WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

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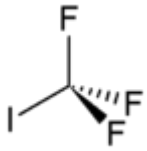
Trifluoroiodomethane (CF_3I) (2018)

I. IDENTIFICATION (Wikipedia Encyclopedia, 2017)

Chemical Name: Trifluoroiodomethane
Synonyms: Trifluoromethyl iodide, Perfluoromethyl iodide, Freon 13T1, CF_3I, Iodotrifluoromethane
CAS Number: 2314-97-8
Molecular Formula: CF_3I
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES (Matheson Tri-Gas, 2017; NRC, 2004)

Molecular Weight: 195/91 g/mol
Physical State and Appearance: Colorless, odorless gas
Conversion Factors: 1 mg/m^3 = 0.12 ppm; 1 ppm = 8.01 mg/m^3
Melting Point: -110 °C (-166 °F)
Boiling Point: -22.5 °C (-8.5 °F)
Vapor Pressure: 78.4 psia at 25 °C (77 °F)
Vapor Density: 6.9 (Air = 1)
Flammability Limits: Not flammable
Flash Point: Not applicable
Autoignition Temperature: Not applicable
Density: 2.5485 g/cm^3 at -78.5°C (-109.3 °F)
Log K_{ow}: Not available
Solubility in Water: Slightly soluble
Stability: Stable at normal temperatures and pressure, may form acid halides (e.g., hydrogen fluoride, hydrogen iodide) on decomposition
Reactivity and Incompatibilities: Will not polymerize, incompatible with oxidizing materials

III. USES

CF_3I is used as a fire suppressant. CF_3I may also be mixed with flammable hydrofluorocarbons to reduce flammability (Dodd, Kinkead et al., 1997)

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Lethality Data

Table 1. Inhalation Lethality Data for Rats (NRC, 2004)

Duration	LC_{50} (ppm)
4-Hour	> 10,000
4-Hour	> 128,000; < 200,000
4-Hour	274,000
15-Minutes	> 33,000 ppm

2. Eye Irritation

CF_3I has not been tested for eye irritation. As CF_3I will rapidly evaporate, ocular irritation related to frostbite may occur.

3. Skin Absorption

No data are available for skin absorption. The chemical is a gas so dermal absorption would be expected to be negligible relative to evaporation.

4. Skin Irritation

CF_3I has not been tested for skin irritation. As a gas, the chemical is unlikely to be present on the skin surface. Skin damage related to frostbite may occur.

5. Skin Sensitization

No data are available for skin sensitization. The chemical is a gas and is not expected to penetrate the skin, a necessary step for inducing skin sensitization.

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6. Inhalation Toxicity

Male Fischer 344 rats (30 per dose) were exposed nose-only for 4 hours to CF_3I at concentrations of 0, 5000 or 10,000 ppm (Dodd, Kinkead et al., 1997; ManTech, 1994).[1] Blood samples for clinical pathology parameters were collected immediately following the 4-hour exposure and at 3 and 14 days following exposure. No deaths or clinical signs of toxicity were observed immediately following exposure or during the 14-day observation period. There were some statistically significant effects on clinical chemistry and hematology parameters but these were within historical control ranges and showed no relationship to dose or time point of blood collection following exposure. No histopathology findings were noted in the rats at each time point. The LC_{50} was above the highest test concentration of 10,000 ppm.

In a second acute toxicity study, Sprague Dawley rats (5/sex/dose) were exposed whole body for 4 hours to 0, 100,000, 128,000, 200,000 or 320,000 ppm CF_3I. All rats exposed at 200,000 and 320,000 ppm died within 20 minutes of exposure initiation. The deaths at these concentrations were attributed to hydrogen fluoride (HF) contamination (7 ppm) of the test article. At necropsy, rats exposed to these higher concentrations exhibited dark red and "puffy" lungs that were considered to be consistent with HF exposure. After implementation of an HF scrubber, exposures were conducted at 100,000 ppm and 128,000 ppm. Animals in these groups experienced narcosis during the exposure but appeared normal within about 3 minutes once exposure ceased. All animals at these concentrations survived through the 14-day observation period with no other clinical signs of toxicity. Upon necropsy, 2 rats exposed to 128,000 ppm exhibited redness in the lung. No other treatment-related effects were noted (Ledbetter, 1994).

In a third acute toxicity study, Sprague Dawley rats (5/sex/dose) were exposed nose-only to 242,000 or 288,000 ppm CF_3I for 15 minutes. All female and two male rats died at the higher concentration and one male rat died at the lower concentration. All surviving animals exhibited a clinical sign "shaky" (not further defined) when removed from the inhalation chamber but did not subsequently display this or other clinical signs of toxicity. No necropsy results were reported nor the duration of the post-exposure period (Ledbetter, 1994).

In a cardiac sensitization study, beagle dogs (6 males, not all animals used for all doses) were exposed, muzzle-only, to CF_3I at concentrations of 1000, 2000, 4000 or 10,000 ppm for 5 minutes while attached to electrocardiographic (ECG) leads. The study was conducted in compliance with Good Laboratory Practice (GLP) regulations. Prior to exposure, an individual response to intravenous epinephrine administration was established for each dog. After a period of approximately 5 minutes of exposure to CF_3I, the dogs received a challenge dose of epinephrine. After an additional exposure of approximately 5 minutes to the test substance, the ECG measurements were terminated. One animal experienced a fatal ventricular fibrillation (FVF) at 4000 ppm and 1 animal experienced a non-fatal FVF at 10,000 ppm. The no-observed adverse effect level (NOAEL) was 2000 ppm (Dodd and Vinegar, 1998; Huntington Research Centre, 1995).

B. Subacute Toxicity

1. Inhalation

A 4-week study (TNO, 2007) in male and female Wistar rats (5/sex/dose) was conducted as part of genotoxicity testing (see Section F: Genotoxicity; TNO, 2007). The study was conducted in compliance with GLPs. Animals were exposed nose-only to 0, 10,000, 20,000 or 40,000 ppm CF_3I for 6 hr/day, 5 days/week for 4 weeks. During the study, decreased body weights for male rats were observed at the mid- and high-dose during the study with no effect on body weights observed at the low dose. Changes in red blood cell parameters and clinical chemistry (e.g., cholesterol, aminotransferases, albumin, etc.) were observed in males or females although the changes are not considered to be toxicologically significant. Increases in absolute or relative (percent body weight) liver weights were observed in male or female rats at 20,000 and 40,000 ppm without histopathological changes, and were not considered to be compound-related. Decreased spleen weights were also observed in males and females at 40,000 ppm. Histopathological changes were seen in the 40,000 ppm animals in the adrenals (vacuolation), spleen (lymphoid depletion), thymus (atrophy, necrotic lymphocytes) and testes (multinucleated giant cells). The NOAEL was 10,000 ppm; effects on bone marrow were not considered for the NOAEL (see Section F: Genotoxicity).

Potential thyroid hormone effects in a species other than the rat was evaluated by Wang (2017). Male B6C3F1 mice were exposed whole body to CF_3I at concentrations of 2500 ppm, 5000 ppm or 10,000 ppm for up to 28 days (7 days/week,

[1] Kinkead et al. (1994) refers to the actual laboratory study report, the results of this and a number of other studies were subsequently published as a peer-reviewed journal article as Dodd et al., 1997.

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6 hr/day). Study outcomes included clinical signs, body and organ weights, serum iodide and thyroid-related hormones (T3, T4 and TSH), clinical and gross pathology and thyroid histopathology. No adverse clinical signs were observed in any animals throughout the study. Slight changes in liver weight were observed, particularly on day 14, but were resolved by day 44 and were not accompanied by changes in liver enzymes. Serum iodide levels were unaffected by exposure. Serum T4 was slightly increased at 5000 and 10,000 ppm after 14 days of exposure but was similar to controls after 28 days of exposure. Serum T3 was significantly increased at 10,000 ppm on day 28 but T4 and TSH were unaffected. TSH was decreased at the mid dose on day 14 but not different from controls at any other dose or time point. No clear dose dependence was observed for these changes. No effects on thyroid hormones were seen in the recovery group. There were no clear effects on thyroid weight nor any differences in thyroid histology compared to controls. The study NOAEL was 10,000 ppm.

2. Oral

No data are available following oral administration. The chemical is a gas so an oral exposure study is not practical.

3. Dermal

No data are available following dermal administration. The chemical is a gas so a dermal exposure study is not practical.

C. Subchronic Toxicity

1. Inhalation

A subchronic exposure study was conducted in male and female Fischer 344 rats (15/sex/dose) exposed nose-only to CF_3I concentrations of 0, 20,000, 40,000 or 80,000 ppm for 2 hr/day, 5 days/week for up to 13 weeks (Dodd, Kinkead et al., 1997; ManTech, 1996). At day 30 after initiation, 5 rats/sex/dose were sacrificed for interim evaluation. During the study, one male rat in the high-dose and seven male rats in the mid-dose group died or were found dead. The cause of death was attributed to the restraint system and not the CF_3I exposure. Body weights of rats in the highest dose group were significantly decreased throughout the study. Transient decreases in some blood parameters (hemoglobin, red cell count and lymphocyte percentage) were reported in the 80,000 ppm group at 30 and 90 days of exposure. Among thyroid parameters, T3 was decreased in both sexes in all exposed animals in a dose dependent manner, and TSH, TBG and rT3 were similarly increased across dose groups. T4 was significantly increased in all exposed animals, although the increase was not dose dependent. Histopathological evaluation of thyroids at the end of the study showed a mild increase in thyroid follicular colloid in all treated animals, with some evidence of dose dependence. Relative thyroid weight was increased in females at all doses and in males at the higher two doses. Changes in the relative weight of several other organs were observed at 80,000 ppm (e.g., brain, liver, thymus, ovaries and testes). Relative thymus weight was also decreased at 40,000 ppm in both sexes. Histopathology also revealed a significant increase in nasal epithelial necrosis and testicular atrophy in the high dose group males. Overall, the lowest observed adverse effect level (LOAEL) based on thyroid related effects was 20,000 ppm. Excluding thyroid effects, the NOAEL (based on body weight changes, organ weight changes and changes in blood cell parameters) was also 20,000 ppm.

D. Chronic Toxicity/Carcinogenicity

No chronic or carcinogenicity studies have been conducted for CF_3I.

E. Reproductive/Developmental Toxicity

A reproduction/developmental inhalation study (Dodd et al., 1999) of CF_3I was conducted with male and female Sprague-Dawley rats (16/sex/dose). The animals were exposed whole body at target exposure concentrations of 0, 2000, 7000 or 20,000 ppm. Rats were exposed for 4 weeks (6 hr/day, 5 days/week) prior to mating and then exposed 6 hr/day, 7 days/week during mating, gestation and lactation. No exposure occurred on Gestation Day 21 through Postnatal Day 4 to allow for delivery. Clinical observations were obtained during the exposure period. A subset of males was sacrificed at week 7 (after mating), the remainder of the animals were sacrificed at the conclusion of the study (week 14). Bone marrow samples were collected for determination of micronuclei formation (see Section F: Genotoxicity).

CF_3I exposure had no significant effects on reproductive parameters (e.g., mating indices, fertility index, gestation length, pups per litter or pup survival). Male to female pup sex ratio was significantly reduced at 20,000 ppm. This same parameter was increased at 7000 ppm and decreased at 2000 ppm relative to controls, but not significantly (i.e., a dose-related change was not observed). Pup weights, pup survival and total number of pups/litter also were not significantly different from controls at any dose. The change in sex ratio was reported to be within the range of the laboratory's historical control incidence. Hence, the sex ratio is considered to be a spurious finding.

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The authors reported no treatment-related clinical findings. A significant decrease in body weight was observed in female parental rats in the 20,000 ppm group over the last 3 days of the study (days 93-95, an 11% decrease relative to the prior measurement in this group) but was not observed at earlier time points. No effects on body weights were observed in male animals. Sporadic changes in blood chemistry or hematology were observed but were stated by the authors not to be treatment-related as they did not exhibit a dose-response relationship or were not toxicologically significant. There were some substantial changes at 20,000 ppm: increases in white blood cells and neutrophils and decreases in eosinophils in males (16%, 33%, and 50% respectively) and decreases in white blood cells and blood urea nitrogen (14% and 11%, respectively) in females. Serum cholesterol was significantly increased at 7000 ppm and 20,000 ppm in female rats (29% and 34%, respectively). Most of these changes, while statistically significant were less than 10% relative to control values.

Significant effects were observed on thyroid hormones in both male and female rats. At the 7-week time point (only males evaluated), TSH, T4, T3 and rT3 were all significantly altered at all doses compared to controls. At the 14-week time point, T4, T3 and rT3 were significantly affected at all doses in both sexes compared to controls (e.g., T4 was increased by approximately 200% in males and 250% in females at the highest dose). TSH was significantly increased in the 2000 and 20,000 ppm in females; at 7000 there was an increase relative to controls but the increase was not statistically significant. In males, TSH was significantly increased only at 20,000 ppm. No morphological changes were observed in the thyroid.

Evaluation of organ weights of parental animals did indicate some effects at higher doses. Liver weights were increased (6-10%) in male rats at 7 and 14 weeks in the 20,000 ppm group and epididymal weights were increased at 7000 ppm and 20,000 ppm at 7 weeks (23% and 16%, respectively) but not at 14 weeks. In females, the mean relative (to body weight) weights of brain, kidney and liver were decreased at 20,000 ppm for the first two and 7000 ppm for the last. These changes were less than 10% relative to controls. Relative ovary weight was decreased at 20,000 ppm (0.03 g vs 0.04 g, a difference of 25%).[2] Histopathology of tissues in the 20,000 ppm group did not indicate any abnormal findings, tissues from lower doses were not evaluated. Based on the lack of histopathological effects, the study authors described these organ weight effects as not CF_3I treatment related.

The authors of the study concluded that CF_3I was not a reproductive toxicant as no significant effects were observed at concentrations that did not produce parental toxicity. Notably, despite thyroid hormone effects in parental animals at doses as low as 2000 ppm, no developmental effects were seen at doses as high as 20,000 ppm. The LOAEL for parental toxicity based on thyroid hormone effects was 2000 ppm. Excluding thyroid hormone effects, 7000 ppm constituted the NOAEL.

F. Genotoxicity/Mutagenicity

Data are summarized in Tables 2 and 3.

Table 2. Summarized Data for Point Mutations

Author	Study Design	Dose (ppm)	Results
Dodd, Ledbetter et al. (1997)	Ames - Bacterial	1000-86,000	**Strongly Positive** (+/-) S9 (TA1535, TA1538, TA1537, weakly positive TA100, TA98)
	Mouse Lymphoma - L5178Y cells	80-518,000	**Negative**
Genesys Research (1995b)	Mouse Lymphoma - L5178Y cells	125,000 to 100% CF3I	**Negative**
BioReliance (2017)	"BigBlue" Mutagenicity - Transgenic Rats	1250, 2500, 5000	**Negative**

Table 3. Summarized Data for Chromosome Damage

Author	Study Design	Dose (ppm)	Results
Dodd, Kinkead et al., (1997)	Micronucleus - Rats (F-344, m/f) - Nose-only - 2 hr/day - 5 days/week - 13 weeks	20,000 40,000 80,000	**Positive** 30- and 90-day endpoints were positive in both genders, females were negative at 30 days, 20,000 ppm

[2] The authors also indicate ovary weight was significantly different from controls at 7000 ppm but the reported mean value (0.04 g) is the same as the control value.

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Author	Study Design	Dose (ppm)	Results
Genesys Research (1995a)	Micronucleus - Mice (Swiss-Webster) - Nose-only - 6 hr/day - 3 days	25,000 50,000 74,000	**Positive** Showed a clear dose response at 50,000 and 75,000 ppm.
Dodd et al. (1999)	Micronucleus (Part of Repro/Dev Study) - Rats (Wistar) - Sprague-Dawley - Whole-body - 6 hr/day - 5 days/week - 14 weeks	2,000 7,000 20,000	**Negative** No increased micronuclei at any concentration; no effect on mitotic index
TNO (2006)	Chromosomal Aberration - Rats (Wistar) - Nose-only - 4 hour	20,000 40,000 200,000 (animals died)	**Negative** 20,000 NOAEL Mitotic index decreased at all doses
TNO (2007)	Chromosomal Aberration - Rats (Wistar) - 6 hr/day - 5 days/week - 4 weeks	10,000 20,000 40,000	**Negative** mitotic index decreased at all doses, no chromosomal aberrations
TNO (2007)	Unscheduled DNA - Same study as above	20,000 40,000	**Negative**

CF_3I was examined in a GLP compliant bacterial reverse mutation (Ames) assay with *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 in the absence and presence of S9 metabolic activation. Test concentrations up to a maximum of 8.6% (86,000 ppm) in air were studied via an exposure chamber. In initial range finding tests, exposure concentrations above this level produced cytotoxicity. In the absence of S9 activation, positive results were observed with strains TA1535, TA98 and TA100. Strain TA1537 also gave a positive result at exposure concentrations above 23,000 ppm. In the presence of S9 activation, strains TA1535 and TA100 gave positive results. Strains TA1537 and TA98 also gave positive results at concentrations at or above 23,000 ppm. Positive and negative controls performed appropriately (Dodd, Ledbetter et al., 1997).

A GLP compliant mouse lymphoma assay was conducted using CF_3I and L5178Y cells in the presence or absence of S9 metabolic activation. Cells were exposed to the compound in an exposure chamber using concentrations ranged from 8% to 51.8%. The authors reported no significant increase in induced mutant frequency in this assay at any concentration regardless of the presence or absence of metabolic activation. A clear increase in mutant frequency was observed with the positive controls (Dodd, Ledbetter et al., 1997).

A second mouse lymphoma assay was conducted using exposure concentrations ranging from 125,000 to 1,000,000 ppm (i.e., 100% CF_3I). These assays were performed in sealed 15 mL round-bottom glass blood tubes sealed with serum stoppers. The authors reported no significant increase in mutation frequency at any concentration tested with or without S9 metabolic activation. An increase in mutation frequency was observed with the positive control as expected (Genesys Research, 1995b).

A "BigBlue" mutagenicity assay was conducted in transgenic rats. In this assay, rats containing a recoverable target gene are exposed to the test substance and, after exposure, the target gene is recovered and transfected into *E. coli*. Mutated genes cause the resulting bacterial colonies to have a blue color, signaling the *in vivo* exposure lead to a mutagenic response. Rats were exposed by inhalation for 6 hr/day, 7 days/week for 28 days to target concentrations of 1250, 2500 or 5000 ppm CF_3I (actual average concentrations 1250, 2510 or 4938 ppm). The recovered transgene was obtained and tested from bone marrow, liver and lung. The authors reported that CF_3I treatment did not cause an increase in mutant frequencies relative to air exposed controls whereas a mutagenic response was observed with the positive control, ethyl nitrosourea (BioReliance, 2017).

Three micronucleus assays have been conducted with CF_3I.

Dodd, Ledbetter et al. (1997) conducted an assay with Fischer 344 rats using nose-only exposure and concentrations of 20,000, 40,000 or 80,000 ppm (this study was part of the 13-week study described above). Separate sets of animals were evaluated at 30 days and 90 days. The authors reported that exposure for 30 days and 90 days each significantly increased the micronuclei frequency in a dose dependent manner in both sexes, with the exception of the 20,000 ppm dose which did not produce a significant increase in females at 30 days, but did produce an increase at 90 days.

In a second study, male and female Swiss Webster mice (5/sex/group) were exposed to CF_3I nose-only by inhalation at 0, 25,000, 50,000 or 75,000 ppm for 6 hr/day for 3 consecutive days (Genesys Research, 1995a). The positive control, triethylene melamine, was administered by intraperitoneal injection on day 3. Results were obtained by scoring the number of polychromatic erythrocytes (PCE) per 1000 erythrocytes and the number of micronuclei observed in approximately 200 PCEs and 100 normochromatic erythrocytes. Positive and negative controls gave the expected results. All animals, including controls, were observed to lose weight over the course of the

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study and the authors reported a greater degree of weight loss in CF_3I exposed animals. CF_3I exposure was observed to decrease the number of PCEs/100 erythrocytes and to increase the number of micronuclei per 1000 PCEs in both the male and female mice. The increase in micronuclei exhibited a clear dose-response relationship statistically significant at 50,000 and 75,000 ppm.

A third micronucleus assay was conducted with male and female Sprague-Dawley rats by whole-body inhalation as part of the reproductive toxicity screen discussed earlier (Dodd et al., 1999). As described earlier, exposure concentrations were 0, 2000, 7000 or 20,000 ppm for 6 hr/day, 5 days/week. Bone marrow smears were collected from femurs at the end of the study and the frequency of micronucleated cells per 1000 polychromatic erythrocytes (PCE) was determined. Bone marrow toxicity was determined by calculating the ratio between PCE and normochromatic erythrocytes (NCE). No increase in micronuclei was observed relative to controls at any exposure concentration and there was no indication of exposure producing bone marrow toxicity.

Subsequent to the micronucleus evaluations, two chromosomal aberration studies were conducted. In the first study (TNO, 2006) male Wistar rats were exposed nose-only to 20,000, 80,000 or 200,000 ppm CF_3I for 4 hours. At the highest dose, 8 of 14 animals died approximately 30 minutes into the test (an occurrence that was apparently not unexpected given the larger group size at this dose) and exposure was halted at this concentration after 35 minutes. The surviving animals at this dose and those at 80,000 ppm exhibited trembling and piloerection for a short time after exposure but recovered. No adverse signs were seen in the 20,000 ppm group. Colchicine was administered 2 hours prior to sacrifice to produce metaphase arrest, bone marrow cells were extracted from femurs and cells were Giemsa stained for analysis. The positive control, mitomycin C, gave the expected results. The authors reported a significant decrease in mitotic index, an indication the substance reached the bone marrow and caused cytotoxicity, at 200,000 ppm and a decrease at 80,000 ppm (84% of controls) that was not statistically significant. No effects on mitotic index were seen at 20,000 ppm. No increase in chromosomal aberrations was seen at any dose relative to controls.

In the second chromosomal aberration study (TNO, 2007), part of the 4-week study described above, male Wistar rats (5 per group) exposed to CF_3I doses of 10,000, 20,000 or 40,000 ppm for 6 hr/day, 5 days/week for 4 weeks. Decreases in mitotic index were seen at all doses (69%, 65% and 53%, respectively) but there was no increase in chromosomal aberrations relative to controls. The positive control, mitomycin C, performed as expected. The second chromosomal aberration study also evaluated the potential for unscheduled DNA synthesis (UDS) using both male and female rats. Rats in the higher two exposure groups had liver cells harvested at necropsy for evaluation of unscheduled DNA synthesis. The study author reported that no indications of unscheduled DNA synthesis were observed.

Genotoxicity Summary: CF_3I has been extensively studied for potential genotoxicity and presents mixed test results. In terms of mutagenicity, there are positive Ames results but negative results in two *in vitro* mouse lymphoma studies and an *in vivo* Big Blue transgenic rodent mutation assay. Results from these tests of mammalian cells, particularly the *in vivo* Big Blue assay, are generally considered more informative of human risk than the results of tests in bacteria (i.e., the Ames assay). It is therefore reasonable to conclude that the weight of evidence indicates a low human mutagenicity risk for CF_3I.

In terms of non-mutagenic outcomes there are negative results for both the *in vivo* unscheduled DNA synthesis assay and two *in vivo* chromosomal aberration assays. There are two positive *in vivo* micronucleus assays (one in rats, one in mice) at doses at or above 20,000 ppm. The one negative *in vivo* micronucleus assay was performed in whole body chambers at doses at or below 20,000 ppm. The two positive *in vivo* micronucleus assays were nose-only inhalation exposures. In nose-only exposure systems, animals need to be restrained inside a tube, which leads to stress. Stress is known to cause changes in body temperatures in rodents. A study of physiological changes caused by nose-only exposures by van Eijl et al. (2006) reported that mice exhibited a pronounced hypothermia when compared to unrestrained littermates. A study that evaluated both mice and rats reported an increase in body temperature by 2 °C in mice. In the same study, the body temperature of rats was unchanged, but heart rates were elevated for both species. It took two weeks of fixed-duration daily restraint for the animals to adapt to nose-only restraint (Narciso et al., 2003). It is possible that the positive micronucleus results were the result of altered body temperature, an effect which has been reported in the literature (Asanami et al., 1998; Asanami and Shimono, 1997, 1999). It is worth noting that body temperatures were reported to be significantly but reversibly decreased in the transgenic rats during exposures in the Big Blue assay at the 2500 and 5000 ppm exposure level. In this study, body temperatures were decreased by approximately 1-1.5 °C. Although the body temperature decreases studied by Asanami and Shimono were more pronounced (approximately 4 °C), it is

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not known how body temperatures were affected at the substantially higher doses used in the positive micronucleus studies where the lowest dose tested was 20,000 ppm. It is suggestive micronuclei alterations were not seen in the lower dose study (Dodd et al., 1999) due to both differences in body restraint and dose. It is noted that in reviewing CF_3I for fire suppression use, the National Research Council (NRC, 2004) recommended that the micronucleus findings be confirmed via a chromosomal aberration study which is less sensitive to such effects. Both chromosomal aberration studies were negative.

G. Metabolism/Pharmacokinetics

Metabolism data for CF_3I are limited. No study specific data addressing the half-life or rate of metabolism were located. Researchers built physiologically based pharmacokinetic models for fire suppressants in general and some of this work included CF_3I (e.g., Vinegar et al., 1999). The models all postulate a low degree of CF_3I metabolism and indicate that CF_3I concentrations reach equilibrium between air and blood within minutes. Partition coefficient studies done during model development have indicated a higher blood:air partition coefficient for rats compared to humans, 1.75 vs 0.97, suggesting that for a given CF_3I concentration in the lungs, more would be taken up into systemic circulation of rats compared to humans (Vinegar and Jepson, 1996).

H. Other Information

Studies with CF_3I in rats (Dodd et al., 1999; Dodd, Kinkead et al., 1997) have shown that thyroid hormone perturbation is the most sensitive effect compared to other clinical chemistry endpoints. Dodd et al. (1999) reported that 6 hour daily exposures to CF_3I for 7 and 14 weeks at 2000 ppm resulted in altered thyroid hormone perturbation in both male and pregnant female rats (Table 4). The changes were substantial, dose-related and persisted throughout the treatment period.

Table 4. Thyroid Hormone Changes in Male Rats Relative to Controls after 7 weeks of CF_3I Exposure*

Hormone	CF_3I Concentration (ppm)		
	2000	7000	20000
TSH	↑ 54%	↑ 66%	↑ 66%
T4	↑ 58%	↑ 118%	↑ 153%
T3	↓ 12%	↓ 18%	↓ 22%
rT3	↑ 43%	↑59%	↑ 205%

* Percent change relative to concurrent control

At 2000 ppm, the changes in thyroid hormone levels resulted in a LOAEL, since these changes were observed at all concentrations examined a NOAEL was not established (Dodd et al., 1999). The specific pattern of thyroid hormone perturbation (increased T4, TSH and rT3, decreased T3) is suggestive of inhibition of peripheral deiodinase inhibition rather than suppression of hormone production via iodide uptake inhibition. It should also be noted that an earlier study, (Dodd, Kinkead et al., 1997), reported thyroid hormone effects after 4 weeks of exposure to 20,000, 40,000 or 80,000 ppm CF_3I. T4 and TSH were significantly increased at 20,000 ppm in female rats, each by about 50%. These effects persisted when observed at the end of exposure at week 13.

Rats are well known for being particularly susceptible to thyroid hormone perturbation due to unique physiological conditions related to thyroid homeostasis (Choksi et al., 2003). Therefore, they are not considered a suitable model for evaluating human health risks of thyroid perturbation. Chronic exposures to drugs and other chemicals that affect thyroid homeostasis produce thyroid hyperplasia and eventually thyroid follicular cell tumors in rats but produce no such effects in humans, even with chronic exposure (McClain, 1995). An evaluation of interspecies susceptibility to thyroid hormone perturbation by the goitrogen perchlorate indicated that rats were more sensitive than mice, rabbits, monkeys or humans (Lewandowski et al., 2004). Similarly, rats appeared to be more sensitive than mice following exposure to erthyrosine, an iodine-containing food dye that inhibits certain aspects of thyroid hormone metabolism (Borzelleca et al., 1987; Borzelleca and Hallagan, 1987). Taken together, these data calls into question whether the thyroid hormone effects of CF_3I observed in rats are an appropriate basis for evaluating human health risks.

To further explore this question, a 28-day inhalation study of CF_3I was conducted in male mice (Lovelace Biomedical, 2017). The object was to compare results in mice to the results obtained by Dodd et al. (1999) in male rats. This 28-day study (OECD Test Guideline 407, (OECD, 2008)) included analysis of thyroid hormones at 2 and 4 weeks, serum iodide analysis at 2 weeks and limited histopathology examinations of the thyroid. The study also included a 44-day time point, approximately 2 weeks after the end of exposure, to assess reversibility of any effects observed.

Exposures of male mice to CF_3I at concentrations up to 10,000 ppm for 28 days resulted in no clinical or gross pathological effects. There was no difference in serum iodide concentration between dosed animals and controls, suggesting a minimal degree of metabolic deiodination of CF_3I. Thus, CF_3I exposure

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in humans is not expected to affect thyroid homeostasis via changes in iodine status. The data also support the idea that the effect of CF_3I on thyroid hormone homeostasis is not due to iodide uptake inhibition and is more likely, if any, due to downstream effects on thyroid hormone metabolism.

After 14 days of exposure, there were slight and transient changes in T4 at 5000 ppm and 10,000 ppm but these returned to control values by day 28 of exposure. Although significantly different from controls, the magnitude of the changes was modest, e.g., no more than a 33% increase from control values, which is less than the effects observed in rats by Dodd et al. (1999). On study day 14, TSH was significantly decreased relative to controls at the mid-dose only but not at the high-dose, and TSH levels were not different from controls at the end of the exposure period on day 28. TSH is a key biomarker for thyroid hormone perturbation due to a sensitive feed-back mechanism (the Hypothalamic-Pituitary-Thyroid [HPT] axis) in mammals. As the serum TSH level was similar to controls after 28 days of exposure suggests that the thyroid hormone system was not adversely impacted. This is also supported by the absence of hypertrophy and hyperplasia in the thyroid glands. TSH stimulation can cause hypertrophy and hyperplasia in thyroid follicles via the HPT feed-back pathway.

During the exposure period in the current study in mice neither T4 nor TSH were different from controls on day 28. This finding is in contrast with Dodd et al. (1999) where perturbation was seen throughout the dosing period, again suggesting no adverse effect on the mouse thyroid. The lack of any notable differences in thyroid hormones on day 44 (recovery period) further supports the idea that the T4 changes observed only at day 14 were at most an adaptive rather than an adverse response.

Serum T3, which was not different from controls at any dose on day 14, was increased at the high dose (10,000 ppm) on study day 28. The magnitude of the change was 33%. No trend was apparent at the lower doses. Note that an increase in T3 is opposite to the effect observed in rats by Dodd et al. (1999). The fact that the T3 was not accompanied by changes in T4 or TSH makes this finding of questionable relevance. T3 levels in all CF_3I exposed animals were similar to controls on study day 44.

Histopathological evaluation of thyroids did not indicate any differences relative to controls. The only other significant finding was an increase in absolute and relative liver weight on study day 14 at all doses and an increase in relative liver weight only at the 10,000 ppm dose on study day 28. All liver weights were similar to controls at study day 44. In the previous study in rats, although liver weights were affected by CF_3I exposure, these effects were not considered biologically relevant when gross and microscopic pathological results were absent in these organs (Dodd, Kinkead et al., 1997). The change in liver weight is considered adaptive and not adverse. It should be noted that transitory increases in liver weights are not uncommon during xenobiotic exposure.

In conclusion, subtle effects on thyroid hormones at certain time points and doses are considered be biologically non-relevant and non-adverse. Overall, the study authors concluded that the top dose in the study, 10,000 ppm, represents a NOAEL.

V. HUMAN USE AND EXPERIENCE

Data on human exposure are limited. Vinegar et al. (1999) report on a follow up of two humans who had inhaled pure CF_3I from a balloon and then exhaled onto a flame to demonstrate the extinguishing properties of CF_3I. The authors report both men were in their mid-30s and in good health. They suffered no apparent acute effects from the CF_3I exposure which consisted of occasional single breaths. Given the lack of detailed examination of these individuals and the brevity of exposure, these case reports contribute little to occupational exposure limit development.

VI. RATIONALE

CF_3I has very low acute inhalation toxicity. In addition, as a gas that evaporates quickly and may cause frostbite, no eye or skin studies have been performed. This substance, however, has been shown to cause cardiac sensitization in dogs and to have effects on thyroid hormone homeostasis.

CF_3I has been extensively studied for potential *in vitro* and *in vivo* genotoxicity with positive and negative test results observed. However, the overall weight of evidence indicates that CF_3I has low human genotoxic risk.

Pharmacokinetic modeling suggested there would be limited CF_3I metabolism. Also, partition coefficient studies indicate that for a given CF_3I concentration in the lungs, more would be taken up into systemic circulation of rats compared to humans.

There are four potential points of departure for derivation of an occupational exposure limit (OEL): cardiac sensitization study conducted in dogs (NOAEL = 2000 ppm); parental thyroid hormone changes in the rat reproductive toxicity screening study (LOAEL = 2000 ppm); clinical chemistry, immune cell and terminal body weight changes in the same study (NOAEL =

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7000 ppm); or bone marrow toxicity observed in several studies (NOAEL = 7000 ppm). Each of these studies would call for different assessment/uncertainty factors for WEEL development.

Cardiac sensitization is an effect observed with most halogenated hydrocarbons. However, this effect is highly conservative with minimal risk to workers in an occupational setting (Brock et al., 2003). Furthermore, based on the physiologically-based pharmacokinetic modeling of fire suppression systems, the NRC concluded that humans could be exposed to 3000 ppm of CF_3I which would reach peak arterial concentrations within minutes and would never reach the blood concentrations associated with cardiac sensitization (i.e., the LOAEL of 4000 ppm from the dog study). The dose of epinephrine used is considered supra-physiological (NRC, 2004). Therefore, systemic levels of CF_3I would not be expected to occur that would represent a potential risk of cardiac sensitization to humans. Hence, the results of the cardiac sensitization study as well the low acute toxicity of CF_3I inform establishing a short-term occupational exposure limit.

In the 14-week reproductive screening study in rats (Dodd et al., 1999), effects were seen on various thyroid parameters (TSH, T3, T4, and rT3) at the lowest dose of 2000 ppm. However, it is recognized that rats are more sensitive to thyroid perturbation relative to humans. As described above, Lewandowski et al. (2004) noted that the rat is a more sensitive animal model for evaluating thyroid-hormone associated risks in humans due to species differences in thyroid hormone economy and suggested that if rat thyroid hormone data are used for human health risk assessment, an interspecies uncertainty factor of less than 1.0 may be appropriate. It is also recognized that rodent thyroid tumors associated with exposure to agents that alter thyroid hormone levels do not pose a thyroid tumor risk for humans for these reasons (Dellarco et al., 2006; Capen, 1994). Based on this information, it is more appropriate to base the occupational exposure limit on another health endpoint derived from animal studies.

The results from the 13-week repeat exposure toxicity study and the 14-week reproductive screening study represent studies that are used for establishing the WEEL. The adverse effects at the higher dose in each study (40,000 ppm in the 13-week study and 20,000 ppm in the reproductive screening study) consisted of body weight changes and changes in some red blood cell parameters. For the 13-week study, the NOAEL was 20,000 ppm based on a daily exposure duration of 2 hr/day. Conversion of this NOAEL to an 8 hr/day equivalent results in a NOAEL of approximately 5000 ppm, an estimated NOAEL similar to the 5250 ppm that can be derived from the 7000 ppm NOAEL reported for the 14-week, 6 hr/day reproductive screening study. The 7000 ppm NOAEL in the reproductive study also was the apparent NOAEL for bone marrow toxicity when looking across studies. Therefore, the 7000 ppm NOAEL is used as the point of departure for establishing the WEEL with subsequent adjustment to account for an 8-hour exposure time. Uncertainty factors to account for interspecies extrapolation, sensitive populations, and duration of exposure (described by Dankovic et al., 2015) were included in the determination of the WEEL. An 8-hour time-weighted average (TWA) WEEL of 500 ppm is recommended. A 15-minute Short-term Exposure Limit (STEL) of 1500 ppm was also developed to address the possible cardiac sensitization effect observed in dogs.

VII. RECOMMENDED WEEL GUIDE

8-hour Time-Weighted Average (TWA): 500 ppm

15-minute Short-Term Exposure Limit (STEL): 1500 ppm

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