Nagy (1987).

When replicated data exist, best professional judgement will be used in the selection of a single value. Barring that, the geometric mean of the data points will be utilized as the representative value.

III. Parameters of the Hazard Component of the Wildlife Criteria Methodology

A. *Minimum Toxicity Database for Tier I Criteria Development*

The 90-day requirement for mammalian studies and the 28-day requirement for avian studies are to ensure that the toxicity data on which a wildlife criterion is based exceeds an acute exposure, which may underestimate the potency a compound would have following a chronic exposure. These minimum test length requirements are to be applied to both field and laboratory studies.

B. *Minimum Toxicity Database for Tier II Wildlife Value Development*

For those substances for which Tier I criteria cannot be derived, all data from avian and mammalian species may be considered in the development of Tier II values. Subchronic or chronic toxicity data shall be used whenever available to derive a no observable adverse effect level (NOAEL) for Tier II values. There are two major differences in data requirements for Tier II values: (1) The minimum database requirements presented for the derivation of a Tier I wildlife criteria must only be met for one of the two taxonomic classes in order to derive a Tier II wildlife value; and (2) a Tier II value may also be based on a mammalian study which fulfills the requirements set forth for Tier I criteria excepting it may have only a 28-day duration.

LD50 and eight-day LC50 data may be used in support of subchronic and chronic toxicity data; however, neither a Tier I criteria nor a Tier II value shall be calculated solely on the basis of LD50 or eight-day LC50 data.

C. *LOAEL to NOAEL Extrapolations*

If a NOAEL in proper units is available from the scientific literature, it may be substituted directly into the equation. In many instances, however, a NOAEL is unavailable and a LOAEL is available for a particular animal. In these instances the LOAEL must be adjusted to estimate a NOAEL and converted to proper units before being substituted into the equation.

The LOAEL is adjusted by dividing by an uncertainty factor which typically ranges in value from 1.0 to 10 to lower the LOAEL into the range of the NOAEL. Experimental support of this concept is provided by Weil and McCollister (1963). A discussion and endorsement of this concept can be found in Stokinger (1972) and Dourson and Stara (1983). In addition, this concept is endorsed by EPA in the *Federal Register* for Water Quality Criteria Documents (45 FR 79353-79354, November 28, 1980) and in the National Drinking Water Regulations (50 FR 46944-46946, November 13, 1985). Additional discussion on the use of a LOAEL to NOAEL uncertainty factor and the determination of its magnitude is also

provided in appendix A to the Great Lakes Water Quality Initiative (GLWQI) Technical Support Document for Human Health Criteria and Values, which is available in the administrative record for this rulemaking.

D. *Subchronic to Chronic Extrapolations*

In certain instances where only subchronic data are available, a subchronic to chronic uncertainty factor may be used to account for the uncertainty in extrapolating from a subchronic NOAEL to a chronic NOAEL. The value of the uncertainty factor is within the range of 1.0 to 10, depending on the dose-response of the adverse effect. The subchronic NOAEL is divided by the uncertainty factor. This factor may be used when assessing highly bioaccumulative chemicals, where toxicokinetic considerations suggest that a bioassay of limited length may underestimate hazard. This concept and the use of a 10-fold uncertainty factor is endorsed by EPA in the *Federal Register* for Water Quality Criteria Documents (45 FR 79353-79354, November 28, 1980) and in the National Drinking Water Regulations (50 FR 46944-46946, November 13, 1985). Additional discussion on the use of a subchronic to chronic uncertainty factor is also provided in appendix A to the Great Lakes Water Quality Initiative Technical Support Document for Human Health Criteria and Values, which is available in the administrative record for this rulemaking.

E. *Species Sensitivity Factor*

The NOAEL shall be adjusted to accommodate differences in interspecies toxicity with the use of an uncertainty factor. This adjustment may be necessary since the toxicity information upon which a criterion is developed will not necessarily be based on a study using the representative wildlife species or the species identified as requiring greater protection. In order to provide protection for the representative species or the species requiring greater protection, an uncertainty factor called the species sensitivity factor (SSF) shall be used the value of which shall be based on the physicochemical, toxicokinetic and toxicodynamic properties of the substance in question. The value of the SSF shall also be based on the amount and quality of available toxicological data--both the duration and quality of available studies and the diversity of species for which data is available. Toxicity information for chemicals which operate by the same mode of action can also be considered in deriving the SSF for a given chemical. The SSF is not intended to adjust for potential differences with regard to body weight and food and water consumption rates between the test species and the representative species or species requiring greater protection. The factor selected shall reflect the uncertainty with which the available toxicity data are appropriate for the representative species or the species requiring greater protection.

For Tier I wildlife criteria, the SSF generally shall be used for extrapolating toxicity data across species within a taxonomic class and have a value within the range of 0.01 and 1.0. Use of a SSF outside of this range is prohibited unless approved by EPA. An interclass extrapolation employing a SSF may be used for a specific chemical if is can be supported by a validated biologically-based dose-response model, incorporating acceptable endpoints, for a chemical analog that acts under the same mode of toxic action.

For Tier II wildlife values, interclass extrapolations are permitted. Because of the uncertainties in performing interclass extrapolations, the SSF for calculating Tier II values may not be greater than 1.0 but may be lower than 0.01 without requiring a written justification. It is stressed that Tier II values are by definition and design conservative. Tier II values can be derived when subchronic or chronic data are available from only one taxonomic class; however, because there is more uncertainty in performing interclass extrapolation, a more conservative SSF may be applied.

To determine the proper range for the species sensitivity factor, LD50 data were reviewed for approximately 50 chemicals and chronic toxicity data were reviewed where available. Table I of the annex contains LD50 data for nine pesticides, PCBs (Aroclor 1242) and 2,3,7,8-tetrachlorodibenzo-p-dioxin. This table demonstrates how toxicity from certain chemicals differs among species. Table II of this annex contains chronic toxicity data for organomercury compounds in mammalian species. These data support both the use of an interspecies uncertainty factor and the range of the SSF established within this procedure.

In application, a database containing both chronic and reproductive/developmental data for a diversity of species may require a SSF of between 0.1 and 1.0. If these data are from numerous species and represent the most sensitive mammalian and avian species, the SSF may be equal to 1.0.

IV. Parameters of the Exposure Component of the Wildlife Criteria Methodology

A. Bioaccumulation Factors

A bioaccumulation factor (BAF) is necessary to estimate the concentration of the chemical in the wildlife food source based on its concentration in the water source. The procedure to derive the BAF is specified in appendix B to part 132 of this rule. This methodology specifies that, in general, trophic level three and four BAFs are used in the derivation of wildlife values, although options to use plant or other trophic level BAFs are permitted based on the identification of species requiring greater protection which are not obligate piscivorous or are not likely to consume only fish species at trophic levels three or four.

V. Determination of Species Identified for Protection and Associated Exposure Parameters

Wildlife exposure to environmental contaminants in aquatic systems can be quite variable depending on natural history characteristics of species and on animal physiology. Furthermore, for most species there are few data to estimate exposure in nature (e.g., ingestion rates of natural foods, field metabolic rates). The procedure outlined below integrates appropriate exposure information for a broad array of species with variable exposure scenarios and was used to determine representative species identified for protection in deriving the Great Lakes Wildlife Criteria. This analysis also supports the WV derivation procedure which reflects an approach similar to the human non-carcinogen water quality criteria derivation procedure.

A. *Selection of Species Identified for Protection*

The analysis described in this section was performed to determine representative avian and mammalian species of the Great Lakes basin which are likely to experience significant exposure to contaminants in aquatic ecosystems through the food chain. As a consequence, emphasis is on species with foraging behaviors and trophic levels of their forage sources which suggest high exposure to contaminants. Therefore, the wildlife species of primary concern are piscivorous.

In general, small endotherms have a higher ingestion rate relative to body mass than large endotherms, because small animals generally have a larger surface area to volume ratio and lose proportionately more energy as heat. This suggests that small animals would be exposed to contaminants to a greater degree than large animals, and would always be at a higher level of risk. However, small piscivorous are generally size-limited predators and feed on smaller fish in a lower trophic status than larger piscivorous. Since the concentration of bioaccumulative pollutants is usually less at lower trophic levels, it can not be assumed that small animals have a greater exposure. Therefore, to adequately predict exposure, information on animal size, food habits, and behavior is needed.

Determinations were made of representative species that reside in the Great Lakes basin, based on animal size (small, medium, and large) and foraging style. Animals with different foraging styles may also have different morphologies and activity patterns that ultimately influence food or water ingestion rates and other factors that determine exposure to contaminants.

1. *Selection of Avian Species.* Piscivorous avian species can be classified into three general types of foraging styles; raptorial predators, diving and swimming predators, and wading, "sit-and-wait" predators. Some species which reside in the Great Lakes basin and exhibit each of these foraging styles are listed here:

a. Raptorial: bald eagle, osprey, kingfisher and common tern;
b. Diving: double-crested cormorant, common loon, common merganser and red-breasted merganser; and
c. Wading: great blue heron and green-backed heron.

Exposure data with sufficient detail to make reasonable exposure estimates for six Great Lakes basin piscivorous birds was obtained: bald eagle, osprey, common merganser, common loon, double-crested cormorant and belted kingfisher. These species represent two of the three foraging styles identified. Analysis of these data indicate that the ingestion rates are proportional to the animal mass and the differing foraging styles do not contribute to differences in the ingestion rate. A representative sample of the variability in bird exposure to contaminants in water can be gained by calculating WVs for the three raptorial species (eagle, osprey and kingfisher) which represent the range and extremes in body size. The additional data, since it is only for a small number of species, was not used because it could skew the distribution.

2. *Selection of Mammalian Species.* Two mammals were identified in the Great Lakes basin which are piscivorous and therefore likely to experience significant exposure to contaminants in aquatic food chains--the mink and river otter. The two species have different body sizes (adult otters are six-to-eight times larger than adult mink), and different food habits. Wildlife Values should be calculated for both mammal species. The mink has a larger food ingestion rate relative to body size than the otter. However, it is unlikely that mink have a diet that is comprised solely of fish from the higher trophic level as is predicted for the otter. Therefore, calculating WVs for both mammals may account for the variability in exposure that likely occurs in mammals.

B. *Derivation of Exposure Parameters and Body Weights for Species Identified for Protection*

1. *Bald Eagle (Haliaeetus leucocephalus).* Adult eagles weigh from 3.0 to 6.3 kg with an average adult weighing about 4.5 kg. (Bortolotti, 1984; Stalmaster and Gessaman, 1984; Palmer, 1988).

There have been several estimates of food ingestion rates of captive and free-ranging eagles. Stalmaster and Gessaman (1982) found that captive eagles consumed about 9.2 percent of their body mass in fish each day (approximately 414 g/d). However, by weighing fish carcasses before and after they were fed upon by free-ranging eagles, Stalmaster and Gessaman (1984) estimated that eagles wintering on the Nooksack River, WA, consumed about 490 g of fish each day. Using models produced by Gessaman and Stalmaster (1984), Craig et al. (1988) estimated that adult eagles wintering along the lower Connecticut River, CT, consume about 520 g of food per day. Therefore, it is assumed that a typical adult eagle consumes about 500 g of fish per day.

The water ingestion rate is derived from the allometric equation presented in appendix D to part 132 and is 0.16 L/d.

2. *Ospery (Pandion haliatus).* Adult ospreys weigh from 1.1 kg to 2.0 kg with a typical adult weighing approximately 1.5 kg (Newell et al., 1987; Palmer, 1988; Poole, 1989).

As reviewed by Palmer (1988), adult osprey consume 286 kcal/d. Assuming the metabolizable energy in fish is approximately 1 kcal/g (Palmer, 1988; Stalmaster and Gessaman, 1982), osprey require 286 g of fish per day. A review of data for European Ospreys, summarized by Palmer, 1988, suggested that food requirements were about 300 to 400 g/d. Nagy (1987) presents models to calculate field metabolic rates (FMRs) of birds and mammals based on body weights. The equation for calculating the FMR (in kcal/bird-d) of a non-passerine bird is as follows:

$$\log \text{FMR (kcal/bird-d)} = 0.0594 + 0.749 \log \text{Wt (g)}$$

where Wt is in g, wet weight.

The Nagy (1987) model predicts that osprey require 274 g of fish per day, assuming osprey weigh 1500 g and the metabolizable energy in fish is 1 kcal/g. Also, Newell et al.

(1987) estimated that osprey would require 300 g/d assuming birds consume 20% of their body weight each day. Therefore, it appears that a reasonable estimate of food ingestion rate for adult ospreys is approximately 300 g/d.

The water ingestion rate is derived from the allometric equation presented in appendix D to part 132 of this rule and is 0.077 L/d.

3. *Belted Kingfisher (Ceryle alcyon).* The average adult belted kingfisher weighs approximately 0.15 kg (Fry, 1980; Dunning, 1984).

Alexander (1977) reviewed the literature and estimated that adult Belted Kingfishers may consume up to 50 percent of their body weight in fish each day. This would equate to approximately 75 g/d. Since this was an estimate, the Nagy (1987) model was applied to calculate the FMR in kcal/d for a non-passerine bird:
log FMR (kcal/bird-d) = 0.0594 + 0.749 log Wt (g).

Assuming kingfishers weigh 150 g, and that the metabolizable energy in fish is 1 kcal/g (Stalmaster and Gessaman, 1982; Palmer, 1988), the Nagy model predicts that birds would require about 50 g/d. Therefore, a reasonable estimate of the kingfisher food ingestion rate would be about 75 g of fish per day.

The water ingestion rate is derived from the allometric equation presented in appendix D to part 132 and is 0.017 L/d.

4. *Mink (Mustela vison).* Adult male mink range from 0.9 to 1.6 kg, and females range from 0.6 to 1.1 kg (Linscombe et al., 1982). Therefore, it is assumed that an average adult mink has a body mass of 1.0 kg (see also Newell et al., 1987).

Estimates of food ingestion rates of captive mink range from about 12 percent to 16 percent of the adult body weight per day (Aulerich et al., 1973; Bleavins and Aulerich, 1981). Therefore, it will be assumed that a one kg adult mink consumes about 150 g of food per day (Aulerich et al., 1973; Newell et al., 1987).

The water ingestion rate is derived from the allometric equation presented in appendix D to part 132 and is 0.099 L/d.

5. *River Otter (Lutra canadensis).* Adult otters range from 5 kg to 15 kg, with a typical adult weighing 8 kg (Lauhachinda, 1978; Toweill and Tabor, 1982).

Toweill and Tabor (1982) reviewed two studies reporting food ingestion rates of captive otters. North American otters were reported to require about 700 to 900 g of prepared food each day, while European otters consumed 900 to 1000 g of live fish each day. Therefore, it is assumed that otter consume about 900 g of food per day.

The water ingestion rate is derived from the allometric equation presented in appendix D to part 132 and is 0.64 L/d.

C. *Derivation of Dietary Trophic Levels for Species Identified for Protection*

1. *Bald Eagle (Haliaeetus leucocephalus).* Bald Eagles are known to consume a variety of foods including fish, waterfowl, small mammals, and carrion. However, if available, fish are their principal food and large fish may make up 100 percent of their diet (Newell et al., 1987; Palmer, 1988; Kozie and Anderson, 1991). Therefore, it is assumed that eagles consume only trophic level 4 fish.

2. *Ospery (Pandion haliatus).* The diet of Osprey is almost 100 percent live fish, concentrating on fish weighing 150-300 g (Palmer, 1988 and Poole, 1989). Therefore, it is assumed that Osprey are consuming only trophic level 3 fish.

3. *Belted Kingfisher (Ceryle alcyon).* Kingfishers may eat a variety of foods including fish, amphibians, and insects. However, small fish are known to comprise roughly 90 percent of their total diet (Alexander, 1977). Therefore, it is assumed that kingfishers have a diet of only trophic level 3 fish.

4. *Mink (Mustela vison).* Mink are opportunistic carnivores (Linscombe et al., 1982); however, aquatic organisms sometimes comprise almost 100 percent of their diet with fish usually making up less than 50 percent of their total intake (Aulerich, 1973; Alexander, 1977; Linscombe et al., 1982; Newell et al., 1987). It is assumed that the diet of mink foraging in habitats comprising the shores of the Great Lakes and major tributaries is made up of trophic level 3 fish.

5. *River Otter (Lutra canadensis).* The bulk of the otter's diet is composed of fish (typically greater than 90 percent) with other aquatic organisms making up lesser portions (Toweill and Tabor, 1982; Newell et al., 1987). It is assumed that otters consume a diet composed of 50 percent trophic level 3 and 50 percent trophic level 4 fish.

TABLE I
SENSITIVITY OF SPECIES BASED ON LD_{50} DATA

Chemical	Species	D_{50} (mg/kg)	[95% Conf. Int.]
Aldrin	Fulvous whistling duck	29.2	[22.2-38.4]
	Mallard	520	[229-1,210]
	Bobwhite	6.59	[5.00-8.66]
	Pheasant	16.8	[14.1-20.0]
	Mule Deer	18.8-37.5	
Chlordane	Mallard	1,200	[954-1,510]
	California Quail	14.1	[9.14-21.7]
	Pheasant	24.0-72.0	
DDT	Bullfrog	72,000	
	Mallard	72,240	
	California Quail	595	[430-825]
	Japanese Quail	841	[607-1,170]
	Pheasant	1,334	[894-1,990]
	Sandhill Crane	71,200	
	Rock Dove	74,000	
Dieldrin	Canada Goose	< 141	
	Fulvous Whistling Duck	100-200	
	Mallard	381	
	California Quail	8.78	[6.47-11.9]
	Japanese Quail	69.7	[40.0-121]
	Pheasant	79.0	[21.6-289]
	Chukar	25.3	[15.2-42.2]
	Gray Partridge	8.84	[1.24-62.8]
	Rock Dove	26.6	[19.2-36.9]
	House Sparrow	47.6	[34.3-66.0]
	Mule Deer	75-150	
	Domestic Goat	100-200	
Endrin	Mallard	5.64	[2.71-11.7]
	Sharp Tailed Grouse	1.06	[0.552-2.04]
	California Quail	1.19	[0.857-1.65]
	Pheasant	1.78	[1.12-2.83]
	Rock Dove	2.0-5.0	
	Mule Deer	6.25-12.5	
	Domestic Goat	25.0-50.0	

TABLE I (continued)

Hexachlorobenzene	Mallard	71,414	
	Pheasant	118	[93.6-148]
Parathion	Fulvous Whistling Duck	0.125-0.250	
	Mallard	2.40	[1.67-4.01]
	Mallard	1.90	[1.37-2.64]
	Mallard	2.34	[1.88-2.92]
	Mallard	1.44[	[1.13-1.83]
	Mallard	1.44[	[1.16-1.80]
	Mallard Duckling (MM)	0.898	[0.770-1.05]
	Sharp Tailed Grouse	5.66	[3.46-9.24]
	California Quail	16.9	[12.2-23.5]
	Japanese Quail	5.95	[3.38-10.5]
	Pheasant	12.4	[10.1-15.2]
	Pheasant	>24.0	
	Chukar	24.0	[16.8-34.2]
	Gray Partridge	16.0	[4.00-64.0]
	Rock Dove	2.52	[1.82-3.50]
	House Sparrow	3.36	[2.43-4.66]
	Mule Deer	22.0-44.0	
	Domestic Goat	28.0-56.0	
PCB	Mallard Duck	2,098	
(Aroclor 1242)	Pheasant	2,078	
	Mink	1.0-8.6	
	Ferret	>20	
	Rat	0.8-11.0	
	Rabbit	8.7	
Temephos	Bullfrog	>2,000	
	Mallard	79.4	[38.5-163]
	California Quail	18.9	[15.0-23.8]
	Japanese Quail	84.1	[60.6-116]
	Pheasant	35.4	[25.5-49.0]
	Chukar	240[	[110-521]
	Rock Dove	50.1	[16.7-150]
	House Sparrow	35.4	[8.85-141]
2,3,7,8-TCDD	Guinea Pig	0.6-2 ug/kg	
	Rat	22-45 ug/kg	
	Rhesus Monkey	<70 ug/kg	

TABLE I (continued)

2,3,7,8-TCDD (cont.)	Dog	100-200 ug/kg	
	Mouse	114-284 ug/kg	
	Rabbit	115 ug/kg	
	Hamster	1,157-5,051 ug/kg	
Toxaphene	Fulvous Whistling Duck	99.0	[37.2-264]
	Mallard Duckling	30.8	[23.3-40.6]
	Mallard	70.7	[37.6-133]
	Sharp Tailed Grouse	19.9	[14.1-28.2]
	Bobwhite	85.5	[59.3-123]
	California Quail	23.7	[11.9-47.4]
	Pheasant	40.0	[20.0-80.0]
	Gray Partridge	23.7	[20.0-28.3]
	Sandhill Crane	100-316	
	Horned Lark	581	[425-794]
	Mule Deer	139-240	
	Domestic Goat	>160	

Adopted from Eisler, 1986a,b and Hudson, et al. 1984.

TABLE II
TOXICITY OF ORGANOMERCURY COMPOUNDS TO SELECTED MAMMALIAN SPECIES

Species	Dose	Effect
Dog	0.1-0.25 mg/kg	Stillbirths
Cat	0.25 mg/kg	Death
Pig	0.5 mg/kg	Stillbirths
Rhesus Monkey	0.5 mg/kg	Maternal Toxicity
Mink	1.0 mg/kg	Death
River Otter	>2.0 mg/kg	Death

Adopted from Eisler, 1987.

VI. References

Alexander, G. 1977. Food of vertebrate predators of trout waters in north central lower Michigan. Michigan Academician. 10:181-195.

Aulerich, R. J., R. K. Ringer and S. Iwamoto. 1973. Reproductive failure and mortality in mink fed on Great Lakes fish. J. Reprod. Fert. (Suppl.) 19:365-376.

Bleavins, M. R. and R. J. Aulerich. 1981. Feed consumption and food passage in mink (Mustela vison) and European ferrets (Mustela putorius furo). Lab. Animal Sci. 31:268-269.

Bortolotti, G. R. 1984. Sexual size dimorphism and age-related size variation in bald eagles. J. Wildl. Manage. 48:72-81.

Calder III, W. A., and E. J. Braun. 1983. Scaling of osmotic regulation in mammals and birds. American Journal of Physiology. 244:601-606.

Craig, R. J., E. S. Mitchell and J. E. Mitchell. 1988. Time and energy budgets of bald eagles wintering along the Connecticut River. J. Field Ornithol. 59:22-32.

Dourson, M. L. and J. F. Stara. 1983. Regulatory history and experimental support of uncertainty (safety) factors. Regulatory Toxicology and Pharmacology. 3:224.

Dunning, J. B. 1984. Body weights of 686 North American birds, Monograph #1, Western Bird Banding Association.

Eisler, R. 1986a. Dioxin hazards to fish, wildlife, and invertebrates: a synoptic review. U.S. Fish and Wildlife Service Biological Report. 85(1.8): 37pp.

Eisler, R. 1986b. Polychlorinated biphenyl hazards to fish, wildlife, and invertebrates: a synoptic review. U.S. Fish and Wildlife Service. Biological Report. 85(1.7): 72 pp.

Eisler, R. 1987. Mercury hazard to fish, wildlife and invertebrates: a synoptic review. U.S. Fish and Wildlife Service Biological Report. 85(1.10): 90pp.

Fry, C. 1980. The evolutionary biology of kingfishers (Alcedinidea). In: The Living Bird, 1979-1980. The Laboratory of Ornithology, Cornell Univ., Ithaca. pp. 113-160.

Great Lakes Water Quality Initiative. Appendix A: Uncertainty Factors. in Great Lakes Water Quality Criteria Initiative Technical Support Document for Human Health Criteria and Values. NTIS #PB93-15468. ERIC: 3940.

Hudson, R. H., R. K. Tucker, and M. A. Haegele. 1984. Handbook of toxicity of pesticides to wildlife, U.S. Fish and Wildlife Service, Resource Publication #153, 90 pp.

Kozie, K. D. and R. K. Anderson. 1991. Productivity, diet, and environmental contaminants in bald eagles nesting near the Wisconsin shoreline of Lake Superior. Arch. Environ. Contam. Toxicol. 20:41-48.

Lauhachinda, V. 1978. Life history of the river otter in Alabama with emphasis on food habits. Ph.D. dissertation. University of Alabama, Auburn, AL. 169 pp.

Linscombe, G., N. Kinler and R. Aulerich. 1982. Mink. In: J. Chapman and G. Feldhamer (eds.), Wild Mammals of North America: Biology, management and economics. John Hopkins Univ. Press, Baltimore. pp. 629-643.

Nagy, K. A. 1987. Field metabolic rate and food requirement scaling in mammals and birds. Ecological Monographs. 57(2):111-128.

National Institute for Occupational Safety and Health. Latest edition. Registry of Toxic Effects of Chemical Substances (available only on microfiche or as an electronic data base). Cincinnati, OH.

Newell, A. J., D. W. Johnson and L. K. Allen. 1987. Niagara River biota contamination project: Fish flesh criteria for piscivorous wildlife. New York State, Division of Environmental Contaminants. Technical Report 87-3.

Palmer, R. S. Editor. 1988. Handbook of North American birds: Volume 4. Yale University Press. 433 pp.

Poole, A. F. 1989. Ospreys: A natural and unnatural history. Cambridge, MA: Cambridge University Press.

Registry of Toxic Effects of Chemical Substances. Latest edition. National Institute for Occupational Safety and Health. Cincinnati, OH.

Stalmaster, M. V. and J. A. Gessaman. 1982. Food consumption and energy requirements of captive bald eagles. J. Wildl. Manage. 46:646-654.

Stalmaster, M. V. and J. A. Gessaman. 1984. Ecological energetics and foraging behavior of overwintering bald eagles. Ecol. Monogr. 54:407-428.

Stephan, C. E., D. I. Mount, D. J. Hansen, J. H. Gentile, G. A. Chapman, and W. A. Brungs. 1985. Guidelines for deriving numerical national water quality criteria for the protection of aquatic organisms and their uses. PB85-227049. National Technical Information Service. Springfield, VA.

Stokinger, H.E. 1972. Concepts of thresholds in standard setting. Arch. Environ. Health. 25:153-157.

Toweill, D. E. and J. E. Tabor. 1982. River otter. In: J. Chapman and G. Feldhammer (eds.), Wild Mammals of North America. John Hopkins Univ. Press, Baltimore. pp. 688-703.

U.S. EPA. 1980. Appendix C. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. pp. 79347-79357 in Water Quality Criteria Documents; Availability. 45 FR 79318-79378. Friday, November 28, 1980.

U.S. EPA. 1985. Section V.C. Evaluation of Health Effects and Determination of RMCLs pp. 46944-46950 in National Primary Drinking Water Regulations; Synthetic Organic Chemicals; Inorganic Chemicals and Microorganisms. 50 FR 46936-47022. Wednesday, November 13, 1985.

Weil, C.S., and D.D. McCollister, 1963. Relationship between short and long-term studies in designing an effective toxicity test. Agric. Food Chem. 11:486-491.

CHAPTER 4
Section VIII of Preamble to Great Lakes Water Quality Guidance: General Implementation Procedures

A. *Site-Specific Modifications to Criteria*

National guidance provided in the "Water Quality Standards Handbook" (1983) (the Handbook) indicates that States may modify generally applicable State criteria and set site-specific water quality criteria for the protection of aquatic life when: the local water quality parameters such as Ph, hardness, temperature, color, etc., alter the biological availability and/or toxicity of a pollutant; and/or the sensitivity of the local aquatic organisms (i.e., those that would live in the water absent human-induced pollution) differs significantly from the species actually tested in developing the criteria. This Handbook is available in the administrative record for this rulemaking. Copies are also available upon written request to the address listed in section XIII of this preamble. State-wide water quality criteria for aquatic life may be unnecessarily stringent or underprotective in a given water body if the physical and chemical characteristics of the water body ameliorate or enhance the biological availability and/or toxicity of a given chemical. In addition, species capable of living at a particular site, if there were no human-induced pollution, may be more or less sensitive than those species represented in the development of the State-wide criteria. Developing site-specific criteria for aquatic life is a way of taking unique conditions of a specific portion of a water body into account so that criteria adequately protect aquatic life from acute and chronic effects. Chapter 4 of the Handbook provides procedures for setting site-specific criteria for aquatic life which may be utilized as a basis for establishing water quality standards. Using those procedures, the resulting chronic or acute aquatic life criteria may be more or less stringent than the otherwise applicable State criteria.

There is presently no such specific guidance regarding site-specific modifications to human health water quality criteria. Additionally, there is presently no National guidance for deriving wildlife water quality criteria or site-specific modifications to wildlife criteria. However, present regulations do allow States to modify any criteria to reflect site-specific conditions provided that the modified criteria are protective of designated uses and based on sound scientific rationale (40 CFR 131.11). One of the issues that States might consider in developing site-specific modifications to human health criteria, for example, is local fish consumption rates. (See, generally, memorandum from LaJuana S. Wilcher to Regional Water Management Division Directors, dated January 5, 1990, which is available in the administrative record for this rulemaking.)

National water quality criteria are based upon data from, and assumptions specifically applicable to, the entire United States. The Great Lakes criteria/values proposed in the proposed Guidance differ from the National criteria in part because they were derived using data and assumptions relevant to the Great Lakes System. For example, certain aquatic life criteria/values have been lowered to protect commercially or recreationally important species within the Great Lakes System (e.g., steelhead rainbow trout). As another example, BAFs used in developing human health criteria/values for the Great Lakes System assume a fish

lipid content of five percent based on Great Lakes-specific data instead of the National average lipid content of three percent used for the derivation of National criteria. The purpose of using Great Lakes-specific data and assumptions in deriving criteria/values is to more accurately calculate ambient criteria levels that are protective of aquatic life, wildlife and humans within the Great Lakes System.

Even though the Great Lakes criteria/values already reflect Great Lakes-based modifications of the National criteria, there may be local areas within the Great Lakes System where conditions vary sufficiently from the assumptions underlying the methodologies for deriving Tier I criteria and Tier II values to merit the application of more narrowly applicable site-specific criteria. Procedure 1 of the proposed Implementation Procedures specifies the circumstances where a State may develop site-specific modifications to the Great Lakes aquatic life, human health and wildlife criteria as well as bioaccumulation factors. The proposed Implementation Procedures allow modifications to be made to acute or chronic aquatic life criteria/values in a manner consistent with Chapter 4 of the Handbook. This Handbook only covers site-specific water quality criteria for the protection of aquatic life. Consistent with that guidance, site-specific modifications to acute and chronic aquatic life criteria/values for the Great Lakes System under the proposed Guidance may result in more or less stringent aquatic life criteria/values than those calculated using the Great Lakes aquatic life methodology.

The Handbook only sets forth procedures for developing site-specific modifications to aquatic life criteria when such modifications are appropriate because either local water quality parameters alter the biological availability or toxicity of a pollutant, or the sensitivity of local aquatic organisms differ significantly from the species actually tested in developing criteria. Proposed implementation procedure 1, however, goes beyond the Handbook by also allowing the Great Lakes States and Tribes to develop site-specific modifications to chronic aquatic life criteria/values for the Great Lakes System to reflect local physical and hydrologic conditions. Specifically, the Great Lakes States and Tribes would be allowed to also develop site-specific modifications to chronic aquatic life criteria/values by showing that either hydrologic conditions or physical conditions related to the natural features of a water body, such as lack of a proper substrate, cover, flow, depth, pools, riffles, and the like, unrelated to ambient water quality, preclude aquatic life from remaining in the site for 96 hours or more. These site-specific conditions may also be taken into account in determining whether a discharge must comply with the chronic whole effluent toxicity requirements specified in proposed procedure 6.A.2. This provision is discussed in section VIII.F of the preamble.

As explained above in the section of this preamble on the Applicability of the Tier I and Tier II Criteria/Values, the Initiative Steering Committee intended that the States be given additional flexibility to modify chronic aquatic life criteria/values where physical and hydrologic conditions prevent aquatic life from remaining in a specific water body for 96 hours or more. The Steering Committee was concerned that the chronic aquatic life criteria/values would be unnecessarily stringent in protecting aquatic life in such locations because the chronic aquatic life methodologies assume that aquatic life are exposed to pollutants in a specific water body for at least 96 hours. Consistent with the Steering Committee deliberations, the proposed Guidance allows the States to develop site-specific

modifications to the chronic aquatic life criteria/values to reflect local physical and hydrologic conditions.

EPA believes that it is possible that there may be sites within the Great Lakes System where aquatic life will not remain at the site for more than 96 hours. Consequently, aquatic life can be protected from suffering chronic health effects at such sites by criteria/values less stringent than those developed under the proposed Great Lakes Guidance. Similarly, in sites where conditions preclude all but a few forms of aquatic life from living in a specific site, it is possible that the few forms of aquatic life living at the site may be protected by less stringent criteria/values. Because the physical and hydrologic condition justification for the exception to procedure 6.A.2 of appendix F is functionally equivalent to a justification for the removal of a designated use at 40 CFR 131.10(g)(2), (4) and (5), EPA expects this exception will typically be used for waters where a full aquatic life use is unattainable. States must ensure that the application of this exception does not impair the water quality of downstream waters.

The proposed Great Lakes Guidance does not provide for the same flexibility in terms of site-specific modifications to the wildlife and human health criteria/values or to bioaccumulation factors as is available for aquatic life criteria/values. The proposed Guidance restricts site-specific modifications to human health criteria/values, wildlife criteria/values, or bioaccumulation factors to only those which would increase the level of protection for humans and wildlife. The proposed Guidance, in allowing States to adopt less stringent criteria/values for aquatic life, but not for human health and wildlife, is consistent with the Steering Committee's proposal.

EPA believes that although less stringent site-specific criteria/value modifications can be justified for aquatic life, similar justifications may not exist with respect to less stringent wildlife and human health criteria/values or BAFs. For example, EPA does not believe that there are natural conditions in the Great Lakes System which preclude humans and wildlife from consuming fish and recreating in specific sites. Similarly, even if there may be local populations of humans and wildlife less exposed to toxicants than assumed in deriving the State-wide criteria, a less stringent site-specific modification may not be appropriate given the mobility of humans and wildlife into and out of these localized areas. Instead, EPA assumes that, due to their mobility, humans and wildlife feed from and recreate in all portions of the Great Lakes System. EPA believes that these assumptions are reasonable and appropriate in light of the goals and objectives of the Clean Water Act and the Great Lakes Water Quality Agreement. However, EPA requests comment on these assumptions.

The proposed Guidance allows Great Lakes States and Tribes to adopt site-specific modifications allowing for application of less stringent aquatic life criteria/values where local water quality parameters alter the biological availability and/or toxicity of a pollutant, but does not allow similar site-specific modifications for human health and wildlife criteria/values. This proposal is consistent with the proposal of the Steering Committee. In those cases where the biological availability and/or toxicity of a pollutant is decreased by local water quality conditions (e.g., pH, hardness, alkalinity, suspended solids), a less stringent criteria/value for aquatic life will adequately protect aquatic organisms. The

proposed Guidance reflects a more conservative approach with respect to humans and wildlife by allowing only more stringent site-specific modifications. EPA believes that this conservative approach is appropriate because of the mobility of humans and wildlife and their potential for exposure to these pollutants in different areas of the Great Lakes basin. In addition, there is not adequate information to quantify the total environmental uptake by humans and wildlife from different exposure routes. In light of these uncertainties, EPA proposes to use an approach that may result in human health and wildlife criteria/values which are somewhat overprotective in those cases where local water quality parameters decrease the biological availability and/or toxicity of a water body. This approach would err on the side of being overprotective rather than underprotective. EPA invites comment on whether the proposed approach for humans and wildlife is reasonable or whether less stringent site-specific modifications should be allowed under certain circumstances.

Specifically, EPA requests comment on whether the proposed Guidance should be modified to allow for development of less stringent site-specific modifications to all types of criteria/values (including human health and wildlife) and BAFs under any of the scenarios described below or under any other scenarios. Comment is requested on whether less stringent site-specific modifications should be allowed for human health and wildlife criteria/values where local water quality parameters decrease the biological availability and/or toxicity of a pollutant. EPA invites specific comment on adding to the human health and wildlife provisions the same text as appears in section A.1.a of procedure 1 of appendix F for aquatic life. EPA also invites comment on whether less stringent site-specific modifications should be allowed for bioaccumulative pollutants where local physical or hydrologic conditions do not allow aquatic life that may be consumed by humans or wildlife to be present in the water body long enough to reach steady-state bioaccumulation. EPA further invites comment on whether less stringent site-specific modifications should be allowed for bioaccumulation factors if reliable data shows that local bioaccumulation is lower than the system-wide value.

EPA also invites comment on whether it should allow in the final Great Lakes Guidance the development of less stringent site-specific modifications to the aquatic life criteria/values, as proposed today. Eliminating the option would enhance consistency of criteria in the Great Lakes System.

The proposed Guidance for wildlife criteria/values states that modifications may be made on a site-specific basis to provide an additional level of protection for a species determined to require greater protection, for any reason. The proposed Guidance specifies that such site-specific modifications may be accomplished through the incorporation of an additional uncertainty factor in the equation for the wildlife value. The text presented below provides additional guidance on the equation for the calculation of the wildlife value and is in keeping with the intent of the Initiative Committees. EPA requests comment on the use of the following alternate text to replace the text of procedure 1.A.2 of appendix F of the proposed Guidance.

Wildlife criteria or values may be modified on a site-specific basis to provide an additional level of protection for a species determined to require greater protection, for any

reason. This may be accomplished through the use of an additional uncertainty factor in the equation for the wildlife value as presented below:

$$WV = \frac{(NOAEL \times SSF \times ISF) \times Wt_A}{W_A + (F_A \times BAF)}$$

where:
The terms are defined in appendix D, section II of the proposed Guidance except that:

NOAEL = No Observed Adverse Effect Level in milligrams per kilogram body weight per day (mg/kg/d) determined for the taxonomic class to which the species requiring greater protection belongs.

Wt_A = Average weight in kilograms (kg) of the species requiring greater protection.

W_A = Average daily volume of water consumed by the species requiring greater protection, in liters per day.

F_A = Average daily amount of food consumed by the species requiring greater protection, in kilograms per day (kg/d).

BAF = Aquatic life bioaccumulation factor in liters per kilogram (L/kg) for the trophic level(s) at which the species requiring greater protection feeds. The BAF is chosen using guidelines for wildlife presented in appendix B, section V.B of the proposed Guidance.

ISF = Intraspecies sensitivity factor. An uncertainty factor to account for differences in toxicological sensitivity among members of the population of the species requiring greater protection (may be 0.1 or less).

The equation presented above for the calculation of a site-specific wildlife criterion for species requiring greater protection incorporates the use of the NOAEL determined for the taxonomic class to which the species requiring greater protection belongs. It is possible that the site-specific wildlife criterion may be based on a species from a different taxonomic class than the wildlife value used to derive the State-wide wildlife criterion. However, site-specific modifications may only be made when the site-specific wildlife criterion which results is more stringent than the State-wide wildlife criterion. In addition, the above equation for the wildlife value includes an intraspecies sensitivity factor (ISF) to provide additional protection to individuals in a population since the proposed wildlife methodology is derived to protect wildlife populations, not individuals within the population. Therefore, EPA highlights the use of site-specific modifications for the protection of individuals within a population for species requiring greater protection for public comment.

Section II.K of today's preamble states that EPA has initiated informal consultation with the FWS to ensure that the requirements in part 132 are not likely to cause jeopardy for

threatened or endangered species in the Great Lakes System. EPA invites comments on whether procedure 1 in appendix F to part 132 should contain specific text requiring modification on a site-specific basis of aquatic life and wildlife criteria/values to provide protection appropriate for threatened or endangered species.

Individual Great Lakes States may make a decision to modify any aquatic life, human health or wildlife criterion/value consistent with the requirements of this guidance. Site-specific modifications to criteria must be submitted to EPA for approval or disapproval in accordance with section 303(c) of the Clean Water Act and 40 CFR 131.20. In addition, the proposed Guidance would require that the State share information concerning site-specific modifications to Great Lakes criteria/values with other Great Lakes States. The State must notify the other Great Lakes States at the time a State proposes any site-specific modification and supply a justification for any less stringent site-specific modification. The State may send a notice to the appropriate State agency designees and/or notify the EPA Region V Clearinghouse to comply with this requirement. The purpose of the notice is to allow other Great Lakes States to comment on proposed site-specific modifications to criteria/values since a primary objective of today's proposed Guidance is to provide consistency among the Great Lakes States.

EPA invites comment on two possible alternatives to the proposed procedure 1 of appendix F. Under the first alternative, site-specific modifications as provided in procedure 1 would be available only for tributaries and connecting channels, not the open waters of the Great Lakes. This first alternative was developed by the Technical Work Group, which felt that the Great Lakes criteria provide appropriate protection for the open waters of the Great Lakes and that the proposed procedure 1 should only be used for rather small localized areas to provide needed additional protection of specific subpopulations within those areas and, for aquatic life, limited less stringent modifications. The reason for the Work Group's proposal was to ensure that a consistent set of requirements is applied throughout the open waters of the Great Lakes.

Although EPA recognizes that one of the goals expressed in the legislative history of the Great Lakes Critical Programs Act of 1990 is to promote consistency in Great Lakes water quality standards, EPA does not view this goal as overriding the authority specifically reserved to States and Tribes in section 510 of the Clean Water Act to enact more stringent requirements than necessary to implement Clean Water Act requirements. Furthermore, Article IV(a) of the Great Lakes Water Quality Agreement also clearly provides that the Agreement is not intended to preclude adoption of more stringent requirements. Consequently, EPA is not authorized under the Clean Water Act to prohibit States from adopting more stringent criteria/values for the open waters of the Great Lakes System. For these reasons, EPA is not proposing this first alternative in today's proposed Guidance. Nevertheless, EPA invites comment on this first alternative, and on EPA's interpretation of the Clean Water Act.

A second alternative would provide that the site-specific modification procedures in procedure 1 of appendix F would differ for pollutants that are not bioaccumulative chemicals of concern (BCCs). For non-BCCs, this alternative approach would allow site-specific

modifications for human health and wildlife criteria/values that are either more stringent or less stringent than the criteria/values derived using the proposed Guidance methodologies, depending on local considerations (e.g., water quality characteristics). This alternative approach would provide additional flexibility to the States in conducting site-specific modifications for non-BCCs.

This second alternative was not viewed favorably by the Great Lakes Steering Committee. EPA is proposing today that only those site-specific modifications which result in more stringent human health and wildlife criteria/values be allowed under the proposed Great Lakes Guidance, consistent with the Steering Committee proposal. However, EPA invites comment on this possible alternative approach.

D. Additivity

1. Introduction

Traditionally, EPA has developed numerical criteria on a single pollutant basis. However, many instances of contamination in surface waters involve mixtures of two or more pollutants. Such mixtures can interact in various ways which may affect the magnitude and nature of risks or effects on human health, aquatic life and wildlife. With respect to impacts on aquatic life, the interactive effects of discharged pollutants on organisms is ascertained through direct exposure of test organisms to a point source effluent in whole effluent toxicity (WET) tests as described in procedure 6 of appendix F of the proposed Guidance. The use of such tests to determine additive pollutant effects on aquatic organisms is a well-established component of existing Clean Water Act regulatory programs. EPA currently has no guidance regarding consideration of additive effects of pollutants on wildlife.

EPA has considered mechanisms for assessing effects resulting from human exposure to pollutant mixtures. On September 24, 1986, the EPA published "Guidelines for the Health Risk Assessment of Chemical Mixtures (51 FR 34014)," which is available in the administrative record for this rulemaking. These guidelines set forth principles and procedures for human health risk assessment of chemical mixtures. Although the calculation procedures in these guidelines differ for carcinogenic and non-carcinogenic effects, both procedures assume dose additivity in the absence of information on specific mixtures. Dose additivity is based on the assumption that the components in a mixture have the same mode of action and elicit the same types of effects. Because information on the interaction of pollutants and on the modes of action is so sparse, EPA recommends in the 1986 guidelines that risk assessments of mixtures be based on an assumption of additivity, as long as the components elicit similar effects. Dose additivity could result in errors in risk estimates if synergistic or antagonistic interactions occur (i.e., additivity assumptions could result in overestimates or underestimates of the actual risks). Thus, the assumption is not a "worst-case" assumption, but a reasonable assumption within the bounds of possibility when specific information on pollutant interaction is not available.

In an effort to address the concurrent human exposure to combinations of carcinogens, three Great Lakes States (Illinois, Minnesota and Wisconsin) assume in criteria development that the risk of a combination of carcinogens in a mixture is equal to the sum of risks associated with exposure to each individual pollutant in the mixture. These three States have adopted an acceptable cancer risk level of 10^{-5} for exposures to individual pollutants. In Minnesota and Wisconsin, the total risks associated with exposure to mixtures is not to exceed 10^{-5} while Illinois allows a total cancer risk level of 10^{-4} for exposure to mixtures.

The Great Lakes Water Quality Agreement addresses this issue in Annex 12, which states that "The Parties shall establish action levels to protect human health based on multimedia exposure and the interactive effect of toxic substances." In addition, Annex 12 of the Agreement recommends that research efforts on the interactive effects of residues of toxic substances on aquatic life, wildlife, and human health be intensified. A supplement to Annex 1 of the Agreement also provides for the development of specific objectives addressing synergistic and additive effects of pollutants.

2. Approaches Considered

The Committees of the Initiative sought to develop a consistent approach to additivity within the Great Lakes States. Their deliberations resulted in proposals for the use of additivity for the protection of aquatic life, wildlife and human health. EPA evaluated the Committees' proposals as well as other alternatives; both the Committees' proposals and alternatives are discussed below.

EPA's traditional approach is to address each pollutant on an individual basis in the derivation of criteria and values. However, EPA has provided guidance in the past on how to take additivity into account for the protection of aquatic life and human health. With respect to the proposed Great Lakes Water Quality Guidance, EPA invites comment on the additivity-related issues discussed below and on whether a specific procedure, should be either required or set fourth as a guidance in the final rule.

a. *Aquatic Life.* As proposed by the Committees of the Initiative, the proposed Guidance accounts for additive effects on aquatic life through establishment of whole-effluent toxicity (WET) limitations. WET requirements are proposed under procedure 6 of appendix F of the proposed Guidance.

b. *Human Health - Carcinogens.* For carcinogenic effects on human health, the 1986 guidelines for mixture recommend that in the absence of contrary information it be assumed that the total cancer risk posed by a mixture of chemicals is the sum of risks posed by exposures to individual chemicals. Since information on the interaction of pollutants in a mixture is generally rather limited, the 1986 guidelines recommend the use of the additivity assumption under most circumstances. However, the guidelines indicate a preference for relying on actual data on the interaction of pollutants in mixtures whenever adequate data are available. Therefore, EPA recommends that in those cases where it can be demonstrated that the carcinogenic risks of a mixture are not additive, the additivity assumption should not be used.

In its December 16, 1992, report, "Evaluation of the Guidance for the Great Lakes Water Quality Initiative," the EPA's Science Advisory Board (SAB) stated that additivity should not be used as a default, but rather multiple carcinogens should be considered on a case-by-case basis. This is because additivity assumes a common mechanism of action and carcinogens are known to act by a wide variety of mechanisms and to target different organs. The SAB report goes on to say that for compounds that act at the same receptor (such as dioxin, furans and PCBs) an assumption of additivity might well be defensible. EPA invites comment on whether the assumption of additivity for carcinogens should be limited to those situations when adequate data are available on the mechanisms of action.

EPA invites comment on whether the narrative criteria of the States and Tribes providing that waters be free from substances that injure or are toxic to humans, animals or plants should be interpreted to account for the additive effects of chemicals. The purpose of this approach would be to prevent the total risk associated with carcinogens in ambient waters from exceeding a non-appreciable level. As discussed elsewhere in the proposed Guidance, EPA is proposing criteria/values for single pollutants based on a 10^{-5} cancer risk level. EPA believes that the use of a risk level on total risk associated with chemical mixtures would enhance protection of human health, and consistency in addressing additive impacts throughout the Great Lakes System. It would also be consistent with the provisions of the Great Lakes Water Quality Agreement calling for consideration of the interactive effects of toxic substances. Insofar as it may require greater reductions of pollutant discharges than would be required through implementation of individual chemical criteria alone, it would also further the "virtual elimination" goal of the Agreement. EPA requests comments on the possible use of 10^{-5} as a cap on the cancer risk associated with mixtures and on alternative risk levels (e.g., 10^{-4}) that may be considered. A specific option that would require interpretation of narrative criteria to establish a 10^{-5} cap on cancer risk associated with chemical mixtures is set forth in section 3 of this preamble discussion.

EPA also requests comments on whether the additivity concept should be applied only to a limited (i.e., finite) number of the carcinogens in ambient waters that individually pose the greatest cancer risk to exposed populations rather than to all detected carcinogens. For example, the narrative criteria could be interpreted such that the cumulative cancer risk posed by the presence of five (or some other number of) carcinogens in any given waterbody or segment would not exceed 10^{-5}. Such a modification would reflect the fact, recognized in EPA's 1986 Guidelines for the Health Risk Assessment of Chemical Mixtures, that as the number of pollutants covered by the additivity assumption increases, the uncertainty associated with the resulting risk assessment is also likely to increase. This approach could also greatly ease the administrative burden of preparing total maximum daily loads (TMDLs) and water quality-based effluent limits (WQBELs) based on the additivity assumption, since it would provide a cut-off to what otherwise might be an extended inquiry and would relieve regulatory authorities of the burden of identifying risks and sources associated with carcinogens that pose a relatively insignificant risk to human health. Finally, EPA requests comments on whether a separate water quality criterion (WQC) should be established for carcinogenicity (e.g., total cancer risk for ambient waters not to exceed 10^{-4}, 10^{-5}, or some other cancer risk level) rather than the approach discussed above for implementing narrative criteria.

These alternatives differ considerably from the proposal of the Committees of the Initiative with respect to considering additivity for carcinogens. The Committees proposed that the additivity assumption be applied only with respect to facilities otherwise requiring WQBELs for individual carcinogens, and only as to those carcinogens requiring WQBELs. Thus, the Committees did not propose application of the additivity assumption in setting or interpreting ambient water quality criteria. Rather, their proposed approach would have resulted in further limitations beyond WQBEL levels so that the carcinogens covered by WQBELs from a given facility would not, after mixing with receiving waters, represent a total cancer risk greater than 10^{-5}. Thus, the Committees' approach did not address carcinogens for which WQBELs were not needed. In addition, because not all sources discharging a pollutant for which WQBELs are needed necessarily need WQBELs in order to provide for attainment of water quality standards, not all sources discharging a given carcinogen would have the additivity assumption applied to their discharges.

Although EPA agrees that the approach proposed by the Committees of the Initiative offers certain administrative advantages as compared with other alternatives, EPA is concerned that the Committees' approach could be inequitable in its application. The full text of the proposal of the Committees is reproduced below under section 4 of this preamble. EPA invites comment on the possible use of that approach in the final rule to account for the additive effects of carcinogens in the Great Lakes.

c. *Human Health - Non-carcinogens.* The 1986 EPA guidelines on chemical mixtures acknowledge that additivity of effects for non-carcinogens is most appropriate when pollutants in a mixture elicit the same type of effect by the same mechanism of action. However, because information on the mechanism of action is rather limited for many pollutants, the 1986 EPA guidelines on chemical mixtures recommend that when two or more compounds produce adverse effects on the same organ system (i.e., target organ) the effects should be considered additive. The 1986 guidelines additionally state that additivity for dissimilar effects does not have strong scientific support. Thus, the underlying assumption in the 1986 guidelines is that the components of a mixture which produces adverse effects on the same target organ are additive. This approach could overestimate or underestimate the actual risks due to possible antagonistic or synergistic interactions among components in a mixture.

The 1986 guidelines recommend the use of a hazard index (HI) approach for non-carcinogenic toxic agents. The hazard index indicates if there is a concern with a mixture by providing a rough measure of likely toxicity. However, it does not define dose-response relationships (i.e., its numerical value is not a direct estimate of risk).

EPA solicits comment on the HI approach for applying additivity to non-carcinogenic effects, as described in the 1986 guidelines. This approach assumes that multiple, simultaneous exposures to a chemical could result in an adverse health effect and that the magnitude of the effect is proportional to the sum of the ratios of the actual exposures to "acceptable" exposures. When the HI exceeds unity (i.e., 1) a potential for adverse health effects exists. While any single chemical with an exposure level greater than the toxicity

value (i.e., threshold or Reference dose (RfD)) will cause the HI to exceed unity, for mixtures, the HI can also exceed unity even if no single chemical exceeds its RfD.

The hazard index approach assumes dose addition for those compounds that induce the same target organ response and, therefore, a separate hazard index should be developed for each end point. Dose addition (additivity) for dissimilar effects does not have strong scientific support. For estimating the "HI" of a mixture of non-carcinogens based on additivity, the following equation may be applied:

$$HI = \frac{E_1}{RfD_1} + \frac{E_2}{RfD_2} + \ldots + \frac{E_n}{RfD_n}$$

Where, for i = 1 through n:

E_i = exposure level of the chemical in the mixture.

RfD_i = The Reference dose for that chemical.

Since publication of the 1986 guidelines, EPA has published a "Technical Support Document on Risk Assessment of Chemical Mixtures (November 1988)", which discusses the hazard index approach as well as an alternative "toxicity equivalency factor" (TEF) approach. This document is available in the administrative record for this rulemaking. The "toxicity equivalency factor" approach was not discussed in the 1986 guidelines but has since been recommended by EPA for risk assessment of certain chemical classes. One advantage of the TEF approach is that it allows the use of data to assess and quantify the toxicity of mixtures that are not used to quantify the risk from exposure to single chemicals (i.e., acute data, data from atypical routes of environmental exposure and *in vitro* data). The 1988 Technical Support Document states that the TEF approach should be applied only to compounds that have the same mode of action or act independently. The approach described in the 1988 Technical Support Document is more restrictive than the 1986 guidelines in the use of the additivity assumption for non-carcinogens but it is consistent with the proposal for the use of TEFs made by the Committees of the Initiative. EPA also believes that the approach in the 1988 Technical Support Document is not inconsistent with the original 1986 guidelines which state: "No single approach can be recommended to risk assessments for multiple chemical exposures."

The preferred approach presented in the 1986 guidelines for conducting risk assessment of mixtures is to use *in vivo* toxicity data on the mixture itself based on the route of exposure and duration period of concern. However, this approach is not practical in most cases because adequate toxicity data are available on very few complex mixtures. The "toxicity equivalency factor" approach involves estimating the potency of less well-studied components in a mixture relative to the potency of better studied components, using data from comparable types of *in vitro* and short-term *in vivo* assays. So far, this approach has been used only to estimate the toxicity of mixtures of chlorinated dioxins and dibenzofurans by using extensive data on the *in vitro* activity of these compounds. Today's proposal requests comments on whether EPA should consider the "toxicity equivalency factor" approach for these chemical classes and for any other mixtures for which TEFs may

reasonably be calculated in the future as this area of research progresses and EPA is able to develop additional TEFs.

EPA specifically solicits comment on two possible approaches to addressing additivity for non-carcinogens, set forth in sections 3 and 4 of this preamble. Both would require that mixture of CDDs and CDFs be considered additive, in accordance with specific TEFs described in more detail in section 2.d. of the preamble. In addition, the option described in section 3 would require use of bioaccumulation equivalency factors (BEFs) (discussed in detail below) to account for differences in bioaccumulation potential of different CDDs and CDFs. The alternative set forth in section 3 would require generally that noncancer effects be considered additive for those pollutants for which available scientific information supports a reasonable assumption that the pollutants produce the same adverse effects through the same mode of action, and for which TEFs and BEFs may reasonably be calculated. Thus, this option would establish a general requirement for States and Tribes to develop specific additivity protocols for classes of pollutants when sufficiently supported by scientific information.

The second option which EPA specifically solicits comment on is set forth in section 4. It would require application of additivity assumptions only for those pollutants for which TEFs are set forth as part of the Great Lakes Guidance. Pollutants covered initially would include CDDs and CDFs, but more pollutants could be addressed through future revisions to the rule. This option would best promote consistency among the Great Lakes States and Tribes, but may involve more lag time between availability of scientific support for application of additivity and use in water quality management than would the option set forth in section 3.

d. *TEFs and BEFs for Chlorinated Dibenzo-p-dioxins (CDDs) and Chlorinated Dibenzofurans (CDFs).* Chlorinated dibenzo-p-dioxins and dibenzofurans (CDDs/CDFs) constitute a family of 210 structurally related chemical compounds. During the late 1970s and early 1980s, EPA encountered a number of incidents of environmental pollution in which the toxic potential of CDDs and CDFs figured prominently. Initially, concern was focused solely on 2,3,7,8-TCDD, which was produced as a low level by-product during the manufacture of certain herbicides.

During the past 20 years, many studies have been conducted to elucidate the toxic effects of 2,3,7,8-TCDD. The data obtained from these studies are summarized in a number of reviews (U.S. EPA, 1984; U.S. EPA, 1985; U.S. EPA, 1988; WHO, 1977; NRCC, 1981), which are available in the administrative record for this rulemaking. EPA is currently engaged in a major effort to generate more data on dioxin toxicity, and to update its analysis of existing data. While research efforts to date have not answered all of the questions, the data do show that 2,3,7,8-TCDD can produce a variety of toxic effects, including cancer and reproductive effects in laboratory animals at very low doses.

Data on the toxicity of other CDDs and for CDFs is considerably more limited. These data are summarized in two EPA documents entitled "Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins

and -Dibenzofurans (CDDs and CDFs)", (October 1986), and "1989 Update to the Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-Dioxins and-Dibenzofurans (CDDs and CDFs)", (March 1989) (the "1989 TEF Update"), which are available in the administrative record for this rulemaking. While data available from long-term in vivo studies are limited for the majority of CDDs and CDFs, a much larger body of data is available on short-term in vivo studies and a variety of in vitro studies. These experiments cover a wide variety of end points; e.g., developmental toxicity, cell transformation, and enzyme induction (aryl hydrocarbon hydroxylase [AHH]). While the doses necessary to elicit the toxic response differ in each case, the relative potency of the different compounds compared to 2,3,7,8-TCDD is generally consistent from one end point to another.

This information, developed by researchers in several laboratories around the world, reveals a strong structure-activity relationship between the chemical structure of a particular CDD or CDF congener and its ability to elicit a biological or toxic response in various *in vivo* and *in vitro* test systems. (Bandiera et al., 1984; Olson et al., 1989; U.S. EPA 1989; NATO/CCMS 1988a,b). Research has also revealed a mechanistic basis for these observations. That is, a necessary (but not sufficient) condition for expression of much of the toxicity of a given CDD or CDF congener is its ability to bind with a particular protein receptor located in the cytoplasm of the cell. This congener receptor complex then migrates to the nucleus of the cell, where it initiates reaction leading to expression of toxicity (Poland and Knutson, 1982).

Based on this type of information, scientists suggested the development of numerical factors ("toxic equivalency factors" or "TEFs") that could be used to equate the toxicity posed by various CDDs and CDFs to 2,3,7,8-TCDD for purposes of conducting risk assessments including mixtures of the chemicals. EPA developed an interim procedure that was reviewed and approved by EPA's Science Advisory Board, and published as a monograph of EPA's Risk Assessment Forum in 1987. The procedure was modified in certain respects in the 1989 TEF Update, and has been adopted for international use by the North Atlantic Treaty Organization.

EPA solicits comment on whether EPA should require use of the specified TEF-based approach to equate mixtures of CDDs and CDFs to a concentration of 2,3,7,8-TCDD for purposes of implementing the human health and wildlife criteria for 2,3,7,8-TCDD. Specific options are set forth in sections 3 and 4 of this preamble. The TEFs are the same as those set forth in EPA's 1989 TEF Update, and that Update provides the technical basis for the proposal. EPA also invites comment on whether other TEFs should be used rather than those listed in the 1989 TEF Update.

The CDD/CDF TEFs address the toxicity of various chemicals as compared to 2,3,7,8-TCDD, but do not address differences in bioaccumulation potential between the chemicals. Because the criteria for 2,3,7,8-TCDD are largely driven by the relatively large bioaccumulation factor for the chemical, and because available information suggests that other CDDs and CDFs have different bioaccumulation factors, EPA believes that it may be appropriate to use factors accounting for the different BAFs in converting concentrations of

CDDs and CDFs to equivalent concentrations of 2,3,7,8-TCDD. The option set forth in section 3 incorporates this approach. The technical rationale for the particular "bioaccumulation equivalency factors" (BEFs) selected is provided in a "Draft Technical Support Document for Bioaccumulation Equivalency Factors," which is available in the administrative record for this rulemaking.

The Committees of the Initiative did not propose use of bioaccumulation equivalency factors; their proposal would have assumed that BAFs for all CDDs and CDFs are identical to that calculated for 2,3,7,8-TCDD. Because available information on BAFs for other CDDs and CDFs suggests that BAFs for those chemicals are generally smaller than for 2,3,7,8-TCDD, the Committee's proposal would be a conservative, as well as a simplifying, approach. EPA solicits comment on this option, set forth in section 4 of this preamble.

e. *Wildlife.* As stated earlier, EPA has no present policy on the use of additivity for wildlife effects. EPA solicits comment, however, on whether additivity with respect to wildlife effects should be treated in a manner consistent with the options described above for noncancer human health effects and for mixtures of CDDs and CDFs. EPA believes that an argument can be made that the TEFs for CDDs and CDFs developed for use in human health risk assessments should generally be applicable to wildlife, since the TEFs are based largely on animal studies. Using the TEF approach, the total allowed exposure level for mixtures of these congeners would not exceed the level established by the wildlife criteria for 2,3,7,8-TCDD, based on 2,3,7,8-TCDD equivalents. Two specific alternatives regarding application of additivity principles to wildlife effects are set forth in sections 3 and 4 of this preamble. EPA requests comment on these options, and on possible alternatives to them.

In developing this proposed Guidance, the use of TEFs for polychlorinated biphenyls (PCB) congeners for wildlife was considered. In December 1990, EPA's Risk Assessment Forum held a workshop to specifically address the use of TEFs for PCBs (Risk Assessment Forum, Workshop Report on Toxicity Equivalency Factors for Polychlorinated Biphenyl Congeners, June 1991, EPA/625/3-91-020). This workshop concluded that the application of TEFs to PCBs is not as straightforward as it is in the case of CDDs and CDFs, but that TEFs for dioxin-like PCB congeners are feasible and may be considered additive with those for CDDs and CDFs. Further, the workshop concluded that current dioxin-like TEFs appear to be useful in assessing traditional measures of wildlife toxicity. The workshop, however, recommended that a TEF scheme for PCBs should be seen as an interim procedure and promising bioassay approaches should also be vigorously pursued.

On March 19-20, 1992, a Dioxin Ecotox Subcommittee of the Ecological Processes and Effects Committee of the Science Advisory Board met to review EPA's research proposals to support the development of an ambient aquatic life water quality criterion for 2,3,7,8-TCDD. At that meeting, the Subcommittee addressed the general issue of research needed to support the use of TEFs for aquatic life and wildlife. In their final report dated August 1992, the Committee stated that the TEF approach appears promising for aquatic life and wildlife but more studies are needed to show phylogenetic variability. The Committee concluded that at the present time there are insufficient data available to judge the reliability and the accuracy of the TEF approach.

A recent study of the potencies of CDDs, CDFs and PCBs relative to 2,3,7,8-TCDD for producing early life stage mortality in rainbow trout calculated TEFs for each of these classes of chemicals (Walker and Peterson, 1991). The TEFs calculated in this study for CDDs and CDFs were similar to those proposed by Safe (1990). However, the TEFs for the PCB congeners were 14 to 80 times less than those proposed in Safe (1990). The results of the Walker and Peterson study illustrate the significant uncertainties in applying TEFs across species and endpoints for PCB congeners. Further, another recent study concluded that the TEFs proposed in Safe (1990) for the "dioxin-like" PCBs overestimate the potency of these compounds by a factor of 10-1,000 (DeVito et al., 1992).

EPA solicits comments on whether TEFs for PCBs should be included together with those for CDDs and CDFs in the use of the additivity concept for wildlife effects. Table VIII.D-1 presents TEFs for PCB congeners from Safe, 1990. EPA specifically requests comment on the inclusion of these TEFs for wildlife in the Great Lakes Guidance.

Table VIII.D-1
Toxic Equivalency Factor Values for PCBs

	IUPAC #	TEF Value
(a) Coplanar PCBs		
3,3',4,4',5-PeCB	126	0.1
3,3',4,4',5,5'-HxCB	169	0.05
3,3',4,4'-TCB	77	0.01
(b)Monoortho Coplanar PCBs		
2,3,3',4,4'-PeCB	105	0.001
2,3,4,4'-PeCB	114	0.001
2',3,4,4',5-PeCB	123	0.001
2,3',4,4',5-PeCB	118	0.001
2,3,3',4,4',5-HxCB	156	0.001
2,3,3',4,4',5-HxCB	157	0.001
2,3',4,4',5,5'-HxCB	167	0.001
2,3,3',4,4',5,5'-HpCB	189	0.001

3. Request for Comment on Approach Considered for Implementing the States' Narrative Criteria

The text presented below represents one approach that would specify that the narrative criteria be interpreted to account for the additive effects of chemicals. EPA requests comments on whether the language below should be added to the Implementation Procedures of the final Guidance.

The following procedures establish the manner in which the additive effects of chemical mixtures shall be treated when interpreting the narrative criteria of the States and Tribes requiring that all waters be free from substances that injure or are toxic or produce adverse physiological responses in humans, animals or plants.

A. *Aquatic Life Effects.* Whole-effluent toxicity requirements established under procedure 6 of appendix F of part 132 shall be used to account for additive effects to aquatic organisms.

B. *Wildlife Effects.* The effects of individual pollutants shall be considered additive for chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans, and for other pollutants for which available scientific information supports a reasonable assumption that the pollutants produce the same adverse effects through the same mechanism of action, and for which toxic equivalency factors and bioaccumulation equivalency factors may reasonably be calculated. For chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans, additivity shall be accounted for in accordance with section E. For other pollutants, toxic equivalency factors and bioaccumulation equivalency factors shall be developed and thereafter applied in a manner similar to that described in section E based either on a relationship to 2,3,7,8-TCDD or to some other chemical, as appropriate.

C. *Human Health - Non-cancer Effects.* The effects of individual pollutants shall be considered additive for chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans, and for other pollutants for which available scientific information supports a reasonable assumption that the pollutants produce the same adverse effects through the same mechanism of action, and for which toxic equivalency factors and bioaccumulation equivalency factors may reasonably be calculated. For chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans, additivity shall be accounted for in accordance with section E. For other pollutants, toxic equivalency factors and bioaccumulation equivalency factors shall be developed and thereafter applied in a manner similar to that described in section E based either on a relationship to 2,3,7,8-TCDD or to some other chemical, as appropriate.

D. *Human Health - Cancer Effects.* The incremental cancer risk of each carcinogen shall be considered to be additive and the total cancer risk shall not exceed 10^{-5}. However, the State or Tribe may determine, based on information submitted by a permittee or otherwise available to the State or Tribe, that the carcinogenic risk for a given mixture is not additive.

E. *Toxicity Equivalency Factors.* The following TEFs shall be used when implementing human health or wildlife criteria for 2,3,7,8-TCDD. The concentration of each CDD and CDF in an effluent shall be converted to a 2,3,7,8-TCDD equivalent concentration by multiplying the concentration of the CDD or CDF by the TEF shown in Table VIII.D.2 below, and multiplying that product by the bioaccumulation equivalency factor in Table VIII.D.3 below. All resultant concentrations shall be added to produce an equivalent 2,3,7,8-TCDD concentration. The equivalent 2,3,7,8-TCDD concentration shall be used to establish TMDLs (including wasteload and load allocations) pursuant to procedure 3. This equivalent 2,3,7,8-TCDD concentration shall also be used as the concentration of 2,3,7,8-TCDD for purposes of assessing the total cancer risk of carcinogens pursuant to section 4.D.

Table VIII.D-2
Toxic Equivalency Factor Values for CDDs and CDFs

Congener	TEF
2,3,7,8-TCDD	1.0
1,2,3,7,8-PeCDD	0.5
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0001
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.05
2,3,4,7,8-PeCDF	0.5
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-HpCDF	0.01
OCDF	0.001

Table VIII.D-3
Bioaccumulation Equivalency Factors (BEFs)

Congener	TCDD BEF
2,3,7,8-TCDD	1.0
1,2,3,7,8-PeCD	≤0.8
1,2,3,4,7,8-HxCDD	<0.3
1,2,3,6,7,8-HxCDD	≤0.2
1,2,3,7,8,9-HxCDD	≤0.2
1,2,3,4,6,7,8-HpCDD	≤0.03
OCDD	≤0.02
2,3,7,8-TCDF	1.2
1,2,3,7,8-PeCDF	0.3
2,3,4,7,8-PeCDF	1.8
1,2,3,4,7,8-HxCDF	≤0.3
1,2,3,6,7,8-HxCDF	≤0.3
2,3,4,6,7,8-HxCDF	≤0.5
1,2,3,7,8,9-HxCDF	≤0.5
1,2,3,4,6,7,8-HpCDF	≤0.003
1,2,3,4,7,8,9-HpCDF	≤0.1
OCDF	≤0.005

Notes:
1. $^{x}BEF \times {}^{TCDD}BAF = {}^{x}BAF$
2. ^{x}BAF = lipid-based bioaccumulation factor for total congener concentration in water.

The TEFs provided in Table VIII.D-2 are the same as those set forth in EPA's 1989 TEF Update. However, this Table has been reorganized to make it consistent with Table VIII.D-3 above (which lists the BEFs for specific congeners and does not include CDDs and CDFs with TEF values of zero).

4. Request for Comment on Alternative Approach

The text presented below represents the proposal for additivity of the Committees of the Initiative, modified by EPA to delete the application of TEFs for PCBs to wildlife. EPA requests comments on whether the language below should be added to the implementation procedures of the final Guidance.

The toxic action of some pollutants in mixtures is additive in their effects on organisms. The following procedure establishes the manner in which the additive effects of chemical mixtures shall be treated. This provision shall be applied to point source discharges.

A. *Aquatic Life Effects.* Whole-effluent toxicity requirements established under procedure 6 of appendix F of part 132 shall be used to account for additive effects to aquatic organisms.

B. *Wildlife Effects.* When establishing wasteload allocations (WLAs) for the protection of wildlife, the effects of individual pollutants shall be considered additive for the pollutants for which toxicity equivalency factors (TEFs), as provided in section E of this procedure, are available.

C. *Human Health - Non-cancer Effects.* When establishing wasteload allocations (WLAs) for the protection of human health for non-carcinogens, the effects of individual pollutants shall be considered additive for the pollutants for which toxicity equivalency factors, as provided in part F of this procedure, are available.

D. *Human Health - Cancer Effects.* When establishing wasteload allocations (WLAs) for the protection of human health for carcinogens, the following shall apply:

(1) Except as noted in (2) below, in cases where an effluent contains detected levels of more than one pollutant for which a Tier I criterion or Tier II value exists and for which a water quality-based limitation is required under Procedure 5, the incremental risk of each carcinogen shall be considered to be additive and the total cancer risk shall not exceed 10^{-5}. The wasteload allocation (WLA) for each carcinogen shall be established in a permit to protect against potential additive effects associated with simultaneous, multiple-chemical human exposure such that the following condition is met:

$$\frac{C_1}{WLA_1} + \frac{C_2}{WLA_2} + \ldots + \frac{C_n}{WLA_n} \leq 1$$

Where:
$C_1 \ldots n$ = the monthly average effluent limitation expressed as concentration of each separate carcinogen in the effluent.

$WLA_1 \ldots n$ = the wasteload allocation concentration calculated for each substance at each permitted facility independent of other carcinogens that may be present in the receiving waters based on the human cancer criterion for each respective carcinogen.

(2) If the permitting authority determines, based on information submitted by the permittee, that the carcinogenic risk for a mixture is not additive, the permitting authority may establish wasteload based on that information.

E. *TEFs applied to Wildlife Effects.* The permitting authority shall use toxicity equivalency factors when establishing wasteload allocations for the protection of wildlife for chlorinated dibenzodioxins (CDDs) and chlorinated dibenzofurans (CDFs). The concentration of each CDD and CDF in an effluent shall be converted to a 2,3,7,8-TCDD equivalent concentration by multiplying the concentration of the CDD or CDF by the TEF shown in Table VIII.D.4. All resultant concentrations shall be added to produce an

equivalent 2,3,7,8-TCDD concentration. The equivalent 2,3,7,8-TCDD concentration shall be used to establish a wasteload allocation consistent with procedure 3. Whenever one or more CDDs and/or CDFs are present in an effluent, the permitting authority shall establish a wasteload allocation for 2,3,7,8-TCDD. The permittee shall be considered in compliance only if the sum of the effluent concentration times the TEF for all the CDDs and CDFs are less or equal to the wasteload allocation for 2,3,7,8-TCDD. If there are carcinogens other than CDDs and CDFs in the effluent, the sum calculated for the equivalent 2,3,7,8-TCDD concentration must be used in the formula in D(1) above for C_k, where k represents 2,3,7,8-TCDD.

F. *TEFs applied to Human Health - Cancer Effects.* The permitting authority shall use toxicity equivalency factors when establishing wasteload allocations for human health-based criteria for CDDs and CDFs. The concentration of each CDD and CDF in an effluent shall be converted to a 2,3,7,8-TCDD equivalent concentration by multiplying the concentration of the CDD or CDF by the TEF shown in Table VIII.D.4. All resultant concentrations shall be added to produce an equivalent 2,3,7,8-TCDD concentration. The equivalent 2,3,7,8-TCDD concentration shall be used to establish a wasteload allocation consistent with procedure 3. Whenever one or more CDDs and/or CDFs are present in an effluent, the permitting authority shall establish a wasteload allocation for 2,3,7,8-TCDD. The permittee shall be considered in compliance only if the sum of the effluent concentration times the TEF for all the CDDs and CDFs are less or equal to the wasteload allocation for 2,3,7,8-TCDD. If there are carcinogens other than CDDs and CDFs in the effluent, the sum calculated for the equivalent 2,3,7,8-TCDD concentration must be used in the formula in D(1) above for C_k, where k represents 2,3,7,8-TCDD.

Table VIII.D-4
Toxic Equivalency Factor Values for CDDs and CDFs

Compound	Tef Value
1. Dioxins	
Mono-, Di-, and TriCDDs	0
2,3,7,8-TCDD	1
other TCDDs	0
2,3,7,8,-PeCDD	0.5
other PeCDDs	0.0
2,3,7,8-HxCDDs	0.1
other HxCDDs	0.0
2,3,7,8-HpCDD	0.01
other HpCDDs	0.0
OCDD	0.001
2. Furans	
Mono-, Di-, and TriCFDs	0
2,3,7,8-TCDF	0.1
other TCDFs	0.0
2,3,4,7,8-PeCDF	0.5
1,2,3,7,8-PeCDF	0.05
other PeCDFs	0.0
2,3,7,8-HxCDFs	0.1
other HxCDFs	0.0
2,3,7,8-HpCDFs	0.01
other HpCDFs	0.0
OCDF	0.001"

5. Request for Comments

EPA requests comment on each element of the text for the two approaches to additivity presented in sections 3 and 4 above, including all subjects and issues raised in the preamble discussion whether or not specific regulatory text has been provided in the proposed Guidance, and any suggested alternative requirements or combinations of requirements to address these elements and issues in the final rule. EPA may promulgate final rules based on any of the issues or subjects discussed in this preamble or based on a combination of possible requirements to address these subjects and issues.

CHAPTER 5
Portions of Appendix F to Part 132--Great Lakes Water Quality Initiative Implementation Procedures

Procedure 1: Site-specific Modifications to Criteria/Values

A. *Requirements for Site-specific Modifications to Criteria/Values*
Criteria or values may be modified on a site-specific basis to reflect local environmental conditions as restricted by the following provisions. Any such modifications must be: protective of designated uses and aquatic life, wildlife and human health; and submitted to EPA for approval/disapproval. In addition, any site-specific modifications that result in less stringent criteria must be based on sound scientific rationale.

1. *Aquatic Life.* Aquatic life criteria or values may be modified on a site-specific basis to provide an additional level of protection, pursuant to authority reserved to the States and Tribes under Clean Water Act section 510.

a. Less stringent site-specific modifications to chronic or acute aquatic life criteria or values may be developed when:

i. The local water quality parameters such as pH, hardness, temperature, color, etc., alter the biological availability and/or toxicity of a pollutant; and/or

ii. The sensitivity of the local aquatic organisms (i.e., those that would live in the water absent man-induced pollution) differs significantly from the species actually tested in developing the criteria.

Guidance on developing site-specific criteria in these instances is provided in Chapter 4 of the U.S. EPA Water Quality Standards Handbook.

b. Less stringent modifications also may be developed to the chronic aquatic life criteria or values to reflect local physical and hydrological conditions.

2. *Wildlife.* Wildlife criteria or values may be modified on a site-specific basis to provide an additional level of protection, pursuant to authority reserved to the States and Tribes under Clean Water Act section 510. This may be accomplished through the use of an additional uncertainty or other documented factor in the equation for the Wildlife Value.

3. *Bioaccumulation.* Bioaccumulation factors may be modified on a site-specific basis to larger values than derived pursuant to authority reserved to the States and Tribes under Clean Water Act section 510. Bioaccumulation factors shall be modified on a site-specific basis where reliable data shows that local bioaccumulation is greater than the system-wide value.

4. *Human Health.* Human health criteria or values may be modified on a site-specific basis to provide an additional level of protection, pursuant to authority reserved to the States and Tribes under Clean Water Act section 510. Human health criteria or values shall be modified on a site-specific basis to provide additional protection appropriate for highly exposed subpopulations.

B. *Notification Requirements.* When a State proposes a site-specific modification to a criterion or value as allowed in section A above, the State shall notify the other Great Lakes States of such a proposal and, for less stringent criteria, supply appropriate justification.

C. *References.* U.S. EPA. 1983. Water Quality Standards Handbook. Chapter 4. U.S. Environmental Protection Agency, Office of Water Resource Center (RC-4100), 401 M Street, S.W., Washington, D.C. 20460.

Procedure 4: Additivity

[Reserved]

APPENDIX A:

INTRODUCTORY MATERIAL
AND OUTLINE FROM PREAMBLE
TO GREAT LAKES
WATER QUALITY GUIDANCE PACKAGE

in

58 *Federal Register* 20802-21047

Friday, April 16, 1993

40 CFR parts 122 et al.

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 122, 123, 131, and 132

[FRL 4205-6]

RIN 2040-AC08

Proposed Water Quality Guidance for the Great Lakes System

AGENCY: U.S. Environmental Protection Agency.

ACTION: Proposed rule.

SUMMARY: This document provides opportunity for comment on the proposed Water Quality Guidance for the Great Lakes System ("Guidance") developed under section 118(c)(2) of the Clean Water Act (CWA), as amended by section 101 of the Great Lakes Critical Programs Act of 1990 (CPA). This Guidance, once finalized, will establish minimum water quality standards, antidegradation policies, and implementation procedures for waters within the Great Lakes System in the States of New York, Pennsylvania, Ohio, Indiana, Illinois, Minnesota, Wisconsin, and Michigan, including the waters within the jurisdiction of Indian tribes. Today's proposal also is intended to satisfy the requirements of section 118(c)(7)(C) of the Clean Water Act that EPA publish information concerning the public health and environmental consequences of contaminants in Great Lakes sediment and that the information include specific numerical limits to protect health, aquatic life, and wildlife from the bioaccumulation of toxins.

The proposed Guidance specifies numeric criteria for selected pollutants to protect aquatic life, wildlife and human health within the Great Lakes System and methodologies to derive numeric criteria for additional pollutants discharged to these waters. The proposed Guidance also contains specific implementation procedures to translate the proposed ambient water quality criteria into enforceable controls on discharges of pollutants, and a proposed antidegradation policy for the Great Lakes System.

The Great Lakes States and Tribes must adopt water quality standards, antidegradation policies, and implementation procedures for waters within the Great Lakes System which are consistent with the final Guidance. If a Great Lakes State or Tribe fails to adopt consistent provisions within two years of EPA's publication of the final Guidance, EPA will promulgate such provisions within the same two-year period.

DATES: EPA will accept public comments on the proposed Guidance until September 13, 1993. Comments postmarked after this date may not be considered.

A public hearing on the proposed Guidance will be held on August 4 and 5, 1993, in Chicago, Illinois, beginning at 9 a.m. on August 4, 1993. The hearing officer reserves the right to limit oral testimony to 10 minutes, if necessary.

In addition, EPA and the States plan to hold a series of public informational meetings across the Great Lakes Basin to provide a general overview of the various elements in the proposed Guidance. Members of the public should call the following numbers for information on the dates and locations of these meetings: (1) In Illinois, Indiana, Michigan, Minnesota, Ohio and Wisconsin—800-621-8431; (2) in Pennsylvania—215-597-6911; (3) in New York—716-285-8842.

ADDRESSES: An original and 4 copies of all comments on the proposed Guidance should be addressed to Wendy Schumacher, Water Quality Branch (WQS-16J), U.S. EPA, Region V, 77 West Jackson Blvd., Chicago, Illinois, 60604 (telephone: 312-886-0142).

The public hearing on the proposed Guidance will be held in room 331, 77 W. Jackson Blvd., Chicago, Illinois.

Materials in the public docket will be available for inspection and copying at the U.S. EPA Region V Records Center, 77 W. Jackson Blvd., Chicago, Illinois, by appointment only. Appointments may be made by calling Wendy Schumacher (telephone 312-886-0142). A reasonable fee will be charged for photocopies.

Selected documents supporting the proposed Guidance will also be available for viewing by the public at the following locations:

Illinois: Lincoln Library, Lincoln Library Reference Center, 326 South 7th Street, Springfield, Illinois, 62701 (217-753-4945).

Indiana: Indiana Department of Environmental Management, Office of Water Management, 6th Floor, 105 Meridian Street, Indianapolis, Indiana, 46206 (317-232-8671).

Michigan: Library of Michigan, Government Documents Service, 717 West Allegan, Lansing, Michigan, 48909 (517-373-1300); Detroit Public Library, Sociology and Economics Department, 5201 Woodward Avenue, Detroit, Michigan, 48902 (313-833-1440).

Minnesota: Minnesota Pollution Control Agency, Library, 320 Lafayette, St. Paul, Minnesota (612-296-7719).

New York: U.S. EPA Region II Library, room 402, 26 Federal Plaza, New York, New York, 10278 (212-264-2881); U.S. EPA Public Information Office, Carborundum Center, Suite 530, 345 Third Street, Niagara Falls, New York, 14303 (716-285-8842); New York State Department of Environmental Conservation (NYSDEC), room 310, 50 Wolf Road, Albany, New York, 12233 (518-457-7463); NYSDEC, Region 6, 7th Floor, State Office Building, 317 Washington Street, Watertown, New York, 13602 (315-785-2513); NYSDEC, Region 7, 615 Erie Boulevard West, Syracuse, New York, 13204 (315-426-7400); NYSDEC, Region 8, 62 74 East Avon-Lima Road, New York, 14414 (716-226-2466); NYSDEC, Region 9, 270 Michigan Avenue, Buffalo, New York, 14203 (716-851-7070).

Ohio: Ohio Environmental Protection Agency Library—Central District Office, 1800 Watermark Road, Columbus, Ohio, 43215 (614-644-3024); U.S. EPA Eastern District Office, 25809 Central Ridge Road, Westlake, Ohio, 44145 (216-522-7260).

Pennsylvania: Pennsylvania Department of Environmental Resources, 1012 Water Street, Meadville, Pennsylvania, 16335; U.S. EPA Region III Library, 8th Floor, 841 Chestnut Building, Philadelphia, Pennsylvania, 19107-4431 (215-597-7904).

Wisconsin: Water Resources Center, University of Wisconsin-Madison, 2nd Floor, 1975 Willow Drive, Madison, Wisconsin (608-2620-3069).

Selected documents supporting the proposed Guidance are also available by mail upon request for a fee (see section XIII of the preamble for additional information).

FOR FURTHER INFORMATION CONTACT: Kenneth A. Fenner, Water Quality Branch Chief (WQS-16J), U.S. EPA Region V, 77 W. Jackson Blvd., Chicago, Illinois, 60604 (Telephone: 312-353-2079).

SUPPLEMENTARY INFORMATION:

Preamble Outline

APPENDIX B:

APPENDIX A

UNCERTAINTY FACTORS

to

DRAFT

Technical Support Document

Methodologies for

Human Health Criteria and Values

Great Lakes Initiative

January 1993

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. A 10-fold factor is recommended when extrapolating from valid experimental results from human studies of prolonged exposure.

2. 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).

3. 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.

4. An additional uncertainty factor or 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.

5. 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).

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.

1. <u>A 10-fold factor is recommended when extrapolating from valid experimental results from human studies of prolonged exposure.</u> 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.

2. 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.

3. 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 onger 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 new 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.

4. 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).

5. 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-dayrodentNOAEL). 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.

REFERENCES:

Bigwood, E. 1973. The Acceptable Daily Intake of Food Additivies. CRC Crit. Rev. Toxicol. June 41-93. As cited in: Dourson, M. and J. Stara. 1983. Regulatory History and Experimental Support of Uncertainty (Safety) Factors. Regulatory Toxicology and Pharmacology. 3:224-238.

Calabrese, E. 1985. Uncertainty Factors and Interindividual Variation. Regulatory Toxicology and Pharmacology. 5:190-196.

Chan, P., O'Hara, G. and A. Hayes. 1982. Principles and Methods for Acute and Subchronic Toxicity. In: Hayes, A. (Ed.) 1982. Principles and Methods of Toxicology. 1982. Raven Press. New York, NY.

Dourson, M. 1987. U.S. EPA. Environmental Criteria and Assessment Office. Personal communication with Robert Sills, Michigan Department of Natural Resources.

Dourson, M. and J. Stara. 1983. Regulatory History and Experimental Support of Uncertainty (Safety) Factors. Regulatory Toxicology and Pharmacology. 3:224-238.

Frederick, G. 1986. The Evidence Supporting 18 Month Animal Studies. In: Walker, S. and A. Dayan. 1986. Long-Term Animal Studies; Their Predictive Value for Man: Proceedings of the Centre for Medicines Research Workshop held at the Ciba Foundation, London, 2 October 1984.

Glocklin, V. 1986. Justification for 12 Month Animal Studies. In: Walker, S. and A. Dayan. 1986. Long-Term Animal Studies; Their Predictive Value for Man: Proceedings of the Centre for Medicines Research Workshop held at the Ciba Foundation, London, 2 October 1984.

Klaassen, C. 1986. Principles of Toxicology. In Doull, J., Klaassen, C. and M. Amdur (Eds.). 1986. Casarett and Doull's Toxicology - The Basin Science of Poisons. 3rd Edition. Macmillan Publishing Co., Inc. New York, NY.

Layton, D.W., et al. 1987. Deriving allowable daily intakes forsystemic toxicants lacking chronic toxicity data. Regulatory Toxicology and Pharmacology. 7:96-112.

McNamara, B., 1971. Concepts in Health Evaluation of Commercial and Industrial Chemicals. In: Mehlman, M., Shapiro, R. and H. Blumenthal (Eds.). 1971. Advances in Modern Toxicology. Volume 1, Part 1: New Concepts in Safety Evaluation. Chapter 4. John Wiley and Sons. New York, NY.

National Academy of Sciences. 1980. Drinking Water and Health. Vol. 2. National Academy Press. Washington, D.C.

National Academy of Sciences. 1977. Drinking Water and Health. Vol. 1. National Academy Press. Washington, D.C.

National Cancer Institute, 1976. Guidelines for Carcinogen Bioassay in Small Rodents. U.S. DHEW. Technical Report Series No. 1.

Organization for Economic Cooperation and Development (OECD). 1981. OECD Guidelines for Testing of Chemicals. Section 4: Health Effects. Paris, France.

Stevens, K. and M. Gallo. 1982. Practical Considerations in the Conduct of Chronic Toxicity Studies. In: Hayes, A. (Ed.) 1982. Principles and Methods of Toxicology. 1982. Raven Press. New York, NY.

U.S. Environmental Protection Agency (EPA). 1986. Human Variability in Susceptibility to Toxic Chemicals - I. Noncarcinogens. EPA/600/8-86/033.

U.S. Environmental Protection Agency (EPA). 1985. Health Effects Testing Guidelines. 40 CFR Part 798. Federal Register, v. 50, n. 188, September 27, 1985.

U.S. Environmental Protection Agency (EPA). 1980. Water Quality Criteria Documents: Availability. Appendix C - Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register, v. 45, n. 231, November 38, 1980. 79347-79357.

Venman, B. and C. Flaga. 1985. Development of an Acceptable Factor to Estimate Chronic End Points from Acute Toxicity Data. Toxicology and Industrial Health. 1(4): 261-269.

Vettorazzi, G. 1976. Safety Factors and their Application in the Toxicological Evaluation. In: The Evaluation of Toxicological Data for the Protection of Public health. Permagon, Oxford. As cited in: Douson, M. and J. Stara. 1983. Regulatory History and Experimental Support of Uncertainty (Safety) Factors. Regulatory Toxicology and Pharmacology. 3: 224-238.

Weil, C. and D. McCollister. 1963. Relationship Between Short- and Long-Term Feeding Studies in Designing an Effective Toxicity Test. Agricultural and Food Chemistry. 11(6): 486-491.