MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

APRIL 17, 1995

TO: File for Talc (CAS# 14807-96-6)

FROM: Michael Depa, Toxics Unit

SUBJECT: Screening Level Determination

The Scientific Advisory Panel reviewed the risk assessment for talc and recommended the following screening levels: the initial risk screening level (IRSL) is 0.8 $\mu g/m^3$ (respirable; i.e. mmad $\leq 10\mu m$) based on annual averaging time. In like manner, the secondary risk screening level for talc is 8 $\mu g/m^3$ (respirable) based on annual averaging time. See the final recommendations of the Scientific Advisory Panel for talc (attached) for a detailed discussion of the screening level determination. The screening levels recommended by the Scientific Advisory Panel will be used by the Air Quality Division for implementation of Rules 230-232.

DNR

Final Recommendation of the Scientific Advisory Panel

TALC

(CAS# 14807-96-6)

Thursday, July 20, 1995

Basis for Screening Level

The available data for talc indicates that this substance meets the definition of a carcinogen (Rule 103(c)) for the purposes of Michigan's air toxic rules. In reviewing the available data for talc, staff of the Air Quality Division recognized that several issues related to the regulation of this substance as a carcinogen needed to be evaluated before developing a final screening level. These issues included such things as the appropriate tumor response data to use in the risk assessment, how the human equivalent dose should be determined, and mechanisms of carcinogenicity. Because evaluation of these issues could take some time, and given that the emissions of talc for the permit application that had precipitated the review of this substance were so low, the emissions were approved without finalizing a screening level. The basis for this approval was that the predicted ambient impact of talc for this application was below a concentration corresponding to an increased cancer risk of 1×10^{-6}, using the most conservative risk assessment methodology. Specifically, this value was 0.0004 $\mu g/m^3$ (annual) based on the increased incidence of adrenal medulla (benign or malignant) pheochromocytomas in male F344/N rats. The dose was measured as mg/m^3 and a surface area correction of $(70/0.45)^{1/3}$ was used.

Summary of Public Comment

Public comment was received by the Upjohn Company who felt the screening level was overly restrictive and should be reviewed by the Scientific Advisory Panel. The basis for Upjohn requesting a review of the screening level by the Panel included the following: 1) the NTP report, on which the risk assessment was based, was not unanimously accepted by the review committee; and 2) reviews by other organizations (ISRTP, USFDA, ACGIH) were planned in the near future. Upjohn commented that sufficient time should be allowed to evaluate the findings of these upcoming reviews prior to establishing a new screening level.

Response to Public Comment

Careful consideration of the talc risk assessment was undertaken by the Air Quality Division and the Scientific Advisory Panel. Several issues that developed during deliberation merit discussion. These include the strength of the evidence relating to the potential carcinogenicity of talc, evidence for a threshold mechanism for the carcinogenic effects, the appropriateness of the linearized multistage (LMS) model, the method for determining the effective dose and what particle size fraction of talc should be considered for determining compliance with the screening level. These issues warrant elaboration and are presented below.

The Panel evaluated pertinent data regarding the carcinogenic potential of talc. First, it was recognized that chronic inhalation of talc in the NTP bioassay produced a statistically significant increase in the incidence of lung tumors in female F344/N rats. Second, since there is insufficient knowledge concerning the mechanism of carcinogenicity no conclusion can be drawn as to whether female rats are uniquely susceptible to lung tumors due to the inhalation of talc. Finally, under the air toxics rules talc meets the definition of a carcinogen. Given the above information the Panel concluded that talc be regulated as a carcinogen.

The Panel spent considerable time discussing the issue of whether talc causes cancer by a threshold mechanism. The Panel believes that talc is likely to be a threshold carcinogen. However, very little is known about the mechanism of pulmonary carcinogenicity of talc. Related to the mechanism issue is the issue of the appropriateness of the linearized multistage model. Whereupon were talc to be proven a threshold carcinogen the use the LMS model would not be appropriate. With this in mind a discussion of the possible mechanisms of carcinogenicty follows.

The search for mechanistic information was expanded to include particles other than talc which may cause pulmonary neoplasms by the same mechanism. One hypothesis was put forth by the National Toxicology Program (NTP, 1993). The NTP stated:

> A potential mechanism for the development of pulmonary neoplasms associated with insoluble particulate substances is that the prolonged stimulus for cell replication, due not only to cell injury but to the release of mitogenic growth factors from alveolar macrophages, provides a favorable environment for the promotion and progression of spontaneously initiated cells. The interim evaluations in the NTP talc study clearly demonstrate a progressive impairment of homeostatic growth regulation in the areas of chronic inflammation and fibrosis associated with talc deposition in rats. Hyperplasia of the alveolar epithelium was evident at 6 months and became more extensive and sever with duration of exposure. Not only were there increased numbers of cells (hyperplasia), but some cells assumed morphologic features atypical of regenerating or differentiated type II cells (epithelia dysplasia). The altered or

> dysplastic epithelium was particularly evident in areas of fibrosis. The squamous metaplasia observed in female rats also represents altered differentiation of populations of alveolar epithelial cells and is notable in light of the development of squamous cysts and squamous cell carcinomas.

A related hypothesis asserts that particle "overload" of the clearance mechanisms leads to excessive particle deposition and the chronic inflammation necessary for the formation of tumors. This hypothesis assumes that the threshold for the "overload" is likewise the threshold for carcinogenesis. This "overload" event was considered with respect to the lung talc burden. The NTP stated concerning the talc bioassay and the F344/N rat, "Lung talc burdens of females exposed to 18 mg/m^3 increased progressively from 6 to 24 months, while those of males exposed to 18 mg/m^3 remained the same after 18 months." Furthermore, the doses as measured in mg/kg/day at the 18 mg/m^3 exposure concentration were 8.4 for male rats and 9.6 for female rats. These data give credence to the possibility that tumors were seen in the female rat and not the male because the dose in the male was insufficient to overload the clearance mechanisms. Similar evidence for the "overload" threshold theory can be found in the dose-response data of the NTP bioassay of talc. The incidence of lung tumors in the high dose female rats was increased, while the incidence of tumors in the low dose group was actually lower than that of controls. Despite the evidence for clearance "overload" in the female rat the relationship between "overload" and carcinogenicity is still uncertain at best.

However plausible the threshold hypothesis is, due to the lack of specific information concerning the mechanism, the Panel recommends that the traditional non-threshold risk assessment methodology be used to determine the screening level. This includes the use of the linearized multistage model to determine the unit risk because specific scientific supporting evidence for a threshold mechanism was considered inadequate.

The Panel examined different measurements of the dose with the intent on choosing the appropriate *effective* dose. For example, the dose can be measured as mg/m^3, mg/kg, RDDR, or lung burden. The effective dose is the dose measurement thought most likely to be associated with the biologic effect. The criteria for choosing the effective dose included how well the dose described 1) the cumulative deposited dose, 2) the differences between the rat and human respiratory rate and 3) the clearance mechanism "overload" event thought to take place during heavy particle exposures. The Appendix provides a summary of the methods considered, and the resulting screening level using each method. The Panel felt that the mg/m^3 and the mg/kg dose measurements did not address the cumulative deposited dose and the overload event, however, they could be adjusted to take into account the respiratory rate differences. Similarly, the RDDR did not take into account the overload event. The Panel therefore, recommends the use of the talc lung burden measurement of dose because it takes into account the overload event as well and the cumulative deposited dose, and can easily be adjusted for the respiratory rate differences between rats and humans. Using the lung burden as the

dose measurement, the initial risk screening level (IRSL) was determined (see part d of the Appendix) to be 0.8 $\mu g/m^3$ (annual) and the secondary risk screening level (SRSL) was determined to be 8 $\mu g/m^3$ (annual).

Regarding the particle size of talc, the Panel recommends that the IRSL should apply only to the respirable particle fraction of talc consisting of 10 μm or less mass mean aerodynamic diameter (MMAD). Only those particles able to reach the small airways in the lung are suspected of causing the alveolar/bronchiolar adenomas or carcinomas observed in the NTP inhalation bioassay.

Appendix - Risk Assessment Methodological Considerations

Summary of National Toxicology Program Bioassay

The National Toxicology Program performed a chronic inhalation bioassay to evaluate the carcinogenic potential of talc (NTP, 1993). Groups of 47 to 49 male mice and 48 to 50 female mice were exposed to aerosols containing 0, 6, or 18 mg/m^3 talc for up to 104 weeks. There was no evidence of carcinogenic activity of talc in male or female mice. However, there was carcinogenic activity in male and female rats. The NTP bioassay in female rats was used to develop the screening levels described in this document.

Groups of 50 male and 49 or 50 female rats were exposed to aerosols containing 0, 6, or 18 mg/m^3 talc for 6 hours per day, 5 days a week until mortality in any exposure group reached 80% (113 weeks for male rats and 122 weeks for female rats). Talc aerosols had a median aerodynamic diameter of 2.7 μm in the 6 mg/m^3 chamber and 3.2 μm in the 18 mg/m^3 chamber. The average daily exposure concentrations were calculated in the following manner:

Average Daily Exposure Conc. = Chamber Conc. x 6 hours/24 hours x 5 days/7 days

Average Daily Exposure Conc. = 6 mg/m^3 x 6/24 x 5/7

Average Daily Exposure Conc. = 1.07 mg/m^3/day

The average daily dose for the 18 mg/m^3 chamber was calculated in the same way. To calculate the incidence of alveolar/bronchiolar adenoma or carcinoma the number of animals that died before the occurrence of the first tumor was subtracted from the number of animals in that dose group. The raw and adjusted incidences are shown in Table 1.

Table 1. Raw and Adjusted Incidence Rates of Alveolar/Bronchiolar Adenoma or Carcinoma

Dose	Raw Incidence	Adjusted Incidence
0 mg/m^3/day	1/50	1/22
1.07 mg/m^3/day	0/48	0/48
3.21 mg/m^3/day	13/50	13/33

a) Traditional AQD Risk Assessment - Dose in terms of mg/m³

The data from Table 1. were used as input in the Global 82 (linearized multistage model) which generated the Upper 95% Confidence Limit (CL) and the Maximum Likelihood Estimate (MLE) at the 1 x 10^{-6} risk level. The Upper 95% CL and the MLE[1] were used in the following way to calculate the animal inhalation unit risk q_1*:

$$q_1^* = \frac{\text{Upper 95\% CL}}{\text{MLE (mg/m}^3\text{)}} \times \sqrt[3]{\frac{W_H}{W_A}} \times \frac{1\text{ mg}}{1000\ \mu\text{g}}$$

$$q_1^* = \frac{2.00852 \times 10^{-4}}{5.08427 \times 10^{-3}} \times \sqrt[3]{\frac{70\text{ kg}}{0.30\text{ kg}}} \times \frac{1\text{ mg}}{1000\ \mu\text{g}}$$

$$q_1^* = 0.039505 \frac{\text{m}^3}{\text{mg}} \times 6.16 \times \frac{1\text{ mg}}{1000\ \mu\text{g}}$$

$$q_1^* = 2.43 \times 10^{-4}\ (\mu\text{g/m}^3)^{-1}$$

Where W_H = 70 kg, the default weight of a human, and
W_A = the weight of the female F344/N rat.

Based on this unit risk value, the concentration of talc in air resulting in an increased risk of one in a million (1 x 10^{-6}) is 0.004 μg/m³ (annual averaging time). The final calculation is presented below:

$$\text{IRSL} = \frac{1 \times 10^{-6}}{q_1^*}$$

$$\text{IRSL} = \frac{1 \times 10^{-6}}{2.43 \times 10^{-4}\ (\mu\text{g/m}^3)^{-1}}$$

IRSL = 4 x 10^{-3} μg/m³ (based on annual averaging time)

SRSL = 4 x 10^{-2} μg/m³ (based on annual averaging time)

b) Traditional AQD Risk Assessment - Dose in terms of mg/kg

This method differs from the method described above in that the average daily exposure concentration is converted to mg/kg/day instead of using mg/m³. A sample calculation for the low dose is shown below:

[1] The chi-square goodness of fit statistic is 4.70381 as indicated in the Global82 output.

$$\text{Dose (mg/kg/day)} = \frac{\text{Adj. Dose x Tidal Vol. x Breathing Frequency}}{\text{Body Wieght}}$$

$$\text{Dose (mg/kg/day)} = \frac{1.07\ \text{mg/m}^3 \times 1.39\ \text{ml} \times 54.44\ \text{breaths/min} \times 60\text{min/hr} \times 24\text{hr/day} \times (\text{m}/100\text{cm})^3}{\text{Body Wieght}}$$

Dose = 0.3886 mg/kg/day

The unit risk was calculated as follows:

$$q_1^* = \frac{\text{Upper 95\% CL}}{\text{MLE (mg/kg)}} \times \sqrt[3]{\frac{W_H}{W_A}} \times \frac{20\ \text{m}^3}{70\ \text{kg}} \times \frac{1\ \text{mg}}{1000\ \mu\text{g}}$$

$$q_1^* = \frac{2.05564 \times 10^{-4}}{1.95022 \times 10^{-3}} \times \sqrt[3]{\frac{70}{0.3}} \times \frac{20\ \text{m}^3}{70\ \text{kg}} \times \frac{1\ \text{mg}}{1000\ \mu\text{g}}$$

$$q_1^* = 0.10541\ \frac{\text{kg}}{\text{mg}} \times 6.16 \times 0.2857\ \frac{\text{m}^3}{\text{kg}} \times \frac{1\ \text{mg}}{1000\ \mu\text{g}}$$

$$q_1^* = 1.855 \times 10^{-4}\ (\mu\text{g/m}^3)^{-1}$$

Based on this unit risk value, the concentration of talc in air resulting in an increased risk of one in a million (1×10^{-6}) is 0.005 μg/m^3 (annual averaging time). The final calculation is presented below:

$$\text{IRSL} = \frac{1 \times 10^{-6}}{q_1^*}$$

$$\text{IRSL} = \frac{1 \times 10^{-6}}{1.855 \times 10^{-4}\ (\mu\text{g/m}^3)^{1}}$$

IRSL = 5×10^{-3} μg/m^3 (based on annual averaging time)

SRSL = 5×10^{-2} μg/m^3 (based on annual averaging time)

c) RfC Method for Determination of Human Equivalent Dose

The conversion of the rat bioassay exposure dose (NTP, 1993) to a human equivalent dose is calculated using data compiled by the EPA in the Draft Interim Methods for the

Development of Inhalation Reference Concentrations (EPA, 1990). The ratio of the rat regional deposited dose to the human regional deposited dose is used to adjust the exposure level between rats and humans. The thoracic region (thoracic = tracheo-bronchial + pulmonary) was used for the region of interest to account for the development of alveolar/bronchiolar adenomas. This ratio of deposited doses is then used to calculate the Human Equivalent Concentration (HEC). Data used to calculate the HEC is shown in Table 2. The calculation of the HEC is done as follows:

$$Dose_{[HEC]}\ mg/m^3 = Dose_{[ADJ]} \times RDDR$$

Where $Dose_{[HEC]}$ is dose used in the linearized multistage model (see below),
$Dose_{[ADJ]}$ is the animal exposure multiplied by 5 day/7 day and 6 hrs/24 hrs,
and RDDR is the regional deposited dose ratio ($RDDR = RDD_{animal}/RDD_{human}$)

Table 2. Data used to Calculate Human Equivalent Concentration

Exposure Dose (mg/m^3)	$Dose_{[ADJ]}$[a] (mg/m^3)	MMAD[b] (geometric standard deviation)	RDDR[c] (Thoracic)	$Dose_{[HEC]}$ (mg/m^3)
6	1.07	2.7 (1.9)	0.57	0.6099
18	3.21	3.2 (1.9)	0.47	1.5087

a Adjusted Dose = Exposure Dose x 5 days/7 days x 6 hours/24 hours.
b MMAD = mass median aerodynamic diameter (NTP, 1993)
c RDDR was estimated from MMADs and geometric standard deviations in Table H-1 (EPA, 1990)

The unit risk (q_1^*) was calculated using the linearized multistage model Global82. Table 3 presents data used to calculate q_1^* including the incidences of alveolar/bronchiolar adenomas and carcinomas in the lung of female rats from the NTP chronic inhalation bioassay.

Table 3. Data Used to Calculate the Unit Risk

Exposure Dose	$Dose_{[HEC]}$	Incidence of Lung Tumors
0 mg/m^3	0 mg/m^3	1/22
6 mg/m^3	0.6099 mg/m^3	0/48
18 mg/m^3	1.5087 mg/m^3	13/33

Data out-put from the Global82 computer model was used to calculate q_1^*. This data included the Upper 95% Confidence Limit (CL) of Risk and the Maximum Likelihood Estimate (MLE) of dose[2]. This calculation is shown below:

$$q_1^* = \frac{\text{Upper 95\% CL}}{\text{MLE (mg/m}^3\text{)}} \times \frac{1\ \text{mg}}{1000\ \mu\text{g}}$$

[2] The chi-squared goodness of fit statistic is 5.86870 as indicated in the Global82 output.

$$q_1^* = \frac{1.9317 \times 10^{-4}}{2.4096 \times 10^{-3}} \times \frac{1\ mg}{1000\ \mu g}$$

$$q_1^* = 8.0167 \times 10^{-5}\ \ (\mu g/m^3)^{-1}$$

Based on this unit risk value, the concentration of talc in air resulting in an increase risk of one in a million (1×10^{-6}) is 0.01 $\mu g/m^3$ based on an annual averaging time. The final calculation is presented below:

$$IRSL = \frac{1 \times 10^{-6}}{q_1^*}$$

$$IRSL = \frac{1 \times 10^{-6}}{8.0167 \times 10^{-5}\ (\mu g / m^3)^{-1}}$$

IRSL = 0.01 $\mu g/m^3$ (based on annual averaging time)

SRSL = 0.1 $\mu g/m^3$ (based on annual averaging time)

d) Lung Talc Burden for Determination of Animal Dose

In order to determine the animal dose the lung talc burden is converted to body talc burden (mg/kg). The lung talc burden per gram of control lung is presented in table G2 of the NTP bioassay. The body talc burden is shown in Table 4.

Table 4. Calculations for Determination of Talc Burden per Body Weight

Exposure Dose	Lung Talc Burden[a] (mg talc/g control lung)		Lung to Body Weight Ratio[b] (g dose lung/Kg BW)		Body Talc Burden[c] (mg talc/Kg BW)
6 mg/m³	9.1	x	4.88	=	44.4
18 mg/m	29.4	x	12.73	=	374.3

a Taken from Table G2 (page 221) of the NTP talc inhalation bioassay.
b Taken from Table E4 (page 197) of the NTP talc inhalation bioassay.
c Body Talc Burden = Lung Talc Burden x Lung to Body Weight Ratio

Using the body talc burden data along with the incidence data presented in Table 3. the Upper 95% CL of Risk and the MLE[3] of dose was again calculated from the Global82 computer program. The q_1^* was calculated as follows:

[3] The chi-squared goodness of fit statistic is 2.52661 as indicated in the Global82 output.

$$q_1^* = \frac{\text{Upper 95\% CL}}{\text{MLE (mg/kg)}} \times \sqrt[3]{\frac{W_H}{W_A}} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g}$$

$$q_1^* = \frac{3.91748 \times 10^{-4}}{0.54407} \times \sqrt[3]{\frac{70}{0.3}} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g}$$

$$q_1^* = 7.2003 \times 10^{-4}\ \frac{kg}{mg} \times 6.16 \times 0.2857\ \frac{m^3}{kg} \times \frac{1\ mg}{1000\ \mu g}$$

$$q_1^* = 1.267 \times 10^{-6}\ (\mu g/m^3)^{-1}$$

The IRSL was calculated below:

$$IRSL = \frac{1 \times 10^{-6}}{q_1^*}$$

$$IRSL = \frac{1 \times 10^{-6}}{1.267 \times 10^{-6}\ (\mu g/m^3)^{-1}}$$

IRSL = 0.8 $\mu g/m^3$ (based on annual averaging time)

SRSL = 8 $\mu g/m^3$ (based on annual averaging time)

Summary of Screening Levels

Table 5. Summary of Screening Levels Derived from the NTP Bioassay

Method	Initial Risk Screening Level (annual ave.)
Traditional AQD ...with dose as mg/m^3	0.004 $\mu g/m^3$ (SRSL = 0.04 $\mu g/m^3$)
Traditional AQD...with dose as mg/kg	0.005 $\mu g/m^3$ (SRSL = 0.05 $\mu g/m^3$)
RfC Method for Determining HEC	0.01 $\mu g/m^3$ (SRSL = 0.1 $\mu g/m^3$)
Lung Talc Burden as Animal Dose	0.8 $\mu g/m^3$ (SRSL = 8 $\mu g/m^3$)

References

ACGIH. 1993. Documentation of Threshold Limit Values and Biological Exposure Indices. Cincinnati, OH.

EPA. 1990. Interim Methods for Development of Inhalation Reference Concentration (Draft Review). US Environmental Protection Agency. Office of Research and Development. EPA/600/8-90/066A

NIOSH. 1990. National Institute for Occupational Safety and Health Pocket Guide to Chemical Hazards. US DHHS, Center for Disease Control.

NTP. 1993. Toxicology and Carcinogenisis studies of talc (CAS No. 14807-96-6) in F344/N rats and B6C3F1 mice (inhalation studies). US DHHS, Public Health Service, National Institutes of Health, NIH Publication No. 93-3152, NTP TR 421.