GUIDESHEET V

GUIDANCE FOR PROVIDING TOXICITY INFORMATION TO DETERMINE A RULE 2222(5) STANDARD

Applicants for a groundwater discharge authorized under Part 31, Water Resources Protection, of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended (Part 31), are required pursuant to the administrative rules for Part 31 [Rule 2206(1); Rule 2218(3)(a)(v)] to provide the information necessary to determine a standard for a substance in the discharge if a standard has not already been developed by the Michigan Department of Environmental Quality (MDEQ) for the substance. The MDEQ toxicologists will use the toxicity information provided to determine a standard for the substance. If there is no toxicity information available by which to base a standard, the substance shall not be discharged, except in limited circumstances [Rule 2222(5)(e)]. The best available toxicity data on the adverse health effects of a chemical must be used when developing Rule 2222(5) standards. The following guidance is provided to assist the applicant in providing all potentially relevant toxicity information for developing the standard to the MDEQ.

Identifying Relevant Toxicity Information

The primary pathway of concern for the development of a Rule 2222(5) standard is human drinking water ingestion. All relevant human and animal toxicity data for a substance must be reviewed and evaluated. Relevant studies generally require oral exposure (water, feed, or gavage) and mammalian species. Aquatic toxicity information is not relevant for human drinking water ingestion standards and therefore will not be accepted to fulfill this requirement. Ideally, the toxicity information should include data from well-conducted human epidemiological studies and/or animal studies that provide chemical information on carcinogenic (cancer causing) and non-carcinogenic effects. If toxicity data are available for both carcinogenic and non-carcinogenic effects, the Rule 2222(5) standard will be the lower of the cancer value or the non-cancer value. In a few cases, toxicity data from an inhalation or dermal study may be used if the critical effect(s) are systemic and there is sufficient data to determine an equivalent oral dose. Appendix A provides additional information on the derivation of cancer and non-cancer values.

A more relevant toxicity study will produce less uncertainty in developing a protective standard and that generally results in a higher standard. Therefore, it is important for the applicant to identify the most preferred studies available. Preference is given to chronic studies which identify critical adverse effects as well as a cancer slope factor (CSF) and/or “no observed adverse effect level” (NOAEL). In the absence of a CSF and/or NOAEL, a lowest observed adverse effect level (LOAEL) may be used. For most chemicals, a NOAEL from a long-term study will result in a higher standard (i.e., less restrictive) due to less uncertainty (see Appendix B for information about uncertainty factors). The minimum toxicity data set for developing a Rule 2222(5) standard is an

acute oral rat LD_{50} (dose that is lethal to 50% of the test species) however, standards based on acute data are generally much more conservative and highly restrictive.* The following hierarchy represents the preference for toxicological data necessary for developing a Rule 2222(5) standard:

1) Lifetime bioassay, sufficient to develop a cancer slope factor and/or a NOAEL for noncancer effects
2) Other chronic studies identifying a NOAEL or LOAEL
3) Subchronic studies (ex: not less than 90-day study) identifying a NOAEL or LOAEL
4) Short-term repeated dose studies (ex: not less than 28-day study)
5) Acute oral rat LD_{50} studies

In addition, reproductive and developmental toxicity studies are important and may decrease the uncertainty and result in a higher standard. Appendix A provides additional information on the type of toxicity data necessary to derive the Rule 2222(5) standards, including in-depth descriptions of the types of studies listed above.

Required Information from Relevant Toxicity Studies

The applicant must provide all available relevant (**oral, mammalian**) toxicity information to the MDEQ for development of the standard. **Material Safety Data Sheets (MSDS) do not provide sufficient information, even if some toxicity data is included.** The sources of toxicity information must be referenced, including databases searched and the search strategy. The basic information necessary from the key study(ies) is as follows:

- **SUBJECTS:** Species and strain, age, number of subjects (by dose, group, and sex), body weight
- **EXPOSURE/DOSES:** Route of exposure, duration of exposure, frequency of exposure, doses (e.g., milligrams of toxicant per kilogram of body weight per day or mg/kg/day), any dose conversion necessary, control group(s)
- **EFFECTS EVALUATED:** Tests administered, observations performed
- **RESULTS:** Any effects observed in the dose groups, effects with statistical significance including statistical methods used and the statistical significance of the effects (e.g., p-values, percent difference)

The bulleted items (above) must be provided for toxicity information to be considered sufficient to determine a standard.

Sources of Information

The preferred source of information on the toxicity of chemicals is the United States Environmental Protection Agency's (EPA) database entitled "Integrated Risk Information System (IRIS - http://www.epa.gov/iris/)." Since a limited number of chemicals are included in IRIS, it may be necessary to use additional sources of information. Additional sources of toxicity information include published scientific literature, and other informational databases, studies, or reports that contain adverse health effects data of adequate quality for use in developing a standard. Other than IRIS, good sources of published toxicity information may be found from the following sources:

- National Toxicology Program (https://ntp.niehs.nih.gov/)
- International Agency for Research on Cancer (http://www.iarc.fr/)
- National Library of Medicine, Toxnet (https://toxnet.nlm.nih.gov/)
- Chemical Abstracts Service (http://www.cas.org/)

When sufficient information is not available in the published literature, it is advisable to contact the manufacturer(s) of the substance to determine if there are relevant unpublished toxicity data. A source for information for chemical manufacturers listed by CAS # is found at EPA's Chemical Right to Know, High Production Volume Challenge website: (https://comptox.epa.gov/dashboard/chemical-lists/EPAHPV).

If you have any questions regarding this guidance, please contact Dennis Bush at 517-335-3308.

** Any Part 22 standard that is developed using an acute oral rat LD_{50} value listed on a Material Safety Data Sheet (MSDS) will be considered only an estimate until the actual LD_{50} study can be evaluated by the toxicologist to determine the appropriateness and adequacy of the methods of the study and the LD_{50} determination.*

Appendix A: Additional Information about Relevant Toxicity Studies

Toxicity Information for Carcinogenic Effects

Cancer values will be derived if there is adequate evidence of potential human carcinogenic effects for a chemical. Carcinogens will be classified, depending on the weight of evidence, as either known human carcinogens, probable human carcinogens, or possible human carcinogens for which there are data sufficient for quantitative risk assessment.

The fundamental principles for the development of human health cancer values are as follows:

- A non-threshold mechanism of carcinogenesis will be assumed unless biological data adequately demonstrate the existence of a threshold on a chemical-specific basis.
- All appropriate human epidemiologic data and animal cancer bioassay data will be considered. To the maximum extent possible, data most specific to the environmentally relevant route of exposure should be used. Oral exposure is preferred over dermal and inhalation exposure since, in most cases, the exposure route of greatest concern is drinking water ingestion. If acceptable human epidemiologic data are available for a chemical, these data will be used to derive the value. If acceptable human epidemiologic data are not available, then the value will be derived from available animal bioassay data. Data from a species that is considered most biologically relevant to humans, that is, responds most like humans to toxicant exposures, 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 species that results in the highest potency will generally be used.
- If animal bioassay data are used and a non-threshold mechanism of carcinogenicity is assumed, then the data are fitted to a linearized multistage computer model, for example, a GLOBAL '86 or equivalent model. GLOBAL '86 is the linearized multistage model derived by Howe, Crump, and Van Landingham (1986). The EPA generally uses this model to determine cancer potencies. The upper-bound 95 percent confidence limit on risk, or the lower 95 percent confidence limit on dose, at the 1 in 100,000 risk level will be used to calculate a potency value for individual chemicals. Other models, including modifications or variations of the linear multistage model may be used where scientifically justified.
- If the duration of the study is significantly less than the natural lifespan of the test animal, then the potency may be adjusted on a case-by-case basis to compensate for tumors that may have been expressed if the animal were allowed to live longer.
- A species-scaling factor will be used to account for differences between test species and humans. It is assumed that milligrams per surface area per day is an equivalent dose between species. All doses presented in mg/kg bodyweight will be converted to an equivalent surface area dose by raising the mg/kg dose to the 3/4 power. However, if adequate pharmacokinetic and metabolism studies are available, then these data may be factored into the adjustment for species differences on a case-by-case basis.

- Additional data selection and adjustment decisions should also be made in the process of quantifying risk. Consideration should be given to tumor selection for modeling, that is, pooling estimates for multiple tumor types and identifying and combining benign and malignant tumors. All doses should be adjusted to give an average daily dose over the study duration. Adjustments in the rate of tumor response should be made for early mortality in test species. The goodness-of-fit of the model to the data should also be assessed.
- If human or animal data, or both, indicate that a chemical causes cancer via a threshold mechanism, then the value may, on a case-by-case basis, be calculated using a method that assumes a threshold mechanism is operative.

Toxicity Information for Noncarcinogenic Effects

For noncarcinogenic values, all available toxicity data will be evaluated. The full range of possible health effects of a chemical will be considered in order to best describe the dose-response relationship of the chemical, and to calculate values that will be protective of the most sensitive endpoint. Although it is desirable to have an extensive database that considers a wide range of possible adverse effects, these data exist for only a very limited number of chemicals. Although toxicity information from peer-reviewed publications is preferred, this information is not always available. It may be necessary to request unpublished toxicity data from the manufacturer of the chemical if sufficient information is not found in the published literature.

The fundamental principles for the development of human health noncancer values are as follows:

- Noncarcinogenic effects will generally be assumed to have a threshold dose or concentration below which no adverse effects are expected to be observed. Therefore, the noncancer value is the maximum water concentration of a substance at or below which exposure from drinking the water is likely to be without appreciable risk of adverse effects.
- For some noncarcinogenic effects, there may not be a threshold dose below which adverse effects will not be observed. For example, chemicals acting as genotoxic teratogens and germline mutagens may produce reproductive or developmental effects, or both, through a genetically linked mechanism that may have no threshold. Values for chemicals that do not exhibit a threshold effect level will be established on a case-by-case basis using appropriate assumptions reflecting the likelihood that no threshold exists.
- All appropriate human and animal toxicologic data must be reviewed and evaluated. To the maximum extent possible, data most specific to the environmentally relevant route of exposure should be used. Oral exposure is preferred over dermal and inhalation exposure since, in most cases, the exposure route of greatest concern is drinking water ingestion. If acceptable human epidemiologic data are not available, then animal data from species most biologically relevant to humans should be used. In the absence of data to distinguish the most relevant species, data from the most sensitive animal species tested, that is, the species showing a toxic effect at the

lowest administered dose given a relevant route of exposure should generally be used.

Toxicity data preferences are specified below. To help facilitate the selection of the best available data, it is helpful to establish a hierarchy in the type of data preferred to develop standards. Preference is given to chronic studies of sensitive and relevant endpoints, which identify critical adverse effects as well as a "no observed adverse effect level" (NOAEL). In the absence of a NOAEL, a lowest observed adverse effect level (LOAEL) may be used if based on mild to moderate effects. This hierarchy also reflects the extent that uncertainty factors are necessary in developing a standard to compensate for the limitations of the data. For most chemicals, a NOAEL from a long-term study will result in a higher standard (i.e., less restrictive) due to less uncertainty. The uncertainty factors used to develop a standard are provided in Appendix B. The following hierarchy represents the preference for toxicological data necessary for developing a Rule 2222(5) standard:

(A) Route of exposure – Drinking water studies are preferred. Other oral exposure studies may also be used (e.g., gavage, feeding studies). When appropriate, studies using other routes of exposure (inhalation, dermal) may be used if there are relevant systemic effects and there are sufficient toxicokinetic data to perform a route to route extrapolation.

(B) Acceptable chronic studies will include at least one well-conducted human epidemiologic study or animal study. A well-conducted epidemiologic study should quantify exposure levels and demonstrate an association between exposure to a chemical and adverse effects in humans. A well-conducted study in animals should demonstrate a dose-response relationship involving one or more critical effects biologically relevant to humans. Ideally, 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. Chronic studies are conducted for one year or longer with rodents or 50 percent of the lifespan or longer with other appropriate test species, and should demonstrate a NOAEL or LOAEL

(C) Subchronic studies, such as 90-day studies, may be used to extrapolate to longer exposures or to account for a variety of adverse effects. A subchronic study should be conducted for not less than 90 days in rodents or for 10 percent of the lifespan of other appropriate test species and should demonstrate a NOAEL or LOAEL.

(D) A well-conducted short-term repeated dose study. The study should be conducted with animals, be of not less than 28 days duration, demonstrate a dose-response, and involve effects biologically relevant to humans.

A well conducted repeated dose, subchronic or chronic toxicity study should include the following:

- a minimum of three doses administered and an adequate control group.
- a minimum of ten animals per sex, per dose group.

- a highest dose level which ideally elicits some signs of toxicity without inducing excessive lethality and a low dose which ideally produces no signs of toxicity.
- ideal dosing regimes of five-seven days per week.
- animals which are dosed by the same method during the entire experimental period.
- animals which are observed for at least 90 days.
- appropriate statistical methods relative to the experimental design.
- toxicity tests which allow for the detection of general toxic effects including neurological, physiological, biochemical and hematological as well as morphological (pathological) effects (ideally these will include immune function and reproductive function endpoints).

(E) Reproductive and developmental toxicity studies must also be considered when available. A well conducted developmental study should include the following:

- At least 20 young adult and pregnant rats, mice or hamsters or 12 young adult and pregnant rabbits at each dose level.
- At least three dose levels and a control group.
- The highest dose which induces some slight maternal toxicity but no more than 10 percent mortality, and a low dose which does not produce grossly observable effects in dams or fetuses. The middle dose level, in an ideal situation, produces minimal observable toxic effects.
- A dosing period which includes the gestational period or at least covers the major period of organogenesis; gestation days 6 to 15 for the rat and mouse, 6 to 14 for the hamster, and 6 to 18 for the rabbit.
- Daily observations on dams including weekly food consumption and body weight measurements.
- Necropsy which includes both gross and microscopic examination of the dams; uterine examination including a count of the number of embryonic or fetal deaths and the number of viable fetuses; fetal weight.
- One-third to one-half of each litter are to be prepared and examined for skeletal anomalies and the remaining for soft tissue anomalies.

(F) The minimum toxicity data set for developing a Rule 2222(5) standard is an oral rat LD_{50} (dose that is lethal to 50 percent of the test species). It should be noted that an acute to chronic NOAEL extrapolation factor of 10,000 is applied in addition to the 10x each for intraspecies and interspecies uncertainty for a total extrapolation factor of 1,000,000. The following conditions must be evaluated to determine if a study is adequate for this purpose:

- Animal age and species identified.

- A minimum number of five animals of each sex per dose level.
- A 14 day or longer observation period following dosing.
- A minimum of three dose levels that are appropriately spaced. Most statistical methods require at least three dose levels.
- Identification of purity or grade of test material used. This is particularly important in older studies.
- If a vehicle is used, the selected vehicle should be known to be non-toxic at the doses tested.
- Gross necropsy of test animals.
- Animal acclimation period before the study begins.
- Dosing route; gavage or capsule.
- Total volume of vehicle plus test material should remain constant for all dose levels.
- Animals should be fasted before dosing.

Appendix B: Uncertainty Factors

Uncertainty factors will 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. The uncertainty factors will be determined as follows:

(1) An intraspecies uncertainty factor of 1 to 10 will be used when extrapolating from valid experimental results from studies of prolonged exposure to average healthy humans. This factor of up to ten is used to protect sensitive members of the human population.

(2) An interspecies uncertainty factor of 1 to 10 will 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. When considered with the intraspecies uncertainty factor above, a factor of up to one hundred is used in extrapolating data from the average animal to protect sensitive members of the human population.

(3) A subchronic to chronic uncertainty factor of 1 to 10 will be used when extrapolating from animal studies for which the exposure duration is less than chronic, but more than subchronic (90 days or more in length), or when other significant deficiencies in study quality are present, and when useful long-term human data are not available. When considered with intraspecies and interspecies uncertainty factors above, a factor of up to one thousand is used when extrapolating data from less than chronic, but more than subchronic, studies for average animals to protect sensitive members of the human population from chronic exposure.

(4) An uncertainty factor of 1 to 3 will be used when extrapolating from animal studies for which the exposure duration is less than subchronic (less than 90 days). When considered with the intraspecies, interspecies and subchronic to chronic uncertainty factors above, a factor of up to three thousand is used in extrapolating data from less than subchronic studies for average animals to protect sensitive members of the human population from chronic exposure.

(5) An additional uncertainty factor of 1 to 10 may be used when deriving a value from a LOAEL. The UF accounts for the lack of an identifiable NOAEL. The level of additional uncertainty applied may depend upon the severity and the incidence of the observed adverse effect.

(6) An additional uncertainty factor of 1 to 10 may be applied when there are limited effects data or incomplete subacute or chronic toxicity data, for example, reproductive/developmental data. The level of quality and quantity of the experimental data available and structure-activity relationships may be used to determine the factor selected.

(7) An additional acute to chronic factor of 10,000 will be used when extrapolating from acute lethal effects (e.g., oral rat LD_{50}) to a chronic NOAEL. The total factor of 1,000,000 is generally used for this type of data set, that includes the intraspecies and interspecies uncertainty factors above.