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REVIEW AND COMPARISON OF DETERMINING ACCEPTABLE AMBIENT AIR CONCENTRATIONS FOR VINYL CHLORIDE BASED ON CARCINOGENICITY IN TWO EPA REPORTS

There are two recent EPA documents in which estimates were derived for q1* values for vinyl chloride. In the first document (Health Effects Assessment for Vinyl Chloride, EPA, 1984, Office of Health and Environmental Assessment, EPA/540/1-86-036) the animal q1* was given as 4.23×10^{-3} (mg/kg/day) and the human q1* was given as 2.5×10^{-2} $(mg/kg/day)^{-1}$ (see Appendix 1 for determination of animal q1* value using GLOBAL86). Inhalation studies in rats were used and total tumors were used as the toxicological end point. This q1* value can be converted to units of ppm^{-1} or $(ug/m^3)^{-1}$ as follows by employing the same conversion factors used by EPA in converting animal exposures in ppm to human equivalent exposures in mg/kg/day:

1. Correction for surface area between humans and rats

$[(1/(70\text{-kg human}/.35 \text{ kg rat}))^{1/3}] * 2.5 \times 10^{-2} = 4.27 \times 10^{-3}$ $(mg/kg/day)^{-1}$

2. Adjustment for body weight of rat

$4.27 \times 10^{-3}/.35$ kg rat $= 1.22 \times 10^{-2}$ $(mg/day)^{-1}$

3. Adjustment for breathing rates of rats

$.233\ m^3/d * 1.22 \times 10^{-2} = 2.72 \times 10^{-3}$ $(mg/m^3)^{-1}$ or

2.72×10^{-6} $(ug/m^3)^{-1}$ or

2.56×10^{3} $(ug/m^3 * ppm) * 2.72 \times 10^{-6}$ $(ug/m^3)^{-1}$ =

6.96×10^{-3} ppm^{-1} (EPA84 calculation was 6.80×10^{-3} ppm^{-1})

4. It was assumed that all the vinyl chloride inhaled was absorbed into systemic circulation. This is a conservative estimate.

In a more recent update (Health and Environmental Effects Profile for Chloroethene, EPA, 1985, Environmental Criteria and Assessment Office ECAO-Cinn-P155) the rat q1* was determined to be 5.04×10^{-2} (mg/kg/day) (see Appendix 2 for determination of the rat q1* value using GLOBAL86) and the human q1* was determined to be 2.95×10^{-1} $(mg/kg/day)^{-1}$. Animal studies from the same

investigator were used as in the EPA 1984 report; instead of using total tumor incidence, however, angiosarcomas of the liver were used as the only toxicological end point. Corrections to the dose were made since the observation period was extended after exposure stopped and an assumption was made that only 50% of the inhaled vinyl chloride was being absorbed. By using the same conversion factors above and correcting for % uptake the following inhalation q1* was determined.

1. Correction for surface area between humans and rats

$[(1/(70/.35))^{1/3}]*2.95x10^{-1}$ $(mg/kg/d)^{-1}$ = $5.05x10^{-2}$ $(mg/kg/d)^{-1}$

2. Adjustment for body weight and breathing rate of rats

$[5.05x10^{-2}$ $(mg/kg/d)^{-1}/.35kg]*.223$ m^3/d = $3.22x10^{-2}$ $(mg/m^3)^{-1}$

or $3.22x10^{-5}$ $(ug/m^3)^{-1}$

3. In this assessment EPA assumed that only 50% of the vinyl chloride was absorbed through the lungs. To correct for this the q1* value has to be multiplied by .5.

$(.5)*3.22x10^{-5}$ $(ug/m^3)^{-1}$ = $1.61x10^{-5}$ $(ug/m^3)^{-1}$

or $4.12x10^{-2}$ ppm^{-1}

The state of Mississippi is recommending a q1* value of $4.2x10^{-5}$ $(ug/m^3)^{-1}$. This value is derived from the more recent EPA report just described from the q1* value of $2.95x10^{-1}$ $(mg/kg/d)^{-1}$. This number is 2.6-fold greater than the number calculated above ($1.61 x0^{-5}$). Mississippi derived their number as follows.

$[2.95x10^{-1}$ $(mg/kg/d)^{-1}]*(.5)*(20$ $m^3/d)*(10-3mg/ug)/70$ kg = $4.21x10^{-5}$ $(ug/m^3)^{-1}$

This calculation is incorrect, since the same conversion factors used by EPA to convert experimental levels (ppm) to human exposure equivalents (mg/kg/day) were not used by the state of Mississippi to back-calculate from (mg/kg/day) to ppm or ug/m^3.

Analysis of the data used by EPA in determining a human q1* of $2.95x10^{-1}(mg/kg/day)^{-1}$ in their 1985 report

Figure 1 illustrates the relationship between liver angiosarcoma and vinyl chloride exposure in rats. No dose-response relationship is obvious. Furthermore, EPA did not use all the data in determining the q1* value. It only selected data points 0, .172, .344 and .86 mg/kg/day. There was no rationale provided why other data points were omitted. In addition, the data points

are not even taken from the same experiment. For example, data points .344 and .86 were from Maltoni et al. experiment BT15 and data point 1.719 was taken from Maltoni et al. experiment BT1. Therefore, the manner in which the q1* value was calculated is scientifically incorrect and meaningless.

In the 1985 report the length of the experiment was reported to be up to 1029 days, whereas the exposure period to vinyl chloride was for 365 days. In the transformation of experimental doses to human equivalent doses an adjustment factor of 365/1029 was used. From a biological sense this dose-averaging approach may not be appropriate. The actual time to tumor data needs to be obtained in order to make the appropriate adjustments to dose.

The first q1* value established by EPA in 1984 was based on total tumors rather than liver angiosarcomas. Although in some instances total tumors may not provide the most sensitive assessment of cancer risk, the data as shown in figure 2 do show a linear dose response relationship up to 239.1 mg/kg/day. Therefore, these data provide a much better data base to determine a human q1* value, than the data base given in the EPA 1985 report.

Discussions with EPA's Cancer Assessment Group

EPA's Office of Health and Environmental Assessment often has contractors provide health profiles and reports on various chemicals. These documents are used primarily as guidance to provide available information on the toxicity of various environmental agents and to provide the agency scientists and regulators with initial data to determine what chemicals potentially should take greater priority in being regulated. Although these documents have undergone some peer review within EPA they have not undergone the extensive scientific peer review that is usually necessary to support program office regulations. The more recent 1985 EPA report entitled "Health and Environmental Effects Profile for Chloroethene," which is being used by the State of Mississippi, is a first draft report and has the disclaimer that it is "for review purposes only and does not constitute Agency policy." Discussions with EPA scientists in the Cancer Assessment Group revealed that they are aware of the deficiencies in the approach taken in the 1985 EPA report for calculating a q1* value for vinyl chloride and that additional evaluations of the data base are necessary to derive a more scientifically sound quantitative risk assessment.

Discussion

The state of Mississippi elected to use a unit risk factor of 2.95×10^{-1} $(mg/kg/day)^{-1}$ taken from an EPA report "Health and

Environmental Effects Profile for Chloroethene" September 1985. From this value they converted the units to obtain a q1* value of 4.21x10-5 ug/m^3. This value is not appropriate to use to set acceptable ambient exposure levels to vinyl chloride for the following reasons:

1. The conversion from mg/kg/day to ug/m^3 was done incorrectly (see above). The correct conversion would reduce the unit risk by a factor of 2.6.

2. The calculation was performed using a q1* value that EPA has not endorsed. This is stated in the disclaimer in the 1985 document.

3. The data used in calculating the q1* value in the 1985 EPA report are not of sufficient quality to determine a q1* value.

   a. There is no dose-response relationship.

   b. Results from different experiments were pooled in order to get a dose response relationship without any scientific rationale provided.

   c. Only certain data points were selected for determining the unit risk without any scientific rationale provided.

   d. Two of the data points available in the original Maltoni et al. paper were not included in the 1985 EPA report. No scientific rationale was provided.

4. Vinyl chloride is known to require metabolic activation to the proximate carcinogen. These pharmacokinetic considerations were not incorporated into the dose-response data used in determining the unit risk determination in the 1985 EPA report.

5. Many other studies are available than Maltoni et al. to estimate the carcinogenic risk of vinyl chloride. These other studies should be assessed, and pharmacokinetic/biologically based models should be considered to estimate more accurately the human carcinogenic risk of exposure to vinyl chloride gas.

Conclusions

The use of the unit risk presented in the 1985 EPA report entitled "Health and Environmental Effects Profile for Chloroethene" to establish acceptable ambient levels of vinyl chloride in the air is not scientifically justifiable because of

the misuse of the data, lack of critical peer review of the methods employed in the report, and insufficient use of critical data pertinent in considering the carcinogenic risk of vinyl chloride.

Until a more scientifically sound risk assessment is performed the former q1* value of 2.72×10^{-6} $(ug/m^3)^{-1}$ from the 1984 EPA report entitled "Health Effects Assessment for Vinyl Chloride" should be used to estimate cancer risk for vinyl chloride in the air. Although there are also deficiencies in the data on which this q1* value is based, a solid dose-response relationship for total tumors (figure 2) was used to estimate risk.

APPENDIX 1

GLOBAL 86 (MAY 1986)

BY RICHARD B. HOWE AND CYNTHIA VAN LANDINGHAM

CLEMENT ASSOCIATES, INC
1201 GAINES STREET
RUSTON, LA 71270
(318) 255-4800

vinyl chloride: data taken from EPA 1984 report
(total tumors)

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
CHI-SQUARE TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	.000000	6/ 58	9.81
2	4.90000	10/ 59	10.69
3	23.9000	16/ 59	13.35
4	47.8000	22/ 59	16.50
5	239.100	32/ 59	34.98

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 5.6876

P-VALUE FOR THE CHI-SQ TEST WITH 3 DEGREES
OF FREEDOM IS .1278379359

FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = .185324445807
Q(1) = 2.983355597998E-03
Q(2) = .000000000000

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -163.144925015

CALCULATIONS ARE BASED UPON EXTRA RISK

GLOBAL 86 UPPER CONFIDENCE LIMITS ON RISK FOR FIXED DOSE

DOSE	MLE RISK	UPPER BOUND ON RISK	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.0000	2.97891E-03	4.22255E-03	95.0%	Q(0) = .15535 Q(1) = 4.23149E-03 Q(2) = .00000

NORMAL COMPLETION!

APPENDIX 2

GLOBAL 86 (MAY 1986)

BY RICHARD B. HOWE AND CYNTHIA VAN LANDINGHAM

CLEMENT ASSOCIATES, INC
1201 GAINES STREET
RUSTON, LA 71270
(318) 255-4800

vinyl chloride: data taken from EPA 1985 report
(liver angiosarcomas)

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
CHI-SQUARE TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	.000000	0/363	.00
2	.344000	1/119	1.17
3	.860000	5/120	2.92
4	1.71900	1/ 60	2.89

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 2.8312

P-VALUE FOR THE CHI-SQ TEST WITH 2 DEGREES OF FREEDOM IS .2427793524

FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = .000000000000
Q(1) = 2.867931930907E-02
Q(2) = .000000000000

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -33.1407703774

CALCULATIONS ARE BASED UPON EXTRA RISK

GLOBAL 86 UPPER CONFIDENCE LIMITS ON RISK FOR FIXED DOSE

DOSE	MLE RISK	UPPER BOUND ON RISK	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.0000	2.82720E-02	4.91334E-02	95.0%	Q(0) = .00000 Q(1) = 5.03816E-02 Q(2) = .00000

NORMAL COMPLETION!

Figure 1

EPA85 (liver angiosarcomas)

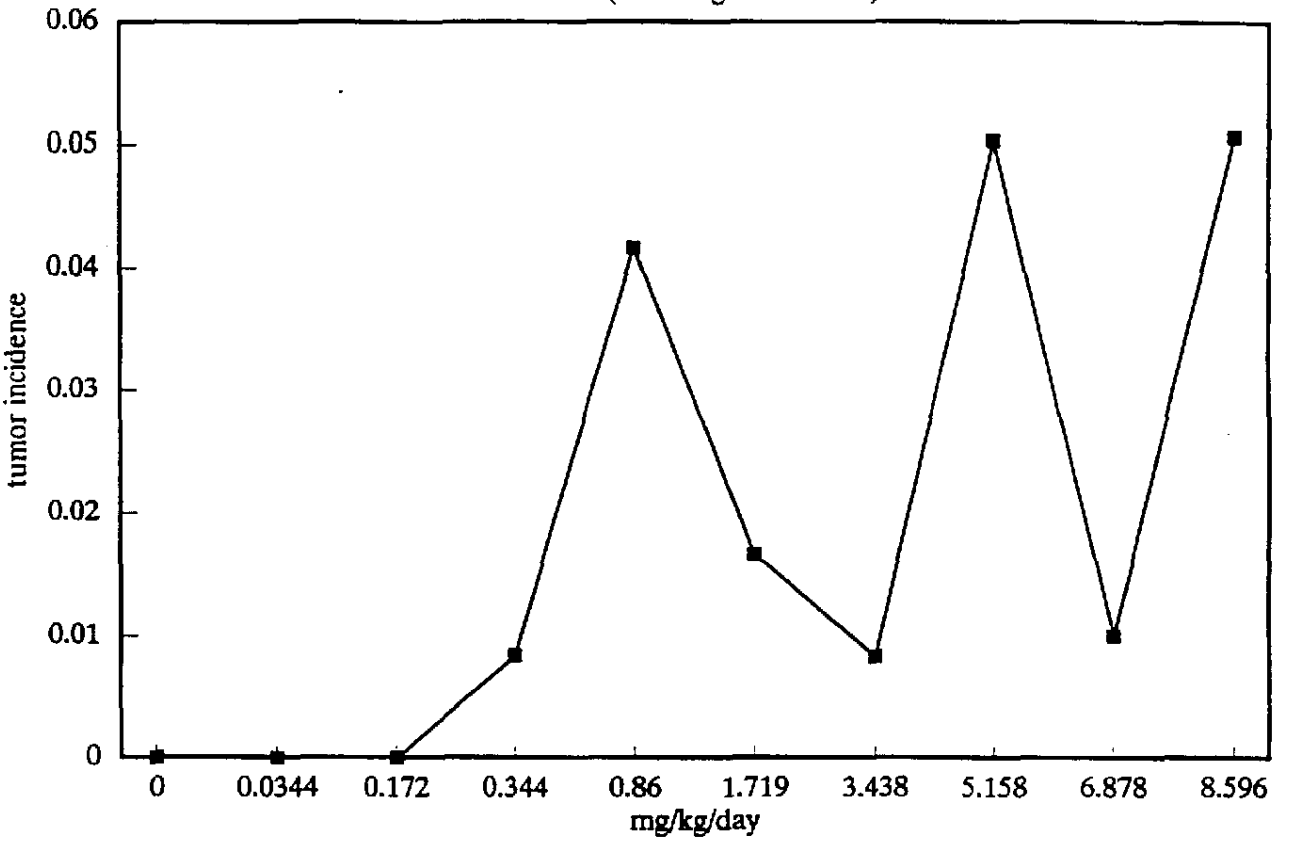

Figure 2