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OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Review of a Carcinogenicity Study on Vinyl Chloride

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At the request of Dr. Marcus of your staff, the Carcinogen Assessment Group (CAG) has reviewed the Feron et al. (1981) dietary administrative study of vinyl chloride in rats. Dr. Larry Anderson has written the qualitative analysis of the study and Dr. Steven Bayard has prepared the unit risk estimate. This review is attached.

Attachment

REVIEW OF A CARCINOGENICITY STUDY ON VINYL CHLORIDE BY FERON et al. (1981)
(Prepared by Drs. Larry Anderson and Steven Bayard, 1983)

The review of the subject study presented herein shows a clear dose-related induction of hepatocellular carcinomas in male and female Wistar rats given chronic doses of vinyl chloride monomer in the diet as well as induction of hepatic angiosarcomas in male and female Wistar rats given a chronic dose of vinyl chloride monomer in soya oil by gavage.

MATERIALS AND METHODS

Vinyl chloride monomer (VCM) used in this study was obtained with the high purity and composition described in Table 1. Polyvinyl chloride (PVC) powder, with a particle size distribution (by weight) of: max 0.1% > 300 um, 4% > 200 um, max 90% > 88 um, max 95% > 40 um, was mixed with liquid VCM before addition of PVC/VCM mixture into the diet. The diet of each dose group contained 10% PVC powder with the desired dose level of VCM. A control group was given a diet containing 10% PVC powder alone; the VCM content of PVC given to the control group was < 0.3 ppm.

Albino Wistar rats (Cpb: WU: Wistar random), initially five weeks old, were randomly allotted to dose groups according to body weight. In the dietary study, the control group (restricted feeding) and the high-dose group each consisted of 80 males and 80 females, and the remaining dose groups, including controls given diet ad libitum, were composed of 60 males and 60 females.

TABLE 1. CHEMICAL COMPOSITION OF VCM
(Feron et al. 1981)

Ingredient	mg ingredient/kg VCM
Vinyl chloride monomer	> 99.97%, W/W)
Acetylene	< 2
Monovinyl acetylene	< 15
1,3-Butadiene	< 10
Methyl chloride	< 75
Ethyl chloride	< 50
Chloroprene	< 1
1,1-Dichloroethane	< 1
1,2-Dichloroethane	< 20 ul/l (gas)
Acetaldehyde	< 5
Hydrochloric acid	< 1
Iron	< 0.5
Water	< 100
Evaporation residue	< 10

These groups were fed a diet containing PVC alone 4 to 6 hours/day for five days before treatment with VCM began. Diets were prepared daily, and diet was available to each group only between 0900 and 1500 hours each day throughout the study. A second control group was offered a diet containing 10% PVC ad libitum. Animals were maintained on control or treatment diets until termination of the study at 135 weeks for males and 144 weeks for females.

Actual doses of VCM ingested from diet were estimated by measuring, by gas-liquid chromatography, the VCM content in the diet during the 4-hour feeding period, the rate of diet consumption during the 4-hour feeding period, and the amount of VCM excreted in feces at the end of feeding and at 4 and 9 hours after termination of feeding. Fecal samples obtained 1 hour before the start of feeding were also analysed. These measurements produced estimates of dietary VCM levels and oral intake of VCM described in Table 2. Intake of VCM was approximately 1.7, 5.0, and 14.1 mg/kg/day in low-, mid-, and high-dose groups, respectively.

A separate treatment group consisting of 80 male and 80 female Wistar rats was given a 10% solution of VCM in soya bean oil by gavage at a dose of 300 mg VCM/kg/day, five days/week, until cessation of treatment at 83 weeks. The VCM solution was prepared by injecting liquid VCM into the oil, and the VCM concentration in oil was checked by gas-liquid chromatography. The group treated with VCM by gavage was offered diet ad libitum. A control group given soya oil alone was not included in this study.

Body weights and food consumption were recorded periodically throughout the study. Blood and urine samples from 10 rats/sex/group at week 13, 26, 52, 78, and 94 were analyzed for hematology, serum biochemistry, and urinalysis.

All animals were necropsied. Complete histopathologic examination of tissues and organs from 20 males and 20 females from the control group

TABLE 2. DESIGNED AND ACTUAL DOSAGE OF VCM IN RATS MAINTAINED ON DIETS CONTAINING PVC POWDER (Feron et al. 1981)

Designed VCM treatment					
Dietary level (ppm)	Intake (mg/kg body weight/day)	Actual initial dietary VCM level (ppm)*	Oral intake of VCM (mg/kg body weight/day)		Actual oral exposure level of VCM§ (mg/kg body weight/day)
			Theoretical†	Actual	
0	0	0	0	0	0
20	1	46	2.3	1.8	1.7
60	3	139	7.0	5.6	5.0
200	10	424	21.2	17.0	14.1

*Average dietary VCM contents determined immediately after preparation of the diets.

†Assuming no loss of VCM by evaporation from the diets.

§Oral intake of VCM diminished by the faecal VCM, which was found to be 8, 10, and 17% of the actual oral VCM intake for the low-, mid-, and high-dose groups, respectively. The VCM excreted in the faeces was considered to be still enclosed in the PVC granules and thus not to have been in contact with the body.

(restricted feeding), the high dose dietary group, and the gavage group was done. Terminally sacrificed animals were supplemented with the longest surviving decedents to yield the 20 rats per group. A limited number of tissues and organs from the remaining rats, except interim sacrificed animals and ad libitum control animals, was histopathologically evaluated. All gross lesions and tumors were microscopically examined.

Ten males and 10 females per group from the control (restricted feeding), the high-dose dietary group, and the gavage group were sacrificed at 26 and 52 weeks. These animals were evaluated for gross pathology, histopathology of the liver, kidney, and Zymbal gland, electron microscopic changes in liver, liver and kidney weights, and liver and kidney function.

The control animals offered diet ad libitum were evaluated for body weight, survival, and gross pathology.

RESULTS

A dose-related decrease in survival of treated rats in the dietary study was evident (Table 3). Death of treated animals was primarily attributed to pulmonary or hepatic insufficiency due to neoplastic or nonneoplastic lesions in these organs. By 80 weeks of gavage treatment with VCM, mortality was becoming high (Table 3), and most of the decedents in this group has lesions or tumors in liver and lung.

Body weights and food consumption were similar between control (restricted feeding) and treated groups given VCM in the diet. Animals allowed diet ad libitum were heavier which appears to be a result of greater food consumption by these animals (Figure 1).

Hematology, serum biochemistry, urinalysis, and organ function tests were negative except for decreased blood clotting times and increased serum α-fetoprotein levels in high-dose dietary- and gavage-treated groups.

TABLE 3. CUMULATIVE MORTALITY OF RATS EXPOSED ORALLY TO VCM FOR UP TO 2.7 YEARS (Feron et al. 1981)

Treatment group (mg VCM/kg body weight/day)	Number of deaths† by end of wk:									
	12	36	52	80	92	105	120	128	134§	143§
					Males					
0	0	0	0	0	2	6	18	40	46	
1.7	0	0	1	1	3	6	13	37	40	
5.0	0	0	0	2	7	12	30*	49	60**	
14.1	0	1	2	8**	22***	40***	56***	60***	60**	
300¶	0	6	6	23	47	53	60	60	60	
0#	0	0	0	1	3	19	28	46	46	
					Females					
0	0	0	0	1	5	6	22	27	32	41
1.7	0	0	1	2	4	13	26	32	34	55**
5.0	0	1	2	7*	16**	31***	55***	60***	60***	60***
14.1	0	0	1	7*	43***	60***	60***	60***	60***	60***
300¶	0	3	7	24	47	58	60	60	60	60
0#	0	0	1	4	10	17	27	42	43	52

†Initial number of rats: 60/sex/group.

§Surviving males were killed in wk 135 and surviving females in wk 144.

¶The figures for this group were not evaluated statistically, because no corresponding control group was included in the study.

#Additional control group housed in a separate room and having constant access to the diet containing 10% PVC without VCM.

Values marked with asterisks differ significantly from those of the controls according to the chi-square test: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

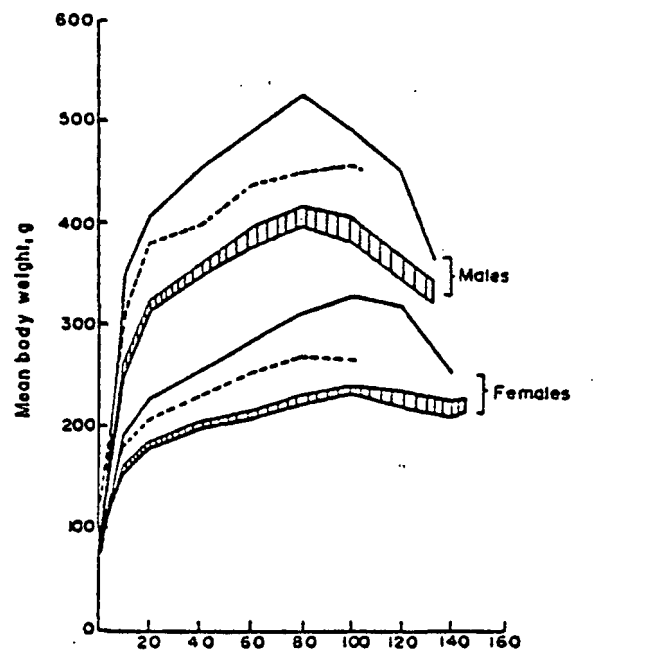

Figure 1. Average body weights of the extra controls fed the 10%-PVC diet ad libitum (-) and of the rats given 300 mg VCM/kg body weight in oil by gavage (--). The weight curves of the rats receiving 0, 1.7, 5.0, or 14.1 mg VCM/kg body weight/day from the 10%-PVC diets fed for 4 hr each day all lie within the shaded area. (Feron et al. 1981)

Liver/body weight ratios were higher in high dose dietary- and gavage-treated rats compared to dietary (restricted feeding) controls at 26 and 52 weeks; however, the evaluation of these results might have been strengthened if liver weights themselves had been reported and if organ weight data had been obtained at other times during the entire study.

Gross lesions in livers of treated rats were described as pronounced swelling, discoloration, varying numbers of cysts, and nodules and nodule-like processes up to 4 cm in diameter. Larger firm and pale nodules with central necrosis, found mainly in completely distorted livers, were diagnosed as carcinomas. Angiosarcomas were mainly multiple soft dark cystic nodules containing blood and granular necrotic material. Neoplastic nodules were small, firm, and compact with no signs of necrosis. Small hemorrhagic or gray nodules were located in pulmonary lobes of treated animals. Nodules in the peritoneum were found in slightly higher incidence in animals given VCM in the diet compared to other groups.

Histopathologic diagnoses of hepatic tumors and lesions are presented in Table 4. A dose-related increase in the incidences of hepatic neoplastic nodules, hepatocellular carcinomas, and hepatic angiosarcomas in both male and female rats given VCM in the diet is clearly evident. Females appear to have been more sensitive to the induction of hepatocellular carcinomas by VCM treatment; however, males were evidently more sensitive to the induction of angiosarcomas. Gavage treatment with 300 mg/kg of VCM effectively induced angiosarcomas but not hepatocellular carcinomas in males and females.

Nonneoplastic lesions common in liver of treated rats were necrosis, cysts, and polymorphism (Table 4). Ultrastructural examination of liver specimens from high dose dietary- and gavage-treated rats sacrificed at 26 and 52 weeks revealed hepatocytes with foci or vacuolated cytoplasm.

TABLE 4. TYPE AND INCIDENCE OF TREATMENT-RELATED HISTOPATHOLOGICAL CHANGES IN THE LIVER OF RATS EXPOSED ORALLY TO VCM
(Feron et al. 1981)

Type of change†	Treatment group (mg VCM/kg/day)...	Incidence of change									
		Males					Females				
		0	1.7	5.0	14.1	300§	0	1.7	5.0	14.1	300§
Animals killed after 26 wk											
	No. of rats examined...	10	--¶	--	10	9	10	--	--	10	10
Clear-cell foci		0	--	--	1	1	0	--	--	5**	2
Animals killed after 52 wk											
	No. of rats examined...	9	--	--	10	9	9	--	--	10	8
Clear-cell foci		1	--	--	8**	0	0	--	--	8**	0
Basophilic foci		0	--	--	0	0	0	--	--	4	1
Eosinophilic foci		0	--	--	2	0	0	--	--	5**	0
Neoplastic nodule		0	--	--	1	0	0	--	--	2	0
Hepatocellular carcinoma		0	--	--	1	0	0	--	--	1	0
Cystic proliferation of bile ducts		0	--	--	0	0	0	--	--	4*	0
Animals found dead or killed in extremis or teminally											
	No. of rats examined...#	55	58	56	59	55	57	58	59	57	54
Clear-cell foci		0	9**	16***	21***	9	4	24***	22***	36***	10
Basophilic foci		8	18	21*	22**	12	0	33***	17	28***	19
Eosinophilic foci		3	23***	27***	33***	11	8	35***	20*	29***	6
Neoplastic nodule		0	1	7**	23***	3	2	26**	39***	44***	2
Hepatocellular carcinoma		0	1	2	8**	1	0	4	19***	29***	0
Angiosarcoma		0	0	6*	27***	27	0	0	2	9**	29

(continued on the following page)

TABLE 4. (continued)

Type of change†	Treatment group (mg VCM/kg/day)...	Incidence of change									
		Males					Females				
		0	1.7	5.0	14.1	300§	0	1.7	5.0	14.1	300§
Proliferation of atypical sinusoidal cells only		2	0	4	7	6	4	6	3	4	7
Extensive necrois		4	4	8	23***	21	5	6	19***	27***	24
Cysts		2	3	4	16***	3	9	30***	41***	49***	3
Liver-cell polymorphism		4	16*	28***	42***	36	34	51*	38	41	41
Centrilobular degeneration		0	0	0	1	1	1	2	3	1	18
Focal haematopoiesis		0	1	0	10**	8	1	3	1	6	12

†Specific hepatocellular lesions were classified according to Squire and Levitt (1975).

§The figures of this group were not evaluated statistically, because no corresponding control group was included in the study.

¶Not examined.

#The initial number of animals was 60/sex/group. A number of rats could not be examined because of cannibalism or advanced autolysis.

Values marked with asterisks differ significantly from those of controls according to the chi-square test: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Vacuoles were identified as swollen mitochondria.

Lung angiosarcomas were found in treated rats (Table 5). Most of these angiosarcomas were described as multiple foci of tumor cells with a growth pattern suggestive of metastases, and pulmonary metastases of hepatocellular carcinomas were frequently observed. Conversely, primary neoplasms in the lung were also identified, and lung angiosarcomas were found in seven rats with no liver angiosarcoma.

Although increased incidences of abdominal mesotheliomas in treated rats were not significant ($P > 0.05$, Table 5), a dose-related decrease in latency for development of this tumor type was reported, without presentation of data.

A possible treatment-related nonneoplastic lesion was "very marked" hematopoietic activity in the spleen of 6/40 males and 10/40 females in the high dose dietary- and the gavage-treated groups compared to slight to moderate spleen hematopoiesis in controls.

TABLE 5. SITE, TYPE, AND INCIDENCE OF TUMORS IN THE LUNG AND ABDOMEN IN RATS EXPOSED ORALLY TO VCM FOR OVER 2.5 YEARS
(adapted from Feron et al. 1981)

Site and type of tumor	Treatment group (mg/VCM/kg/day)	Incidence of tumors									
		Males					Females				
		0	1.7	5.0	14.1	300†	0	1.7	5.0	14.1	300†
	Effective no. of rats	55	58	56	59	55	57	58	59	57	54
Lungs											
Angiosarcoma		0	0	4*	19**	19	0	0	1	5*	23
Abdomen											
Mesothelioma		3	1	7	8	1	1	6*	3	3	0

†The figures for this group were not evaluated statistically, because no corresponding control group was included in this study

*Significant difference from controls by chi-square test ($P < 0.05$).

**Significant difference from controls by chi-square test ($P < 0.01$).

DISCUSSION

Results of this study indicate that limiting the animals to a daily 4-hour feeding period did not compromise their health and survival; however, the 4-hour daily treatment with VCM was effective as an inducer of neoplastic and nonneoplastic lesions in liver. Limiting the animals to a 4-hour feeding period reduced the unavoidable exposure to VCM evaporating from diet; however, the rats receiving PVC in the diet for 4 hours each day were housed in a "well-ventilated" room. Rats given VCM in corn oil were separately housed in a "well-ventilated" cabinet.

Ingestion of VCM as a VCM/PVC mixture in diet produced a dose-related increase in the incidence of neoplastic nodules and carcinomas in liver in all treated groups of male and female rats. In contrast, gavage administration of VCM in soya oil produced a high incidence of hepatic angiosarcomas but few hepatocellular carcinomas. Nonneoplastic liver lesions common to treated rats were necrosis, centrilobular degeneration, and mitochondrial damage. Slight increases in liver/body weight ratios and α-fetoprotein levels in treated rats may also reflect liver damage. Most pulmonary angiosarcomas were metastases from hepatic angiosarcomas.

Induction of hepatic angiosarcomas in male and female Wistar rats given 300 mg/kg of vinyl chloride in soya oil by gavage for 83 weeks in the study by Feron et al. (1981) is supportive of the similar finding in male and female Sprague-Dawley rats given doses of 50 mg/kg or less of vinyl chloride in olive oil by gavage for 52 weeks by Maltoni et al. (1981). Feron et al. (1981) used only one dose, whereas Maltoni et al. (1981) used six doses to provide evidence for a dose-response.

The contrast between the effect of VCM administered by gavage in oil and orally in diet on the spectrum of neoplastic and nonneoplastic liver lesions induced in rats in this study is not clear and should be further investigated. Additionally, possible differences in the sensitivity of rats to the liver toxicity of VCM when given in the diet during daily restricted 4-hour feedings and when offered in the diet ad libitum could also be explored; however, evaporation of VCM from diet should be considered in designing a study for such a comparison. The evaluation of rats treated with VCM by gavage could have been strengthened if a concurrent control group treated with soya oil alone had been included in the study.

Feron et al. (1975) analyzed VCM solutions in soya oil and various dietary preparations of VCM for stability and reactivity. These investigators reported a slow evaporation of VCM from soya oil at room temperature, e.g., a 5.6% solution lost 10%, 16%, and 29% of its VCM after 1, 4, and 8 hours, respectively, and no evidence of reaction products from storage of a 10% VCM solution in soya oil was noted. Feron et at. (1975) compared the following diets: a) diet mixed with a solution of 3% VCM in soya oil in an open vessel; b) diet mixed with soya oil and liquid VCM, individually, in a closed vessel; c) diet mixed with PVC containing 1,850 ppm or 4,400 ppm VCM. Storage of these diets in open vials at room temperature revealed loss of VCM from diets a and b to undetectable levels by 1 and 2 hours, respectively, after mixing. The VCM in diet c evaporated more slowly, thus indicating greater stability, with 1,850 ppm reduced to 750 ppm by 6 hours and 4,400 ppm decreased to approximately 2,600 ppm by 4 hours after mixing. The rate of VCM evaporation from diet in the study by Feron et al. (1981) discussed herein corresponds to the results by Feron et al. (1975) in that

the initial 49, 139, and 424 ppm VCM levels in Table 2 decreased to approximately 25, 75, and 225 ppm, respectively, by the end of the 4-hour feeding period. Feron et al. (1981) and Feron et al. (1975) concluded that VCM was released from PVC during transport in the gastrointestinal tract, and the percentage of VCM eliminated in feces in rats fed VCM in diet, as described in Table 2 herein, indicates an 83 to 92% absorption of VCM which is close to the estimated 92% absorption of VCM in soya oil given to rats in the study by Feron et al. (1975).

UNIT RISK ASSESSMENT FOR VINYL CHLORIDE

The data used to estimate a unit risk for oral exposure to vinyl chloride are based on the Feron et al. (1981) study. The statistically significant increases reported for liver and lung tumors were considered biologically significant. For the liver tumors, neoplastic nodules were considered a progression toward hepatocellular carcinomas, and these are included in the analysis in Tables 6 and 7. Extrapolations using the linearized multistage model show values of q_1^* for the individual tumors ranging from 8.8×10^{-2} to 1.3×10^{-1} for the males and from 5.8×10^{-2} to 1.3 for the females. The value of q_1^* based on males was 3.0×10^{-1} for liver tumors and 2.9×10^{-1} based on all tumors combined. For the females the value of q_1^* based on liver tumors was 1.9 and for all tumors combined was 2.3. All units of q_1^* are per mg/kg/day.

Before proceeding with the unit risk estimates an explanation of the total tumor counts in Tables 6 and 7 is necessary. For the liver all animals with hepatocellular carcinomas were assumed to also have the neoplastic nodules. Thus, only the neoplastic nodules and liver angiosarcomas were added to derive the total liver tumors. Otherwise, the totals would have exceeded the number of animals examined. Also, in adding the lung and liver tumors, the totals were not allowed to exceed one less than the number examined. The result of this latter restriction was to raise the value of q_1^* slightly due to increased variance. In fitting the response data in Tables 6 and 7 with the human equivalent dosages, the human equivalent dosages were derived by dividing the corresponding animal dosages by $(W_h/W_a)^{1/3}$. The human weight (W_h) was assumed to be 70 kg; the male rats

TABLE 6. TYPE AND INCIDENCE OF STATISTICALLY SIGNIFICANT TREATMENT-RELATED CHANGES IN THE LIVER AND LUNG OF MALE WISTAR RATS EXPOSED TO VCM IN THE DIET. VALUES OF q_1^* AND CONCENTRATION FROM MULTISTAGE EXTRAPOLATION MODEL INCLUDED

	Treatment group (mg/kg/day)				q_1^* [a]	95% lower-limit concentration ug/l associated with risk [b]		
	0	1.7	5.0	14.1	$(mg/kg/day)^{-1}$	10^{-4}	10^{-5}	10^{-6}
Number of rats examined[c]	55	58	56	59				
LIVER								
Neoplastic nodules	0	1	7	23	2.1×10^{-1}	16.7	1.7	0.2
Hepatocellular carcinomas	0	1	2	8	8.8×10^{-2}	39.8	4.0	0.4
Angiosarcomas	0	0	6	27	1.3×10^{-1}	27.0	2.7	0.3
TOTAL LIVER TUMORS[d]	0	2	13	50	3.0×10^{-1}	11.7	1.2	0.1
LUNG								
Angiosarcomas	0	0	4	19	1.1×10^{-1}	31.8	3.2	0.3
TOTAL ANIMAL WITH TUMORS[e]	0	2	17	58	2.9×10^{-1}	12.1	1.2	0.1

[a] Human equivalent $q_1^* = q_1^*(a)(W_h/W_a)^{1/3}$ in $(mg/kg/day)^{-1}$.

[b] Concentration in ug/l $= (-35000/q_1^*)\ln(1-R)$.

[c] Found dead or killed in extremis or terminally.

[d] Sum of neoplastic nodules and liver angiosarcomas.

[e] Total must be at least less than total examined.

TABLE 7. TYPE AND INCIDENCE OF STATISTICALLY SIGNIFICANT TREATMENT-RELATED CHANGES IN THE LIVER AND LUNG OF FEMALE WISTAR RATS EXPOSED TO VCM IN THE DIET. VALUES OF q_1^* AND CONCENTRATION FROM MULTISTAGE EXTRAPOLATION MODEL INCLUDED

	Treatment group (mg/kg/day)				q_1^* [a]	95% lower-limit concentration ug/l associated with risk[b]		
	0	1.7	5.0	14.1	$(mg/kg/day)^{-1}$	10^{-4}	10^{-5}	10^{-6}
Number of rats examined[c]	57	58	59	57				
LIVER								
Neoplastic nodules	2	26	39	44	1.3	2.7	0.3	0.03
Hepatocellular carcinomas	0	4	19	29	5.0×10^{-1}	70.0	0.7	0.07
Angiosarcomas	0	0	2	9	8.8×10^{-2}	39.8	4.0	0.4
TOTAL LIVER TUMORS[d]	2	26	41	53	1.9	1.8	0.2	0.02
LUNG								
Angiosarcomas	0	0	1	5	5.8×10^{-2}	60.3	6.0	0.6
TOTAL ANIMAL WITH TUMORS[e]	2	26	42	56	2.3	1.5	0.2	0.02

[a] Human equivalent $q_1^* = q_1^*(a)(W_h/W_a)^{1/3}$ in $(mg/kg/day)^{-1}$.

[b] Concentration in ug/l = $(-35000/q_1^*)\ln(1-R)$.

[c] Found dead or killed in extremis or terminally.

[d] Sum of neoplastic nodules and liver angiosarcomas.

[e] Total must be at least less than total examined.

were estimated to weigh 350 grams and the female rats were estimated to weigh 200 grams (Figure 1). Thus, the corresponding human equivalent dosages were 0, 0.29, 0.85, and 2.41 mg/kg/day based on the male rats, and 0, 0.24, 0.71, and 2.00 mg/kg/day based on the female rats.

When the response and human equivalent dose data were fit to the linearized multistage model, the 95% upper limit on the largest linear term (Table 7) was

$$q_1^* = 2.3 \text{ (mg/kg/day)}^{-1}$$

To derive an estimate of the 95% lower level of concentration, d, corresponding to a 95% upper level of risk, R, the following equation is used

$$R = 1-e^{-q_1^* d}$$

where d is the lower limit on dose in mg/kg/day. To solve for d in ug/liter, we use the transformation

$$1 \text{ mg/kg/day} \times (70 \text{ kg}/2 \text{ liter}) \times 1000 \text{ ug/mg} = 35000 \text{ ug/liter}$$

If we set $R = 10^{-5}$ then

$$d = (-35000/q_1^*) \ln (1-10^{-5}) \text{ (ug/liter)}.$$

For the highest value of $q_1^* = 2.3 \text{ (mg/kg/day)}^{-1}$ (Table 7), setting $R = 10^{-5}$ yields a value of d = 0.15 ug/liter. Setting $R = 10^{-4}$ or 10^{-6} yields values of d = 1.5 ug/liter and d = 0.015 ug/liter, respectively.

For comparison purposes only we compare the potency of vinyl chloride by the diet versus the inhalation routes. A previous memo we sent you

estimated the 95% upper limit of potency for VCM as $q_1^* = 1.7 \times 10^{-2}$ $(mg/kg/day)^{-1}$ based on an inhalation study showing angiosarcomas and other tumors in rats. That potency estimate was derived for water quality criterion purposes. In that document an inhalation to ingestion by gavage relationship of 1 ppm inhaled = 2.28 mg/kg/day ingested was derived for 200 gram rats based on a VCM uptake study. Without that adjustment for route differences, a direct transformation based on a 70 kg human breathing 20 m^3/day would have yielded a 1 ppm inhaled = 0.76 mg/kg/day relationship and a $q_1^* = 5.2 \times 10^{-2}$ mg/ kg/day, still 44 times less than the estimate from the diet study.

In summary, the VCM potency estimates are reported below.

Route	Potency	95% lower limit concentration ug/liter associated with risk		
	$q_1^*(mg/kg/day)^{-1}$	10^{-4}	10^{-5}	10^{-6}
Oral				
Based on diet study	2.3	1.5	0.15	0.015
Based on inhalation study	1.7×10^{-2}	200	20.0	2.0
Inhalation				
Based on inhalation study	5.2×10^{-2}	67.3	6.7	0.7

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