MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

August 24, 2005

TO: File for decahydronaphthalene (CAS #91-17-8)

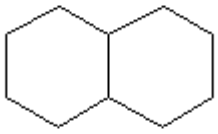
FROM: Anne Kim, Air Quality Division, Toxics Unit

SUBJECT: Cancer Risk Assessment

The IRSL for decahydronaphthalene is 0.03 µg/m³ and the SRSL is 0.3 ug/m^3, both based on an annual averaging time.

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 decahydronaphthalene. The molecular weight of decahydro-naphthalene is 138.3 g. The molecular structure of decahydronaphthalene is shown in Figure 1.

Figure 1



Decahydronaphthalene (or decalin) is a naturally occurring hydrocarbon found in petroleum and coal. Emissions from “petroleum refining, coal tar distillation, gasoline and diesel engines, and combustion” are potential sources of exposure to decalin (NTP, 2005). Exposure may also occur through other industrial uses of decalin, such as use as a solvent for fats, resins, and waxes; use as a turpentine substitute in paints and varnishes; and use as a motor fuel/lubricant constituent. (ChemFinder.com, 2005; NTP, 2005)

Animal Toxicity

A study conducted by Gaworski et al. (1985) reported the effects of decalin by continuous inhalation exposure in male and female beagle dogs, male and female F344/N rats, and female C57BL/6 mice. The animals were exposed to 0, 5, or 50 ppm decalin for 90 days in inhalation chambers. After exposure termination, all dogs and one-third of the rats and mice were necropsied, and the remaining rats and mice were held for post-exposure observation until the 24th month of the study. The dogs showed no gross or microscopic effects from decalin vapor exposure.

The body weight gain and survival of exposed mice were comparable to the control group. The most evident change in mice was hepatocellular cytoplasmic vacuolization which was found in 94% of the 50 ppm group, 87% of the 5 ppm group, and only 6% of the control group. Mice also developed pituitary carcinomas, cysts in the mammary gland, and hyperplasia in the thyroid gland. The mammary gland and thyroid lesions were both attributed to the neoplastic activity of the pituitary gland.

Male rats exposed to decalin had lower body weights compared to control, but the response was not considered dose-related. The only significant exposure-related effect was observed in the kidneys of exposed male rats. After 90 days of exposure, tubular nephrosis was evidenced by hyaline droplets in the proximal tubular epithelium and granular casts in the outer medulla. Rats exposed to decalin developed neoplasms approximately at the same rate as control. The incidence of pituitary adenomas, however, was significantly increased ($p<0.05$) in male rats exposed to 5 ppm and 50 ppm when compared to control.

Although the focus of this study was not to search for neoplastic lesions, they were found and, thus, reported. The increase in pituitary tumor incidence was concluded to be significant in male F344/N rats and female C57BL/6 mice. The authors, however, discounted the significance of the pituitary adenoma and carcinoma incidence rates by noting the historical occurrence of pituitary tumors in their lab:

> A slightly greater incidence of pituitary tumors was noted in both male rats and female mice exposed to decalin. These tumors have been shown to be common in aged Fischer rats and virgin female C57BL/6 mice, and it has been the experience in our laboratory that the background incidence of pituitary tumors in Fischer rats and C57BL/6 mice is usually quite high, approximately 40%. Thus the apparent increase of pituitary tumors in rodents exposed to decalin is considered to be a result of an unusually low control group incidence rather than a response to decalin exposure. (Gaworski et al., 1985)

While the historical control values in their lab may be usually quite high, the 40% value is neither a species-specific nor a sex-specific number. It is generally found that historical control values are species-specific and sex-specific. It is, thus, difficult to give credence to the authors' rationale for discounting the significance of the increased incidence of pituitary lesions in both the male F344/N rats and the female C57BL/6 mice.

Another inhalation study, conducted by NTP (2005), reported the effects of decalin exposure in F344/N rats, B6C3F1 mice, and male NBR rats. F344/N rats and B6C3F1 mice were exposed via inhalation 6 hours/day, 5 days/week for 2 weeks, 3 months, or 2 years, while the male NBR rats were exposed 6 hours/day, 5 days/week for only 2 weeks.

The male NBR rats were used to determine the influence of the male-specific and rat-specific protein, α2u-globulin. In F344/N rats, α2u-globulin is naturally produced in the liver under the hormonal regulation of testosterone. After circulating in the blood system, it reaches the glomerulus where it is partially reabsorbed; the rest is excreted via urine. The reabsorbed fraction is broken down by lysosomes. The binding of hydrocarbons, such as decalin, to α2u-globulin, however, inhibits the lysosomes from catabolizing the protein, thus inducing renal toxicity with the accumulation of α2u-globulin. The male NBR rats, which do not produce this protein, were used to determine whether any evidence of renal toxicity was due to the species-specific and sex-specific occurrence of α2u-globulin accumulation.

A comparison between the results from the 2-week decalin inhalation exposure in male NBR rats and male F344/N rats revealed that renal toxicity in the form of hyaline droplet accumulation, degeneration and regeneration of renal cortical tubules, and granular casts occurred in F344/N rats only. This supports the conclusion that any tumor formation in the kidney of male rats would only occur secondary to α2u-globulin accumulation.

In the 2-year study, 50 male F344/N rats were exposed to 0, 25, 50, 100, or 400 ppm decalin 6 hours/day, 5 days/week for 105 weeks (only 20 male rats were in the 400 ppm group). 50 female F344/N rats and 50 male and female B6C3F1 mice were exposed to 0, 25, 100, or 400 ppm decalin 6 hours/day, 5 days/week for 105 weeks. Neoplastic lesions developed as a result of decalin vapor exposure in the renal tubule and adrenal medulla of male F344/N rats. These lesions included significant increases in the incidences of renal tubule adenoma or carcinoma and benign or malignant pheochromocytoma of the adrenal medulla. Neoplastic lesions resulting from decalin exposure in female B6C3F1 mice included marginally increased incidences of hepatocellular adenoma or carcinoma and uterine stromal polyp or sarcoma. Biologically significant neoplastic lesions were not found in female rats and male mice.

Thus, NTP concluded that:

> Under the conditions of these studies, there was clear evidence of carcinogenic activity of decalin in male F344/N rats based on increased incidences of renal tubule neoplasms. The increased incidences of benign or malignant pheochromocytoma (combined) of the adrenal medulla in male rats were also considered to be exposure related. There was no evidence of carcinogenic activity of decalin in female F344/N rats exposed to 25, 100, or 400 ppm. There was no evidence of carcinogenic activity of decalin in male mice exposed to 25, 100, or 400 ppm. There was equivocal evidence of carcinogenic activity of decalin in female B6C3F1 mice based on marginally increased incidences of hepatocellular and uterine neoplasms. (NTP, 2005)

Regarding the "clear evidence of carcinogenic activity" in male F344/N rats, special attention must be drawn to the NTP report comment section:

> Dr. Drinkwater asked whether the proposed conclusion based on kidney neoplasms should carry a qualifying comment that the neoplasms were a secondary effect of α2u-globulin accumulation. Dr. J.R. Bucher, NIEHS, replied that the standard practice had been simply to mention the occurrence of both lesions and permit future readers to draw their own inferences about causality based on the evolving hypothesis and knowledge. (NTP, 2005)

Based on the analysis of the NTP study report, the inference drawn about the relationship between the kidney neoplasms found in the male F344/N rats and the accumulation of α2u-globulin was that the neoplasms occurred as a secondary effect of the α2u-globulin accumulation. Regarding the increased incidences of benign and malignant pheochromocytoma of the adrenal medulla, the NTP report stated that previous NTP studies have revealed similar significant correlation between severe nephropathy and pheochromocytoma in male F344/N rats. The authors emphasized that the occurrence of pheochromocytoma was more strongly correlated with the severity of nephropathy than the increase in exposure concentration. Nevertheless, the significant positive association between exposure concentration and incidence of pheochromocytoma lesions cannot be dismissed. Thus, only the significant increased incidences of neoplastic lesions in the kidney of male F344/N rats were excluded from further analysis for subsequent decalin initial risk screening level (IRSL) and secondary risk screening level (SRSL) calculations; pheochromocytoma lesions of the adrenal medulla were included in the assessment.

The following neoplasms were found to be decalin-exposure-dependent:

- pituitary adenoma and carcinoma – Gaworski et al., 1985;
- pheochromocytoma of the adrenal medulla (benign and malignant) – NTP, 2005;
- hepatocellular adenoma and sarcoma – NTP, 2005; and
- uterine stromal polyp and sarcoma – NTP, 2005.

The data from these neoplasms were entered into the Global 82 linearized multistage (LMS) model to attain a q_1* risk factor slope with which further calculations would be made to derive an IRSL and SRSL. Table 1 shows the study data adjusted for low dose extrapolation modeling.

The Global 82 model determined whether the multistage model adequately fit the input data by the Chi-square goodness-of-fit statistical test. If the data fit the model, further analysis and calculations were made; if the data did not fit the model, no further analysis or calculations were made. Only data from hepatocellular adenomas and carcinomas in female B6C3F1 mice were unacceptable as determined by the goodness-of-fit Chi-square test. Pursuant to Rule 231(3)(b), the highest dose data values were dropped and modeled again. This was repeated until the data set was acceptable by Chi-square test.

The input of the LADD and adjusted incidence rates into the Global 82 model resulted in q_1* (human) unit risk values in units of $(mg/m^3)^{-1}$. The q_1* (human) unit risk values are 1.29×10^{-2}, 5.69×10^{-3}, 2.15×10^{-3}, 3.44×10^{-2}, and 5.13×10^{-4} $(mg/m^3)^{-1}$, respectively based on male F344/N rat pituitary adenomas, female C57BL/6 mice pituitary carcinomas, male F344/N rat pheochromocytoma tumors, female B6C3F1 mice hepatocellular adenomas and carcinomas, and female B6C3F1 mice stromal polyps and sarcomas.

Table 1. Global 82 LMS model input data.

Study	Strain	Tumor Type	Doses (ppm)	Doses* (mg/m^3)	LADD†‡ (mg/m^3)	Incidence Rates	No. Died Before First Incidence§	Adjusted Incidence Rates**
Gaworski et al., 1985	F344/N male rats	Pituitary adenoma	0	0	0	5/50	-	-
			5	28.75	3.54	16/49	-	-
			50	287.5	35.4	16/48	-	-
	C57BL/6 female mice	Pituitary carcinoma	0	0	0	0/77	-	-
			5	28.75	3.54	3/81	-	-
			50	287.5	35.4	8/80	-	-
NTP, 2005	F344/N male rats	Pheochromocytoma benign and malignant tumors	0	0	0	8/49	2	8/47
			25	143.75	25.67	9/49	1	9/48
			50	287.5	51.34	13/49	1	13/48
			100	575	102.68	16/49	2	16/47
			400	2300	410.7	8/20	1	8/19
	B6C3F1 female mice	Hepatocellular adenoma and carcinoma	0	0	0	11/49	2	11/47
			25	143.75	25.67	27/50	2	27/48
			100	575	102.68	47/50	2	14/48
			400	2300	410.7	20/50	3	20/47
	B6C3F1 female mice	Stromal polyp and sarcoma	0	0	0	0/49	10	0/39
			25	143.75	25.67	0/50	16	0/34
			100	575	102.68	2/50	9	2/41
			400	2300	410.7	4/50	8	4/42

* The doses were converted given: 1 ppm = 5.75 mg/m^3.

† The lifetime average daily dose (LADD) for pituitary lesions was calculated given: LADD = administered dose (mg/m^3) x (90 days of exposure ÷ 731 days total in study).

‡ The lifetime average daily dose (LADD) for hepatocellular and stromal lesions was calculated given: LADD = administered dose (mg/m^3) x (6 hours /24 hours) x (5 days/7 days).

§ The day of first appearance of a female mouse pituitary carcinoma in a treatment group was not given. The day of first appearance of a female mouse hepatocellular adenoma or carcinoma in a treatment group was day 488. The day of first appearance of a female mouse stromal polyp or sarcoma in a treatment group was day 714.

** The adjusted incidence rates are the rates with the denominator reflecting the number of animals which did not expire before the date of the first appearance of the tumor type of focus in a treated group.

Rule 231(3)(h) mandates that an appropriate adjustment factor be applied to the q_1* risk slope factor. According to EPA (1994), decalin is a Category 3 gas. As such, the dose equivalency factor defaults to the value of 1, because there is no information for the blood:gas partition coefficient for decalin specific to humans.

The IRSL and SRSL are typically derived from the highest unit risk value, which, in this case, is 3.44×10^{-2} $(mg/m^3)^{-1}$. This value is based on the increased incidence of female B6C3F1 mice hepatocellular adenomas and carcinomas observed by NTP (2005). The calculation of the screening levels is presented in Figure 2 below.

Figure 2. Derivation of Screening Levels

Hepatocellular adenoma and carcinoma in B6C3F1 female mice:
>Global 82 LMS model given results:
Chi-squared stat = 12.7148 > 3 degrees of freedom = 11.344 – *therefore **un**acceptable*.

Rerun model after dropping highest dose:
>Global 82 LMS model given results:
Chi-squared stat = 12.6886 > 2 degrees of freedom = 9.210 – *therefore **un**acceptable*.

Rerun model after dropping next highest dose:
>Global 82 LMS model given results:
Chi-squared stat = 1.097×10^{-23} << 1 degree of freedom = 6.637 – *therefore acceptable*.
q_1* human = 3.44×10^{-2} at 1×10^{-6}

>Calculation of risk-specific dose (D):
$D = 1 \times 10^{-6} / q_1$* human
$D = 1 \times 10^{-6} / 3.44 \times 10^{-2}$
$D = 0.000029$ mg/m^3
$D = 0.03$ ug/m^3 IRSL – 0.3 ug/m^3 SRSL

The q_1* (human) unit risk value of 3.44×10^{-2} $(mg/m^3)^{-1}$ was chosen for the derivation of the final IRSL and SRSL for decalin.

Therefore, the IRSL and SRSL for decalin (91-17-8) are 0.03 ug/m^3 and 0.3 ug/m^3, respectively, both based on an annual averaging time.

References

ChemFinder.com – Internet World Wide Web. 2005. Chemical and physical properties for decahydronaphthalene. http://chemfinder.cambridgesoft.com/.

EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. United States Environmental Protection Agency, Office of Research and Development. Washington D.C. 20460. EPA/600/8-90/066F.

National Toxicology Program (NTP). Jan 2005. Toxicology and Carcinogenesis Studies of Decalin (CAS NO. 91-17-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). *NTP Technical Report Series* No. 513.

Gaworski, C.L., Haun, C.C., MacEwen, J.D., Vernot, E.H., Bruner, R.H., Amster, R.L., and Cowan, M.J. 1985. A 90-Day Vapor Inhalation Toxicity Study of Decalin. *Fundamental and Applied Toxicology*. 5: 785 – 793.

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Pituitary adenoma in F344/N male rats:
>Global 82 LMS model given results:
Chi-squared stat = 6.80662 < 2 degrees of freedom = 9.210 – *therefore acceptable*.
q_1* human = 1.286×10^{-2} $(mg/m^3)^{-1}$ at 1×10^{-6}

>Calculation of risk-specific dose (D):
D = $1 \times 10^{-6}/q_1$* human
D = $1 \times 10^{-6}/1.286 \times 10^{-2}$
D = 0.00007776 mg/m^3
D = 0.08 ug/m^3 IRSL – 0.8 ug/m^3 SRSL

Pituitary carcinoma in C57BL/6 female mice:
>Global 82 LMS model given results:
Chi-squared stat = 2.31387 < 2 degrees of freedom = 9.210 – *therefore acceptable*.
q_1* human = 5.686×10^{-3} $(mg/m^3)^{-1}$ at 1×10^{-6}

>Calculation of risk-specific dose (D):
D = $1 \times 10^{-6}/q_1$* human
D = $1 \times 10^{-6}/5.686 \times 10^{-3}$
D = 0.00017587 mg/m^3
D = 0.2 ug/m^3 IRSL – 2 ug/m^3 SRSL

Pheochromocytoma benign and malignant tumors in F344/N male rats:
>Global 82 LMS model given results:
Chi-squared stat = 1.85109 < 4 degrees of freedom = 13.277 – *therefore acceptable*.
q_1* human = 2.153×10^{-3} $(mg/m^3)^{-1}$ at 1×10^{-6}

>Calculation of risk-specific dose (D):
D = $1 \times 10^{-6}/q_1$* human
D = $1 \times 10^{-6}/2.153 \times 10^{-3}$
D = 0.000464 mg/m^3
D = 0.5 ug/m^3 IRSL – 5 ug/m^3 SRSL

Stromal polyp and sarcoma in B6C3F1 female mice:
>Global 82 LMS model given results:
Chi-squared stat = 0.943486 < 3 degrees of freedom = 11.344 – *therefore acceptable*.
q_1* human = 5.133×10^{-4} $(mg/m^3)^{-1}$ at 1×10^{-6}

>Calculation of risk-specific dose (D):
D = $1 \times 10^{-6}/q_1$* human
D = $1 \times 10^{-6}/5.133 \times 10^{-4}$
D = 0.001948 mg/m^3
D = 2 ug/m^3 IRSL – 20 ug/m^3 SRSL