3745-1-42 **Methodologies for development of human health criteria and values for the lake Erie drainage basin.**

[Comment: For dates of non-regulatory government publications, publications of recognized organizations and associations, federal rules and federal statutory provisions referenced in this rule, see rule 3745-1-03 of the Administrative Code.]

This rule applies to water bodies located in the lake Erie drainage basin. All pollutants or combinations of pollutants, for which human health criteria have not been adopted in rule 3745-1-33 or 3745-1-34 of the Administrative Code, shall not exceed the water quality criteria or values derived using the procedures contained in this rule.

(A) General provisions.

(1) The purpose of this rule is to describe procedures for calculating human health criteria and values that provide protection of humans from unacceptable exposure to toxicants through consumption of contaminated fish and drinking water and from ingesting water as a result of participation in water-oriented recreational activities.

(2) Level of protection. The criteria and values developed shall provide a level of protection likely to be without appreciable risk of carcinogenic or noncarcinogenic effects. Ambient criteria and values for single carcinogens shall not be set at a level representing a lifetime upper-bound incremental risk greater than one in one hundred thousand of developing cancer using the hazard assessment techniques and exposure assumptions described in this rule. Criteria and values affording protection from noncarcinogenic effects shall be established at levels that, taking into account uncertainties, are considered likely to be without an appreciable risk of adverse human health effects (i.e., acute, subchronic and chronic toxicity including reproductive and developmental effects) during a lifetime of exposure, using the risk assessment techniques and exposure assumptions described in this rule.

(3) Two-tiered classification. Chemical concentration levels in surface water protective of human health shall be derived based on either a tier I or tier II classification. The two tiers are primarily distinguished by the amount of toxicity data available for deriving the concentration levels and the quantity and quality of data on bioaccumulation.

(B) Minimum data requirements. The best available toxicity data on the adverse health effects of a chemical and the best data on bioaccumulation factors shall be used when developing human health tier I criteria or tier II values. The best available toxicity data shall include data from well-conducted epidemiologic or animal studies which provide, in the case of carcinogens, an adequate weight of evidence of potential human carcinogenicity and, in the case of noncarcinogens, a

dose-response relationship involving critical effects biologically relevant to humans. Such information shall be obtained from the U.S. EPA integrated risk information system (IRIS) database, scientific literature, and other informational databases, studies and reports containing adverse health effects data of adequate quality for use in this rule, when available. Strong consideration shall be given to the most currently available guidance provided by IRIS in deriving criteria or values, supplemented with any recent data not incorporated into IRIS. The best available bioaccumulation data shall include data from field studies and well-conducted laboratory studies.

(1) Carcinogens.

(a) Tier I human cancer criteria (HCC) and tier II human cancer values (HCV) shall be derived using the methodologies described in paragraph (C)(1) of this rule when there is adequate evidence of potential human carcinogenic effects for a chemical. The U.S. EPA classification system for chemical carcinogens, which is described in "Guidelines for Carcinogen Risk Assessment, Risk Assessment Forum, U.S. Environmental Protection Agency" shall be used in determining whether adequate evidence of potential carcinogenic effects exists. Carcinogens are classified, depending on the weight of evidence, as carcinogenic to humans, likely to be carcinogenic to humans, or having suggestive evidence of carcinogenic potential. The human evidence shall be considered inadequate and therefore the chemical cannot be classified as a human carcinogen, if any of the following conditions exists:

(i) There is little or no pertinent information.

(ii) Some studies provide evidence of carcinogenicity but other studies of equal quality with animals of the same sex and strain are negative.

(iii) There are negative results that are not sufficiently robust for the descriptor "not likely to be carcinogenic to humans."

(iv) There is animal evidence that demonstrates lack of carcinogenic effect in both sexes in well-designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects).

(v) There is convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans.

(vi) There is convincing evidence that carcinogenic effects are not likely by a particular exposure route.

(vii) There is convincing evidence that carcinogenic effects are not likely below a defined dose range.

(b) Chemicals are described as "carcinogenic to humans" when either: there is convincing epidemiological evidence of a causal association between human exposure and cancer; or when all of the following conditions are met:

(i) There is strong evidence of an association between human exposure and either cancer or the key precursor events of a chemical's mode of action but not enough for a causal association.

(ii) There is extensive evidence of carcinogenicity in animals.

(iii) The mode or modes of carcinogenic action and associated precursor events have been identified in animals.

(iv) There is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on biological information.

(c) Chemicals described as "likely to be carcinogenic to humans" include chemicals for which the weight of evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "carcinogenic to humans." Chemicals with weight of evidence demonstrating carcinogenic potential to humans can include, but are not limited to:

(i) Chemicals for which a plausible association is demonstrated between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments.

(ii) Chemicals that tested positive for carcinogenicity in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans.

(iii) Chemicals for which positive tumor study results are demonstrated that raise additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy or an early age of onset.

(iv) Chemicals for which a rare animal tumor response in a single experiment is demonstrated that is assumed to be relevant to humans.

(v) Chemicals for which positive tumor study results are demonstrated that are strengthened by other lines of evidence, for example, either plausible association between human exposure and cancer or evidence that the chemical or an important metabolite causes events generally known to be associated with tumor formation likely to be related to tumor response in this case.

(d) "Suggestive evidence of carcinogenic potential" is evidence used to describe chemicals where the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. Chemicals with weight of evidence suggestive of carcinogenicity can include, but are not limited to:

(i) Chemicals with studies that show a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor "likely to be carcinogenic to humans."

(ii) Chemicals with studies that show a small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not to the chemical being assessed.

(iii) Chemicals with evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion, but where the carcinogenic potential is strengthened by other lines of evidence.

(iv) Chemicals with studies that show a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend.

(e) Tier I. Weight of evidence of potential human carcinogenic effects sufficient to derive a HCC shall generally include chemicals that are carcinogenic to humans and likely to be carcinogenic to humans and can include, on a case-by-case basis as determined by the director, chemicals with suggestive evidence of carcinogenic potential if studies have been well-conducted when compared to studies used in classifying chemicals that are carcinogenic to humans or likely to be carcinogenic to humans. The decision to use data on a chemical with suggestive evidence of carcinogenic potential for deriving tier I criteria shall be a case-by-case determination. In determining whether to derive a HCC, additional evidence that shall be considered includes but is not limited

to available information on mode of action, such as mutagenicity/genotoxicity (determinations of whether the chemical interacts directly with DNA), structure activity, and metabolism.

(f) Tier II. Weight of evidence of chemicals with effects suggestive of carcinogenic potential sufficient to derive a HCV shall include those chemicals with suggestive evidence of carcinogenic potential for which there are, at a minimum, data sufficient for quantitative risk assessment, but for which data are inadequate for tier I criterion development due to a tumor response of marginal statistical significance or inability to derive a strong dose-response relationship. In determining whether to derive tier II human cancer values, additional evidence that shall be considered includes but is not limited to available information on mode of action such as mutagenicity/genotoxicity (determinations of whether the chemical interacts directly with DNA), structure activity and metabolism. As with the use of data on chemicals with suggestive evidence of carcinogenic potential in developing tier I criteria, the decision to use data on chemicals with suggestive evidence of carcinogenic potential to derive tier II values shall be made on a case-by-case basis by the director.

(2) Noncarcinogens.

(a) All available toxicity data shall be evaluated considering the full range of possible health effects of a chemical, i.e., acute/subacute, chronic/subchronic and reproductive/developmental effects, in order to best describe the dose-response relationship of the chemical, and to calculate human noncancer criteria (HNC) and human noncancer values (HNV) which will protect against the most sensitive endpoint of toxicity. Paragraphs (B)(2)(b) and (B)(2)(c) of this rule provide the minimum data sets necessary to calculate HNC and HNV, respectively.

(b) Tier I. The minimum data set sufficient to derive an HNC shall include at least one well-conducted epidemiologic study or animal study. A well-conducted epidemiologic study for an HNC must quantify exposure level and demonstrate positive association between exposure to a chemical and adverse effect in humans. A well-conducted study in animals must demonstrate a dose response relationship involving one or more critical effect biologically relevant to humans. The duration of a study should span multiple generations of exposed test species or at least a major portion of the lifespan of one generation. By the use of uncertainty adjustments, shorter term studies (such as ninety-day subchronic studies) with evaluation of more limited effect may be used to extrapolate to longer exposures or to account for a variety of adverse effects. For an HNC developed pursuant to this rule, such a limited study must be conducted for at least ninety days in rodents or ten per

cent of the lifespan of other appropriate test species and demonstrate a no observable adverse effect level (NOAEL). Chronic studies of one year or longer in rodents or fifty per cent of the lifespan or greater in other appropriate test species that demonstrate a lowest observable adverse effect level (LOAEL) may be sufficient for use in tier I criterion derivation if the effects observed at the LOAEL were relatively mild and reversible as compared to effects at higher doses. This does not preclude the use of a LOAEL from a study (of chronic duration) with only one or two doses if the effects observed appear minimal when compared to effect levels observed at higher doses in other studies.

(c) Tier II. When the minimum data for deriving tier I criteria are not available to meet the tier I data requirements, a more limited database may be considered for deriving tier II values. As with tier I criteria, all available data shall be considered and shall address a range of adverse health effects with exposure over a substantial portion of the lifespan (or multiple generations) of the test species. With the use of appropriate uncertainty factors to account for a less extensive database, the minimum data sufficient to derive a tier II value shall include a NOAEL from at least one well-conducted short-term repeated dose study. This study shall be of at least twenty-eight days duration, in animals demonstrating a dose-response, and involving effects biologically relevant to humans. Data from studies of longer duration (greater than twenty-eight days) and LOAELS from such studies (greater than twenty-eight days) may be more appropriate in some cases for derivation of tier II values. Use of a LOAEL shall be based on consideration of the following information: severity of effect, quality of the study and duration of the study.

(3) Bioaccumulation factors (BAFs).

(a) Tier I for carcinogens and noncarcinogens. To be considered a tier I cancer or noncancer human health criterion, along with satisfying the minimum toxicity data requirements of paragraphs (B)(1) and (B)(2) of this rule, a chemical shall have the following minimum bioaccumulation data. For all organic chemicals either: A field-measured BAF; a BAF derived using the BSAF methodology; or a BAF less than one hundred twenty-five regardless of how the BAF was derived. For all inorganic chemicals, including organometals such as mercury, either: a field-measured BAF; or a laboratory-measured BCF.

(b) Tier II for carcinogens and noncarcinogens: a chemical is considered a tier II cancer or noncancer human health value if it does not meet either the minimum toxicity data requirements of paragraph (B)(1) or (B)(2) of this rule or the minimum bioaccumulation data requirements of

paragraph (B)(3)(a) of this rule.

(C) Principles for development of tier I criteria or tier II values. The fundamental components of the procedure to calculate tier I criteria or tier II values are the same. However, certain aspects of the procedure designed to account for short-duration studies or other limitations in data are more likely to be relevant in deriving tier II values than tier I criteria.

(1) Carcinogens.

(a) A non-threshold mechanism of carcinogenesis shall be assumed unless biological data adequately demonstrate the existence of a threshold on a chemical-specific basis.

(b) All appropriate human epidemiologic data and animal cancer bioassay data shall be considered. Data specific to an environmentally appropriate route of exposure shall be used. Oral exposure should be used preferentially over dermal and inhalation since, in most cases, the exposure routes of greatest concern are fish consumption and drinking water/incidental ingestion. The risk associated does shall be set at a level corresponding to an incremental cancer risk of one in one hundred thousand. If acceptable human epidemiologic data are available for a chemical, they shall be used to derive the risk associated dose. If acceptable human epidemiologic data are not available, the risk associated dose shall be derived from available animal bioassay data. Data from a species that is considered most biologically relevant to humans is preferred where all other considerations regarding quality of data are equal. In the absence of data to distinguish the most relevant species, data from the most sensitive species tested, i.e., the species showing a carcinogenic effect at the lowest administered dose, shall be used.

(c) When animal bioassay data are used and a non-threshold mechanism of carcinogenicity is assumed, the data shall be fitted to a linearized multistage model. The upper-bound ninety-five per cent confidence limit on risk (or, the lower ninety-five per cent confidence limit on dose) at the one in one hundred thousand risk level shall be used to calculate a risk associated dose (RAD). Other models, including modifications or variations of the linear multistage model, which are more appropriate to the available data may be used where scientifically justified.

(d) If the duration of the study is significantly less than the natural lifespan of the test animal, the slope may be adjusted on a case-by-case basis to compensate for latent tumors which were not expressed. In the absence of alternative approaches which compensate for study durations

significantly less than lifetime, the process described in "Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health, Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency" shall be used.

(e) A species scaling factor shall be used to account for differences between test species and humans. It shall be assumed that milligrams per surface area per day is an equivalent dose between species. All doses presented in mg/kg body weight shall be converted to an equivalent surface area dose by raising the mg/kg dose to the two-thirds power. However, if adequate pharmacokinetic and metabolic studies are available, these data may be factored into the adjustment for species differences.

(f) Additional data selection and adjustment decisions must also be made in the process of quantifying risk. Consideration shall be given to tumor selection for modeling. All doses shall be adjusted to give an average daily dose over the study duration. Adjustments in the rate of tumor response shall be made for early mortality in test species. The goodness-of-fit of the model to the data shall also be assessed.

(g) When a linear, non-threshold dose response relationship is assumed, the RAD shall be calculated using the equation

$$RAD = \frac{0.00001}{q_1^*}$$

Where:

RAD = risk associated dose in milligrams of toxicant per kilogram body weight per day (mg/kg/day).

0.00001 (1×10^{-5}) = incremental risk of developing cancer equal to one in one hundred thousand.

q_1^* = slope factor $(mg/kg/day)^{-1}$.

(h) If human epidemiologic data or other animal biological data indicate that a chemical causes cancer through a threshold mechanism, the risk associated dose may be calculated using a method which assumes that a threshold mechanism is operative.

(2) Noncarcinogens.

(a) Noncarcinogens shall generally be assumed to have a threshold dose or concentration below which no adverse effects should be observed.

Therefore, the tier I criterion or tier II value shall be the maximum water concentration of a substance at or below which a lifetime exposure from drinking the water, consuming fish caught in the water, and ingesting water as a result of participating in water-related recreation activities is likely to be without appreciable risk of deleterious effects. For some noncarcinogens, there may not be a threshold dose below which no adverse effects are observed. Chemicals acting as genotoxic teratogens and germline mutagens are thought to possibly produce reproductive or developmental effects via a genetically linked mechanism which may have no threshold. Other chemicals also may not demonstrate a threshold. Criteria and values for these types of chemicals shall be established on a case-by-case basis using appropriate assumptions reflecting the likelihood that no threshold exists.

(b) All appropriate human and animal toxicologic data shall be reviewed and evaluated. To the maximum extent possible, data most specific to the environmentally relevant route of exposure shall be used. Oral exposure data should be used preferentially over dermal and inhalation since, in most cases, the exposure routes of greatest concern are fish consumption and drinking water/incidental ingestion. When acceptable human data are not available (e.g., well-conducted epidemiologic studies), animal data from species most biologically relevant to humans shall be used. In the absence of data to distinguish the most relevant species, data from the most sensitive animal species tested, i.e., the species showing a toxic effect at the lowest administered dose (given a relevant route of exposure), shall be used.

(c) Minimum data requirements are specified in paragraph (B)(2) of this rule. The experimental exposure level representing the highest level tested at which no adverse effects were demonstrated (NOAEL) from studies satisfying the provisions of paragraph (B)(2) of this rule shall be used for criteria calculations. In the absence of a NOAEL, the LOAEL from studies satisfying the provisions of paragraph (B)(2) of this rule may be used if it is based on mild and reversible effects.

(d) Uncertainty factors shall be used to account for the uncertainties in predicting acceptable dose levels for the general human population based upon experimental animal data or limited human data.

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

(ii) An uncertainty factor of one hundred shall be used when

extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. In comparison to paragraph (C)(2)(d)(i) of this rule, this represents an additional ten-fold uncertainty factor in extrapolating data from the average animal to the average human.

(iii) An uncertainty factor of up to one thousand shall be used when extrapolating from animal studies for which the exposure duration is less than chronic, but greater than ninety days length, or when other significant deficiencies in study quality are present, and when useful long-term human data are not available.

(iv) An uncertainty factor of up to three thousand shall be used when extrapolating from animal studies for which the exposure duration is less than twenty-eight days.

(v) An additional uncertainty factor of between one and ten may be used when deriving a criterion from a LOAEL. The level of additional uncertainty applied shall depend upon the severity and the incidence of the observed adverse effect.

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

(vii) When deriving an uncertainty factor in developing a tier I criterion or tier II value, the total uncertainty, as calculated following the guidance of paragraphs (C)(2)(d)(i) to (C)(2)(d)(vi) of this rule, shall not exceed ten thousand for tier I criteria and thirty thousand for tier II values.

(e) All study results shall be converted, as necessary, to the standard unit for acceptable daily exposure of milligrams of toxicant per kilogram of body weight per day (mg/kg/day). Doses shall be adjusted for continuous exposure.

(3) Criteria and value derivation.

(a) Carcinogens. The tier I HCC and tier II HCV shall be calculated using the equation

$$HCV = \frac{RAD \times BW}{WC + [(FC_{TL3} \times BAF^{HH}_{TL3}) + (FC_{TL4} \times BAF^{HH}_{TL4})]}$$

Where:

HCV = human cancer value in milligrams per liter (mg/l).

RAD = risk associated dose in milligrams toxicant per kilogram body weight per day (mg/kg/day) that is associated with a lifetime incremental cancer risk equal to one in one hundred thousand.

BW = weight of an average human (seventy kilograms).

WC = per capita water consumption (two liters/day for surface waters designated as public water supplies and 0.01 liters/day for surface waters not designated as public water supplies).

FC_{TL3} = mean consumption of trophic level three of regionally caught freshwater fish (0.0036 kilogram/day).

FC_{TL4} = mean consumption of trophic level four of regionally caught freshwater fish (0.0114 kilogram/day).

BAF^{HH}_{TL3} = bioaccumulation factor for trophic level three fish, as derived using the BAF methodology contained in rule 3745-1-37 of the Administrative Code.

BAF^{HH}_{TL4} = bioaccumulation factor for trophic level four fish, as derived using the BAF methodology contained in rule 3745-1-37 of the Administrative Code.

(b) Noncarcinogens. The tier I HNC or tier II HNV shall be calculated using the equation

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

Where:

HNV = human noncancer value in milligrams per liter (mg/l).

ADE = acceptable daily exposure in milligrams toxicant per kilogram

body weight per day (mg/kg/day).

RSC = relative source contribution factor of 0.8. An RSC derived from actual exposure data may be developed using the methodology outlined in "Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health, Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency."

BW = weight of an average human (seventy kilograms).

WC = per capita water consumption (two liters/day for surface waters designated as public water supplies and 0.01 liters/day for surface waters not designated as public water supplies).

FC_{TL3} = mean consumption of trophic level three fish by regional sport fishers of regionally caught freshwater fish (0.0036 kilogram/day).

FC_{TL4} = mean consumption of trophic level four fish by regional sport fishers of regionally caught freshwater fish (0.0114 kg/day).

BAF^{HH}_{TL3} = human health bioaccumulation factor for edible portion of trophic level three fish, as derived using the BAF methodology contained in rule 3745-1-41 of the Administrative Code.

BAF^{HH}_{TL4} = human health bioaccumulation factor for edible portion of trophic level four fish, as derived using the BAF methodology contained in rule 3745-1-41 of the Administrative Code.

(D) Application of criteria and values. The HCC, HCV, HNC and HNV shall be applied as thirty-day average concentrations outside the mixing zone.

Replaces: 3745-1-38

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