Attachment 5 (11/9/93)

Risk Assessment Issue Paper for:
Evaluation of Subchronic Oral Systemic Toxicity
for Vinyl Chloride (CASRN 75-01-4)

SUBCHRONIC ORAL TOXICITY

Groups of 15 weanling male and female Wistar rats were administered 0, 30, 100, or 300 mg/kg vinyl chloride (purity not reported) in soybean oil by gavage 6 day/week for 13 weeks (Feron et al., 1975). The duration expanded doses are 0, 26, 86, and 257 mg/kg-day. Weekly body weight measurements, hematological parameters (blood clotting time, hemoglobin, packed cell volume, and erythrocyte and leukocyte counts), clinical chemistry parameters (glucose, SGOT, SGPT, BUN, total protein, albumin), organ weights, histopathology of major organs and tissues (control and high-dose groups only), and electron microscopy of the liver (2/sex/group) were used to assess toxicity. In addition, urinalysis (specific gravity and GOT in the urine) was conducted in 10 rats/sex in the control and high dose group. Urinary pH, glucose, protein, occult blood, ketones and microscopic constituents were measured from pooled urine samples from 10 rats/sex in each group. Slight but significant ($p < 0.05$) decreases in blood glucose, total leukocytes (mid- and high-dose females), SGOT, SGPT, and urinary GOT (high-dose males) levels were observed. Increases ($p < 0.05$) in relative liver and adrenal (males only) weights were observed in the high-dose group. Foci of hyperbasophilic hepatocytes were observed in 2/30 in each of the 100 and 300 mg/kg groups, this slight increase was not statistically significant. This study identifies a NOAEL of 300 mg/kg.

CHRONIC ORAL TOXICITY

Groups of 110 female and 110 male Wistar rats were fed diets containing 0, 0.014, or 0.13 mg/kg-day vinyl chloride and groups of 60 female and 60 male Wistar rats were fed 1.3 mg/kg-day vinyl chloride for over 3 years (Til et al., 1983). The diets were prepared by incorporating polyvinyl chloride powder with varying proportions of vinyl chloride monomer-containing powder (4600 ppm) or vinyl chloride-free powder. The concentration of polyvinyl chloride in the diet was 1%. The rats had access to the diet for 4 hour/day. Til et al. (1983) calculated mg/kg-day doses from the rate of evaporation of vinyl chloride monomer from the diet, food intake, and body weight data. After 9 and 18 months, 5 female and 5 male rats in each group were killed for measurement of glutathione levels in the liver. Daily observations of clinical signs, monthly body weight and bimonthly food consumption measurements, hematological measurements (thrombocyte count and prothrombin time) in 10 rats/sex/group after 9 and 18 months of exposure, gross examination of major tissues and organs, and histopathological examination of the liver were used to assess toxicity. Increased mortality was observed in the high dose group during the last 6 and 9 months of the study. No compound-related effects on general appearance, food intake, body weight, hematological parameters, or glutathione levels were observed. The only

compound-related alteration observed during the gross examination was a significant ($p<0.05$) increase in the incidence of liver cysts in the high dose group. An increase in the incidence of foci of basophilic cellular alterations in the liver were observed in all groups of vinyl chloride-exposed female rats, the incidence was not dose-related. Other compound-related liver alterations observed in the high-dose group include cell polymorphism, eosinophilic cellular alterations, clear cell foci of alterations, and cysts. A statistically significant increase in the incidence of neoplastic tumors in the liver and mammary glands were observed in the high-dose group.

Groups of 80 (control and high dose groups) or 60 male and 80 or 60 female Wistar rats were fed diets containing 0, 1.7, 5.0, or 14.1 mg/kg-day vinyl chloride for 135 (males) or 144 (females) weeks (Feron et al., 1981). The diets were prepared by combining polyvinyl chloride powder (10% in diet) and varying proportions of vinyl chloride monomer. Actual levels of vinyl chloride monomer in the diet were measured. The diet was available for 4 hours each day; another control group that had ad libitum access to a diet containing 10% polyvinyl chloride was also used. A group of 80 male and 80 female rats received 300 mg/kg vinyl chloride in corn oil by gavage 5 day/week for 2 years (expanded dose of 214 mg/kg-day). The following measurements were used to assess toxicity: monthly body weights and bimonthly food consumption measurements; hematological (hemoglobin, hematocrit, thrombocyte, RBC, and WBC counts, BUN, blood glucose) and clinical chemistry (alkaline phosphatase, SGOT, SGPT, total protein, alpha-fetoprotein, and albumin) parameters (blood samples taken from 10 rats/sex/group in week 13, 26, 52, 78, and 94); urinalysis (urine samples collected same as blood samples); and gross and histopathological examinations (major organs and tissues - 20 rat/sex in control, 14.1 and 214 mg/kg-day groups at termination; liver, Zymbal glands, lungs, kidneys, spleen, pituitary, thyroid, and adrenals - all rats killed at termination; and liver, kidneys and Zymbal glands - 10 rats/sex in control, 14.1 and 214 mg/kg-day groups killed after 26 or 52 weeks). The data for animals in the 214 mg/kg-day group were not analyzed statistically because no corresponding control group was included in the study. Rats in the 214 mg/kg-day gavage group died or were killed in a moribund condition by week 84. Lethargy and severe lesions in the liver, lungs and other organs, were observed in this group. In the 5.0 and 14.1 mg/kg-day groups, lethargy, emaciation, and general poor condition were observed after 18 months of exposure. A significant ($p<0.05$) increase in mortality was observed in the female rats in the 5.0 and 14.1 mg/kg-day groups after 80 weeks and in the 1.7 mg/kg-day group after 143 weeks; in the male rats increased mortality was observed in the 14.1 mg/kg-day group after 80 weeks of exposure and in the 5.0 mg/kg-day group after 134 weeks of exposure. A decrease in body weight gain was observed in the 214 mg/kg-day group compared with the ad libitum control group. No differences in the body weight gain of the other groups were observed. Decreased ($p<0.05$) prothrombin times and increased alpha-fetoprotein levels were observed in the 14.1 and 214 mg/kg-day groups after 26 (prothrombin time only) and 52 weeks of exposure. Significant ($p<0.05$) increases in the incidence of clear cell foci, neoplastic nodules (females only), and cystic proliferation of the bile ducts (females only) were observed in rats exposed to 14.1 mg/kg-day for 26 or 52 weeks. In animals killed at termination, dying early, or killed in extremis, statistically significant increases in the incidence of clear-cell, basophilic, and eosinophilic foci of cellular alterations, neoplastic

nodules, cysts, and liver cell polymorphism (all treated groups), and hepatocellular carcinomas, extensive necrosis, cysts, and focal hematopoiesis (14.1 mg/kg-day) were observed in the liver. The severity and incidence of the lesions were generally higher in the females than the males. Marked hematopoietic activity was observed in the spleen in rats exposed to the 2 highest concentrations. Significant increases of neoplastic tumors were also observed in the lung, abdomen, and pituitary gland.

Male and female Wistar rats (total of 10-20 rats/group) received daily gavage doses of 0, 3, 30, or 300 mg/kg-day of vinyl chloride in corn oil for 95-125 weeks (Knight and Gibbons, 1987). Increased mortality was observed in the 300 mg/kg-day group after 60 days. Mortality in the low- and mid-groups was 1/15 and 5/16, respectively. The incidence of liver tumors, primarily hepatic angiosarcomas, were 1/16, 11/15, and 10/10 in the low-, mid-, and high-dose groups, respectively; the incidence in the control group was not reported. The chemical composition of the skin from 9 control group rats and 8 rats exposed to 30 mg/kg-day was analyzed. Significant increases in moisture content and collagen content were observed in the vinyl chloride treated rats. A significant increase in the number of collagen cross-links was also observed in the treatment group, indicating an increase in collagen synthesis. Thus, exposure to 30 mg/kg-day vinyl chloride for 2 years resulted in a thickening of the skin due to increased collagen. Scleroderma-like syndrome has been observed in individuals exposed to vinyl chloride. Characteristics of this syndrome include thickening and increased rigidity of the skin, poor circulation in the extremities, and hypersensitivity to the cold.

SUBCHRONIC INHALATION TOXICITY

Hong et al. (1981) exposed groups of CD rats (4-16/sex/group) and CD-1 mice (8-28/sex/group) by inhalation to 0, 50, 250, or 1000 ppm vinyl chloride 6 hour/day, 5 day/week for 1, 3, 6, or 10 months (rats only). Animals were sacrificed 12 months after termination of exposure. Clinical signs, biweekly body weight and weekly food consumption measurements, hematological (RBC, reticulocyte, platelet, and WBC counts, hemoglobin, hematocrit, methemoglobin, and Heinz bodies) and clinical chemistry [SGPT and BUN (both species), prothrombin time, SGOT, alkaline phosphatase, bilirubin, creatinine, LDH, immunoglobulin IgA, IgB-A, IgB-B, and IgM, total protein, albumin, globulin, and collagen contents of liver and lungs (rats only)] parameters, gross examination of major tissues and organs, and histopathological examination of mammary gland, lung, liver, spleen, kidney and tissues with gross pathological changes were used to assess toxicity. During the recovery period for rats, significant ($p<0.05$, Fisher exact test performed by EPA) increases in mortality were observed in rats exposed to 1000 ppm for 6 months and all groups of rats exposed to vinyl chloride for 10 months. Increased incidence of neoplastic nodules (mid-concentration group exposed for 6 or 10 months), hemangiosarcomas in the liver (mid-concentration group exposed for 10 months), fibroadenoma (low-concentration group exposed for 6 or 10 months), and bronchioloalveolar tumor and hemangiosarcomas in the lungs (mid- and high-concentration groups) were observed. During the recovery phase for mice, significant ($p<0.05$, Fisher exact test performed by EPA) dose- and duration-related increases in mortality were observed. Increased mortality was observed in mice exposed to

1000 ppm for 1 month, in the 250 and 1000 ppm groups exposed for 3 months, and all vinyl chloride exposed groups exposed for 6 months. Rough coat hair, lethargy, and the appearance of external tumor masses were observed in animals dying early. Increased incidence of bronchioloalveolar tumors (mid- and high-concentration groups exposed for 1 month; all vinyl chloride exposed groups after 3 and 6 months of exposure), hemangiosarcoma in the liver (mid- and high-concentration groups after 3 and 6 months of exposure), and adenocarcinoma/carcinoma in mammary gland (low-, mid- and high-concentration females after 3 months of exposure and mid-and high-concentration females after 6 months of exposure) were observed.

Groups of male Wistar rats were exposed by inhalation to nominal concentrations of 0, 10, 100, or 3000 ppm (0, 26, 256, 7669 mg/m^3) vinyl chloride 6 hour/day, 6 day/week for 12 months (Bi et al., 1985). Equivalent oral doses using a TWA body weight of 0.200 kg, an inhalation rate of 0.2136 m^3/day (calculated using the allometric equation in U.S. EPA, 1987), inhalation absorption rate of 0.42 (Krajewski et al., 1980) and oral absorption rate of 0.83 (Feron et al., 1981). The equivalent oral doses are 0, 3, 30, 888 mg/kg-day, respectively. Following 3, 6, and 9 months of exposure, 8, 30, 6, and 10 rats per dose group, respectively, were killed. The remaining animals were killed 6 months after exposure termination. Histopathological examination of the testes, lungs, liver, heart, kidneys, spleen, and brain were performed. During the study, the body weights of rats in the 100 and 3000 ppm groups were greater than 20% lower ($p<0.05$) than in the control group. Transient increases in relative kidney, spleen, liver, and heart weights were observed; in general, the changes were not dose- or duration-related. After 6 months of exposure, a significant ($p<0.05$) decrease in relative testes weight was observed in the 100 and 3000 ppm groups; this effect was not observed after 12 months of exposure. In the 100 and 3000 ppm groups, significant increases in the incidence of damage of the testicular seminiferous tubules were observed. Significant ($p<0.05$) increases in the incidence of tumors (predominantly in the liver and lung) were observed in the two highest-concentration groups. A significant increase in hepatic angiosarcomas was observed in the 3000 ppm group.

Groups of 36 male and 36 female CD rats and CD-1 mice were exposed by inhalation to 0, 50, 250, 1000 ppm (0, 128, 639, 2556 mg/m^3) vinyl chloride 6 hour/day, 5 day/week for 12 months (Lee et al., 1977, 1978). Equivalent oral doses can be estimated using TWA body weights of 0.580 kg (rat) and 0.032 kg (mouse), inhalation rates of 0.5116 (rat) and 0.0537 m^3/day (mouse) (calculated using the allometric equation in U.S. EPA, 1987), inhalation absorption rate of 0.42 (Krajewski et al., 1980) and oral absorption rate of 0.83 (Feron et al., 1981). The equivalent oral doses for rats are 0, 10, 51, and 204 mg/kg-day, respectively, and 0, 20, 98, 392 mg/kg-day, respectively, for mice. Four animals/species/sex/group were killed after 1, 2, 3, and 9 months of exposure. Clinical signs, biweekly body weight and weekly food consumption measurements, hematological (RBC, reticulocyte, platelet, and WBC counts, hemoglobin, hematocrit, methemoglobin, and Heinz bodies) and clinical chemistry [SGPT and BUN (both species), prothrombin time, SGOT, alkaline phosphatase, bilirubin, creatinine, LDH, immunoglobulin IgA, IgB-A, IgB-B, and IgM, total protein, albumin, globulin, and collagen contents of liver and lungs (rats only)] parameters, and gross and histopathological examination of major tissues and organs

were used to assess toxicity. In rats, increased mortality was observed in the vinyl chloride exposed rats; 0, 2, 14, and 21 animals died or were killed in a moribund state between months 8 and 12 in the 0, 50, 250, and 1000 ppm groups, respectively. Rough hair coats, loss of muscle tone, lethargy, and weight loss were observed in the animals prior to death. A slight decrease in body weight gain was observed in the high-concentration group (statistical significance not reported). No persistent alterations in hematological or clinical chemistry parameters were observed. Hepatic and/or pulmonary hemangiosarcomas were observed in the rats exposed to 250 and 1000 ppm vinyl chloride. In mice, increased mortality was observed in the vinyl chloride treated animals after 6 months of exposure. The number of animals dying early or killed due to morbidity in the 0, 50, 250, and 1000 ppm groups are 2, 20, 38, 34, respectively. All mice in the 1000 ppm and females in the 250 ppm groups were killed at the end of the ninth month. During the first 8 months of exposure, no differences in body weight gain were observed; in the ninth month, decreases in body weight were observed in the high concentration group. No persistent changes in hematological or clinical chemistry parameters were observed. A number of tumors including bronchiolo-alveolar adenomas, hemangiosarcoma in the liver, and mammary tumors were observed in the vinyl chloride exposed rats. The statistical significance of the tumor incidence were not reported.

INHALATION DEVELOPMENTAL TOXICITY

John et al. (1981) exposed groups of pregnant Sprague-Dawley rats (17-33/group) and New Zealand white rabbits (7-18/group) by inhalation to 0, 500, or 2500 ppm (0, 1278, 6391 mg/m^3) vinyl chloride for 7 hour/day on gestational days 6-15 or 6-18, respectively. Groups of 29-37 CF-1 mice were exposed 7 hour/day on days 6-15 of gestation to 0, 50 or 500 ppm (0, 128, 1278 mg/m^3) vinyl chloride. The pregnant rats, mice, and rabbits were sacrificed on day 21, 18, or 29 of gestation, respectively. Equivalent oral doses can be estimated using initial body weights of 0.250, 0.025, and 3.5 kg for rats, mice, and rabbits, respectively, inhalation rates of 0.2565 (rat), 0.0414 (mouse), and 1.302 (rabbit) m^3/day (calculated using the allometric equations in U.S. EPA, 1987), inhalation absorption rate of 0.42 (Krajewski et al., 1980) and oral absorption rate of 0.83 (Feron et al., 1981). The equivalent oral doses are 0, 194, 968 mg/kg-day; 0, 31, 312 mg/kg-day; and 0, 70, 351 mg/kg-day for rats, mice, and rabbits, respectively. Decreased body weight gain was observed in the rat dams exposed to 500 ppm, this effect was not observed in the high-concentration group. At 2500 ppm, decreased food intake and liver weight were observed; 1/17 rats died. Decreased mean fetal body weight and increased crown-rump length was observed in the 500 ppm group but not the 2500 ppm group. Lumbar spurs in the vertebrae (500 ppm) and dilated ureter (2500 ppm) were observed. Increased incidence of maternal deaths and decreases in body weight gain, food consumption and absolute liver weight were observed in mice exposed to 500 ppm. The incidence of resorption was significantly increased in the high-concentration group, but, the incidence was within the range for historical controls. A decrease in litter size was also observed in the high-concentration group. A statistically significant ($p < 0.05$) increase in fetal crown-rump length (50 ppm group) and decrease in mean fetal body weight (500 ppm group) were observed. Skeletal anomalies (delayed ossification in skull and sternebrae and unfused sternebrae) were observed

in the offspring of mice exposed to 500 ppm vinyl chloride. In the high-concentration group, 1/7 rabbit does died; decreased food intake was observed in the low-concentration group. A significant increase in the incidence of resorption was observed in the low-concentration group. Delayed sternebrae ossification was observed in the offspring of rabbits exposed to 500 ppm vinyl chloride.

CONCLUSION

One subchronic oral toxicity study was located (Feron et al., 1975). In this study, a small but significant increase in relative liver weight (approximately 10%) and slight decreases in SGPT, SGOT, and urinary GOT levels were observed in rats receiving gavage doses of 300 mg/kg (257 mg/kg-day) for 13 weeks. The 300 mg/kg dose is considered a NOAEL. The Hong et al. (1981) study showed that significantly more mice exposed by inhalation to 50 ppm vinyl chloride 6 hour/day, 5 day/week for 6 months (equivalent oral dose of 19 mg/kg-day) died 6-12 months after exposure termination as compared to the control group. No significant increases in the incidence of neoplastic tumors were observed in this group of mice (Fisher exact test performed by EPA). Non-neoplastic effects were not reported, however, it is not known if the tissues were examined for neoplastic endpoints only. No deaths were reported during exposure. Similar effects were observed in rats. However, mice may be more sensitive than rats to the lethal effects of vinyl chloride. The Hong et al. (1981) data suggest that the Feron et al. (1975) study is not adequate for the derivation of a subchronic RfD for vinyl chloride because subchronic exposure to 300 mg/kg may result in increased mortality several months after exposure termination. Furthermore, data from chronic exposure studies should not be used to derive a subchronic RfD. Decreased lifespan and liver damage following chronic oral exposure to vinyl chloride (Til et al., 1983; Feron et al., 1981) have been observed at dose levels greater than 2 orders of magnitude lower than the NOAEL from the Feron et al. (1975) subchronic study.

References

Bi, W., Y. Wang, M. Huang and D. Meng. 1985. Effect of vinyl chloride on testis in rats. Ecotoxicol. Environ. Safety 10: 281-289.

Feron, V.J., A.J. Speek, M.I. Willems, D. van Battum and A.P. de Groot. 1975. Observations on the oral administration and toxicity of vinyl chloride in rats. Food Cosmet. Toxicol. 13: 633-638.

Feron, V.J., C.F.M. Hendriksen, A.J. Speek, H.P. Til and B.J. Spit. 1981. Lifespan oral toxicity study of vinyl chloride in rats. Food Cosmet. Toxicol. 19: 317-333.

Hong, C.B., J.M. Winston, L.P. Thornburg, C.C. Lee and J.S. Woods. 1981. Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: tumor incidence and mortality subsequent to exposure. J. Toxicol. Environ. Health. 7: 909-924.

John, J.A., F.A. Smith and B.A. Schwetz. 1981. Vinyl chloride: inhalation teratology study in mice, rats, and rabbits. Environ. Health Perspect. 41: 171-177.

Knight, K.R. and R. Gibbons. 1987. Increased collagen synthesis and cross-link formation in the skin of rats exposed to vinyl chloride monomer. Clin. Sci. 72: 673-678.

Krajewski, J., M. Dobecki and J. Gromiec. 1980. Retention of vinyl chloride in the human lung. Br. J. Industr. Med. 37: 373-374.

Lee, C.C., J.C. Bhandari, J.M Winston, et al. 1977. Inhalation toxicity of vinyl chloride and vinylidene chloride. Environ. Health Perspect. 21: 25-32.

Lee, C.C., J.C. Bhandari, J.M. Winston, W.B. House, R.L. Dixon and J.S. Woods. 1978. Carcinogenicity of vinyl chloride and vinylidene chloride. J. Toxicol. Environ. Health 4: 15-30.

Til, H.P., H.R. Immel and V.J. Feron. 1983. Lifespan oral carcinogenicity study of vinyl chloride in rats. Conducted by CIVO Institutes TNO. Submitted by Verband Kunststofferzeugende Industrie e.V. to U.S. EPA, Office of Toxic Substances. Fiche No. FYI-AX-1084-0353.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Vinyl Chloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC EPA-440/5-80-078. NTIS PB81-117889.

U.S. EPA. 1984. Health Effects Assessment for Vinyl Chloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, D.C. EPA 540/1-86-036.

U.S. EPA. 1985a. Health and Environmental Effects Profile for Chloroethene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office , Cincinnati, OH, for the Office of Solid Waste and Emergency Response. Washington, D.C. ECAO-CIN-P155.

U.S. EPA. 1985b. Drinking Water Criteria Document for Vinyl Chloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington D.C. PB86-118320.

U.S. EPA. 1987. Health Advisory for Vinyl Chloride. Prepared by Office of Drinking Water, Washington D.C.

Summary Table of the Toxicity Data for Vinyl Chloride

Study	Species	Effect	Reported dose or concentration	Dose (mg/kg/day)	UF/MF	RfD (mg/kg/day)
Subchronic oral toxicity						
Feron et al., 1975	rat		0 (mg/kg, 6 d/wk) 30 100 300	0 26 86 257		
Chronic oral toxicity						
Til et al., 1983	rat	decreased lifespan and liver damage at 1.3 mg/kg/day		0 0.014 0.13 1.3		
Feron et al., 1981	rat	decreased lifespan and liver damage at ≥1.7 mg/kg/day		0 1.7 5.0 14.1 214[a]		
Knight and Gibbons, 1987	rat	decreased lifespan and increased collagen in the skin at 30 mg/kg/day		0 3 30 300		
Subchronic inhalation toxicity studies						
Bi et al., 1985	rat	testicular damage	0 (ppm) 10 100 L 3000	0[b] 3 30 L 888		
Hong et al., 1981	rat	increased mortality; increased incidence of lung tumors	0 (ppm) 50 F 250 1000			
Lee et al., 1977, 1978;	rat	increased mortality	0 (ppm) 50 250 F 1000	0[c] 10 51 F 204		

Study	Species	Effect	Reported dose or concentration	Dose (mg/kg/day)	UF/MF	RfD (mg/kg/day)
Lee et al., 1977, 1978;	mouse	increased mortality	0 (ppm) 50 F 250 1000	0[d] 20 F 98 392		
Inhalation developmental toxicity						
John et al., 1981	rat	developmental toxicity	0 (ppm) 500 L 2500	0[e] 194 L 968		
John et al., 1981	mouse	developmental toxicity and maternal toxicity	0 (ppm) 50 500 L	0[f] 31 312 L		
John et al., 1981	rabbit	developmental toxicity	0 (ppm) 500 2500	0[g] 70 351		

[a] gavage dose of 300 mg/kg 5 day/week
[b] mg/kg/day doses were calculated by multiplying the duration expanded concentration (mg/m^3) by the inhalation rats of 0.2136 m^3/day (using allometric equation, U.S. EPA, 1987) and dividing by a TWA body weight of 0.200 kg. This mg/kg/day dose was multiplied by the ratio of the inhalation absorption rate of 0.42 (Krajewski et al., 1980) and oral absorption rate of 0.83 (Feron et al., 1981).
[c] mg/kg/day doses calculated same as in [b], inhalation rate of 0.5116 m^3/day and body weight of 0.580 kg
[d] mg/kg/day doses calculated same as in [b], inhalation rate of 0.0537 m^3/day and body weight of 0.032 kg
[e] mg/kg/day doses calculated same as in [b], inhalation rate of 0.2565 m^3/day and initial body weight of 0.250 kg
[f] mg/kg/day doses calculated same as in [b], inhalation rate of 0.0414 m^3/day and initial body weight of 0.025 kg
[g] mg/kg/day doses calculated same as in [b], inhalation rate of 1.303 m^3/day and initial body weight of 3.5 kg