SETTING THE OCCUPATIONAL EXPOSURE LIMIT FOR CF_3I*

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Occupational exposure limits are established by a number of organizations. The establishment of an occupational exposure limit involves examining the hazard levels associated with the exposure to a chemical. The hazard profile is determined by performing a battery of toxicity tests, the exact nature of which are dependant on the chemical in question. An example of a test battery would include such tests as acute toxicity tests (limit test, but not necessarily an LC_{50}), genotoxicity battery of tests, subchronic tests, and developmental toxicity tests.

A number of toxicity studies have been performed on trifluoroiodomethane (CF_3I). These toxicity tests have been independently evaluated by ICF Incorporated for the US Environmental Protection Agency and have been found adequate to establish an acceptable "Occupational Exposure Limit" (OEL) for CF_3I. This paper presents the recommended time-weighted average and ceiling OEL as well as the basis and justification for these values. Also, this paper addresses how one utilizes these OELs to assure safe production, transfer, use. and storage of the chemical.

RECOMMENDED ACCEPTABLE OCCUPATIONAL EXPOSURE LIMIT

The recommended time-weighted average (TWA) OEL for CF_3I is 150 ppm. The ceiling limit for CF_3I is 2000 ppm. The TWA OEL applies to chronic or repeated exposures such as those that might be experienced in manufacturing, cylinder filling or transfer operations, or agent recycling operations. The TWA OEL is established to provide guidance to personnel who might he exposed for 8 hrs/day, 40 hrs/wk, over a 35-year work span. The TWA OEL is not applicable to firefighting situations because firefighting situations generally involve infrequent, if not once-in-a-lifetime exposures. Therefore, the ceiling OEL is applied to a firefighting setting and represents a level not to he exceeded for any period of time. The ceiling OEL would also apply to accidental discharge scenarios of fire extinguisher cylinders and storage containers.

Basis for the Time-Weighted Average

A number of toxicological studies were considered when establishing this OEL [1,2,3,4,5,6,7]. Two endpoints in particular were the main focus for setting the TWA OEL (Figure 1): Thyroid hormone alterations and non-dose related, inconsistent changes in male to female pup ratio [1].

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* Based on a report by Harvey Clewell and Greg Lawrence, *Recommendation for an Acceptable Exposure Limit for CF_3I*, ICF Incorporated, for US Environmental Protection Agency, Washington, DC, 1998.

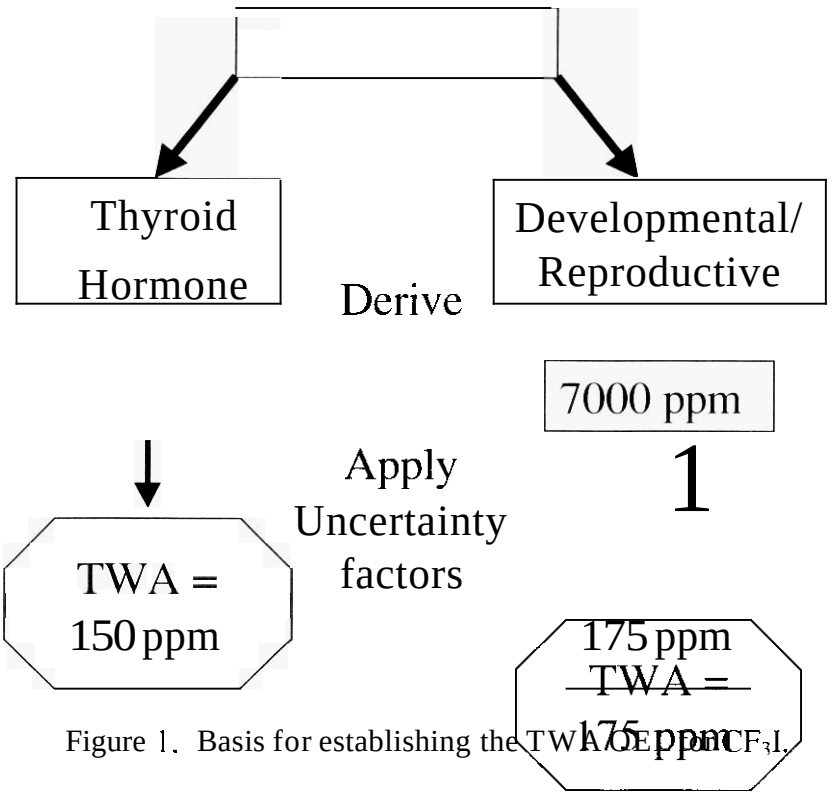

Figure 1. Basis for establishing the TWA/EEL for CF_3I.

Justification for the Time-Weighted Average Rased on Thyroid Effects

Endpoint:	Thyroid hormone alterations, male/female pup ratio changes
Study:	*Reproductive Toxicity Screen of Trifluoroiodomethane (CF3I) in Sprague-Dawley Ruts* [1]
Protocol:	Whole body, 6 hrs/day, 5 or 7 days/wk, I6 animals/sex/dose
Concentrations:	0, 0.2, 0.7 and *2* % (0, 2000. 7000 and 20,000 ppm)
NOAEL:	Not identified
LOAEL:	*0.2%*
LOAEL [adj]:	*2000* ppm x *6* hr / 8 hr = 1500 ppm
LOAEL [HEC]:	*1500* ppm
Uncertainty/Modifying Factors:	1 - animal to human 2 - use of LOAEL, instead of NOEAL 3 - human variability

Dodd et al. [1] and Kinkead et al. [3] have evaluated the potential effects of exposures to CF_3I on thyroid hormone levels. Not surprisingly, the thyroid organ was found to be the site of action for CF_3I, where iodine is utilized to make thyroid hormones. In Sprague-Dawley rats exposed via whole body inhalation to CFjI 6 hrs/day, 5 or 7-days/wk for 7 or 14 weeks [I]. significant concentration-related increases in T_4, rT_3, and TSH. and significant decreases in T_3 were reported in males and females at all cxposure levels, whcn compared to controls. Similar results with regard to TSH. T_4, rT_3, and T_3 levels wcre reported in the study by Kinkead et al. [3] where male and female rats were exposed to 2, 4, or 8% CF_3I vapors for 2 hrs/day, 5 days/wk for I3 weeks via nose-only inhalation.

Rats are considered a highly sensitive species for chemical mediated thyroid disruptions. A brief review of thyroid hormone regulation is useful to explain this fact and to understand the observed spectrum of effects. Iodine is taken up by the thyroid, combined with tyrosine and other components to form thyroglobulin (a high molecular weight glycoprotein), and a series of biochemical transformations results in the formation of the thyroid hormones T_3 and T_4 [8]. Release of these hormones is controlled by a neuroendocrine feedback loop, involving the hypothalamus, pituitary gland, and the thyroid gland. In response to demand for thyroid hormone, the hypothalamus releases thyroid stimulating hormone releasing factor, which in turn stimulates the pituitary gland to release thyroid stimulating hormone (TSH). The thyroid hormones T_3 and T_4 exert similar effects on target tissues, but T_3 is more biologically active. T_4 secreted into the circulation is converted *to* T_3 by the enzyme 5'deiodinase. The enzyme 5-deiodinase can convert excess T_4 to an inactive form of T_3, reverse T_3 (rT_3).

In the bloodstream, thyroid hormones (T_3 and T_4) are hound to carrier proteins, such as albumin and globulins, and when bound are not subject to metabolism or degradation. Conversely, the unbound or free forms are metabolized and degraded. In rats, T_3 and T_4 are hound to albumins, while in humans T_3 and T_4 are hound with a high affinity to globulins, which are not present in rats. In the rat, due to this weaker binding, T_3 and T_4 have a shorter plasma half-life and more rapid turnover than in humans [8,9]. Consequently, the demand on the rat thyroid gland to maintain homeostasis is much greater than in humans, i.e., it would be easier for humans to maintain normal physiological levels of T_3 and T_4. Therefore, rats are more sensitive to thyroid effects produced by the indirect mechanism described. In particular. it seems unlikely that short-term exposures of humans to low concentrations of CF_3I would result in the thyroid effects produced in rodents, due to the differences in protein binding and plasma half-lives. Although it is obvious that the thyroid effects reported in these studies were related to CF_3I exposure; the relevance to human health is questionable, and it is uncertain whether the rat is an appropriate model for the evaluation of potential thyroid effects in humans.

The study authors proposed that the observed effects were likely the result of CF_3I interfering with 5'-deiodinase, the enzyme responsible for the conversion of T_4 to T_3. Such a mechanism could explain the changes in T_4, T_3, rT_3, and TSH levels reported following exposure to CF_3I. The resulting decrease in T_3 could lead to a loss of negative inhibition and a subsequent increase in TSH and T_4, with the excess T_4 partially converted to rT_3.

Dosimetric Adjustments and Uncertainty Factors

It is important to note that a NOEAL for thyroid effects was not observed in the study [1], therefore the calculation of the TWA OEL was performed using a dosimetric adjusted LOAEL. The LOAEL was dosimetrically adjusted to account for an exposure duration of 6 hrs/day instead of the normal 8-hr occupational exposure (2000 ppm x 6 hr/8 hr = 1500 ppm). This adjustment is important, because thyroid toxicity is likely related to the total amount of iodine released by CF_3I metabolism (the area under the curve of the metabolite). No adjustment was made for days/week, because the exposure of interest (occupational) is also 5 days/wk.

The rat appears to be a highly sensitive species for chemicals that cause disruption of thyroid hormone levels, due to an approximate IO-fold slower clearance of T_3 and T_4 compared to the human [9]. Levels of 5'-deiodinase inhibition that cause marked effects in the rat may not cause adverse effects in the human, because the slower turnover in the human allows for a physio-

logical "buffer," making it easier for humans to maintain normal physiological levels of T_3. Therefore. the indirect mechanism by which CF_3I acts would only be active in humans following exposure to concentrations higher than those to which the rats were exposed, making the rats much more sensitive than humans. Thus, an uncertainty factor of 1 was applied for extrapolation from animals to humans.

The default animal-to-human uncertainty factor of 3 for differences in pharmacokinetics was not applied because the rat is more sensitive than the human. Similarly. because the thyroid effects are unlikely to occur in humans, except at very high exposure concentrations. a factor of 3, riithcr than 10, was applied for the use of a LOAEL. A factor of 3 was applied to consider sensitive individuals, rather than a full factor of 10, due to the "healthy worker effect": the most sensitive members of the population are not included in the working population. However, a factor of 3 was retained because the working population may contain people with under- or overactive thyroids, who would exhibit increased sensitivity to the potential thyroid effects *of* CF_3I. An overall uncertainty factor of about 10 (1 by 3 by **3** ≈ 10) was applied yielding a TWA OEL of 150 ppm (1500 ppm/10 = 150 ppm).

Justification for the Time-Weighted Average Rased on Reproductive Effects

Potential reproductive effects associatcd with exposures to CF_3I have been evaluated by Dodd et al. [1] and to a limited extent by Kinkead et al. [3]. The reproductive toxicity study conducted by Dodd et al. [1] suggested that no treatment-related effects resulted from subchronic exposure to CF_3I with regard to male reproduction parameters, such as changes in mating index. fecundity index, fertility index, and gross and histological lesions.

In the study by Dodd et al. [1], male and female rats were exposed in whole body inhalation chambers to 0.0, 0.2. 0.7, and 2.0% CF_3I, ***6*** hrs/day, *5* days/wk for 30 days prior to mating. It is generally customary to expose rats 7 days/wk for ***a*** minimum *of* 70 days prior to mating because spermatogenesis occurs over a period of 48-53 days in the rat. It could, therefore, be argued that the test protocol was inadequate for the assessment of any potential effect on the early stages *of* spermatogenesis: however. based upon the data it is unlikely that any effects were produced in the later stages *of* sperm development. Furthermore. there were no differences in testicular weights or histological observations in any of the high-dose males when compared to the control animals at the 14-week necropsy. These data suggest that under the conditions of this study, there was no evidence of a treatment-related effect on the testes.

Thc reproductive study conducted by Dodd et al. [1] did appear to assess female fertility and prenatal development accurately. Starting with gestation day 0, and continuing throughout the remainder of the study, rats were exposed **6** hrs/day, 7 days/wk. The authors reported no statistically significant differences between control and treated groups in mcan number of pups/ litter, pups with gross lesions. live birth index, or pup survival index for 4, 7. 14, and 21 days post-parturition. A significant decrease in the sex ratio (male pups/litter) for litters from dams receiving 2.0% CF_3I was observed. However, a consistent dose-response for this effect was not evident (the pup sex ratio was 0.99, 0.79, 1.07 and 0.68 for the control, low-, mid- and high-concentration groups, respectively), and this effect was not associated with a statistically significant positive trend. The toxicological significance of this effect is questionable. Additionally, Dodd et al. [1] reported a treatment-related decrease in absolute and relative ovary weights in the

14-wk sacrifice group. Kinkead et al. [3], however, reported no significant difference in ovary weights between control and treated groups.

Dosimetric Adjustments and Uncertainty Factors

Because the uncertainty factors used in deriving a TWA OEL based on thyroid effects were reduced from the default values. a TWA OEL based on reproductive effects observed in rats at higher concentrations than those of the thyroid effects was calculated for comparison. The NOAEL for the reproductive effects reported by Dodd et al. [1] was found to be 0.7% (7000 ppm). To derive an OEL based on these reproductive effects, the NOAEL would be adjusted from a 6 hr/day exposure to occupational exposures (8 hr/day) resulting in a NOAEL [HEC] of 5250 ppm (7000 ppm by 6 hrs/8 hrs). An uncertainty factor of 3 would be applied for extrapolation from animals to humans. An additional uncertainty factor of 10 would be applied in consideration of human variability resulting in a total uncertainty factor of 30. Application of the total uncertainty factor to the NOAEL [HEC] (5250 ppm/30) results in a recommended OEL of 175 ppm, a value that is slightly higher than the TWA OEL based on the thyroid effects, thus the thyroid-based TWA would be protective of both the thyroid and reproductive effects.

Basis *for the* Ceiling Value

The ceiling level is set based on the cardiac sensitization **(CS)** results. The cardiac sensitization study is summarized below along with the dosimetric and uncertainty factor considerations.

Endpoint:	Cardiac sensitization
Study:	Cardiac Sensitization in Dogs [2]
Protocol:	Standard epinephrine challenge, 9 animals
Concentrations:	0.1, 0.2, 0.4, and 1.0% (100, 200, 400, and 1000 ppm)
NOAEL:	0.2%
LOAEL:	0.4%
NOAEL [adj]:	2000 ppm
NOAEL [HEC]:	2000 ppm
Uncertainty/Modifying Factors:	None

The cardiac sensitization (CS) potential of CF_3I was assessed by Kenny et al. [2], and published by Dodd and Vinegar [10]. The **CS** study was divided into three stages and was conducted according to the experimental procedure described by Reinhardt and company (1971). Briefly, experiments lasted for 17 min/dog with dogs receiving an initial challenge dose of adrenalin at 2 min, followed by exposure to the test substance via inhalation starting at 7 min, then dogs received a second challenge dose of adrenalin at 12 min, and lastly, discontinuation of the test substance at 17 min. The first stage of the study was involved in establishing the response of each dog to varying concentrations of adrenaline. A positive response in Stage 1 was defined as an increase in heart rate, followed by a decrease in heart rate and an increase in the height of the T-wave on the ECG. The doses of adrenalin to be administered to each dog in Stages 2 and 3 were determined using the results from Stage 1. The second stage of the study served as a positive control for the experimental protocol. In Stage 2, two beagle dogs were exposed to CFC-11, a known cardiac sensitizer. The positive result was defined as the appearance of a burst of multifocal ventricular ectopic activity or ventricular fibrillation. Stage 3 of the study involved exposing the dogs to increasing concentrations of CF_3I.

All dogs produced negative results when exposed to concentrations of 0.1 and 0.2% CF_3I. One dog produced a positive result and died of ventricular fibrillation when exposed to 0.4%. and one dog produced a positive result and died of ventricular fibrillation when exposed to 1.0%. Exposure of subsequent dogs at concentrations that produced positive results and death were not performed based upon humane considerations.

The results observed in the CF_3I CS study were similar to results observed in studies investigating CS for Freon 11 and Halon 1211. The LOAEL for CF_3I based on CS was established as 0.4%. Likewise, the LOAEL for Freon 11 based upon CS is 0.35%. and the LOAEL for Halon 1211 based upon CS is 1.0%. It is important to note that all the dogs that died in the CF_3I CS study received the highest doses of adrenaline. At least one review article suggests that the dose of adrenalin administered may determine the sensitivity of studies investigating CS. For example, a relatively low dose of 5 µg/kg adrenaline was used in the study investigating CS for Halon 1211. If higher doses of adrenaline were used in the Halon 1211 study, a lower LOAEL would likely have resulted for Halon 1211. Conversely. if the study investigating the CS potential for CF_3I would have used a lower dose of adrenalin, then it is likely that the LOAEL for CF_3I would have been higher.

Because the cardiac sensitization test is considered highly conservative, no uncertainty factors are needed to calculate the human equivalency concentration. In addition, recent studies with CF_3I in unchallenged dogs show that without added adrenaline. these animals can withstand 5% CF_3I without adverse cardiac effects [10]. Therefore, the NOEAL of 2000 ppm is used to establish the ceiling OEL for CF_3I.

OTHER CONSIDERATIONS FOR THE OEL

Evidence of Carcinogenic Potential

Although genotoxicity tests are not used directly in the establishment of OELs, these tests do provide useful indicators of the potential mutagenic effects of a chemical. The potential mutagenicity and genotoxicity of CF_3I have been evaluated in bone marrow micronucleus assays in mice [4] and rats [1.31, the Ames reverse mutation assay [5] and mouse lymphoma forward mutation assay [6]. Mitchell [4] conducted a bone marrow micronucleus assay where male and female mice were exposed to 0, 2.5, 5 or 7.4% CF_3I (0, 25,000, 50,000 or 74,000 ppm) via nose-only inhalation, 6 hrs/day for 3 consecutive days. Statistically significant concentration-related increases in micronucleus frequency (micronuclei/1000 polychromatic erythrocytes) were reported in the mid- and high-concentration male and female mice. In addition, statistically significant concentration-related decreases in the ratio of PCE/1000 erythrocytes were reported at **all** exposure concentrations in female mice.

A bone-marrow micronucleus induction assay was also performed as part of a 13-week nose-only inhalation study where rats were exposed to 0, 2.4. and 8% (0, 20,000, 40,000 and 80.000 ppm) CF_3I for 2 hrs/day, 5 days/wk for 4 or 13 weeks [3]. After 4 weeks of exposure, concentration-related increases in micronucleus frequency were observed in the mid- and high-concentration males and females. with statistically significant positive trends reported for each **sex.** Concentration-related decreases in polychromatic erythrocyte/normochromatic erythrocyte (PCE/NCE) ratios, an indicator of hone marrow toxicity, were observed in all treated males and females and statistically significant trends were reported. After 90 days of exposure. concentration-related

increases in micronucleus frequency and decreases in PCE/NCE ratios were observed in all treated groups, with statistically significant trends also reported for each endpoint. However, in a study by Dodd et al. [1] where male and female rats were exposed to 0, 0.2, 0.7 or 2.0% CF_3I (0, 2000, 7000 or 20,000 ppm) via whole-body inhalation for 7 or 14 weeks, there were no statistically significant changes in micronuclei frequency or in PCE/NCE ratios.

Because the results of these genotoxicity screening tests were mixed, there is an indication that CF_3I might produce mutagenic or carcinogenic effects. Nevertheless, it would be premature *to* assume that, based on the results of these genotoxicity tests, CF_3I is a carcinogen. An accurate assessment of the potential carcinogenicity of CF_3I would require data from a two-year bioassay. However, given the proposed uses of the material as a fire suppressant, exposures (apart from manufacturing) would be rare. or at least infrequent, rather than chronic. Thus, even if CF_3I were found to have a relatively high carcinogenic potency, which appears unlikely given the dose-response for the micronucleus assays, such infrequent exposures would not result in a significant cumulative lifetime risk of carcinogenic effects. Therefore, a general conclusion that CF_3I should not be used as a fire suppressant based on its possible genotoxicity would not be appropriate.

APPLYING OELS

As is the case with all potential chemical exposures, it is the duty of industrial hygienist and chemical safety officers to protect the health of their workers by limiting exposure to chemicals. Safety professionals limit exposure by using common sense. good practice industrial hygiene procedures such as ventilation, or engineering controls.

To determine the safe use of a chemical, the safety professional compares the concentration at which personnel might be exposed to the acceptable exposure limit or OEL. In the case of potential repeated, long-term exposures as might he experienced during the manufacturing process and during cylinder or extinguisher filling for CF_3I, the TWA OEL is compared to measured or predicted exposure concentrations in the workplace. For example, at one extinguisher filling plant, typical exposure concentrations range between 22 and 67 ppm, well below the TWA OEL of 150 ppm.

The TWA OEL is not applicable to firefighting situations. In total-flooding applications, CF_3I is designed to be used in "not normally occupied" applications; thus personnel would not be exposed during firefighting situations. In streaming applications, the manual direction of the stream helps limit the exposure of personnel. Residual breathing zone firefighter measurements of CF_3I in a number of handheld trails using 2.5 to 13-pound extinguishers indicates that a firefighter might be exposed to concentrations ranging between 6 and 1700 ppm, again below the acceptable ceiling OEL.

CONCLUSIONS

An adequate database of toxicological testing exists to assess the hazards associated with exposure to CF_3I adequately. Although additional tests would be useful to characterize more fully the mechanism of action and explore certain toxicological findings, the results of these additional tests would not likely change the OELs that have been established. Based on these

findings and the comparison of likely exposure concentrations in various scenarios with the recommended OEL. it is concluded that CF_3I can be used safely for firefighting purposes in "not normally occupied" areas and for streaming purposcs given that common sense, good practice industrial hygiene procedures are followed.

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