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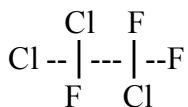
FROM: Alan Stern, Dr.P.H., D.A.B.T

SUBJECT: Development of Interim Specific Ground Water Criterion for Freon 113

DATE: May 4, 2010

As requested, I have investigated the human health risk basis for developing an interim specific groundwater criterion for Freon 113 (1,1,2-trichloro-1,2,2,2-trifluoroethane). As you are aware, there is currently a Reference Dose (RfD) entry for Freon 113 on the USEPA's IRIS database (<http://www.epa.gov/ncea/iris/subst/0123.htm>). The RfD for Freon 113 was last reviewed under IRIS in 1996. Therefore, in addition to reviewing the basis for the RfD as derived by EPA in IRIS, I have also attempted to locate all relevant research that has become available since the time that EPA began its consideration for the IRIS determination (i.e., somewhat prior to 1996). Given the availability of the IRIS review addressing the literature available up to the period of the IRIS review, I have not attempted to review the entire literature. Rather, I have focused on key studies prior to and during the IRIS review period and all relevant subsequent studies.

Physical and Chemical Characteristics



Molecular Weight = 187.38

Boiling Point = 47.7 deg C

Log Octanol/Water Partition Coefficient (log Kow) = 3.16

Water solubility = 170 mg/l @ 25 deg C

Vapor Pressure = 284 mm Hg at 20°C
Henry's Law Constant = 5.3×10^{-1} atm m³/mol

Key Studies

Because of its volatility, nearly all of the toxicological investigations of Freon 113 focused on the inhalation route of exposure. It appears that the only exception is the oral toxicity study of Michaelson and Huntsman (1983). However, this study is not useful for the purposes of this review due to serious reporting discrepancies regarding the administered dose.

The USEPA RfD is based on the study of Imbus and Adkins (1972). This study examined workers who were exposed for 5 days/wk for up to 4 ½ yrs to Freon 113. The mean air concentration was measured at 699 ppm with 17% of samples >1,000 ppm. 50 exposed workers (mean age = 34) were compared to 34 unexposed workers (mean age = 37) on the basis of physical examination (including electrocardiogram), self-reported symptoms, and blood chemistry. The authors state that there were no significant exposure-related symptoms and no differences between exposed and controls with respect to blood chemistry. This study is useful because it directly addresses human exposure and given the use of electrocardiograms, would likely have detected cardiac arrhythmias that have been reported to occur on association to high-level acute exposures (Kaufman et al., 1994; Egeland et al. 1992) and in-vitro in perfused rat heart (Kawakami et al., 1990). On the other hand, this study did not examine effects that are typically examined in animal studies including pathology and histopathology, organ weight, weight loss/gain. In addition, this study did not examine cancer incidence, reproductive, or developmental effects. The USEPA used this study, in which exposure appears to have occurred exclusively or nearly exclusively through inhalation of Freon 113, to derive an ingestion RfD by assuming that ingested Freon 113 would be absorbed twice as efficiently as inhaled Freon 113. This assumption was presumably based on data showing significant concentrations of Freon 113 in exhaled breath (Woollen et al., 1990). However, this is not explicitly stated. Apart from the uncertainty in this assumption, this approach suffers from the fact that ingested Freon 113 that is absorbed from the gastrointestinal tract would largely experience a “first-pass” through the liver, while inhaled Freon 113 would largely experience a “first pass” through the brain before recirculating through the liver. Depending on potential differences in metabolism and retention in the brain and liver, inhalation and ingestion of the same mass of Freon 113 could lead to different concentrations in each organ. The overall half-life for elimination of Freon 113 in breath is 29 hours suggesting that there is retention in one or more tissues, particularly fatty tissues (Woollen et al., 1990). Although it does not appear likely that there is more than a small fraction of Freon 113 that is metabolized, there is currently little or no basis for assessing whether there may be a small but significant amount of toxicologically reactive metabolites produced. Whether such differences could affect the type of toxicity and/or the dose-response relationship for that toxicity is an uncertainty in the use of this study to derive an oral RfD. The USEPA RfD derived from this study should be considered to be weak due to incompleteness of the database and due to the fact that the database is negative with respect to observed adverse effects resulting in an RfD that is derived from a freestanding NOAEL. It should also be noted that while well conducted, this study had only 50 exposed subjects. This study did not, therefore have power to identify effects that might occur relatively infrequently at the levels of exposure experienced by the workers.

Voge (1996) reported a case study of an acute inhalation and dermal (mist on skin) exposure (several hours) inside an airplane cockpit at a concentration between 9,000 and 36,000 ppm. After 1 week of latency, chronic hypertension (14 months duration) was diagnosed. Effects on cognitive function were also seen. Protein was found in the urine leading the author to hypothesize that the hypertension was secondary to renal toxicity.

While this study did not provide sufficient exposure information to allow identification of a LOAEL, it does indicate the potential for Freon 113 to have systemic toxicity

Another indication of the potential of Freon 113 to induce systemic toxicity is the study of McKnight and McGraw (1983) in which Freon 113 was applied to the skin of hairless mice two times per day for 2 or 5 min for 10-40 days. The authors reported vacuolization of liver cytoplasm and increased sinusoidal spaces in the liver at the two highest concentrations. They also noted increased endoplasmic reticulum at all durations/doses and an increased nucleus-to-cytoplasm volume ratio at all durations/doses except the lowest dose. An increased mitochondrial-to-cell volume ratio was observed at the second highest duration/dose, but not at the highest dose. However, the design of this study does not lend itself to estimation of a dose that can be converted to an ingestion dose.

Egeland et al. (1992) conducted personal air monitoring of Freon 113 exposure among workers on high and low exposure days (mean 442 vs. 64 ppm) and investigated association with heart-monitor-based recording of cardiac dysrhythmias. No significant association was observed. These findings are qualitatively and quantitatively consistent with those of Imbus and Adkins (1972). However, it should be noted that there were no unexposed controls. Additionally, the structure of the comparison, with each subject serving as his/her own control on low-exposure days, leaves open the possibility that there were chronic changes in individual electrocardiograms that did not return to pre-exposure baseline on low exposure days.

Neghab et al. (1997) studied a group of workers who were exposed to Freon 113 for an average of 2.5 years. Personal exposure monitoring gave an average air concentration of 66.2 ± 12.6 ppm. No data are provided on the duration or frequency of the air sampling or on the maximum levels. Blood samples were taken from unexposed (control) subjects and from exposed workers pre-shift on a Monday morning ("pre-exposure sample") and a "post exposure" sample on Friday (presumably at the end of the shift). The authors state that the blood samples spanned 4 days of work, although this description suggests 5 days of work. The blood samples were analyzed for standard liver enzymes (e.g., ALP, AST, GGT) and for individual as well as total serum bile acids. There was no significant differences in levels of liver enzymes between post-exposure exposed workers and either controls or pre-exposure workers. There were, however, significant differences between post-exposure workers and both controls and pre-exposure workers for some individual serum bile acids as well as for total serum bile acids. The authors note, however, that pre-exposure serum bile acids were in the normal range and comparable to those of controls. No other adverse effects were noted. The authors suggest that while increases in serum levels of liver enzymes reflect perturbation of hepatocyte membrane integrity, serum bile acids levels reflect blockage of hepatocyte bile acid transport. The authors suggest that such effects on serum bile acid levels are without significant adverse effect and that it is "unlikely that there would be pathological sequelae to these effects." This is supported by the observation that despite the elevation of serum bile acid levels on Friday, the Monday morning levels were comparable to control levels despite the mean employment duration of 2.5 years. The authors suggest that measurement of serum bile acid levels in workers is a tool for monitoring of exposure rather than a significant adverse effect per se. Nonetheless, these results suggest that Freon 113 interacts with hepatocytes and could have more significant liver toxicity at higher doses.

Derivation of the RfD

The USEPA based its oral RfD on the Imbus and Adkins (1972) occupational exposure study. The freestanding NOAEL from this study was taken to be 699 ppm, the mean level of exposure measured in the workplace of the exposed subjects. This is equivalent to 5,358 mg/m³. The air was sampled at unspecified intervals during the

early period of operation of the facility and subsequently, twice daily over a period of three weeks (i.e., 30 samples). Since the authors report a total of 161 samples, the majority of the samples were taken during the unspecified intervals. The distribution of measured concentrations was highly right-skewed with a maximum concentration of 4,700 ppm. The median concentration was 435 ppm and 17% of the samples were greater than 1,000 ppm. Thus, while there is some uncertainty as to the representativeness of the exposure measurements, it appears that the use of the mean value to represent the freestanding NOAEL is reasonably conservative. This inhalation exposure was converted to a hypothetical ingestion exposure by adjusting the 5,358 mg/m³ air concentration to account for exposure during 5 days per week, and by assuming a 70 kg body weight, a 10 m³ daily occupational inhalation volume and by assuming that 100% of ingested Freon 113 would be absorbed versus 50% of inhaled Freon 113. This gives the following conversion:
 $(5,358 \text{ mg/m}^3 \times 10 \text{ m}^3/\text{day} \times 5 \text{ days/wk} / 7 \text{ days/wk} \times 0.5 \text{ inhalation vs. ingestion absorption factor}) / (70 \text{ kg}) = 273 \text{ mg/kg}$. This is the point of departure from which consideration of uncertainty adjustment proceeds.

The USEPA applied an uncertainty factor (UF) adjustment of 10 to account for inter-individual variability in sensitivity in the human population. This gives a value of 27.3 mg/kg/day that was rounded to one significant figure to give an RfD of 30 mg/kg/day.

Discussion and Review of the RfD

My review of the currently available literature on the toxicology of Freon 113 reveals several studies that may not have been available to the USEPA at the time of its RfD derivation. These are summarized above. These studies suggest that Freon 113 has the potential to cause kidney and liver toxicity and cardiac arrhythmia. However, these endpoints appear to be associated with high, acute exposures, and there is no way to estimate a dose-response relationship from the data reported in these studies. It is likely that evidence of these endpoints would have been detected in the Imbus and Adkins (1972) study had they been present significantly above background rates among the exposed population. The study of Neghab et al. (1997) suggests that Freon 113 interacts with hepatocytes to produce transient effects of uncertain toxicological significance. However, the observation of such an interaction raises the possibility of more significant adverse effects at higher doses. Although there are no recent mutagenicity studies or cancer bioassays, earlier mutagenicity studies provide no evidence of a mutagenic or carcinogenic potential (Longstaff, 1988). The Imbus and Adkins (1972) study appears to be the best available basis for an RfD, but for the reasons discussed above, this study provides a weak basis for the derivation of an RfD and the overall confidence in the resulting RfD is judged by the USEPA in its IRIS summary (<http://www.epa.gov/ncea/iris/subst/0123.htm>) as “low”.

The use in the USEPA RfD derivation of a UF of 10 to address uncertainty in inter-individual human sensitivity is appropriate. However, the lack of any data that address reproductive or developmental endpoints is an additional uncertainty that is not addressed in the USEPA’s derivation. The population studied in the Imbus and Adkins (1972) study was adults and appears to be mostly or entirely males. The study provides no information from which the potential for reproductive or developmental effects can be derived. This is a significant shortcoming in the current USEPA RfD for Freon 113. A careful review of the literature provides no indication of human or animal studies that address these endpoints. It is standard procedure in the derivation of RfDs to apply a UF to address the database insufficiencies arising from the lack of studies addressing these endpoints (USEPA, 2002). In addition, the lack of a useable ingestion-specific study should also be viewed as a database insufficiency.

It is recommended that, as per USEPA IRIS guidance (USEPA, 2002), reconsideration of this RfD should address this database insufficiency resulting from a lack of data on reproductive or developmental effects and the lack of an appropriate ingestion study by application of an additional UF of 10. This would result in an RfD of 3 mg/kg/day.

Interim Specific Ground Water Criterion

The interim specific ground water criterion is derived from the recommended RfD, as derived above, using the standard USEPA/NJDEP exposure assumptions of 2 L/day intake and 70 kg body-weight, and applying the default USEPA/NJDEP relative source contribution (RSC) from drinking water of 20%. The use of the RSC is intended to address the fact that the RfD applies to total daily exposure, and that for most drinking water contaminants, drinking water provides only a fraction of that total daily exposure. The default value of 20% is used in the absence of specific data on non-drinking water exposures to a chemical. The use of this default assumption is reasonable since, given its volatility, significant exposure to Freon 113 can occur in air. For example the exposure through showering discussed below is not taken into account except through the application of an RSC. The interim specific groundwater criterion (IGC) is derived as follows:

$$\text{IGC} = \frac{\text{RfD (mg/kg/day)} \times \text{BW (kg)} \times \text{RSC}}{\text{Water Intake (L/day)}}$$

$$\frac{3 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 21 \text{ mg/L or } 21,000 \text{ ug/L}$$

Showering Exposure

Given its volatility, it is likely that a significant fraction of the Freon 113 contained in residential water will volatilize into the air in the shower stall/bathroom during the course of a shower. It is also likely that Freon 113 contained in the water and volatilized to the air will be absorbed through the skin. At present, there is no USEPA RfC for inhalation exposure and no quantitative data on dermal absorption. Therefore, there is no basis for evaluating the health risk associated with showering exposure at the recommended, interim specific groundwater criterion. Nonetheless, it is noted that showering can pose an exposure to Freon 113 additional to exposure from consumption of drinking water.

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