MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

March 1, 2005

TO: File for Resorcinol (CAS #108-46-3)

FROM: Anne Kim, Air Quality Division, Toxics Unit

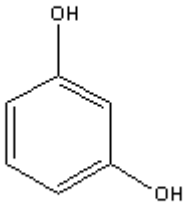
SUBJECT: Screening Level Derivation

Note: This chemical was withdrawn from the permit, PSM-2005-0006, because it is a solid and the process by which the chemical would be used does not require permits for solid compounds.

An initial threshold screening level (ITSL) will not be established at this time due to the crystalline nature of resorcinol. Instead, the National Ambient Air Quality Standard for particulate matter (NAAQS PM) will be emphasized.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 – 2005), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration or reference dose for Resorcinol. The molecular weight of Resorcinol is 110.1 g. The molecular structure of Resorcinol is shown in Figure 1.

Figure 1



Background

Resorcinol is characterized by the physical property of having “white needle-like crystals with a sweetish taste” which are water-soluble (IARC, 1999). Resorcinol is primarily used in the manufacture of rubber tires, wood adhesives, dyes, and pharmaceuticals for skin treatment. Exposure to resorcinol may occur in an occupational setting or in an environment where there is wood smoke or tobacco smoke. (NTP, 1992)

Animal Toxicity

A couple inhalation studies have been performed and was reviewed in a journal dated 1976 (Flickinger, 1976; NTP, 1992; ACGIH, 2001). In one acute inhalation study, six female Harlan-Wistar albino rats per group were exposed to resorcinol in aerosol form at concentrations of 2130 mg/m^3 to 7800 mg/m^3 for one hour or 2000 mg/m^3 to 2800 mg/m^3 for eight hours. Results produced no deaths or gross lesions attributable to resorcinol inhalation (Table 1).

Table 1. Acute inhalation data in rats

mg/m^3	**7800**	**2130**	
1-hour	no toxicity	no toxicity	
mg/m^3	**2800**	**2480**	**2000**
8-hour	no toxicity	no toxicity	no toxicity

Another inhalation study was conducted with rats, guinea pigs, and rabbits, showing no toxic effects after exposure to 34 mg/m^3 (8 ppm) resorcinol 6 hours/day for 2 weeks.

An acute oral study was conducted exposing rats to 0.398, 0.795, 1.58, and 3.16 g/kg by gavage (Flickinger, 1976). All rats died in the 1.58 g/kg and 3.16 g/kg dose groups. All survived in the 0.398 g/kg dose group and only one died from the 0.795 dose. All deaths occurred in less than 2-3 hours (Table 2).

Table 2. Acute oral data in rats

g/kg	**0.398**	**0.795**	**1.58**	**3.16**
No. Died/ No. Dosed	0/5	1/5	5/5	5/5
Day (No. Died)	-	<3 hr (1)	<3 hr (5)	<2 hr (5)

NTP (1992) ran multiple toxicity studies on F344/N rats and B6C3F1 mice: 17-day, 13-week, and 2-year studies. Resorcinol (>99% pure) was administered to all study animal groups by oral gavage. For the 17-day study, rats, in groups of five, were fed 0, 27.5, 55, 110, 225, or 450 mg/kg resorcinol; and mice, in groups of five, were fed 0, 37.5, 75, 150, 300, or 600 mg/kg resorcinol. All of the rats survived the 17-day study, but all female and four male mice in the 600 mg/kg group and one male in the 300 mg/kg group died due to resorcinol-related toxicity. Hyperexcitability and tachypnea were symptoms of toxicity observed in male rats in the 225 mg/kg and 450 mg/kg groups (Table 10). Female rats administered 55 mg/kg and greater presented hyperexcitability and those in the 110 mg/kg and 450 mg/kg groups showed tachypnea. The mean body weights of all dosed rats and mice were equivocal to those of control. Changes observed in organ weights were not biologically significant except for the decrease in absolute and relative thymus weights (relative to body weight) in the female rats (Table 3).

Table 3. 17-day female rat thymus weights and thymus-weight-to-body-weight ratios

mg/kg	0	27.5	55	110	225	450
Absolute (mg)	412.0 ± 15.9	402.0 ± 14.6	396.0 ± 7.5	380.0 ± 6.3	384.0 ± 19.4	344.0 ± 16.6*
Relative (mg/g)	2.71 ± 0.10	2.64 ± 0.08	2.63 ± 0.06	2.52 ± 0.08	2.55 ± 0.12	2.33 ± 0.10*

** P≤0.01

For the 13-week study, rats, in groups of ten, were fed 0, 32, 65, 130, 260, or 520 mg/kg resorcinol; and mice, in groups of ten, were fed 0, 28, 56, 112, 225, or 420 mg/kg resorcinol. All female and eight male rats in the 520 mg/kg group and eight male and eight female mice in the 420 mg/kg group died due to resorcinol-related toxicity. The mean body weights of all dosed rats and mice were equivocal to those of control. Clinical signs of toxicity observed in the high-dose rats included tremors and those observed in the high-dose mice included dyspnea, prostration, and tremors (Table 11). Weight changes in the liver (male and female rats) and adrenal gland (male rats and male mice) were observed (Table 4 – Table 7).

Table 4. 13-week male rat liver weights and liver-weight-to-body-weight ratios

mg/kg	0	32	65	130	260	520
Absolute (g)	10.84 ± 0.30	11.36 ± 0.36	11.32 ± 0.20	11.75 ± 0.24**	11.74 ± 0.18**	-
Relative (mg/g)	32.0 ± 0.7	33.6 ± 0.7	33.1 ± 0.5	34.4 ± 0.5**	34.9 ± 0.5**	-

** P≤0.01

Table 5. 13-week female rat liver weights and liver-weight-to-body-weight ratios

mg/kg	0	32	65	130	260	520
Absolute (g)	4.77 ± 0.16	5.15 ± 0.18	5.43 ± 0.15*	5.41 ± 0.22*	5.49 ± 0.16*	-
Relative (mg/g)	26.0 ± 0.9	28.3 ± 0.8*	29.7 ± 0.5**	28.8 ± 0.8**	30.2 ± 0.7**	-

* P≤0.05
** P≤0.01

Table 6. 13-week male rat adrenal gland weights and adrenal-gland-weight-to-body-weight ratios

mg/kg	0	32	65	130	260	520
Absolute (mg)	4.73 ± 0.24	5.42 ± 0.12**	5.48 ± 0.09**	5.21 ± 0.12**	5.74 ± 0.24**	-
Relative (mg/g)x10	0.14 ± 0.01	0.16 ± 0.00**	0.16 ± 0.00**	0.15 ± 0.00**	0.17 ± 0.01**	-

** P≤0.01

Table 7. 13-week male mice adrenal gland weights and adrenal-gland-weight-to-body-weight ratios

mg/kg	0	28	56	112	225	420
Absolute (mg)	8.30 ± 0.52	6.40 ± 0.34**	5.90 ± 0.18**	5.89 ± 0.20**	5.70 ± 0.26**	9.00[a]
Relative (mg/g)	0.31 ± 0.02	0.25 ± 0.01**	0.22 ± 0.01**	0.23 ± 0.01**	0.23 ± 0.01**	0.36[a]

** P≤0.01
[a] n = 1 due to high mortality

For the 2-year study, male rats and male and female mice, in groups of sixty, were fed 0, 112, or 225 mg/kg resorcinol; and female rats, in groups of 60, were fed 0, 50, 100, or 150 mg/kg. The male rats in the high-dose group had mean body weights that were 10% to 15% lower than control starting from week 87. Similarly, the female rats in the high-dose group had mean body weights that were 11% to 14% lower than control starting from week 95. Survival in the high-dose groups also was decreased due to resorcinol administration. Mice did not show biologically significant changes in organ weights, but the brain and liver weights of rats were significantly increased in the male 112 mg/kg dose group and the female 150 mg/kg dose group, respectively (Table 8 and Table 9).

Table 8. 2-year male rat brain weights and brain-weight-to body-weight ratios

mg/kg	0	112
Absolute (g)	2.00 ± 0.02	2.04 ± 0.04
Relative (mg/g)	4.75 ± 0.07	5.19 ± 0.09

** P≤0.01

Table 9. 2-year female rat liver weights and liver-weight-to-body-weight ratios

mg/kg	0	50	100	150
Absolute (g)	8.55 ± 0.28	8.55 ± 0.23	9.26 ± 0.17	8.72 ± 0.27
Relative (mg/g)	2.95 ± 0.06	2.92 ± 0.06	3.05 ± 0.07	3.19 ± 0.09*

* P≤0.05

The 2-year study depicted neurological effects from resorcinol, including clinical signs such as ataxia, recumbency, and tremors (Table 12). The 2-year study resulted in no increased incidences of neoplasms or nonneoplastic lesions from exposure to resorcinol. In addition, resorcinol was not mutagenic in multiple strains of Salmonella typhimurium. Thus, NTP concluded that there was no evidence for carcinogenic activity of resorcinol in both F344/N rats and B6C3F1 mice.

Table 10. 17-day study - Clinical signs of neurotoxicity

Dose	mg/kg	0	27.5	55	110	225	450
Rats	**Male**	-	-	-	-	hyperexcitability; tachypnea	hyperexcitability; tachypnea
	Female	-	-	hyperexcitability	hyperexcitability; tachypnea	hyperexcitability	hyperexcitability; tachypnea
Dose	**mg/kg**	**0**	**37.5**	**75**	**150**	**300**	**600**
Mice	**Male**	-	-	-	prostration; tremors	prostration; tremors	prostration; tremors
	Female	-	-	-	-	prostration; tremors	prostration; tremors

Table 11. 13-week study - Clinical signs of neurotoxicity

Dose	mg/kg	0	32	65	130	260	520
Rats	**Male**	-	-	-	-	-	tremors
	Female	-	-	-	-	-	tremors
Dose	**mg/kg**	**0**	**28**	**56**	**112**	**225**	**420**
Mice	**Male**	-	-	-	-	-	dyspnea; prostration; tremors
	Female	-	-	-	-	-	dyspnea; prostration; tremors

Table 12. 2-year study - Clinical signs of neurotoxicity

Dose	mg/kg	0		112	225
Rats	Male	-		ataxia; prostration; salivation; tremors	ataxia; prostration; salivation; tremors
Mice	Male	-		recumbency; tremors	recumbency tremors
	Female	-		recumbency; tremors	recumbency; tremors
Dose	**mg/kg**	**0**	**50**	**100**	**150**
Rats	Female	-	-	ataxia; prostration; salivation; tremors	ataxia; prostration; salivation; tremors

IARC (1999) determined that "resorcinol is not classifiable as to its carcinogenicity to humans" after finding no available epidemiological data for resorcinol's carcinogenicity and inadequate evidence for resorcinol's carcinogenicity in experimental animals. Resorcinol is, thus, categorized as a Group 3 chemical.

Human Toxicity

According to a survey, 180 workers exposed to 10 ppm resorcinol had no complaints of irritation or discomfort (ACGIH, 2001).

Discussion

NIOSH's recommended exposure level (REL) and OSHA's permissible exposure level (PEL) are consistent with ACGIH's threshold limit value time-weighted average (TLV-TWA), which is set at 45 mg/m^3 (10 ppm). ACGIH's basis includes industrial experience with resorcinol and the similarity of the toxicity of phenol or catechol to that of resorcinol. (NIOSH, 1997; ACGIH, 2001).

When the oral study results are compared to the inhalation study results, there is indication that oral toxicity from resorcinol exposure may be greater than toxicity caused by inhalation exposure to resorcinol. The inhalation studies, however, were acute or short-term studies, whereas the oral studies conducted by NTP ranged from short-term to chronic studies. A reference dose (RfD) can be calculated from the chronic oral NTP studies, but the acute inhalation studies do not meet the standard requirements for developing a reference concentration (RfC) – the RfD and RfC values can be used to derive health-based screening levels. Since the NTP study can be used to derive a RfD, the screening level calculations will be based on the NTP (1992) oral study.

After analysis of the NTP (1992) study, the lowest-observable adverse effect level (LOAEL) is determined to be 32 mg/kg. The 13-week study in female rats showed a significant weight change in the liver compared to control. Since 32 mg/kg was the lowest dose administered to the rats, a NOAEL cannot be established. The 13-week study in male mice, at a lower concentration dose of 28 mg/kg, showed significant weight change in the adrenal gland compared to control. Analysis of the results, however, shows an inconsistency between the rats and mice in the effect that resorcinol has on the adrenal gland; exposure to resorcinol increased the weight of the male rats' adrenal glands while decreasing the weight of the male mice's adrenal glands. Due to the lack of a consistent dose-response effect on the adrenal gland, the LOAEL derived

from the 13-week female liver weight change results will be used to calculate an initial threshold screening level (ITSL).

Note: LOAEL = 32 mg/kg

Derivations of Screening Level

ITSL = RfD x (70 kg)/(20 m^3)

>where RfD = Reference Dose

During the 13-week study, resorcinol was administered 5 days per week. Therefore, the LOAEL must be adjusted accordingly:

Adjusted LOAEL = 32 mg/kg x (5 days)/(7 days)

Adjusted LOAEL = 22.9 mg/kg

Calculation of RfD:

$$RfD = \frac{LOAEL}{UF}$$

>where RfD = defined above

UF = uncertainty factor

UFs that apply: 1) variation in sensitivity among members of the human population = 10

2) extrapolation from animal data to humans = 10

3) extrapolation from sub-chronic to chronic = 10

4) extrapolation from LOAEL to NOAEL = 3*

*3 is used instead of 10 because there were no histopathologic evidence of gross or microscopic lesions associated with the increase in organ weight

$$RfD = \frac{22.9 \text{ mg/kg}}{10x10x10x3}$$

RfD = 0.00763 mg/kg

ITSL = 0.00763 mg/kg x (70 kg)/(20 m^3)

ITSL = 0.026716 mg/m^3

ITSL = 26.7 ug/m^3 = 27 ug/m^3

Therefore, the ITSL for resorcinol (108-46-3) is 27 ug/m^3 based on a 24-hour averaging time. This calculated ITSL is less than a possible ITSL that can be derived from an occupational exposure limit (OEL). In addition to background particulate matter levels, the above health-based ITSL may, however, be greater than the National Ambient Air Quality Standard for particulate matter (NAAQS PM) (Table 13).

Table 13. National Ambient Air Quality Standard for Particulate Matter

	PM10	PM2.5
annual	50 ug/m^3	15 ug/m^3
24-hour	150 ug/m^3	65 ug/m^3

It is considered inappropriate to set an ITSL for a chemical emitted as particulate matter that is greater than the NAAQS, especially considering the lack of chronic inhalation toxicity data for this compound. Although this ITSL is not greater than the NAAQS PM (standing) alone, the NAAQS PM must still be considered due to potential additive effects from background particulate matter levels. Therefore, as long as the ambient impact of resorcinol combined with the background particulate matter concentration is less than NAAQS PM for both PM10 and PM2.5, then adverse health effects would not be expected to occur, and compliance with health-based screening level requirements of the air toxic rules is satisfied.

References

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