The Vinyl Institute

A Division of The Society of The Plastics Industry, Inc.

June 5, 1991

TO: VI Health, Safety and Environment Committee

RE: Comments to Louisiana DEQ on Proposed Ambient Air Standard for Vinyl Chloride

Enclosed is a copy of the comments filed May 31 with the Louisiana Department of Environmental Quality on the Department's proposed ambient air standard for vinyl chloride of 1.19 ug/m^3. These comments note that none of the unit risk factors calculated for inhalation of vinyl chloride are scientifically defensible and urge the postponement of the formal adoption of an ambient air standard for vinyl chloride.

Many thanks to Joe Ledvina and the members of his unit risk factor task force who worked with Bob Mathews of Keller and Heckman in preparing these submissions.

Meredith

Meredith N. Scheck
Assistant Director

MNS/bg

R&S 143430

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A Division of The Society of The Plastics Industry, Inc.

May 30, 1991

VIA FEDERAL EXPRESS

Mr. David Hughes
Louisiana Department of Environmental Quality
Office of Air Quality and Radiation Protection
Enforcement and Regulatory Compliance Division
7290 Bluebonnet Road
Baton Rouge, Louisiana 70810

Re: Comments Concerning a Proposed Rule to Amend the Air Quality Regulations, LAC 33:III, Chapter 51 Subchapters A, C, E, F, J, M, and V, and LAC 33:III. 6511 and 6523 **(LOG NUMBER AQ12)**

Dear Mr. Hughes:

The Vinyl Institute (VI), a division of the Society of the Plastics Industry, Inc. (SPI)1/ is pleased to submit comments concerning the Louisiana Department of Environmental Quality's (DEQ) Comprehensive Toxic Air Pollutant Emission

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1/ SPI is a 2,000 member not-for-profit trade organization representing all segments of the plastics industry in the United States. The Society's members include processors and manufacturers of plastics and plastic products, suppliers of raw material, processors and converters of plastic resins and manufacturers of accessory equipment for the plastic industry. Founded in 1937, SPI is the major national trade association of the plastics industry.

Members of the Vinyl Institute include the BF Goodrich Company, Borden Chemicals and Plastics Industries, CertainTeed Corporation, The Dow Chemical Company, Georgia Gulf Corporation, Occidental Chemical corporation, PPG Industries, Inc., PW Resins, Shintech, Inc., and Vista Chemical. Members of the Vinyl Institute account for approximately 82% of the domestic production of vinyl chloride and 63% of the domestic production of polyvinyl chloride.

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Control Program: Proposed Rule with Substantive Changes Incorporated (Proposed Rule).2/

On December 31, 1990, VI submitted comments in response to DEQ's initial proposed rule. These comments are intended to supplement and expand our original comments on the proposed rule with specific regard to the proposed ambient air standard for vinyl chloride of 1.19 $\mu g/m^3$ and the Unit Risk Factor (UFR) used to reach this value. LAC 33:III.5105 at Table 51.2.

As discussed more fully below, the proposed ambient air standard is not supported by the administrative record in this rulemaking. Significantly, the URF used to derive the ambient air standard was developed by the Environmental Protection Agency (EPA) using methods inconsistent with its own guidelines. Moreover, DEQ did not provide sufficient notice concerning the state's adoption of a URF and ambient air standard for vinyl chloride so that affected parties could comment on these values.

After examining carefully the information available in the public domain, one must conclude that none of the URF's calculated for inhalation of vinyl chloride are scientifically defensible. Consequently, the formal adoption of an ambient air standard for vinyl chloride must be postponed. At most, an interim standard of 37 $\mu g/m^3$, derived from the 1984 EPA URF of $2.7 \times 10^{-6}/(\mu g/m^3)$ might be temporarily used.3/ However, we urge DEQ to continue to seek a URF that has been determined using a sound scientifically based approach.

A. REGULATORY BACKGROUND

Act 184 requires the Secretary of DEQ to prepare an initial list of 100 toxic air pollutants (TAPs) proposed for regulation under provisions of the Act. See, R.S. 30:2060(a)(1). Vinyl chloride appeared on the proposed list of 100 TAPs to be regulated under Act 1984. See, La. Reg. Vol. 15, p. 73 (January 20, 1990). DEQ published a "Development Document" on March 27, 1990, which was designed to provide details on the information and procedures employed in developing the initial list of 100 TAPs to be regulated under

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2/ The Proposed Rule amends the Air Quality Regulations at LA ADMIN. Code title 33, Part III, Chapter 51, Subchapters A, C, E, F, J, M, and V and LAC 33: III.6511 and 6523 (AQ12).

3/ Health Effects Assessment for Vinyl Chloride, U.S. Environmental Protection Agency (Sept. 1984)(Cincinnati, Ohio, National Technical Information Service PB86-194475.

Act 184.4/ The SARA Title III (Emergency Planning and Community Right-To-Know Act of the Superfund Amendments and Reauthorization Act of 1986) Section 313 list of over 300 substances served as the principal basis for determination of the universe of toxic substances that would be candidates for the list of 100 TAPs. See, D.D. at 4.5/ This list was then reduced to account only for those substances known or reasonable expected to be emitted into the air in Louisiana. See, D.D. at 4. Then, four criteria were used to evaluate whether the remaining substances should be listed. These were: emission levels, human health effects, population exposure, and persistence or accumulation in the environment. See, D.D. at 4.

From the rankings of the three classes of substances, the list was narrowed to the 100 of greatest regulatory concern. The conclusion in the Development Document concerning vinyl chloride and other substances are based on a report by Dr. Barbara Shane and Ms. Suzanne Gardner of Louisiana State University under contract to the DEQ. See, D.D. at 7 and 11.6/

On November 20, 1990, DEQ provided public notice regarding the proposed rule which recommends regulations for the control of emissions of the 100 TAPs, including vinyl chloride, compiled previously. An ambient air standard of 1.19 $\mu g/m^3$ is proposed for vinyl chloride. See, LAC 33:III. 5105 at Table 51.2. No owner or operator of a stationary source may cause, allow, or permit vinyl chloride emissions to cause ambient air concentrations of vinyl chloride off the source's property to exceed this ambient air standard. Id. at § 5105 D.2.

B. THE ADMINISTRATIVE RECORD DOES NOT SUPPORT DEQ's AMBIENT AIR STANDARD FOR VINYL CHLORIDE

Several guideline documents are available that detail the methods adopted by EPA for calculating and adjusting exposure levels, extrapolating animal URFs to humans, and the

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4/ Louisiana Department of Environmental Quality, Office of Air Quality and Nuclear Energy, Development Document for the Initial List of 100 toxic Air Pollutants Proposed to be Regulated Under Act 184 (March 27, 1990).

5/ D.D. refers to the DEQ Development Document.

6/ B. Shane and S. Gardner, Assessment of Air Toxics Released in Louisiana in 1987, (1989) Louisiana State University.

means of calculating URFs from experimental data. The most recently available document expressing EPA's policies on risk assessment is incorporated into Background Document 2 for the Integrated Risk Information System (IRIS).7/ The same procedures described in Background Document 2 are described in EPA's final guidelines for carcinogen risk assessment.8/

The URF used to calculate the proposed air standard does not comply with the EPA guidelines for risk assessments as expressed in its own documents and is therefore not suitable for use in determining an air standard for vinyl chloride. Our primary objections to the bases of the URF are as follows:

1. EPA selectively and incorrectly discarded data points from the experimental database from which the URF was calculated.

2. EPA's criterion for goodness of fit in selecting data to be used was not met.

3. There is a discrepancy between the URF's calculated for total tumors and liver angiosarcomas.

4. EPA's use of a surface area scaling factor from rats to humans is not called for when the chemical in question is not toxic in and of itself but is metabolized to an unstable intermediate.

5. Pharmacokinetic information, although widely available, was not used in the EPA calculation.

C. ORIGINS OF EPA's URFs

1. 1984 URF

EPA's 1984 human inhalation URF, $2.7 \times 10^{-6}/(\mu g/m^3)$, was calculated from the first fully completed vinyl chloride inhalation assay available from which dose-response data

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7/ EPA Approach for Assessing the Risks Associated with Chronic Exposures to Carcinogens. Available from: U.S. Environmental Protection Agency, Office of Research and Development, Environmental Criteria and Assessment Office, Cincinnati, OH 45268.

8/ 51 Fed. Reg.33992 September 24, 1986.

suitable for performing a risk assessment was available.9/ EPA used only the data from the five lowest dose groups: 0, 50, 250, 500, and 2,500 ppm (administered dose) to calculate the 1984 URF. This choice of data points is consistent with what is known about the absorption and metabolism of vinyl chloride.10/ Apparently, EPA chose to exclude from the dose-response evaluation those data points beyond the point of metabolic saturation.

We have determined in a simulation of the EPA calculation that the statistical criterion used by EPA to assure the quality of the "curve-fitting" procedure, i.e., that the chi-square test yields a probability of >99% ($p<0.01$) was not met (actually $p = 0.128$) (See Attachment I).

The strengths of this EPA risk assessment lie primarily in the smooth dose-response curve and in the use of a single set of data obtained from a single experiment. It is important to note that at the time of the 1984 report, EPA had access to all data available that could be of potential use in risk evaluations.

2. 1985 URF

In 1985, EPA published a report entitled Health and Environmental Effects Profile For Chloroethene.11/ The URF for human risk to vinyl chloride by inhalation was recalculated in the 1985 report as 0.295/(mg/kg/day), which is equivalent to 8.4×10^{-5} $\mu g/M^3$. The 1985 URF was derived from data combined from a series of inhalation bioassays on rats as reported by Maltoni, et.al., in 1981.12/ By combining data from several of the Maltoni experiments, the dose-response due to administered doses from one ppm to 30,000 ppm could be evaluated. Of the available data points EPA used only three (10, 25, and 50 ppm) to calculate the 1985 URF.

9/ Carcinogenicity Bioassays of Vinyl Chloride Monomer: A Model of Risk Assessment on an Experimental Basis, C. Maltoni, et. al., Environmental Health Perspectives, 41 (1981) 3-29.

10/ Toxicological Profile for Vinyl Chloride, Agency for Toxic Substances and Disease Registry, U.S. Public Health Service (1989), ASTDR/TP-88/25.

11/ Available from the National Technical Information Service. Publication number PB88-174529.

12/ See footnote 8.

When the data used by EPA to calculate the 1985 URF is evaluated using the linearized multistage model (Global 86 computer program) it is found once again that EPA's criterion for goodness of fit is not met. In this case p = 0.243, which is a poorer fit than that found for the 1984 URF (See Attachment II).

D. IMPROPRIETY OF USING THE 1985 URF

1. Selective Use of Data for Risk Calculations

First, selected data points were excluded from both the 1984 and 1985 calculations. Thus, the 1984 URF excluded data above the administered dose of 2,500 ppm, presumably because experiments on the metabolism of vinyl chloride indicate clearly that the metabolic process becomes saturated. The inclusion of data points beyond this saturation point would yield a URF that underestimates the risk at low concentrations. However, in calculating the 1985 URF, EPA excluded data points at one ppm and five ppm (administered dose). There is no scientific justification (nor an explanation) for this exclusion. Furthermore, data points above 50 ppm were excluded due to a poor fit: in EPA's terms, "the goodness of fit hypothesis was rejected for the data at $\geq$3.438 mg/kg/day.") Once again, there is no scientific justification for this exclusion of data, especially since there is no clear plateauing of responses above 50 ppm (administered dose). Actually, an improved data-fit with a chi-square goodness of fit of >97.5% ($p < 0.025$) is obtained by using all data up to 150 ppm. Given that the data from several experiments were combined to obtain a dose-response curve, a greater variability in data would be expected, especially at low doses.

In fact, the exclusion of data points above the administered dose of 50 ppm results in the anomalous result that the URF is calculated using exclusively data points that are not associated with a statistically significant tumor response.13/ This means that the 1985 URF (the one used to determine the DEQ ambient air standard) was calculated with data representing zero risk and in effect represents only the variability in the data at low dose. The "slope" of such a curve has no meaning whatsoever, even if there are data points corresponding to higher doses that are associated with significant number of tumors.

13/ Archives of Experimental Research on Industrial Carcinogens, Volume 2 (1984), C. Maltoni and M. Mehlman, Editors, Princeton Scientific Publications.

2. EPA's Criterion for Goodness of Fit is Not Met

EPA's approach to quantitative risk assessment has been summarized. This summary states that the fit resulting from the linearized multistage (LMS) program (Global82 or similar programs) is unacceptable whenever chi-square (X^2) is larger than the cumulative 99% point of the chi-square distribution with f degrees of freedom ($p < 0.01$). Where f is defined as the number of dose groups minus the number of non-zero multistage coefficients. As shown in the Global 86 printouts (See Attachments I & II) for both the 1984 URF and 1985 URF this criterion is not met. The 1984 value is actually closer to meeting this criterion.

3. Discrepancy Between URFs Derived from Total Tumors and Liver Angiosarcomas Only

The observation that the risk based on the total tumors observed in the Maltoni BT-1 experiment, on which the 1984 URF is based, is smaller than the risk due to liver angiosarcomas alone from four combined experiments, on which the 1985 URF is based, is the opposite of what is expected.

One explanation of this discrepancy is that after excluding selected data from the combined data sets, the slope of the remaining data points is heavily influenced by the relatively high tumor response at 25 ppm (we stress that this is an apparent response since it is not statistically significant). However, a graphical representation of a larger portion of the data suggests that the high response at 25 ppm can easily be viewed as variation within the data set (or alternatively, variation among the separate experiments as well as within each experimental data set). In this case, a statistical criterion for exclusion of data is clearly inadequate for the intended purpose of calculating the most realistic URF.

4. Extrapolation Using a Surface-area Correction is not Appropriate for Vinyl Chloride

Application of risk calculations to humans using data obtained from experiments on experimental animals is generally referred to as scaling up or extrapolation. EPA has in the past routinely applied a surface area correction to animal URF's to calculate human URF's. The principles on which this surface area correction are based were obtained from studies on drug doses where the active form of the drug was the drug itself, and not a metabolite. However, during the past several years the unquestioned use of the surface area correction has been carefully examined by experts in this field of science.

The results of the question of whether a surface area correction should be incorporated into risk calculations has been published in reports of the Committee on Drinking Water and Health of the National Research Council. In fact, the studies on which the conclusions of this committee are based were done under contract to EPA for purposes of assessing the safety of carcinogens in drinking water. The conclusions of the committee are spelled out in detail in Volume 6 of Drinking Water and Health (1986). The same conclusions are summarized in Volume 8 of Drinking Water and Health (1987). With regard to the application of animal data for the calculation of risks to humans the Committee concluded as follows:

a. Where the parent chemical is the carcinogen the surface area correction should be used.

b. Where a stable metabolite of the parent chemical is the carcinogen no correction factor is required since the dose for different size animals should be identical in units of mg/kg bw/day.

c. Where an unstable metabolite of the parent chemical is the carcinogen the dose (and risk) for larger animals is expected to be smaller than that for smaller animals.

Since vinyl chloride clearly falls into case 3, not only is a surface area correction not indicated, but even without such a correction the estimated animal risk is expected to exaggerate that for a human. That is, a URF calculated using rat data with no surface area correction is expected to exaggerate the human risk without further corrections. Clearly, based on the metabolic properties of vinyl chloride it is inappropriate to use a surface area correction in calculating the human risk.

5. Low-dose Pharmacokinetic Modeling has not been Utilized in EPA Risk Assessments

Early work by Gehring, et. al., demonstrated how information on the absorption and excretion of vinyl chloride could be used in evaluating the risk due to inhalation based on the same animal bioassay data used by EPA in calculation of the 1984 URF.14/ Similarly, Krewski, et. al., calculated a URF of

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14/ Resolution of Dose-Response Toxicity Data for Chemicals Requiring Metabolic Activation: Example -- Vinyl Chloride, P.J. Gehring, et. al., Toxicology and Applied Pharmacology 44 (1978) 581-591.

$1.98 \times 10^{-6}/(\mu g/m^3)$ incorporating pharmacokinetic data and using the same data employed by EPA in calculating the 1985 URF (but without selective exclusion of data).15/ The value calculated by Krewski, et. al., is very similar to the 1984 URF calculated by EPA and is not significantly different from the URF obtained using the one-hit model and the approach of Gehring, et. al. Finally, two EPA scientists have estimated the vinyl chloride URF using a physiologically-based pharmacokinetic (PB-PK) simulation model and employing the same data that EPA used to calculate the 1985 URF.16/ The URF calculated from the PB-PK model was $1.7 \times 10^{-5}/ (\mu g/m^3)$. This last value is clearly larger than the other values estimated using pharmacoknetic data but the point is that, collectively, these methods clearly establish a basis for using pharmacokinetic information in estimating a URF for vinyl chloride.

E. THE BEST CURRENT EPA URF IS THE 1984 VALUE

The URF calculated by EPA in 1984, $2.7 \times 10^{-6}/(\mu g/m^3)$, is based on the most reasonable use by the Agency, so far, of the data available from rat inhalation bioassays. This view is supported by the following:

1. The 1985 URF was calculated after the unjustified rejection of data. This process yielded a URF based on tumor frequencies that are not statistically significant.17/

2. The statistical criterion for goodness of fit in the linearized multistage curve-fitting process is not met by either EPA URF, but the 1984 value does result from a regression line with a better fit (i.e., it represents a better dose response curve) than the 1985 value.

3. The 1984 URF for total tumors is paradoxically lower than the 1985 URF for liver angiosarcomas (LAS). This conclusion is untenable.

15/ The Application of Pharmacokinetic Data in Carcinogenic Risk Assessment, D. Krewski, et. al., in Pharmacokinetics in Risk Assessment Drinking Water and Health, Volume 8 (1987), National Academy Press, Washington, D.C.

16/ Incorporation of Biological Information in Cancer Risk Assessment: Example -- Vinyl Chloride, C.W. Chen and J.N. Blancato, Cell Biology and Toxicology 5 (1989) 417-444.

17/ See footnote 13.

The following criticisms apply to both the 1984 and 1985 values, but support the idea that the 1984 value is the most reasonable.

1. In accordance with National Research Council recommendations, an extrapolation of URF's from rats to humans incorporating relative body surface areas is not required for chemicals that are metabolized to unstable intermediates that act as carcinogens.

2. The impact of pharmacokinetic modeling on either URF using known metabolic information on vinyl chloride was not considered.

3. The implications of epidemiological data have not been openly discussed in accordance with EPA guidelines for risk assessment.

A thorough examination of the available literature suggests that virtually every URF determined for vinyl chloride suffers from some weakness. This applies also to URFs published by EPA. Before promulgating an ambient air standard that can potentially have an adverse effect on industry, DEQ should carefully evaluate the basis for any standard it adopts and provide adequate time for public comment. Since any standard will be derived directly from a URF estimated from experimental data it is incumbent on DEQ to require that the URF is based on sound scientific principles. We have identified six factors that should be considered carefully, and then discussed, prior to the adoption of any URF:

1. Data selection. What are the bases for selecting some data points and rejecting others? Is the data selection in accordance with metabolic and pharmacokinetic data on the chemical?

2. Tumor incidence rates. What tumor rates were used in the calculation? Why were they selected? Are they statistically significant?

3. Calculation model. What model was used to calculate the URF? If the linearized multistage model was used how many terms were incorporated? How good was the fit?

4. Scaling factors. In extrapolating animal URFs to humans was a surface area correction used? If so, why?

5. Pharmacokinetic data. Was pharmacokinetic data or PB-PK simulation used? If not, and PK data is available, why wasn't it used?

6. Epidemiology. If epidemiological data is available why was it (or was it not) used?

After examining carefully the information available in the public domain one must conclude that of the URF's calculated for inhalation of vinyl chloride none address these issues adequately or in such a manner as to permit a full evaluation of the bases for the URF. Because these issues were not addressed or discussed by EPA or DEQ the bases for adopting an ambient air standard for vinyl chloride is inadequate. Consequently, the formal adoption of an ambient air standard for vinyl chloride must be postponed. As noted above, at most an interim standard of 37 $\mu g/m^3$, derived from the 1984 EPA URF of $2.7 \times 10^{-6}/(\mu g/m^3)$ might be temporarily used. However, we encourage DEQ to continue to seek a URF that has been determined using a sound scientifically based approach.

Sincerely,

Roy T. Gottesman/RAM

Roy T. Gottesman,
Executive Director

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Jerome H. Heckman
Peter L. de la Cruz

Technical Advisor:
Robert A. Mathews, Ph.D.

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Enclosures

APPENDIX 1

GLOBAL 86 (MAY 1986)

BY RICHARD B. HOWE AND CYNTHIA VAN LANDINGHAM

CLEMENT ASSOCIATES, INC
1201 GAINES STREET
RUSTON, LA 71270
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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

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RMAIL 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
.0000	2.82720E-02	4.91334E-02	95.0%	Q(0) = .00000 Q(1) = 5.03816E-02 Q(2) = .00000

NORMAL COMPLETION!

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