TOXICITY REVIEW FOR IODOTRIFLUOROMETHANE (CF_3I)

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INTRODUCTION

General

In 1987, 23 countries, including the United States, signed an agreement that would reduce the production of ozone-depleting substances (ODS). Amendments to this agreement, called the "Montreal Protocol on Substances that Deplete the Ozone Layer," have placed controls on the production and consumption of ozone-depleting materials, including the fire suppressants, Halon 1211 and Halon 1301. These compounds are effective and. when used correctly, they have acceptable risk. They have, however, been identified as ozone-depleting substances. This ban has forced a search for suitable replacements for Halon 1211 and Halon 1301, which are both effective and safe, as well as environmentally acceptable. A number of candidate replacement agents for Halon 1301 have been tested for efficacy and safety and are currently in use. Another candidate replacement is CF_3I (iodotrifluoromethane, trifluoroiodomethane, trifluoromethyl iodide). A request for a Toxicology Profile for CF_3I was submitted by the Army Acquisition Pollution Prevention Support Office of the Army Materiel Command.

Physical Properties of CF_3I

Iodotrifluoromethane (CF_3I) is a gas at room temperature with a boiling point of -22.5 °C and a melting point of –110 °C. The vapor pressure of CF_3I at room temperature (25 °C) is 439.2 kPa. These properties indicate that exposure to CF_3I is most likely to occur through inhalation. CF_3I also has a C-I dissociation energy of 53.2 kcal/mol, indicative of a compound that can readily disassociate [1,2].

There is evidence that CF_3I photolyzes in the presence of sunlight and common fluorescent lights [3]. The hazardous potential byproducts of this reaction include carbonyl fluoride (COF_2), hydrogen fluoride (HF), and hydrogen iodide (HI). Nyden states in his conclusion that "the high level of toxicity associated with these compounds merits their inclusion when considering the impacts of accidental releases of CF_3I in well-lit, occupied spaces." These compounds are also produced during fire suppression. In his executive summary. Gann [4] states "exposure to surfaces heated by fire would produce more HF than from an equal amount of the other three chemicals (HFC-227ea, HFC-125, and FC-218)." In a fire situation, however, CF_3I produces far less HF than HFC-227ea, HFC-125, and FC-218.

The long-term stability testing indicates that CF_3I would degrade more rapidly in the presence of moisture, copper, and at temperatures above 100 °C [5]. Yamamoto and his colleagues [6] indicated that fluorinated compounds containing iodine or bromine atoms decomposed easier than perfluoridated compounds. It is unknown how product degradation will affect toxicity. No attempt to identify or evaluate the toxicity of degradation products was conducted for this document.

Regulatory Information

The International Standards Organization (ISO) is developing a standard on Gaseous Fire Extinguishing Systems (ISO, 1999). The standards document draws heavily on both National Fire Protection Association (NFPA) and British Fire Protection Systems Association (BFPSA/UK) code of practice for clean agents. The standard is expected to be published in 1999.

The EPA published a final rule under its Significant New Alternatives Policy (SNAP) program on 13 June 1995 accepting CF_3I as a substitute for Halon 1301 in normally unoccupied areas only. Based on this ruling, any employee who could possibly be in the area must be able to escape within 30 sec, and employers shall ensure that no unprotected employees enter the area during agent discharge [7]. The EPA also published a final rule on 22 May 1997 [8], accepting CF_3I as a substitute for Halon 1211 in nonresidential applications only. Because of the low cardiac sensitization values, EPA prohibits use of this agent in consumer residential applications where the possibility exists of incorrect use by untrained individuals.

The Army does not have a separate policy regarding ozone-depleting substances. Health and safety issues are addressed in Army Regulation 40-5 (AR 40-5) [9]. One of the Preventive Medicine functional areas of AR 40-5 is the Health Hazard Assessment Program (AR 40-10) [IO]. The primary objective of this regulation is to identify and eliminate or control health hazards associated with the life cycle management of weapons, equipment, clothing, training devices. and materiel systems. One objective of this program is to preserve and protect the health of the individual soldier and other personnel. Another objective is to reduce the health hazards due to potential environmental contamination associated with the use of Army systems. This objective is protective of the stratospheric ozone and complies with all federal regulations and guidelines. The Army is in the process of revising both AR 40-5 and AR 40-10.

Efficacy

The minimum extinguishing concentration for a gaseous agent is determined by the ISO Cup Burner Test. The concentration of Halon I301 necessary to extinguish a *n*-heptane fire by this test method is 3.3 vol%. The "best value" for CF_3I as determined by the National Fire Protection Association (NFPA) Cup Burner Data Task Group is 3.2 vol% [I l]. Therefore, for *n*-heptane, the dcsign concentration for CF_3I will be slightly lower than that for Halon 1301 regardless of the applied safety factor. The NFPA 12A requires a minimum 20% safety factor above the cup-burner values with a minimum design concentration of 5.0% for Halon 1301. This safety margin was chosen as a requirement for extinguisument of class A fires. According to Meyer [12], the extinguishing concentration of CF_3I is almost half of the concentration needed by any other gaseous agent under consideration. In a turbulent spray burner test, CF_3I required the lowest mass fraction at extinction of any other compound tested [13].

HEALTH EFFECTS

General

The US Army Environmental Hygiene Agency prepared a toxicity profile for iodotrifluoro-methane (CF_3I) in 1993 [14]. The assessment indicated that no toxicity data were available for CF_3I. Furthermore, it was suggested that a number of toxicity tests be conducted in order to

evaluate fully the safety of CF_3I. These suggestions included a skin and eye irritation test, acute and 14 day inhalation studies, genotoxicity testing, cardiac sensitization, and a full evaluation of combustion, pyrolysis, and decomposition products for this compound. Comprehensive tests, such as reproductive and developmental toxicity as well as subchronic inhalation, were also suggested if projected use scenarios indicated a need. Many of the suggested tests have been conducted, and the data are available for a more comprehensive review of iodotrifluoromethane.

TABLE 1. INFORMATION CONTAINED IN THIS SECTION OF THIS REPORT SUMMARIZES THE FOLLOWING TOXICOLOGICAL STUDIES THAT HAVE BEEN CONDUCTED ON CF_3I.

Date–In—ater	Type of Study	Test System	Actual Concentrations
1993–Ledbetter [15]	15 min (nose-only)	Rat (Sprague-Dawley)	12.7%
1994–Ledbetter [16]	4 hr (whole-body) 15 min. (nose-only)	Rat (Sprague-Dawley)	4 hr: 10, 12.8, 20, 32% 15 min: 24, 28.8%
1994-Kinkead [17]	4 hr (nose-only)	Rat (Fischer-344)	0.0, 0.5, 1.0%
1995–Mitchell [18]	Ames Test	*S. typhimurium*	Ames: 0.1060, 0.2775, 1.0586, 2.3230, 8.5908 %
1995–Mitchell [19]	Micronucleus	Mouse (Swiss-Webster)	Micro: 2.5, 5.0, 7.5%
1995–Mitchell [20]	Genetic Screen Mouse lymphoma	L5178Y cells	Lymph 8.0, 17.7, 30.6, 42.6, 45.4, 49.7, 51.8%
1995–Kenny [21]	Cardiac sensitization (facemask)	Dog	0.1, 0.2, 0.4, 1.0%
1995–Kinkedd [22]	Subchronic screen (14 days)	Rat (Fisher-344)	0.0, 3.0, 6.0, 12.0%
1996–Kinkead [23]	Subchronic (13 wks) (nose-only)	Rat (Fischer-344)	0.0, 2.0, 4.0, 8.0%
1998–Dodd [24]	Reproductive (13 wks) (whole-body)	Rat (Sprague-Dawley)	0.0, 0.2, 0.7, 2.0%

Acute Toxicity

15 Min Acute Exposure

Acute inhalation studies were conducted on CF_3I in August 1993 [IS]. Five male and five female Sprague-Dawley rats were exposed to CF_3I in a "nose-only" inhalation chamber for 15 min at a target concentration of 60,000 ppm (6.0%). The actual measured concentration of CF_3I during the exposure was 127,289∀5,574 ppm (12.7%), an exposure more than twice as high **as** the target concentration. This was due to an error in the wavelength setting for the infrared monitoring system. The rats were observed for 14 days post-exposure. Clinical indications of exposure included severe salivation for all exposed rats and audible respiration (rales) in two rats. All clinical indications seen in exposed rats were within normal limits within one hour after exposure had ceased. Necropsy revealed no gross abnormalities in exposed rats.

Rats (10 per dosage level) were also exposed to concentrations of CF_3I at 28.8 or 24% for 15 min [16]. At 28.8%, 7 of 10 animals died. The lungs of three rats were red and puffy. One rat died at a concentration of 24%. The lungs of two rats had hemorrhagic foci and one rat had red puffy lungs. The median lethal concentration (LC_{50}) derived from the 15 min exposure was estimated to be 27.4%.

Two rats (one male and one female) served as control animals for the Ledbetter studies (15 min nose-only exposures and the 4 hr whole body exposure).

4 Hr Acute Exposure

A 4-hr whole-body exposure was conductcd using CF_3I at concentrations of 32.20, 12.8, and 10% with five rats of each sex for each concentration [16]. All rats exposed to 32% and 20% died within 20 min of exposure. It was determined that the gas for the 32% group was contaminated with hydrogen fluoride (HF). Lungs of rats from these groups were red and puffy. No deaths were observed in the 12.8 or 10% exposure groups, although the lungs of 2 rats exposed to 12.8% were puffy.

Fisher-344 rats were exposed for 4 hrs to CF_3I using a nose-only chamber [17]. The 4 hr exposure portion was conducted on 30 male rats. Concentrations of CF_3I used were 0.0, *0.5,* and 1.0%. No toxic effects were noted during the 4-hr exposure or during the 14 day post-exposure observation period.

14 Day Subacute Exposure

A 2-week range-finding study was conducted using CF_3I concentrations of 0, 3. 6, and 12% [22]. Five male Fischer-344 rats were exposed at each concentration for 2 hrs/day, 5 days/wk (10 exposures). The study revealed a statistically significant decrease in weight gain for rats in the 6 and 12% exposure groups. There was also a 20% decrease in white blood cells of animals exposed in the two highest dosage groups (6 and 12%) CF_3I and an 8% increase in serum albumen of animals exposed to 12% CF_3I. Elevated levels of serum thyroglobulin and reverse triiodothyronine (rT_3) were observed in all animals exposed to CF_3I. No histopathologic lesions were noted in the thyroid and parathyroid glands following examination of CF_3I exposed rats.

Cardiac Sensitization Potential

Cardiac sensitization studies for CF_3I wcrc conducted at Huntington Research Center, Huntington, Cambridgeshire, England (1995) with purebred beagle dogs. This study was based on the experimental procedure developed by Reinhardt and his colleagues [25,26]. Dogs were initially challenged by injecting adrenaline (epinephrine, 0.1 mg/kg/sec) to establish the response of each individual dog to adrenaline alone. The appearance of multifocal ventricular ectopic activity (MVEA). or ventricular fibrillation following exposure indicated a positive response. Dogs were then exposed to CF_3I for 5 niin and challenged again with adrenaline. For this study, selected CF_3I concentrations were 0.1, 0.2. 0.4, and 1.0%. A single dog exposed to CF_3I at a concentration of 1.0% displayed a severe positive response and died. A second dog also died following exposure to 0.4% CF_3I. No other animals werc tested at these concentrations. Dogs exposed to CF_3I concentrations of 0.1 and 0.2% displayed no dysrhythmia following epinephrine challenge. The lowest observed adverse effect level (LOAEL) for this CF_3I was 0.4% and the no observed adverse effect level (NOAEL) was 0.2%.

Genotoxicity

Genetic toxicity testing was conducted in 1995 [18,19,20]. The testing protocol consisted of the *Salmonella typhimurium* histadine reversion assay (Ames Assay), mouse bone marrow erythrocyte micronucleus assay. and mouse lymphoma forward mutation assay using LS158Y cells.

The Ames assay used 5 tester strains of *S. typhimurium* at 5 dilutions of CF_3I. The concentration of CF_3I in the exposure chamber was within 30% of the calculated concentration. Following a range finding study, final concentrations of CF_3I used for exposure purposes were 1060, 2775, 10586, 23230 and 85908 ppm (0.11, 0.28, 1.1, 2.3. and 8.6%). Tester strain TA1538 was not affected by CF_3I. Strains TA1537 and TA98 displayed a weak positive response both with and without activation by the S9 mitochondrial fraction. Strong positive responses were displayed in strains TA100 and TA1535 with and without activation. The results indicate that CF_3I is mutagenic inducing both frame-shift and base-pair mutations in S. *typhimurium*.

For the mouse bone micronucleus assay, Swiss Webster mice were exposed for 6 hrs/day for three consecutive days to either 2.5, 5, or 7.5% concentrations of CF_3I. Positive results were assessed according to criteria set forth by MacGregor et al. [27]. The ratios of polychromatic erythrocytes (PCE)/1000 erythrocytes of female mice were significantly depressed with increasing concentrations of CF_3I. This effect was also observed in male mice, although one outlier prevented statistical significance. The ratio of micronucleated erythrocytes/1000 PCEs was significantly elevated in both genders (5.0 and 7.5% exposure groups). These data are supported by similar information obtained from Fisher-344 rats used in a 90-day inhalation study [23].

The forward mutation assay, using L5158Y *tk* +/- mouse lymphoma cells (clone 3.7.2C) was conducted with 5 concentrations of CF_3I between 8.0 and 51.8%. Tests were conducted with and without metabolic activation by S9. Results indicated no evidence of CF_3I-induced mutations of L5158Y *tk* +/- mouse lymphoma cells at any concentration tested.

Free radical modeling has indicated that CF_3I has the characteristics to be carcinogenic [28]. The model was based on the effects of carbon tetrachloride, which suggested that cellular damage was caused by free radicals produced when an electron was transferred from an enzyme to the carbon tetrachloride molecule. Vertical electron affinities were calculated and indicated that CF_4 was nontoxic, CF_3Cl was equivocal, CF_3Br was considered toxic, and CF_3I was considered to be carcinogenic.

Subchronic Toxicity

13 Wk Subchronic Exposure

A subchronic inhalation (90-day) study of CF_3I exposure of rats was conducted in 1996 [23]. Fisher-344 rats were exposed to 0, 2, 4, or 8% CF_3I vapor for 2 hrs/day, 5 days/wk for 13 weeks in nose-only chambers. This 90-day study examined clinical effects, body weights, hematology, bone marrow toxicity/mutagenicity (micronuclei induction), serum chemistry organ weights, gross pathology, and histopathology. One focus area of this study was the effect of CF_3I on thyroid function. This was accomplished by morphometric analysis and immunoradiometric assays for thyroid hormones. The study indicated a statistically significant, dose-dependent increase in micronucleated bone marrow polychromatic erythrocytes (PCE) in all rats exposed to CF_3I as well as a reduction in the PCE/NCE (normochromatic erythrocytes) ratio. High levels (8%) of CF_3I induced statistically significant reductions in serum levels of calcium, alanine aminotransaminase (ALT), triglycerides (males), and triiodothyronine (T_3) and increases in thyroglobin (rT_3), thyroxine (T_4), and thyroid stimulating hormone (TSH). Rhinitis was noted in all rats exposed to CF_3I concentrations of 4 and 8% after 30 days; however, these lesions were not present following 90 days of exposure. A significant reduction in testicular weight (and organ-to-body weight ratios) with loss of spermatogonia and spermatids, including aspermia, of

male rats was observed after 30 days of exposure to 4 and 8% CF_3I. These lesions were also present but less severe after 90 days of exposure. Death of male animals in the *2%* group prevcntcd examination of this group at 30 days. Female rats exposed to 4 and 8% CF_3I displayed a decrease in ovary weight following 30 days of exposure; howcvcr, ovary to body weight ratios were not statistically different from values obtained from control animals. Decreased ovary weight was observed at 90 days also but only in female rats cxposcd to 8% CF_3I. The authors attributed the deaths observed in the 2% (7 rats) and the 8% (1-rat) exposure groups to effects of restraint rather than a compound-induced effect. It is unknown whether othcr measured parameters werc affected by heat stress.

Reproductive Toxicity

Reproductive toxicity testing was conducted in Sprague-Dawley rats [24]. Four groups composed of 16 rats of each gender were exposed to concentrations of 0.0, 0.2, 0.7, and 2.0% CF_3I in a whole-body exposure chamber. This number would ensure at least 12 pregnant females for each concentration level. Animals were exposcd for 4 weeks at 6 hrs/day, 5 days/wk prior to mating. During mating, gestation and lactation, rats were exposed for 6 hrs/day, 7 days/wk. Females were not exposed from gestation day 21 through lactation day 4 to allow for early parturition. Pups wcre not exposed to CF_3I. Females were once again exposcd to CF_3I for 6 hrs/day, 5 days/wk until the study terminated. Half of the male rats (8) from cach group were sacrificed after 7 weeks. The remaining adult animals were sacrificed after 14 weeks. The rcsults of the study indicated no difference in measured reproductive endpoints between animals exposed to CF_3I and control animals.

A reduction of T_3 and an increase in rT_3 and T_4 observed at both 7 and 14 weeks was also observed in the Dodd study. Both male and female rats exposed to 2.0% CF_3I displayed a significant increase in TSH when compared to control animals. No CF_3I-induced alterations in micronuclei production were observed nor was there a difference in the PCE/NCE ratio between treated and control animals.

REPORTED EXPOSURE SCENARIOS

An exposure assessment to CF_3I in handheld fire extinguishers ***was*** conducted to determine the exposure of firefighters during simulated streaming scenarios. Three different room sizes were used in the study. a 912 ft^3 room, a 3822 ft^3 room, and a 5133 ft^3 room. In cach scenario, the firefighter stood 8 ft from a I-foot target. and fully discharged the extinguisher. The firefighters discharged 2.5, 5.0, 9.0, and 13 lb fire extinguishers in this study. Peak concentrations of CF_3I varied from approximately 10.000 ppm (1%) to 30,000 ppm (3%), depending on the height off of the tloor, size of the room, and amount of CF_3I discharged. Average concentrations for the first 30 min varied from 1040 ppm (0.1%) to 4678 ppm (0.5%) [29].

Exposures from intentional release of CF_3I in an F-IS engine nacelle havc been estimated [30]. Portions of the data were obtained from air sampling conducted during a discharge test of an F-15A engine fire supprcssion system at the Robbins Air Force Base, GA. The fire supprcssion bottle was filled 6.6 lbs of CF_3I and charged with nitrogen at 600 psi. Air sampling for CF_3I concentrations was conductcd using the Halonizer provided accurate data for CF_3I concentrations above 10,000 ppm (1%) and the Triodide Analyzer for concentrations lower than 1%. Two

Fourier Transform Infrared Spectroscopy (FTIR) analyzers were used to sample extremely low concentrations of CF_3I. The samplers were strategically placed in various locations around the aircraft. Blood concentrations of CF_3I were estimated using physiologically based pharmacokinetic modeling (PBPK). Three crew locations appropriate for maintenance activities were identified: (1) kneeling or standing near engine bay, (2) working in or under the engine bay, and (3) prone near the engine bay. Paths of and time to egress were determined for each crew location. The estimated blood concentration acquired from a 5 min exposure to 4000 ppm (0.4%) CF_3I, the LOAEL for cardiac sensitization, was 19 mg/L. Estimated blood concentrations for crewmembers ranged between 6 and 40 mg/L. The highest estimated blood concentration of CF_3I was for individuals at head level inside the open engine nacelle. Concentrations of CF_3I in this area were in excess of 70,000 ppm (7%), which resulted in an estimated blood concentration of 40 mg/L. This estimated blood concentration for the "head-at-the-engine" scenario was obtained following the first breath and remained above the level of cardiac sensitization for more than 30 sec. Levels of CF_3I under the left wing remained above 4000 pprn for more than 5 min.

An event where two salesmen inhaled CF_3I from balloons as part of their sales demonstration was described. The average volume inhaled was 1.25 L, resulting in an estimated peak blood concentration of 2000 mg/L and after 5 min. 71 mg/L. There were no reported adverse effects.

COMMENTS

Trifluoroiodomethane and several other compounds have been screened as potential replacements for Halon 1301. The review of the available data indicates that undesirable health effects could occur following exposure to CF_3I. Potential health hazards appear to exist in the area of cardiac sensitization and mutagenicity. The effect of CF_3I on reproductive parameters is equivocal.

Since it is reasonable to expect that most exposures would be intermittent and of short duration, acute toxicity information is critical. The LC_{50} for CF_3I has been approximated at 27.4%. This approximation was determined using two concentrations (24 and 28.8%) for 15 min exposures. Normally, at least three concentrations are used, and the animals are exposed for 4 to 6 hrs. The report states that "full determination of the LC_{50} was not completed due to the steep mortality curve of the test material." The LD_{50} (or LC_{50}) is an imprecise value; it is not a biological constant and should be de-emphasized for most materials [31]. It has, however, been used to compare toxicity among chemicals. Lethality is only one of many parameters used for the determination of acute toxicity. The slope (response/dose) of the dose-response curve, time to death, pharmacotoxic signs, and pathological findings are probably more critical than the LC_{50} in the evaluation of acute toxicity. This Center recommends that additional testing to determine LC_{50}, and other critical parameters of CF_3I exposure, be considered using three or more concentrations over 4 to 6-hour exposure period.

Abnormal cardiac activity, resulting in death, occurred when a single dog was exposed to CF_3I at 1.0% in the presence of epinephrine. Another dog died after exposure to CF_3I at 0.4% in the presence of epinephrine. This testing procedure, according to the authors, is based on methodology developed by Reinhardt [25]. The human is able to secrete about 0.004 to 0.005 mg/kg/hr. The dose of epinephrine used in most cardiac sensitization testing procedures was more than 10 times the level produced by humans. It is still difficult to reach a conclusion as to the cardiotoxicity of CF_3I based on information from only one dog at each treatment level. Other potential

replacement compounds tested using this methodology resulted in mild to moderate MVEA, and not death [25,26,32,33,34]. Cardiac sensitization data. however, appear to drive the risk associated with the use of CF_3I. This Center believes that a potential health hazard exists in the area of cardiac sensitization following acute exposure to concentrations of CF_3I greater than 0.2%. A cardiac scnsitization test could he perfonned, with a statistically relevant number of animals at each dosage level, in order to assess accurately the potential of CF_3I to cause cardiac arrhythmia in the presence of physiologically relevant levels of epinephrine. This type or testing, although informative from an academic viewpoint, may result in the application of uncertainty factors. which could further reduce the NOEL for cardiac sensitization.

Since the beagle dog model used to measure cardiac sensitization is a conservutivc assessment of human risk, physiologically based pharmacokinetic modeling can be used to provide directly relevant information on CF_3I eoncentralions in human blood that may cause cardiac effects. Physiologically based pharmacokinetic modeling develops a mathematical description of the uptake and disposition of chemicals based on quantitative interrelationships among critical determinates of these processes [35]. The model developed to evaluate blood levels of CF_3I and other halocarbons, may eventually be used to provide extrapolations essential for dose-response assessment of this class of chemicals. For instance, PBPK modeling indicated a blood level of 2000 mg/L for a salesman inhaling CF_3I from a balloon without adverse effects. This level is two orders of magnitude greater than that predicted for a response in humans (19 mg/L) based on cardiac sensitization testing in dogs. PBPK data can. therefore, he used to augment or refine existing animal data or provide presumptive data for risk assessment purposes.

Mutagenic potential was observed with two of three screening techniques. The Ames Salmonella Reverse Mutation assay indicated that CF_3I was a potent mutagen. It induced both frameshift and base-pair mutations in *Salmonella typhimurium* tester strains with and without activation by mitochondrial S9. Positive results were also ohtaincd from the mouse hone marrow micronucleus assay, where elevated polychromatic erythrocyte (PCE) to erythrocyte ratios and micronuclei to PCE ratios were observed. These results indicate that CF_3I is capable of causing structural changes in the chromosomes in vivo. A positive result on a screen would indicate that a potential for mutagenesis exists and that further testing is warranted. Furthermore. the Koski free radical model indicated that CF_3I could potentially be carcinogenic. This model. however, has not been validated. Examination of tissues taken from animals exposed to CF_3I in repeated-dose studies, however. has revealed no preneoplastic lesions. Based on the current data, this Center considers the effect of CF_3I on mutagenicity to he equivocal. To determine developmental effects from inhalation of CF_3I, 40CFR798.43.50 (inhalation developmental toxicity study) is suggested. Carcinogenic potential can be evaluated using 40CFR798.3320 (combined chronic toxicity/oncogenicity) or 40CFR798.3300 (oncogenicity).

The results of the investigation into reproductive effects of CF_3I are difficult to assess. The abbreviated test design did not allow for an accurate interpretation of reproductive toxicity. Spermatogenesis in the rat, for instance, occurs over a period of 48 days. Dosing for the reponed study started only 30 days prior to mating. The EPA suggests that both male and female rats be exposed 10 weeks prior to mating. Interestingly, a previous 90-day study conducted in Fischer-344 rats [23] indicated a complete absence of sperm as well as a reduction in testicular weight and testicular atrophy of males in the two highest dosage groups (4 and 8%). This finding was interpreted as an effect of restraint resulting in heat stress and not associated with CF_3I exposure. The fact that testicular changes were reduced at 90 days may support this hypothesis. Similar

effects from nose-only inhalation systems have been reported with structurally related compounds [36]. This effect, however, was only seen in animals of the two highest dosage groups, not control animals. The reproductive effects observed in the Kinkead study may have been potentiated by heat stress. As the associated pathologist's report states, "[this] suggests a potential reproductive toxicity associated with exposure to the CF_3I at the high and medium dosage levels, and the findings warrant further investigation." The highest dosage level used in the subsequent reproductive toxicity test [24] was 2%. Only partial information was obtained from this group in the Kinkead subchronic study. The exposure time in the Dodd study (6 hrs/day) was 3 times greater than that of the Kinkead study (2 hrs/day). The effects in the Kinkead study were observed in Fischer-344 rats, an inbred strain, while the reproductive study was conducted using outbred Sprague-Dawley rats. Although chronic exposure is not anticipated, this Center interprets the data on reproductive effects as equivocal. The definitive test for reproduction and fertility effects of a compound is Health Effects Testing Guideline 40CFR798.4700 (or 40CFR 799.9380: TSCA Reproduction and fertility effects).

The 90-day (subchronic) inhalation study indicated an increase in thyroid stimulating hormone (TSH). While these effects could be related to exposure to CF_3I, they could also he a result of stress induced by restraint. The alterations observed in thyroid indicators, although significant, were within published normal ranges. The author suggested in his discussion of the results that high levels of TSH could induce carcinomas. Chronic hypersecretion of TSH causes profound thyroid hyperplasia (goiter). which appears to be related to carcinogenesis. In rats, iodine deficiency is a much more effective tumor promoter than it is a carcinogen. This suggests that one role of iodine is to prevent the formation of thyroid tumors in humans and animals [37]. On the other hand, iodine excess also produces colloid goiter with normal T_4 and a slightly reduced TSH level [38]. The human thyroid, however, is much less sensitive to elevated plasma TSH levels than are those of rats or mice [39]. Curran and DeGroot [40] indicate that prolonged stimulation of the human thyroid by TSH will induce neoplasia only in exceptional circumstances, probably by acting together with some other metabolic or immunologic abnormality. This Center does not consider thyroid hormone alterations to be a problem at design concentrations.

CONCLUSIONS

The review of the available data indicates a potential health hazard exists in the area of cardiac sensitization following acute exposure to concentrations of CF_3I greater than 0.2%. The effect of CF_3I on mutagenicity and reproductive parameters is equivocal. However unlikely, human exposure to CF_3I could occur during the manufacturing process, transportation, storage, and packaging. Fire suppression training and accidental releases are also potential sources of exposure. The available data indicate that the toxicity of CF_3I precludes its use in many Army systems without further evaluation.

Individuals are exposed to toxic compounds on a daily basis both at work and at home. The effects of most of these toxic compounds on humans, animals, and the environment have, for the most part, been characterized. Exposure to these compounds is limited by proper labeling and through the use of personal protective equipment. Since the evaluated information indicates that CF_3I is a potential toxicant, the exposure issue must be addressed. Exposure to CF_3I could possibly he reduced through use of personal protective equipment and engineering method-

ologies. These issues could be explored once sufficient data are available to proceed with the required Health Hazard Assessment or a Toxicity Clearance.

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