REVISED
GLEAS PROCEDURE 22.1

PROCEDURE FOR CALCULATING HUMAN CANCER VALUES (HCVs)

I. Introduction

The Human Cancer Value (HCV) is derived under R 323.1057 of the Michigan Water Quality Standards. The HCV is the concentration of a carcinogen in ambient water designed to protect humans from an excessive risk of developing cancer using the exposure assumptions specified in R 323.1057(4). This procedure provides guidance on reviewing cancer bioassays, entering data into the cancer model, and then calculating the HCV when appropriate. The cancer risk assessment procedure generally involves the following eight steps:

1. Review data and determine that cancer risk assessment is appropriate.
2. Prepare and adjust data for model input.
3. Cancer risk modeling.
4. Goodness-of-fit test for adequate fit of the model to the data.
5. Utilize the model output to calculate the slope factor (potency), risk-associated dose, and corresponding criteria for surface waters.
6. Prepare a justification document.
7. Maintain a file documenting the assessment, and add the criteria to the Rule 57 database.
8. Enter the appropriate information into the Environmental Protection Bureau Chemical Criteria Database (EPBCCD).

II. Review Data and Determine that Cancer Risk Assessment is Appropriate

All available and relevant data on the chemical's potential carcinogenicity should be reviewed. This must include a review of the chemical file in the United States Environmental Protection Agency's (USEPA's) IRIS database, if available. For risk assessment, epidemiological data are preferred over animal data if they are adequate for this purpose (guidance is provided by OSTP, 1985; USEPA, 1986). Risk assessment by means of epidemiological data will be conducted on a case-by-case basis (see risk assessment file for benzene for example). The interpretation and evaluation of animal carcinogenicity bioassays shall utilize the protocols and guidelines provided by the OSTP (1985) and USEPA (1980; 1985; and 1986). Considerations shall therefore include the statistical and biological significance of the tumorigenic response, the route of administration, the duration of the exposure period of the study, the number of dose groups, etc. Positive inhalation data are generally utilized only if oral data are insufficient and if the tumorigenic response is systemic (non-respiratory) rather than local. All datasets which are thereby determined to be adequate and appropriate for quantitative risk assessment are generally utilized in the following risk modeling and extrapolation steps.

III. Data Preparation and Adjustment for Model Input

Carcinogenicity bioassays have three key variables which are utilized in risk modeling: the number of animals studied at each dose level; the number of tumor-bearing animals; and the doses administered. For each species, strain, sex, and tumor site/type which provides a positive tumorigenic response, as discussed above, the data are prepared for modeling as follows.

A. The Number of Animals at Each Dose Level

For risk assessment purposes, the number of animals at each dose level for the species, sex, and tumor being assessed includes those that were histopathologically evaluated and that were sufficiently at risk for tumor development. Therefore, exclude animals that were not adequately examined, or that expired prior to the first appearance of the specific tumor type in a treated group. If the obtainable bioassay information does not provide sufficient detail to determine this, it may be assumed that the reported number of animals examined were all at sufficient risk.

For the control group, a vehicle control group is generally preferred over an untreated or sham treated control group if a vehicle is used in administering the test substance.

B. The Number of Tumor-Bearing Animals

The response rate is normally based on the combined number of benign and malignant tumors of the same histogenic origin, unless the benign tumors are not considered to have the potential to progress to malignant tumors. When two or more significantly elevated tumor sites or types are observed in the same study, species, and sex, then the response for the tumor type predicting the highest estimate of the slope factor shall generally be used for the risk assessment. However, in some cases it may be appropriate to pool the data for all tumors which are statistically significant prior to modeling the data.

Since the Global models will not accept a 100% response rate as model input, such data must be adjusted. If the study has two or more treatment groups and the highest dose results in a 100% response, that group should be adjusted or eliminated from the model input. If the 100% response occurs in the sole treatment group, or in an intermediate treatment group, the number of animals responding should be reduced by 1 (the Global 82 modeling will not accept a fractional response). See the risk assessment file for 3,3'-dichlorobenzidine for an example.

C. The Doses Administered

The dose levels for model input should generally be in units of mg/kg/d, although other units are acceptable (e.g., ug/kg/d for 2,3,7,8-TCDD). If the reported exposures are in units of food residue concentration (e.g., ppm) or concentration in air (e.g., mg/m^3), the administered doses in mg/kg/d must be estimated for model input.

The doses for model input must be the average doses over the entire study duration, i.e., the Study Average Dose (SAD). To calculate the SAD, it may be necessary to first adjust for intermittent non-dosing periods, such as weekends, and calculate the time-weighted average dose (TWA). Secondly, it may be necessary to adjust for an observation period following the cessation of treatment. In this case, where the duration of the dosing period (le) is less than the duration of the study (Le), the time-weighted average dose should be multiplied by the fraction le/Le (USEPA, 1980). For example, if a study protocol involves dosing 5 days/week for 102 weeks, followed by a 2-week observation period, the SAD is calculated in two steps as follows:

1. TWA (mg/kg/d) = daily administered dose (mg/kg/d) x 5/7
2. SAD (mg/kg/d) = TWA (mg/kg/d) x $\frac{le = 102}{Le = 104}$

These calculations become somewhat more complicated if the doses to the treatment groups were altered during the course of the study (e.g., increased to achieve a Maximum Tolerated Dose (MTD), or decreased due to overt toxicity). If the conversion of doses to mg/kg/d requires estimation of the animal weights, utilize the study-specific adult weights whenever possible. For example, the growth curves provided in the NTP bioassays allow the estimation of the average adult weight from the midpoint of the flatter (adult-stage) portion of the curve. If the study does not provide body weights, refer to USEPA (1988) for default animal data.

IV. Cancer Risk Modeling

The linearized multistage procedure will be employed for risk modeling and extrapolation in the absence of adequate information to the contrary. Available model versions include Global 79 (Crump and Watson, 1979), Global 82 (Howe and Crump, 1982), and Global 86 (Howe et al., 1986). Criteria derivation shall be based on Global 82 modeling and extrapolation (Global 82 and Global 86 are virtually identical). Other models, including modifications or variations to the linear multistage model that are appropriate to the available data may be used when scientifically justified. Attachment 1 of this procedure describes the operation of the Global 82 model.

Chemical-specific carcinogenicity risk assessments by the USEPA in the IRIS database or in documents of USEPA program offices should be obtained and reviewed to ensure consistency in our approach, unless a divergence is justifiable. It is noted by the USEPA (1986) that "The Agency will review each assessment as to the evidence on carcinogenesis mechanisms and other biological or statistical evidence that indicates the suitability of a particular extrapolation model," and "When longitudinal data on tumor development are available, time-to-tumor models may be used."

V. Goodness-of-Fit Test for Adequate Fit of the Model to the Data

Whenever the multistage model does not fit the data sufficiently, as determined by the chi-square goodness of fit statistical test, the model may be refitted to the data omitting the highest dose (USEPA, 1980). This is continued until an acceptable fit to the data is obtained. Alternatively, a different model may be employed to obtain a better fit to the entirety of the bioassay data. The chi-square statistic (χ^2) is conveniently provided in the output from Global 82 modeling. It is calculated by the equation presented in USEPA (1980). The fit of the model to the data is determined to be unacceptable when chi-square (χ^2) is larger than the cumulative 99% point of the chi-square distribution with f degree of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficients (as presented in the model output). The cumulative 99% point of the chi-square distribution corresponding to various degrees of freedom (df) are:

for 1 df: 6.637
for 2 df: 9.210
for 3 df: 11.344
for 4 df: 13.277
for 5 df: 15.085
for 6 df: 16.812 (reference: Devore, 1982).

VI. Utilize the Model Output to Calculate the Slope Factor (Potency), the Risk-Associated Dose, and Corresponding Criteria for Surface Waters

For each dataset modeled, the slope factor q_1* is calculated as follows:

A. Calculate the plausible upper bound of the slope factor for the animals tested, q_1*(animal). This is done by the following equation, utilizing the values provided by the model.

$$q_1^* \text{ (animal)} = \frac{\text{95\% Upper Confidence Limit on Extra Risk at the } 10^{-5} \text{ risk level}}{\text{Maximum Likelihood Estimate of dose at } 10^{-5} \text{ risk level}}$$

The units for the slope factor q_1* (animal) are dependent on the dose units of the model input. Generally, dose levels are in units of mg/kg/d, and the slope factor units are $(mg/kg/d)^{-1}$.

B. If the duration of the study (Le) is significantly less than the natural lifespan for the species (L), the slope factor is adjusted to account for unobserved tumors due to the short study duration (USEPA, 1980). For mice and rats, the natural lifespan (L) is assumed to be 90 weeks and 104 weeks, respectively. The slope factor adjustment will be made for mice and rat data if the study duration (Le) is less than 78 weeks for mice or 90 weeks for rats, by multiplying the slope factor by the factor $(L/Le)^3$. For other species, this adjustment should also be made whenever appropriate, using species-specific values for L and the Le trigger level. The latter may be determined using the trigger levels for mice and rats as a guideline.

C. Interspecies scaling is generally done by assuming interspecies equivalence of dose per surface area per day. The species sensitivity factor is calculated by dividing the average weight of a human (70 kg) by the weight of the test species (in kg units) and taking the fourth root of the resultant value. The animal slope factor is multiplied by this factor to obtain the human slope factor.

$$q_1^* \text{ (human)} = q_1^* \text{ (animal)} \times (70 \text{ kg} / W(\text{kg}))^{1/4}$$

The weight (w) of the test species should be the average adult weight from the control groups in the particular bioassay if possible, or derived from available data tables or standard assumed weights (e.g., USEPA, 1988).

D. If more than one positive bioassay is available for calculation of q_1* (human), the highest estimate for the slope factor is generally used in the following steps for criteria derivation. However, if two or more positive bioassays exist that are of comparable quality and are identical with regard to species, strain, sex, and tumor type, then the geometric mean of the slope factors may be used for criteria derivation (USEPA, 1980). A more liberal averaging approach is suggested by USEPA (1989): "Occasionally, in situations where no single study is judged most appropriate, yet several studies collectively support the estimate, the geometric mean of estimates from all studies may be adopted as the slope. This practice ensures the inclusion of all relevant data." For an example of this approach, see the IRIS file for DDT.

E. Determine the risk-associated dose (RAD) corresponding to a risk of one in 100,000 (10^{-5}) as follows:

$$RAD = \frac{10^{-5}}{q_1^* \text{ (human)}}$$

RAD is in units of mg/kg/d if $q_1^*$is in units of $(mg/kg/d)^{-1}$. This equation reflects the underlying association of risk = dose x potency, rearranged to the above form of dose = risk/potency. Although "potency" is older terminology, it is often used synonymously with "slope factor," the new terminology.

F. The RAD is then used to derive the HCV for the protection of surface waters used as drinking or nondrinking water resources.

$$HCV \text{ (mg/l)} = \frac{RAD \text{ (mg/kg/d)} \times 70kg}{WC + (FC_{TL3} \times BAF_3) + (FC_{TL4} \times BAF_4)}$$

Where:

HCV =	concentration (mg/l) of the carcinogen in surface waters which is protective of human health
RAD =	10^{-5} risk-associated dose
WC =	daily water consumption of 0.01 L for surface waters protected as a nondrinking water resource; 2 L for surface waters protected as a drinking water resource
FC_{TL3} =	daily fish consumption of a trophic level 3 fish (FC = 0.0036 kg/d)
FC_{TL4} =	daily fish consumption of a trophic level 4 fish (FC = 0.0114 kg/d)
BAF_3 =	bioaccumulation factor for trophic level 3 fish as derived per Rule 57
BAF_4 =	bioaccumulation factor for trophic level 4 fish as derived per Rule 57

VII. Prepare a Justification Document

The justification is a chemical-specific document which presents the rationale behind the choice of the study used for the cancer risk assessment. The document should be titled as the cancer risk justification for the pertinent chemical identified by both name and CAS number. Include the following information in the justification:

A. A brief review of the available cancer data.

B. The rationale behind your choice of a particular study and tumor incidence data set.

C. Any unusual or significant modifications of the data or the process.

Upon finalization of the justification, initialize and date the document.

VIII. Maintain a File Documenting the Assessment, and Add the Criteria to the Rule 57 Database

The final step in the process pertains to maintenance or creation of a risk assessment file and entry of the data into the computerized database. After the HCV calculations have been performed and the justification written, either create a new file or update the old one. The current calculation sheet, the Global printouts, and the justification should be placed loose in the file. Any superseded calculations, criteria, printouts, etc., material should be attached to the back of the file folder. In addition, fill out the Terrestrial

Toxicity and Aesthetics Values Work Sheet and attached it to the inside front cover. Then complete a Rule 57 data entry form. If the HCV has not changed from the last entry, simply enter the current CAS date (as YYMM) to confirm that the data review has been updated. If the HCVs have changed or were calculated for the first time, enter the values in units of μg/l. If HCVs could not be calculated due to insufficient data, enter an I.D. (insufficient data) in the HCV columns. Fill out these sheets after completion of both the HNV and HCV reviews. Once completed, sign and date the forms and have all material reviewed by the appropriate person(s) for finalization.

IX. Enter the appropriate information into the Environmental Protection Bureau Chemical Criteria Database

REFERENCES

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ATTACHMENT 1

Instructions for Operating the Global 82 Cancer Risk Assessment Model

I. For instructions on how to load the Global 82 program using DOS instructions, see Attachment 2 or contact a computer technician.

II. Three general steps to using the Global 82 model:

A. Create a Microsoft Word (MS Word) document file consisting of data to be modeled using Global 82.
   1. Open MS Word.
   2. Use File, Open, and locate the directory called "Global."
   3. Open Global directory and locate a data file (files with .dat ending).
   4. Open data file and modify data set.
      a. See Attachment 3 for example of a data set.
      b. See Attachment 4 for a detailed description of data set.
   5. Save the modified data set in Global directory with a NEW name (e.g., TCERAT.DAT).

   You may open the Global directory to verify that your data set has been saved.

B. Run Global 82 model with new data set (using DOS).
   1. Open MS DOS window and change directory to "Global" directory by typing cd\global {enter} at the prompt (screen should read C:\GLOBAL).
   2. To run program: at the prompt, type global82 {enter}.
   3. At the prompt, type in the data set filename (e.g., TCERAT.DAT) {enter}.
   4. At the prompt, type in a filename for the results (e.g., TCERAT.OUT) {enter} (after the program has run properly, the words "program terminated" appear).
   5. Exit from the MS DOS window.

C. To view results from Global 82 model.
   1. Open MS Word.
   2. Open the output file that you created in DOS during step II.B.4.

D. To print results from Global 82 model.
   1. Open MS Word.
   2. Open the output file that you created in DOS during step II.B.4.
   3. Print results as per MS Word print commands.

ATTACHMENT 2

Loading Global 82 Model onto a Personal Computer

Copy the files in the 3½ inch diskette, "Global 82-Sills" onto the hard drive of the PC. This diskette contains five files:

1. CONVERT.EXE - to convert a wordperfect file into ASCII format (required by the Global program).
2. GLOBAL82.DAT- example datasets.
3. GLOBAL82.EXE - executes the Global 82 program.
4. HYDRAZI1.DAT - hydrazine dataset.
5. GARY.DAT - an example dataset.

Copy it as follows:

1. At the command prompt: C:|> md global {enter} (this makes a directory called global).
2. C:|>cd global {enter} (this switches to the global subdirectory).
3. At the C:\GLOBAL> prompt: copy a:*.* {enter} (this copies the files from the diskette in the "a" drive into the subdirectory "global").

ATTACHMENT 3

Example of Data set for Global 82 Model

GARY.DAT file for use as a template

```
TEST OF GLOBAL82    EXAMPLE 1
5 4 0 2 6 0 0
100 100 100 100 100 100
0 1 20 50 100
1 0 1 7 18
.1 2 .01 2 .1D-2 2 .1D-3 2 .1D-4 2 .1D-5 2
```

NOTES: It is easier to open and modify a data file and then save it with the new name. There are 6 lines of information in the dataset. Each line is also referred to as a "card;" these are described in detail in Attachment 3.

Under normal, routine use, staff only need to modify lines 1, 2 (fields A and B), 3, 4, and 5.

Line 1	The title of your dataset.
Line 2	A: The number of dose groups.
	B: The number of dose groups minus one.
Line 3	The number of animals in each dose groups.
Line 4	The dose levels administered.
Line 5	The number of tumor-bearing animals in each group.

ATTACHMENT 4

DESCRIPTION OF THE 7 CARDS (LINES) OF DATA ENTRY

Card1: The title of your dataset. Type right over the previous title; don't "insert." Include the name of the chemical in the title. You are allowed no more than 64 characters.

Card 2: Parameters A - G separated by commas.

A. The number of dose groups, including controls.

B. The number of dose groups minus one.

C. Specifies whether a background response (Qo) is estimated. This parameter should be set to zero, so that Qo will be estimated.

D. Specifies whether the calculated risks will be "extra risk" or "additional risk." This should be set to 2 for "extra risk;" this was done by GLOBAL82 and is routinely done by the USEPA.

E. Specifies the number of values of extra risk to be analyzed and presented at the end of the printout as lower confidence limits on dose along with values for the Q parameters of the confidence bound. The LCL on dose, however, already appears earlier in the printout, and the Q parameters are of no particular use to us. The template has a value of 3 for this parameter purely for instructive purposes.

F. Specifies the number of environmental doses to be analyzed. This is set at zero currently. However, this function could be useful should we need to evaluate a particular environmental exposure level relative to the animal bioassay data being modeled.

G. Specifies that confidence limits will also be calculated for the linearized procedure employed in GLOBAL82. This is set at zero in order to have these limits calculated.

Card 3: The number of animals in each dose group, i.e., controls, low dose, moderate dose, etc.

Card 4: The dose levels administered, i.e., controls (0), low dose, etc. Units must be consistent and are generally mg/kg/day, although ug/kg/day, mg/m3, or other units may be used.

Card 5: The number of tumor-bearing animals within each dose group.

Card 6: This is a vector of the risks for which you want lower bounds on safe dose calculated, as called for in Card 2E. The first element of the vector is the risk level, which may range from 0.1 to 0.1D-7. The second element of the vector is an integer from 1 to 4 which specifies the desired confidence limit (1=90%; 2=95%; 3=97.5%; 4=99%). The template and the PCB example in Figure 1 call for 3 risk levels to be analyzed: .01 at a 95% limit; .1D-4 at a 95% limit; and .1D-5 at a 95% limit.

Card 7: If you specified in Card 2F an analysis of environmental dose(s), here is where you would list those in vector format. The first element is the desired confidence bound indicated by an integer 1-4 as described under Card 6.