Interim Specific Groundwater Criterion Support Document 1,1-Dichloro-1-Fluoroethane (HCFC141b)*

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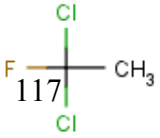
* Some of the information from drafts submitted by R. Shuler, ERM, was used in the preparation of this document

Summary
An interim specific ground water criterion of 500 µg/L is derived for 1,1-dichloro-2-fluoroethane. The risk assessment is based on decreased pup body weight in a 2 generation rat study. 1,1-Dichloro-1-fluoroethane is classified as having Suggestive Evidence of Human Carcinogenicity based on testicular Leydig cell tumors in a chronic rat study. An additional uncertainty factor is used to protect for potential carcinogenic effects.

Physical and Chemical Properties (OECD, 2001, unless otherwise noted)

Chemical Name:	1,1-Dichloro-1-fluoroethane
CAS Number:	1717-00-6
Common name:	HCFC-141b
Synonyms:	Dichlorofluoroethane; R-141b
Empirical Formula:	$C_2H_3Cl_2F$
Structural Formula:	
Molecular Weight:	117

Form:	Clear, colorless liquid
Odor:	Ethereal
Melting Point:	-103.5° C
Boiling Point:	32° C
Vapor Pressure:	76.3 kPa @ 25° C
Water Solubility:	4 g/L @ 20° C
Partition Coefficient:	Log K_{ow} = 2.3
Flammability:	Non-flammable
Liquid density:	1.24 g/cm^3 @ 20° C
Conversion factor:	1 ppm = 4.85 mg/m^3 (20° C, 1013 hPa) (ECETOC, 1994)

Production and Use
Worldwide production of 1,1-dichloro-1-fluoroethane for 1999 was 127,000 tons, most of which was for foam blowing. The remainder was for a variety of uses such as precision cleaning (OECD, 2001). In the most recent publically available data as reported to the Alternative Fluorocarbons Environmental Acceptability Study (AFEAS), the annual world-wide production (exclusive of India and China) of 1,1-dichloro-1-fluoroethane for 2007 was 21,835 metric tons (AFEAS, 2009).

1,1-Dichloro-1-fluoroethane was developed as a substitute for CFC-11, a fully halogenated chlorofluorocarbon mainly for use as a blowing agent for polyurethane and polyisocyanurate insulating foams and as a solvent in electronic and other precision cleaning applications. It is no longer permitted to be used as a blowing agent. 1,1-Dichloro-1-fluoroethane is produced and used as a substitute for fully halogenated chlorofluorocarbons with comparable physical properties since it has less unfavorable environmental properties (ECETOC, 1994; OECD, 2001).

Guidelines, Regulations, and Standards

No criteria or standards for 1,1-dichloro-1-fluoroethane in drinking water, ground water, surface water, or soil remediation developed by other government agencies were located.

An international agreement, known as the Montreal Protocol, controls the production and consumption of substances that can cause ozone depletion. In developed countries, a phase out of 1,1-dichloro-1-fluoroethane and other hydrochlorofluorocarbons (HCFCs) was scheduled as follows: 35% by 2004, 75% by 2010, 90% by 2015, 99.5% by 2020 and total phase out by 2030. For developing countries, a freeze of the production is scheduled by 2013 and a total phase out by 2030 (OECD, 2001 & UNEP, 2007).

Section 605 of the Clean Air Act sets the U.S. phaseout targets for hydrochlorofluorocarbons. In 1993, the USEPA established the phaseout framework and the "worst-first" approach, which focused first on the three HCFCs with the highest ozone depletion potential (HCFC-22, HCFC-141b, and HCFC-142b). To meet the required 2004 reduction, the USEPA phased out production of 1,1-dichloro-1-fluoroethane within the U.S. in 2003 (USEPA, 2010).

Pharmacokinetics and Metabolism

Absorption

1,1-Dichloro-1-fluoroethane is absorbed by inhalation. In male rats exposed to 1000 to 10,000 ppm for 6 hours, there was an initial period of rapid uptake for about 100 minutes followed by slower linear uptake (Loizou and Anders, 1993). From these data, the authors concluded that absorption involves an initial saturable process of equilibration between blood and highly perfused tissues, followed by a first-order process involving further uptake into poorly perfused tissues and metabolism.

No information is available on oral absorption of the compound.

Distribution

No *in vivo* data on the distribution of 1,1-dichloro-1-fluoroethane were located. As would be expected based on its physical and chemical properties, *in vitro* studies showed greater partition into fat than into liver, blood, or muscle (Loizou and Anders, 1993).

Metabolism

In male rats exposed to 1000 to 15, 000 ppm for 6 hours, 1,1-dichloro-1-fluoroethane was excreted in the urine as the glucuronide conjugate of the 2,2-dichloro-2-fluoroethanol metabolite; the urinary concentration of this metabolite increased linearly with exposure concentration (Loizou and Anders, 1993). Lower concentrations of dichlorofluoracetic acid were also found in urine of rats exposed to 40,000 ppm for 4 hours, but not after exposure to 11,500 ppm for 2 hours, suggesting that oxidation of the fluoroethanol metabolite to the acetic acid metabolite occurs at higher exposures, but that the acetic acid metabolite is not produced at detectable concentrations at lower exposures (Harris and Anders, 1991).

The glucuronide conjugate of 2,2-dichloro-2-fluoroethanol, as well as lower concentrations of dichlorofluoracetic acid and another unidentified metabolite, were also found in urine of human volunteers exposed to 250, 500, and 1000 ppm 1,1-dichloro-1-fluoroethane for 4 hours. Metabolites were found in urine collected 0-4, 4-12, and 12-24 hours after exposure, with the highest concentrations at 4-12 hours, and urinary excretion of metabolites increased with exposure level (Tong et al., 1998). Free (unconjugated) 2,2-dichloro-2-ethanol was not detected in the urine of rats or humans exposed to 1,1-dichloro-1-fluoroethane.

Treatment with diallyl sulfide, an inhibitor of cytochrome P450 2E1, reduced the uptake of 1,1-dichloro-1-fluoroethane in rats exposed by inhalation. Diallyl sulfide completely inhibited the urinary excretion of the metabolite in rats exposed to 10,000 ppm, but reduced metabolic excretion by 57% in rats exposed to 30,000 ppm (Loizou and Anders, 1993). 1,1-Dichloro-1-fluoroethane was oxidized to the fluoroethanol metabolite in liver microsomes from rats induced with pyridine, a cytochrome P450 2E1 inducer, but metabolism was not detected in microsomes from control rats (Loizou and Anders, 1993). These findings suggest that 1,1-dichloro-1-fluoroethane is metabolized by cytochrome P450 2E1, as well as by other form(s) of cytochrome P450 with lower affinity for the compound.

No covalent binding of metabolites of 1,1-dichloro-1-fluoroethane to liver proteins was detected in rats exposed to 11,500 ppm for 2 hours (Harris and Anders, 1991). However, destruction of cytochrome P450 and depletion of glutathione occurred *in vitro* in rat liver microsomes incubated with 1,1-dichloro-1-fluoroethane under anaerobic conditions. These effects were prevented by the free radical trapping agent, DBN, and the carbene trapping agent, DMB, suggesting that reactive free radical and carbene metabolites of 1,1-dichloro-1-fluoroethane formed by reductive metabolism were responsible (Tolando et al., 1996). The toxicological relevance of these observations, which occurred under reductive conditions, is unclear. Further studies in isolated rat hepatocytes showed that 1,1-dichloro-1-fluoroethane is cytotoxic (as indicated by the release of the enzyme, lactate dehydrogenase) and also depletes glutathione, under both aerobic and anaerobic conditions. Cytotoxicity and glutathione depletion were found to occur independently, based on data from studies with agents which selectively inhibited cytotoxicity when GSH was depleted, or selectively decreased glutathione levels but without increasing cytotoxicity (Zanovello et al., 2001).

Excretion

As discussed above, metabolites of 1,1-dichloro-1-fluoroethane are excreted in the urine. No information from humans or experimental animals is available on other potential routes of excretion, such as fecal, or on the proportion of the dose which is exhaled unchanged compared to the percentage which is metabolized.

Toxicity

Acute Toxicity

Oral

In three studies in which 10 male, or 5 male and 5 female, rats were administered one oral dose of 2000 or 5000 mg/kg 1,1-dichloro-1-fluoroethane in corn oil and observed for 14 days, no

deaths occurred. Body weight decreased slightly before increasing in the second observation week. No other significant clinical or pathological changes were consistently seen (Brock et al., 1995). Mortality also did not occur at the same doses in two earlier acute oral studies (Jannsen and Pott, 1988; Sarver, 1989). Based on these results, the oral LD_{50} in rats is greater than 5000 mg/kg.

Inhalation

Three acute inhalation studies were conducted in rats by Brock et al. (1995). In a study of 5 male and 5 female rats exposed for 46 hours to 30,000, 46,000, 68,000, and 77,000 ppm, no deaths occurred at the two lower concentrations and the LC_{50} was calculated as 62,000 ppm (59,000 ppm in males and 65,000 ppm in females). In a study of 6 male rats exposed to 32,000-96,000 ppm for 6 hours, no deaths occurred at or below 43,000 ppm, and the LC_{50} was calculated as 57,000 ppm. In a third study of 5 male and 5 female rats exposed to 3000, 6000, and 11,000 ppm for 6 hours, no deaths occurred.

Concentrations above 29,000 ppm caused signs of CNS depression, and concentrations of 45,000 ppm or higher caused tremors, incoordination and/or convulsions. The rats recovered from these effects within one day after exposure ended. Serum phosphate levels were increased in male rats sacrificed two days after exposure to 3000, 6000, and 11,000 ppm; blood chemistry was not evaluated in the other studies of higher concentrations. As in the oral study (above), transient body weight loss occurred after exposure to all concentrations.

The effect of inhalation of 1,1-dichloro-1-fluoroethane on the cardiac sensitization response after an epinephrine challenge was studied in beagle dogs (n=2) using concentrations of 9000-20,000 ppm and cynomolgus monkeys (n=2) at 3000-10,000 ppm. Some response occurred at all concentrations, and the response became more severe as concentration increased. At 20,000 ppm, fatal ventricular fibrillation occurred in one dog (Brock et al., 1995).

A cohort study evaluated a group of 15 workers exposed to elevated airborne concentrations of 1,1-dichloro-1-fluoroethane in the workplace following an accident. The airborne concentration of 1,1-dichloro-1-fluoroethane was not measured at the time of exposure or estimated in the study. Clinical manifestations, radiologic findings and changes in pulmonary function and airway hyperresponsiveness over time were assessed. Cough, shortness of breath and malaise developed in most patients. A high-resolution CT scan of the chest revealed bilateral diffuse ground-glass opacities that were predominant in upper lung zones. Eleven patients showed restrictive ventilatory impairments during the initial tests. Parenchymal lung injury and restrictive impairment improved with time after exposure (Lee, 2009).

Dermal

No deaths occurred in 14 days following dermal dosing for 24 hours with 2000 mg/kg in two studies in rats (5 per sex) and one study in rabbits (5 per sex). As in the oral and inhalation study, transient body weight loss was observed after dosing. In rats, but not rabbits, livers were swollen (with no change in liver weight) at autopsy 14 days following exposure (Brock et al., 1995).

Short Term and Subchronic Toxicity

Oral
No data are available on oral toxicity after subchronic exposure.

Inhalation
In a **2 week** study, male rats (10 per group) were exposed to 0 or 10,000 ppm 1,1-dichloro-1-fluoroethane for 6 hours per day, 5 days per week, for a total of ten exposures. Urine was collected overnight and blood samples were taken after the ninth exposure. Half of the animals in each group were sacrificed after the tenth exposure, and the other half were observed for two weeks after exposures ended. No deaths, clinical changes, or effects on body weight occurred. Hematological changes including increased red blood cells and decreased MCV and MCH, and increased plasma bilirubin, were seen in treated rats after the tenth exposure, but not after the 2 week recovery period. There were no pathological findings in treated rats. An increased incidence of pneumonitis in treated, but not control, rats at the end of the 2 week recovery period may have been related to exposure to the compound (Brock et al., 1995).

In a **4 week/13 week** inhalation exposure study, groups of male and female rats (15 per sex per group) were exposed to 0, 2000, 8000, or 20,000 ppm HCFC -141b for 6 hours per day, 5 days per week. After 4 weeks, 5 rats per sex from each group were sacrificed. The remaining 10 rats per sex in each group were exposed for 9 additional weeks for a total of 13 weeks. Blood samples were taken from all rats prior to sacrifice.

After **4 weeks**, body weight was slightly (<10%) but significantly decreased at all doses in males and at the high dose in females. Rats in the highest exposure groups appeared less alert, and rats in the mid and high dose groups had increased response to being touched. The authors state that these data cannot be clearly interpreted because the chamber temperature for the two higher dose groups was 2-4^{o} C higher than for the controls, and the increased temperature may have contributed to these effects.

After 4 weeks of exposure, serum triglycerides were increased in the mid and high dose males, and cholesterol was increased in the high dose males. The enzymes AST and ALT were decreased in males in the middle and high dose groups. No significant changes in organ weights or gross and microscopic pathology were found.

After **13 weeks**, decreased mean body weight and decreased food consumption occurred in all exposed groups, including the low dose group (for which chamber temperature was not elevated). The data for these effects are not provided. After 13 weeks, cholesterol was increased in both male and females in the high dose (20,000 ppm) groups. In both sexes, absolute liver weight was decreased in the middle (8000 ppm) and high (20,000 ppm) dose groups, and absolute weights of brain, heart, kidney, and lung were decreased in the high dose groups. However, it is stated that "corresponding increases" in relative weights were also seen for these organs. (Note: It is difficult to interpret the statements on organ weights, as the wording seems to imply similar, not opposite, effects on absolute and relative organ weights.) No treatment-related hematologic or histopathologic changes were noted in any exposure level group (Brock et al., 1995).

Based on these data, the No Observed Adverse Effect Level (NOAEL) for the 13 week exposure period was stated by the authors to be 8,000 ppm (approximately 38,400 mg/m^3). It is not clear how the NOAEL was identified, since it was reported that liver weight was decreased at this dose, and body weight, and food consumption were decreased at both this dose and the lower dose of 2000 ppm. The higher exposure level, 20,000 ppm (96,000 mg/m^3), caused increased serum cholesterol and changes in weights of other organs, in addition to reduced body weight and food consumption.

These authors also discuss another previously unpublished 4 week inhalation study in which rats were exposed to 1500, 8000, or 20,000 ppm 6 hours/day, 7 days per week (Y. Hino, 1992). Body weight was decreased in the mid-dose females and high dose males. Decreased thromboplastin time occurred in mid and high dose females, and increased mean corpuscular volume in high dose females. Increased serum calcium occurred in mid dose males, and increased cholesterol, albumin, and albumin:globulin ratio in high dose males.

Neurological Toxicity
Male and female rats (10 per sex per group) were exposed to 1500, 5000, or 15, 000 ppm 1,1-dichloro-1-fluoroethane , 6 hours per day, 5 days per week, for 16 weeks. Neurobehavioral parameters, compared to control rats, were assessed at on the day after exposure ceased, and 2 and 4 weeks later. Five rats per group were sacrificed for histological assessment of the brain, spinal cord, and peripheral nerves at 17 and 21 weeks. No effects on behavior or histology of the nervous system were observed (Brock et al., 1995).

Chronic Toxicity and Carcinogenicity

Oral
A chronic oral study of 1,1-dichloro-1-fluoroethane has not been conducted.

Inhalation
Groups of 80 male and 80 female Sprague-Dawley rats were exposed via inhalation to 1,1-dichloro-1-fluoroethane for 104-106 weeks. Ten (10) of the 80 animals in each group were pre-designated for interim sacrifice at 1 year. Rats were exposed to vapors for 6 hours/day, 5 days/week at concentrations of 0, 1,500, 5,000 and 15,000 ppm for the first 17 weeks, subsequently increased to 20,000 ppm. Blood and urine were collected at 3, 6, 12, 18, and 24 months.

No exposure-related effects of toxicological significance were observed related to survival, clinical signs, ophthalmoscopy, hematology, clinical chemistry, urinalysis or organ weight analysis. Reduced food intake was noted in the high dose group in both sexes through 52 weeks of exposure and in females during the second year of exposure. Body weight gain was decreased significantly in the high dose groups during the first 15 weeks. Serum triglycerides were increased in high dose animals at weeks 13, 26, and 52; this effect was significant in females at the first two time points.

In the animals (10 per group) pre-designated for sacrifice at one year, there were no macroscopic pathology findings. In the animals that died during the study and those that survived until terminal sacrifice at 2 years, there was a treatment-related increased incidence of testicular masses and testicular abnormalities (small, blue, flaccid, and white subtunical striae) in the high dose group compared to controls. Microscopic pathology examinations confirmed the testes as a target organ for toxicity. An increased incidence of testicular interstitial hyperplasia was statistically significant ($p<0.05$) at 5000 ppm and was not statistically significant at 20,000 ppm. The incidence of seminiferous tubular atrophy was marginally (not statistically significant) increased at 20,000 ppm. The incidence of Leydig cell adenomas was 3/70; 4/70; 14/70; and 12/70 in the 0, 1500, 5000, and 20,000 ppm groups respectively; the incidence was significantly increased compared to controls in the two highest exposure group (Millischer, 1995).

Reproductive and Developmental Toxicity

Teratology studies were conducted in both rats and rabbits, and a two-generation reproduction inhalation toxicity study was conducted in rats (Rusch et al., 1995).

In the teratology studies, pregnant rabbits (14-16/group) were exposed 6 hours per day to levels of 0 (control), 1,400, 4,200, 12,600 ppm 1,1-dichloro-1-fluoroethane 6 hours per day from days 7 to 19 of gestation. There was no evidence of developmental or teratogenic effects on the fetuses. Pregnant rats (21-22/group) were exposed to levels of 0 (control), 3,200, 8,000 and 20,000 ppm from days 6 to 15 of gestation. In the dams in the 20,000 ppm exposure group, body weight and food consumption were decreased and water consumption was significantly increased. In the 20,000 ppm exposure group, there was a significant increase in early, late, and total embryonic deaths, and in post-implantation losses. In this group, litter weight and fetal weight were significantly lower than in controls. There was some evidence of delayed ossification in the high dose animals, but there was no evidence of teratogenic effect (Rusch, 1995).

In the reproduction study, male and female rats were exposed to levels of 0, 2,000, 8,000 and 20,000 ppm, 6 hours per day, 7 days per week starting approximately 10 weeks before the first pairing. Adult rats exposed at 20,000 ppm (and, to a lesser extent, those exposed to 8,000 ppm) showed increases in water intake, slight increases in food consumption, and decreases in body weight.

Following the mating of the F_0 parents (32 females paired/group), there were fewer litters in the 20,000 ppm exposure level group than in controls. Mean pup weight in the F_1 offspring from this first F_0 mating was significantly ($p<0.05$) decreased compared to controls on PND 14, 18, and 21 in all treated groups. The magnitude of the change in body weight was not dose-related. Body weights were lower in all treated groups of males than in the controls at weeks 4-24. These decreases were statistically significant at 8000 ppm at week 4, and at all time points at 20,000 ppm. Further statistical analysis (e.g. Benchmark Dose modeling) of these data cannot be performed because standard deviations or similar statistics are not provided. Sexual maturation was somewhat delayed in the high dose F_1 males, but this effect was not statistically significant. When the F_0 parents were subsequently paired with different partners, the number of litters was lower in the 20,000 ppm group, although most of the animals that did not produce litters the first time mated successfully the second time. When the F_1 animals (28 per group) were mated to produce the second generation, the number of litters was comparable for all the groups.

Although Rusch et al. (1995) state that the NOAEL for the pups was 8000 ppm, the data that they present indicates that the low dose, 2,000 ppm, was the LOAEL for decreased body weight in the F_1 pups on days 14, 18, and 21.

Genotoxicity/Mutagenicity

As discussed below, mixed results are seen in the available studies of the genotoxic potential of 1,1-dichloro-1-fluoroethane.

The genotoxic effects of 1,1-dichloro-1-fluoroethane via inhalation exposure were investigated on a group of 10 male and 10 female Sprague-Dawley rats exposed 13 weeks (6 hours per day, 5 days per week) to 0, 1,500, 3,000, and 6,000 ppm concentrations of 1,1-dichloro-1-fluoroethane vapor (Maeng et al., 2004). No exposure-related effects were noted with respect to organ weights, clinical chemistry and histopathology. Statistically significant and dose-dependent increases were found in the micronuclei frequencies of male rats at all doses ($P < 0.01$); increases which were not statistically significant were seen in females. Decreases in the percentage of polychromatic erythrocytes among the total number of erythrocytes were also statistically significant ($P < 0.05$) at the high dose in both sexes, suggesting repression of cell growth at this dose. These effects were observed in the absence of effects on organ weights, clinical chemistry, or histopathology.

In contrast to the results of Maeng et al. (2004) in male Sprague-Dawley rats, negative results at higher exposure levels were obtained in two micronucleus assays in male and female mice. Both gave negative results after a nose-only 6-hour inhalation exposure at concentrations ranging from 2,000 to 20,000 ppm, or a 6-hour whole-body exposure to concentration ranging from 3,600 to 34,000 ppm (Vlachos, 1989).

1,1-dichloro-1-fluoroethane was negative for *in vitro* mutagenicity in Ames assays in S. typhimurium and E. coli (with and without metabolic activation). Tests for chromosomal aberrations were negative in human lymphocytes, but were positive in Chinese hamster ovary cells (Millischer et al., 1995).

Development of Toxicity Factor

Choice of Appropriate Carcinogenicity Descriptor

In the chronic rat study, the incidence of Leydig cell adenomas was 3/70; 4/70; 14/70; and 12/70 in the 0, 1500, 5000, and 20,000 ppm groups respectively; the incidence was significantly increased compared to controls in the two highest exposure group (Millischer, 1995). Some chemicals cause rat Leydig cell tumors through a mode of action (pituitary-testicular axis hormonal disruption and increased luteinizing hormone (LH)) that may not be relevant to humans, while other chemicals cause Leydig cell tumors in rats without affecting LH (Prentice and Meikle, 1995). Millischer et al. (1995) did not evaluate the mode of action for the Leydig cell tumors, and there is no evidence or *a priori* reason to assume that the tumors caused by 1,1-dichloro-1-fluoroethane definitely occur through this hormonal mechanism. Some fluorochemicals structurally related to 1,1,-dichloro-1-fluoroethane have been shown to cause Leydig cell tumors through a mechanism related to peroxisome proliferation or as related to testicular atrophy, possibly caused by a metabolite. However, these modes of action are not

relevant to 1,1-dichloro-1-fluoroethane because it is not a peroxisome proliferators, and does not produce testicular atrophy (Cook et al., 1999). Thus, the mode of action for 1,1-dichloro-1-fluoroethane is not known and there is no clear basis for assuming that the Leydig cell tumors observed in the rats is not relevant to human cancer risk.

Relevant to these considerations, Leydig cell tumors occur in humans, and over 10% of Leydig cell tumors in the historical database for human Leydig cell tumors progressed to metastasis (Heer et al., 2010). Maeng et al. (2004) found that 1,1-dichloro-1-fluoroethane causes genotoxicity (micronuclei in the rat bone marrow), especially in males, at exposures lower than those that cause other toxic endpoints (Maeng et al., 2004). These results suggest that genotoxicity is a potential mechanism for the Leydig cell tumors, especially because the genotoxic effects occurred in the same species, strain, and gender in which the tumors were seen.

Based on the weight of evidence from the data discussed above, it is concluded that the evidence is suggestive of carcinogenicity relevant to humans, and that the appropriate carcinogenicity descriptor for 1,1-dichloro-1-fluoroethane is "Suggestive Evidence of Carcinogenic Potential" (USEPA, 2005). According to USEPA (2005), "This descriptor of the database is appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species."

NJDEP has adopted a risk assessment approach for chemicals with Suggestive Evidence of Carcinogenic Potential (or classified as Possible Human Carcinogens, Group C, under the older USEPA, 1986, guidance) (see NJDWQI, 2009). In this approach, the risk assessment is based on a slope factor at the 10^{-6} risk level if the data supports development of a slope factor, if supportable. Alternatively, the risk assessment is based on a Reference Dose for non-cancer effects with an additional uncertainty factor of 10 to protect against potential carcinogenic effects, if a slope factor is not supported. Although the testicular tumor data for 1,1-dichloro-1-fluoroethane can be modeled to derive a slope factor (see Appendix A), it is recognized that uncertainties exist about the appropriateness of using low dose extrapolation of Leydig cell adenoma data as the basis for risk assessment, when this is the only tumor type observed. Therefore, the alternative approach for risk assessment based on a Reference Dose that includes an additional Uncertainty Factor of 10 to protect for possible carcinogenic effects is recommended.

Derivation of Reference Dose

Because no oral subchronic, chronic, developmental or reproductive studies are available for 1,1-dichloro-1-fluoroethane , the Reference Dose is based on systemic effects (not related to the point of entry) from an inhalation study.

The endpoint used as the basis for the Reference Dose is the LOAEL of 2000 ppm (9,700 mg/m^3) for decreased body weight in the F_1 pups on days 14, 18, and 21 from the rat two-generation study (Rusch et al., 1995). The mean pup weight was decreased by 12%, 10%, and

11%, respectively on days 14, 18, and 21, and the decrease was statistically significant ($p<0.05$) at all three time points. Statistically significant body weight decreases also occurred in the two higher dose groups at all 3 time points. Body weight decreases also occurred at 2000 ppm and above in the subchronic study (Brock et al., 1995), but the data and statistical significance information are not provided.

The inhalation LOAEL can be converted to an oral LOAEL by multiplying by the default daily inhalation volume, 20 m^3/day and body weight, 70 kg, and adjusting for the fact that exposure occurred for 6 hours per day, as follows:

$$\frac{9{,}700\ mg/m^3 \times 20\ m^3/day \times 6\ hrs/24\ hrs}{70\ kg} = 693\ mg/kg/day$$

The uncertainty factors applied to derive the Reference Dose are:

10 – Interspecies, to account for animal-to-human variability
10 – Intraspecies variability, to protect sensitive subpopulations
10 – LOAEL-to-NOAEL
10- Possible carcinogenicity, for Suggestive carcinogens (see above)

Note that an uncertainty factor for less-than-lifetime exposure is not used for developmental endpoints which occur due to exposure during a short time period.

The Reference Dose is: $\frac{693\ mg/kg/day}{10{,}000} = 0.07\ mg/kg/day$

Derivation of Interim Specific Ground Water Criterion

New Jersey ground water criteria are based on the assumptions for chronic drinking water exposure.

The interim specific criterion is derived as follows:

$$\frac{0.07\ mg/kg/day \times 70\ kg \times 0.2}{2\ L} = 0.5\ mg/L = 500\ \mu g/L$$

Where:
0.07 mg/kg/day = RfD
70 kg = assumed body weight of adult
2 L/day = assumed daily drinking water ingestion volume
0.2 = Relative Source Contribution factor to account for non-drinking water exposures

These exposure assumptions are considered to be applicable to pregnant women, the receptor of concern for developmental effects, as well as adults in general.

A cancer slope factor of 1.9 x 10-4 (mg/kg/day)-1 was developed, based on the testicular tumors in Millischer et al. (1995) (Appendix A).

For comparison purposes, the corresponding dose at one-in-one-million (1 x 10-6) risk is 5.3 x 10^{-3} mg/kg/day. This interim specific criterion based on this cancer risk level would be:

$$\frac{0.0053 \text{ mg/kg/day} \times 70 \text{ kg}}{2 \text{ L}} =$$

0.186 mg/L = 0.2 µg/L (rounded to one significant figure)

Discussion of Uncertainties

The interim specific ground water criterion was developed using risk assessment approaches generally used by USEPA and NJDEP. These approaches are based on reasonable, but health protective, assumptions and approaches. Uncertainties in this risk assessment are common to all risk assessments based on animal data, including the assumption that effects observed in experimental animals are relevant to humans and that effects observed at higher levels can be used to develop health-based criteria for environmental exposures to lower levels. Because of uncertainties about using linear low dose extrapolation for rat Leydig cell testicular tumors, the alternative approach for the USEPA descriptor of "suggestive evidence for carcinogenicity" that incorporates an additional uncertainty factor for potential carcinogenicity, was used. An additional uncertainty in this risk assessment is route-to-route extrapolation of inhalation data to develop an oral Reference Dose. However, the endpoints of concern for 1,1-dichloro-1-fluoroethane are not related to the point of entry, and no data are available to suggest that absorption, metabolism, distribution, or excretion differ between inhalation or oral exposure.

Citations

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APPENDIX A

Cancer potency calculations from Millischer et al. (1995) for interstitial cell adenomas

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Tumor incidence

Millischer et al. report testicular interstitial (Leydig cell) adenomas in two categories of male rats, decedents (those rats that died prior to the end of exposure) and those that survived to the termination of the study. However, they do not report the length of survival for those rats that died prior to termination. Thus, the time to an HCFC-141b-associated tumor cannot be estimated. The practical implication of this is that the tumor incidence ratio in rats in the decedent category is likely to be underestimated by the ratio of the total number of rats with tumors divided by the total number of decedent rats since some of the rats that were exposed to HCFC-141b that died without tumors may have died early in the study and may ultimately have developed exposure related tumors had they survived longer.

The tumor incidence ratio is estimated by summing the total number of animals with tumor – whether the tumors were detected in decedent animals or at termination and dividing by the total number of animals in each exposure category. In each case, the total number of animals in each exposure category was 70. Millischer et al. present data for several testicular endpoints in their Table 1. These include "interstitial cell adenomas" and "microscopic masses." The term, "microscopic masses" is not defined in the paper and it is not clear how or whether this observation is related to tumors *per se*. Given the uncertainty about this endpoint, animals with "microscopic masses: are not included in the calculation of the tumor incidence ratio.

	0 ppm (controls)	1,500 ppm	5,000 ppm	20,000 ppm
n	70	70	70	70
Number of animals with tumor (decedents + termination)	3	4	14	12
Incidence ratio	0.043	0.057	0.200	0.171

Calculation of POD

Consistent with USEPA Guidance for Carcinogen Risk Assessment (2005), the point-of-departure (POD) is derived using benchmark dose analysis. (USEPA BMD ver. 2.0 software). All models are dichotomous models and are based on a benchmark response value of 0.1 (i.e., the benchmark dose (BMD) corresponds to dose at the 10% response level predicted by the given model). All models assume "extra risk". Extra risk is defined as $(P_d - P_0)/1-P_0$:
where P_d = the probability of a response at a given dose
P_0 = the probability of a response at zero dose (controls)

The results from the best fitting models are presented in the table below. Detailed information on model fits is presented in the outputs from the BMDS software (attached).

	χ^2	p_{χ^2}	BMD (in linear space)	BMDL (in linear space)
Models with linear dose function				
log-logistic	4.31	0.038	5286.73	55.6239
multistage	1.42	0.2337	3163.34	1817.36
Weibull	4.35	0.0369	5347.37	36.9012
Models with dose expressed as log (dose + 1)				
log-logistic	0.03	0.9860	3792.7	2205.1
log-probit	0.10	0.7573	4017,9	2174.7
Weibull	0.00	0.9971	3813.2	2199.3

By far, the best fitting models (i.e., small χ^2 parameter values, large χ^2 p-values) are those that use log (dose + 1) rather than the linear expression of dose. These models, as a whole produce more stable BMD and BMDL values than the linear models. For the three best-fitting log (dose + 1) models the range of BMDL values is only about 1%. The overall best fit is given by the Weibull model of log (dose + 1). This model gives a BMDL of 2199 ppm. This value is, therefore, selected as the basis for the POD derivation.

In the chronic (104 wk) study of Millishcer et al. (1995), the rats were exposed for 6 hr/day, 5 days/wk. Given the absence of acute or obvious clinical effects in the range of concentrations in the chronic study, it appears appropriate to scale the BMDL concentration in the study to continuous (24 hr/day, 7 days/wk) exposure as:

$C_{continuous} = C_{study}$ (6 hr/24/hr) (5 day/wk/7 day/wk) =
2199 ppm (0.25) (0.71) = 390 ppm.

Assuming conditions of 25°C and 760 mm Hg pressure, this concentration corresponds to 1,865 mg/m^3. This concentration is the adjusted POD (POD_{adj}) in rats.

Based equation 4-48 in the USEPA (1994) guidance, "Methods for Derivation of Inhalation Reference Concentrations (RfCs) and Application of Inhalation Dosimetry," the corresponding

human equivalent concentration (HEC) at the NOAEL (or POD) for Category 3 gases (i.e., gases that are not reactive in the respiratory tract) is estimated as:

$POD_{HEC} = POD_{adj-animal} \times ((Hb/g)_{animal}/(Hb/g)_{human})$

where Hb/g is the blood-gas partition coefficient for each specific chemical. In the absence of specific information on the partition coefficients for a chemical the USEPA guidance recommends assuming that $Hb/g_{animal}/Hb/g_{human} = 1$. HCFC-141b is largely unreactive in general, and there does not appear to be any specific evidence for its reactivity in the respiratory tract. Further, there do not appear to be any data that would permit an estimate of the $Hb/g_{rat}/Hb/g_{human}$ ratio. Therefore, the default value of 1 is assumed. The POD_{HEC} is thus, estimated to be equal to the POD_{rat} (i.e., 1,865 mg/m^3). Note that inherent in this interspecies conversion the allometric scaling occurs implicitly on the basis of the human and rat inhalation rates that are generally proportional to (body weight)$^{3/4}$.

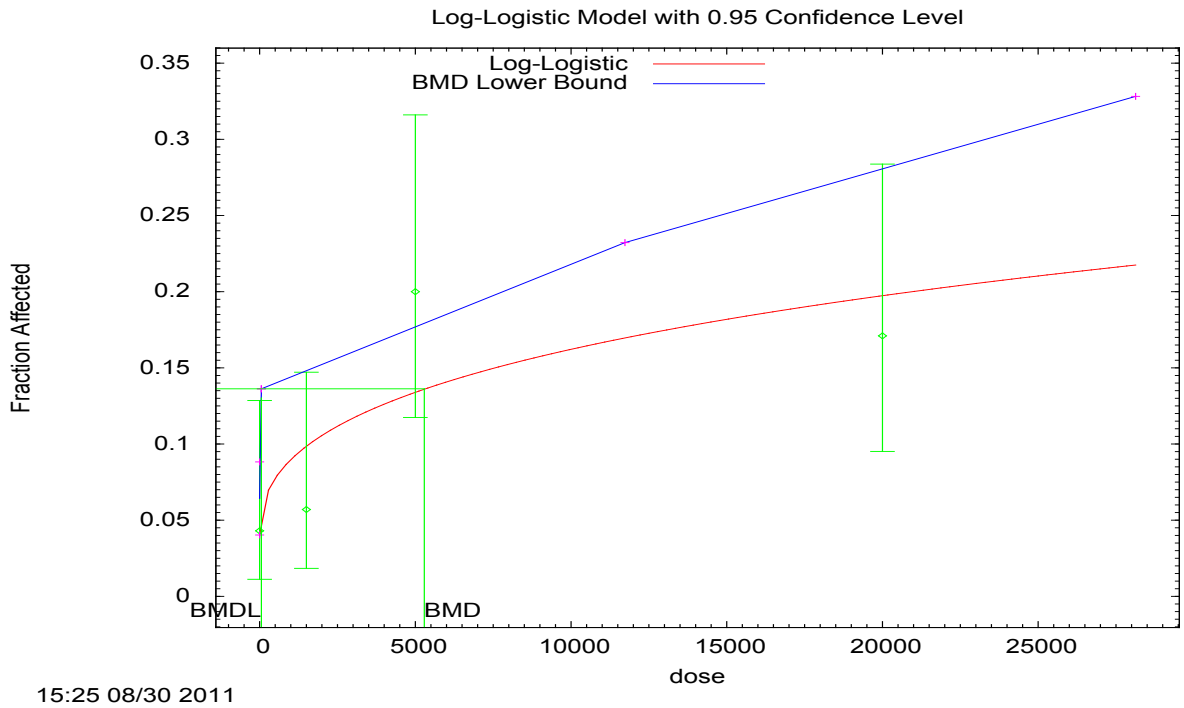
Inhalation dose to ingestion dose extrapolation

Extrapolation of the toxicity of HCFC-141b by the inhalation route of exposure to the risk from the ingestion route of exposure is carried out under the assumption that absorption from the gastrointestinal tract occurs to the same extent as absorption from the respiratory tract. Additionally it is assumed that differences in first-pass metabolism resulting from the different routes of exposure will not significantly affect the toxicology of HCFC-141b. Given the relatively large log K_{ow} of HCFC-141b, the first of these assumptions seems reasonable. Although it appears that the majority of HCFC-141b is excreted without metabolism, the extent of metabolism is unclear. It is also not clear to what extent metabolism occurs in the liver and would therefore be influenced by first-pass liver metabolism with ingestion exposure versus inhalation exposure. Therefore, the accuracy of the second of these assumptions is uncertain.

Under the above assumptions, applying the USEPA default human inhalation rate of 20 m^3/day, the POD concentration of 1,865 mg/m^3 would correspond to a daily inhalation absorption of 37,300 mg/day. Dividing by the USEPA default body weight of 70 kg gives a dose of 533 mg/kg-body wt/day. Recall that the POD is the dose corresponding to the benchmark response level (BMR), in this case, a probability of 0.1.

Estimation of the human equivalent cancer potency

Under the 2005 USEPA Guidance for Carcinogen Risk Assessment, the human equivalent cancer potency under conditions of unknown or uncertain mode-of-action (MOA) is derived from the linear slope of the line extending from the POD (in this case, 533 mg/kg/day, 0.1 prob.) to the origin (0 dose, 0 prob.). This is equal to:
$(0.1 - 0)/(533 \text{ mg/kg/day} - 0) = 1.9 \times 10^{-4} \text{ (mg/kg/day)}^{-1}$. The corresponding dose at one-in-a-million (1×10^{-6}) risk is 5.3×10^{-3} mg/kg/day.



Chi^2 = 4.31 d.f. = 1 P-value = 0.0380

Benchmark Dose Computation

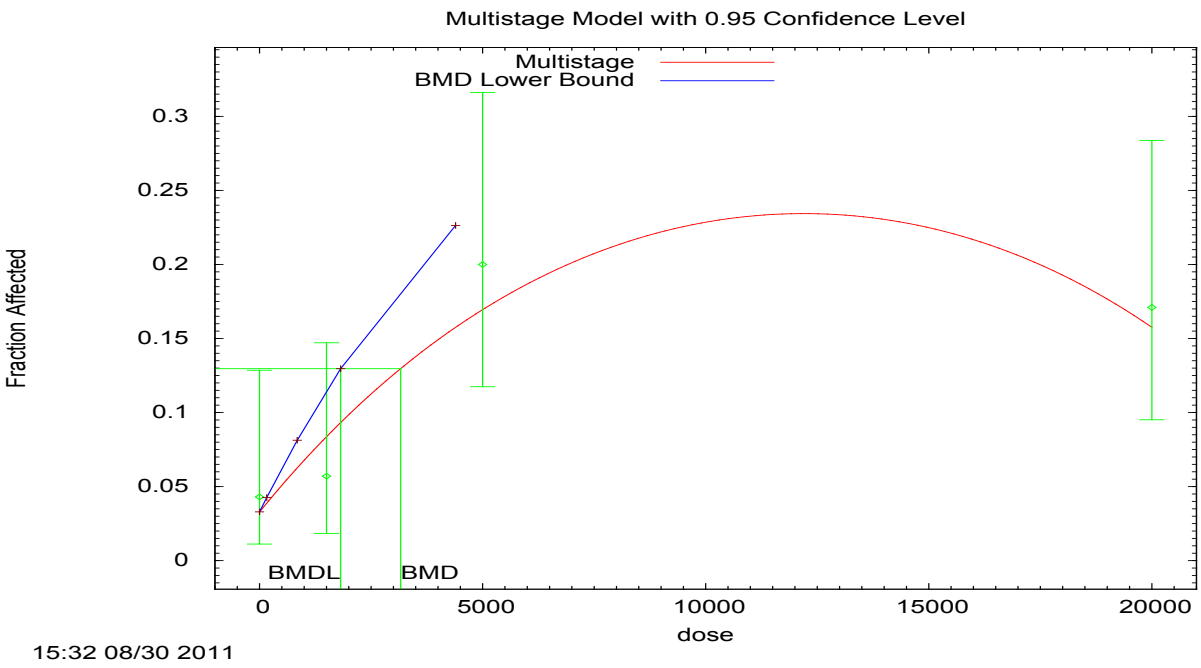
Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 5286.73

BMDL = 55.6239



Chi^2 = 1.42 d.f. = 1 P-value = 0.2337

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

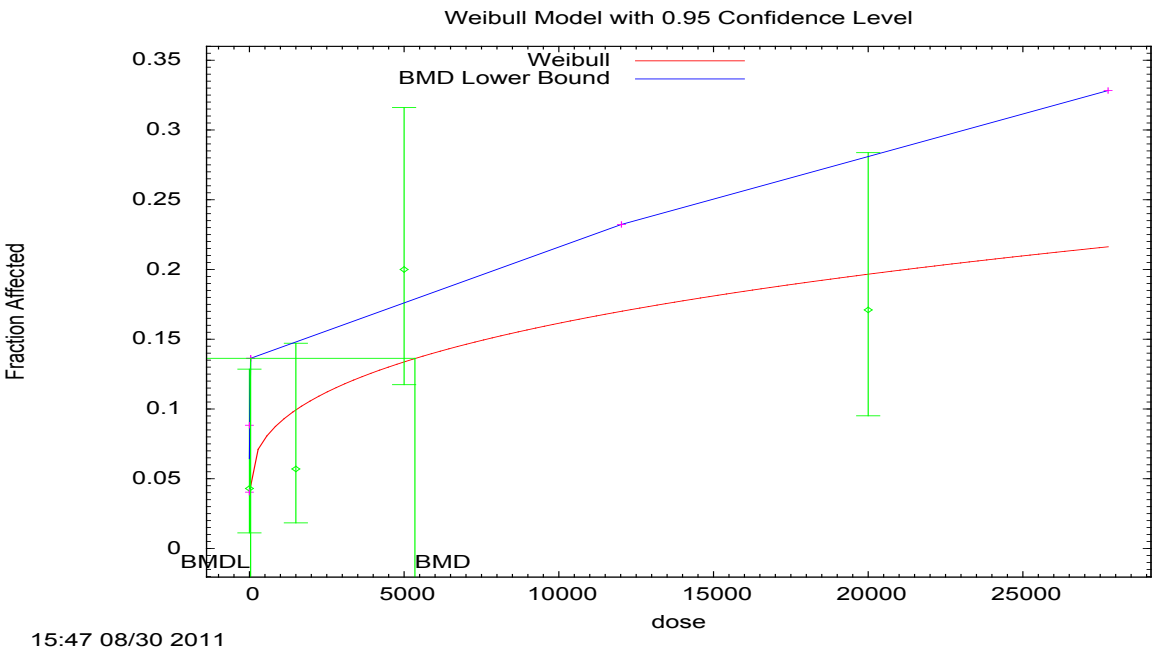
BMD = 3163.34

BMDL = 1817.36

BMDU = 8626.29

Taken together, (1817.36, 8626.29) is a 90 % two-sided confidence interval for the BMD

Warning: BMDL is out of the three times range of dose for some BMR in BMDL curve computation.



Chi^2 = 4.35 d.f. = 1 P-value = 0.0369

Benchmark Dose Computation

Specified effect = 0.1

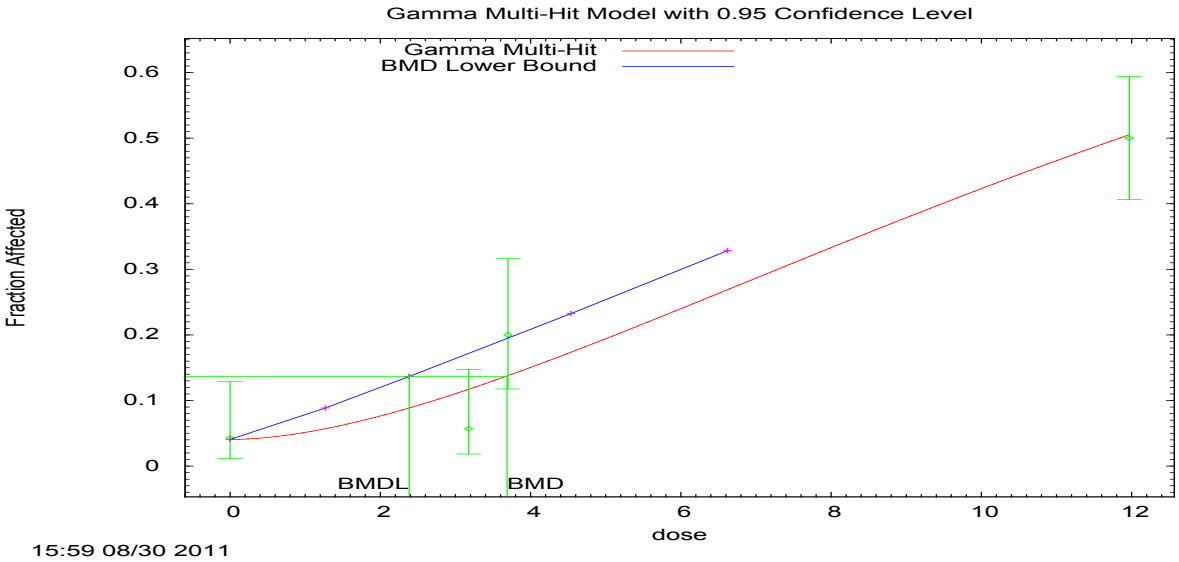
Risk Type = Extra risk

Confidence level = 0.95

BMD = 5347.37

BMDL = 36.9012

Models using log (dose + 1)



Chi^2 = 4.76 d.f. = 1 P-value = 0.0291

Benchmark Dose Computation

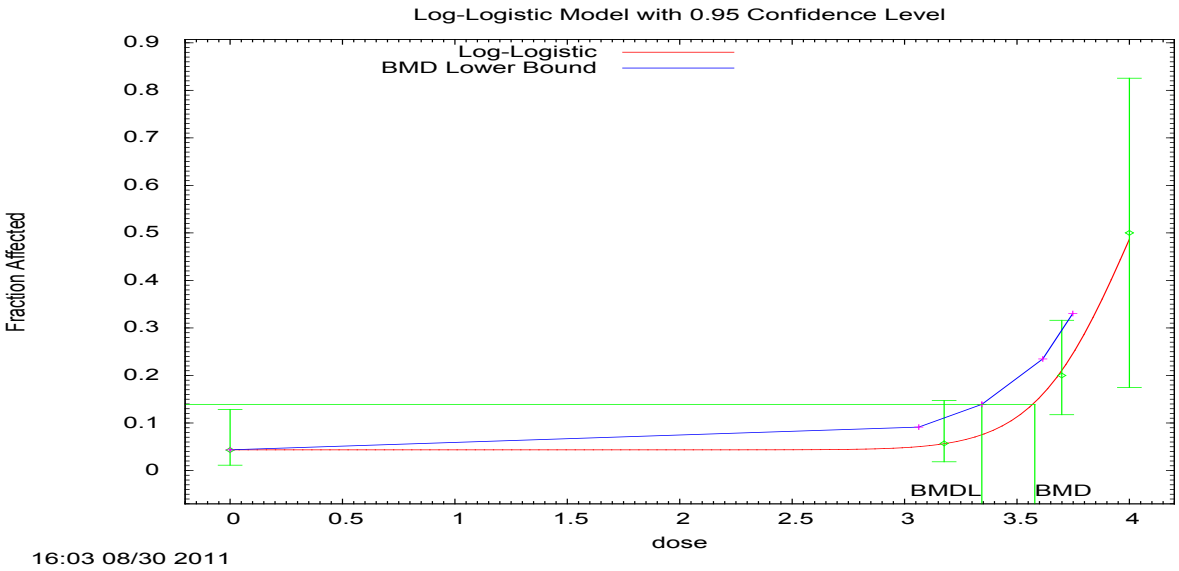
Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.68729

BMDL = 2.38419



Chi^2 = 0.03 d.f. = 2 P-value = 0.9860

Benchmark Dose Computation

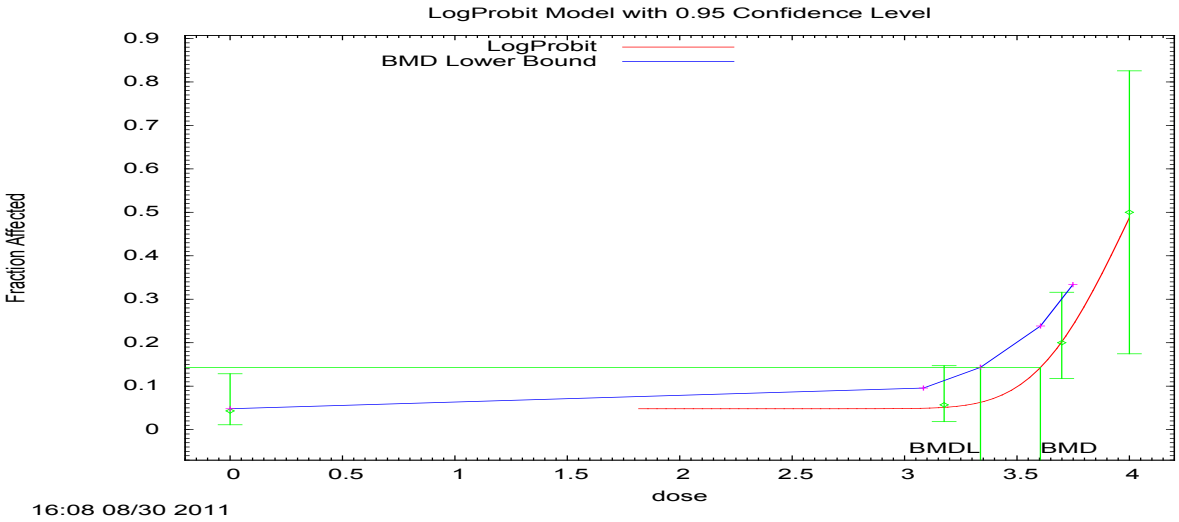
Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.57906

BMDL = 3.34362



Chi^2 = 0.10 d.f. = 1 P-value = 0.7573

Benchmark Dose Computation

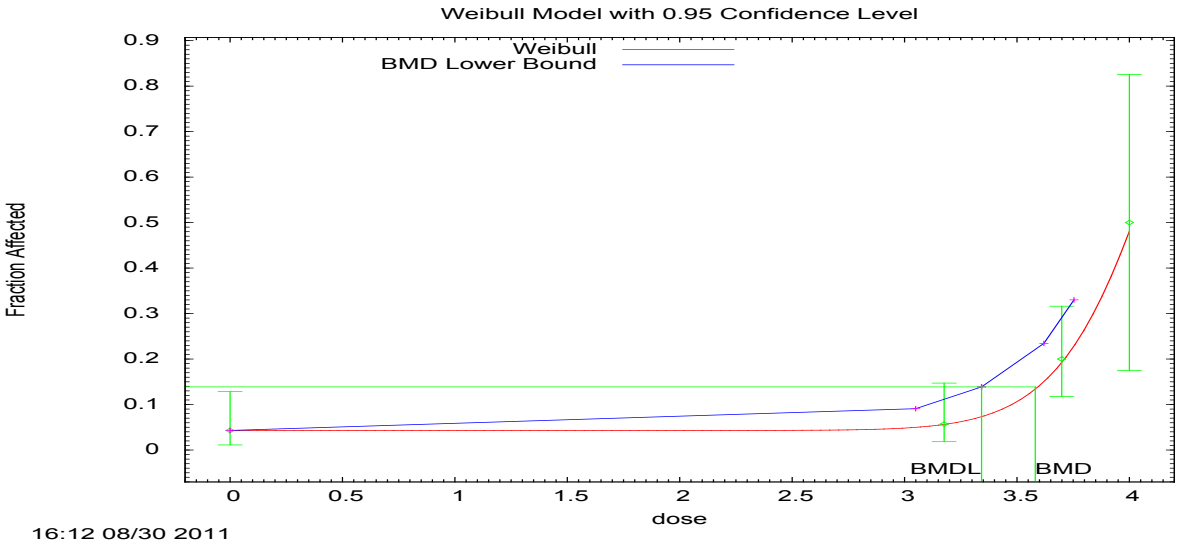
Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.60411

BMDL = 3.33759



Chi^2 = 0.00 d.f. = 1 P-value = 0.9971

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.5814

BMDL = 3.34249