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Recommendation of an Occupational Exposure Level for Perfluoro-N-Butyl Iodide

Darol E. Dodd
CIIT Centers for Health Research
Six Davis Drive
P.O. Box 12137
Research Triangle Park NC 22709

Peter J. John
University of Dayton Research Institute (UDRI)
800 College Park
Dayton, OH 45469-0168

Gary M. Hoffman
Huntingdon Life Sciences
100 Mettiers Road
East Millstone NJ 08875

David R. Mattie
AFRL/HEPB
2729 R Street, Bldg 837, Area B
Wright-Patterson AFB OH 45433-5707

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Air Force Research Laboratory
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FOR THE DIRECTOR

//SIGNED//

MARK M. HOFFMAN
Deputy Chief, Biosciences and Protection Division
Air Force Research Laboratory

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*Darol E. Dodd, **Peter J. John, ***Gary M. Hoffman, ****David R. Mattie

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*CIIT Centers for Health Research, Six Davis Dr,P.O. Box 12137,Research Triangle Park NC 27709
**Univ of Dayton Research Inst (UDRI),800 College Park,Dayton OH 45469-0168
***Huntingdon Life Sciences,100 Mettlers Road, East Millstone NJ 088875

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14. ABSTRACT

Perfluoro-n-butyl iodide (PFBI) is a promising alternative to chlorofluorocarbon solvents used in aircraft ground maintenance operations and other military and commercial operations, because it cleans well, has zero ozone depletion potential and has extremely low global warming properties. The purpose of this technical report was to summarize the toxicity profile of PFBI and propose an occupational exposure level (OEL) for PFBI. Toxicity tests were performed with PFBI to determine and evaluate its health hazard. Results of these investigations were summarized, and lowest-observed-adverse-effect-levels (LOAELs) and no-observed-adverse-effect-levels (NOAELs) were identified. Dosimetric adjustments for daily exposure time and uncertainty factors were selected, discussed, and applied to provide a basis for the proposed OEL. For acute (single event) exposure, a ceiling OEL of 3,900 ppm PFBI was proposed. For repeated exposure, an 8-hr time weighted average of 40 ppm PFBI was proposed.

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PREFACE

This document is a final report in response to University of Dayton Research Institute (UDRI, Dayton, OH) Request for Proposal No. SC305 (Purchase Order R0602522). The Statement of Work was to assess the health hazards of the Freon replacement solvent, perfluoro-n-butyl iodide (PFBI) and to propose occupational exposure limits for this material. The technical point of contact at UDRI was Dr. Peter John. The technical point of contact at CIIT Centers for Health Research was Dr. Darol E. Dodd (formerly at Alion Sciences and Technology, Dayton, OH). Contract and programmatic oversight was provided by Ed C. Snyder and Lois J. Gschwender, of AFRL/MLBT at Wright-Patterson Air Force Base (WPAFB), OH.

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LIST OF ACRONYMS

μg	microgram(s)
AEL	Acceptable Exposure Limit
ALKP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CAS	Chemical Abstracts Service
CF_3I	trifluoroiodomethane
CFC	chlorofluorocarbon
CFR	Code of Federal Regulations
d	day(s)
ECG	electrocardiogram
EPA	U.S. Environmental Protection Agency
HJF	Henry M. Jackson Foundation for the Advancement of Military Medicine
HLS	Huntingdon Life Sciences
hr	hour(s)
iv	intravenous
kg	kilogram(s)
LC_{50}	lethal concentration affecting 50% of the test species
LOAEL	Lowest Observed Adverse Effect Level
min	minutes(s)
mL	milliliter(s)
NOAEL	No Observed Adverse Effect Level
OECD	Organization for Economic Cooperation and Development
OEL	Occupational Exposure Level
OPPTS	Office of Prevention, Pesticides and Toxic Substances (U.S. EPA)
PFBI	perfluoro-n-butyl iodide
ppm	parts per million
SBIR	Small Business Innovative Research
SNAP	Significant New Alternatives Policy
T_3	triiodothyronine
T_4	thyroxine
TSH	thyroid stimulating hormone, thyrotropin
TWA	Time Weighted Average
UDRI	University of Dayton Research Institute
UNEP	United Nations Environment Programme
UF	uncertainty factor
wk	week(s)
WPAFB	Wright-Patterson Air Force Base

INTRODUCTION

The Montreal Protocol agreements initiated in 1987 continue to be the regulatory driver for finding suitable substitutes for currently-used and globally-distributed chlorofluorocarbons (CFCs) (UNEP, 2000). Perfluoro-n-butyl iodide (PFBI), CAS# 423-39-2, is a liquid at room temperature with a boiling point of 67ºC and a vapor pressure of 143 Torr at 20ºC. It is one of several fluoroiodocarbons being considered as a replacement for CFCs in aircraft ground maintenance operations and other military and commercial operations (Glass *et al.*, 1999). Specifically, PFBI is being evaluated as an alternative cleaner for critical liquid and gaseous oxygen aerospace systems. Cleaning studies conducted by the Air Force have shown PFBI to be a superior wipe solvent cleaner. In addition to its performance, compatibility (e.g., reactivity) with existing aerospace systems, and environmental effects, the toxicity potential of PFBI must be assessed before PFBI can be considered to be a desirable replacement candidate.

There are limited citations in the public domain that investigate the toxicity of fluoroiodocarbons. One example is a series of studies with trifluoroiodomethane; a replacement candidate for trifluorobromomethane (Halon 1301) conducted by Dodd and Vinegar (1998) and Dodd *et al.* (1997a; 1997b; 1999). The U.S. Air Force initiated the effort to evaluate PFBI toxicity by requesting and subsequently funding small business innovative research (SBIR) proposals to investigate the development of nonflammable, environmentally compliant (i.e., negligible ozone depletion potential, low global warming potential, and low toxicity) fluoroiodocarbon solvents. Under the U.S. Clean Air Act of 1990, the U.S. Environmental Protection Agency's Significant New Alternatives Policy (SNAP) program makes decisions on the end-use (e.g., household refrigerators) within a sector (e.g., refrigeration and air conditioning) of proposed CFC substitutes. The SNAP program has evaluation criteria for making decisions on health and safety, environmental impact, efficacy, and market potential. Included in the SNAP health hazard evaluation criteria is information on a substitute's acute toxicity, including cardiac sensitization potential (primarily for halogenated hydrocarbons), genotoxicity, and subchronic toxicity (U.S. EPA, 2006). Preliminary ecotoxicity studies (acute toxicity to *Daphnia magna* and fathead minnow) were performed with PFBI (Bell *et al.*, 1996a; 1996b).

The purpose of this technical report was to assess the health hazard potential of PFBI and to propose an occupational exposure level (OEL) for PFBI. The proposed OEL is to assure the safety of occupational workers during the transport and use of PFBI for routine daily operations.

APPROACH

The health hazard assessment of PFBI followed, in general, the U.S. Environmental Protection Agency (EPA) guidelines for assessing risk of health effects other than cancer and gene mutations from chronic chemical exposure (U.S. EPA, 1987). Additional EPA documents of value were Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994) and A Review of the Reference Dose and Reference Concentration Processes (U.S. EPA, 2002).

Toxicity tests were performed with PFBI to evaluate its health hazard. Using standard testing guidelines (e.g., Organization for Economic Cooperation and Development; OECD, 1981a, 1981b, 1981c, 1983a, 1983b, 1983c, 1992), tests included acute (4-hr), 4-week (6 hr/d, 5 d/wk), and 13-week (6 hr/d, 5 d/wk) inhalation (nose-only) toxicity studies in rats, an acute (10-min) inhalation cardiac sensitization study in dogs, *in vitro* chromosomal aberrations experiments in human lymphocytes, and *in vitro* mutagenic experiments in *Salmonella typhimurium* and

Escherichia coli. Details of materials, methods, and results are available (Dodd *et al.*, 2004; Mattie *et al.*, 2006; Narayanan and Mattie, 2006).

In this document, results of these investigations were summarized, and lowest-observed-adverse-effect-levels (LOAELs) and no-observed-adverse-effect-levels (NOAELs) were identified. Dosimetric adjustments for human equivalent dose and uncertainty factors were selected, discussed, and applied to provide a basis for the proposed acute (ceiling value) and chronic (8-hr time-weighted average (TWA)) OELs. Proposed OELs were compared with EPA-derived Acceptable Exposure Limits (AELs) of another iodofluorocarbon, trifluoroiodomethane.

TOXICITY PROFILE

Six toxicity studies were conducted.

- Acute (4-hr) inhalation toxicity study in rats
- Acute (10-min) cardiac sensitization study in dogs
- *In vitro* genotoxicity studies:
    - *Salmonella typhimurium* and *Escherichia coli* mutagenicity
    - Chromosomal aberration in human lymphocytes
- 4-Week inhalation toxicity study in rats
- 13-Week inhalation toxicity study in rats plus 4-week recovery period

All animal studies were conducted by Huntingdon Life Sciences (HLS) at their Testing Facility in East Millstone, NJ, or at Huntingdon Life Sciences Ltd., Cambridgeshire, England. Acceptable practices of good animal husbandry were followed (National Research Council, 1996; *United Kingdom Home Office Code of Practice for Housing and Care of Animals Used in Scientific Procedures*) and principles of Good Laboratory Practice (GLP) were followed. More complete details of materials, methods, and results are available (Dodd *et al.*, 2004; Mattie *et al.*, 2006; Narayanan and Mattie, 2006).

Acute Inhalation Toxicity and Cardiac Sensitization Results

Mean analytical exposure concentrations for the acute (4-hr) inhalation toxicity study in 5 male and 5 female rats were 10,000, 20,000, 35,000 and 100,000 ppm PFBI. No aerosol formation of PFBI was detected during any exposure. Exposure concentrations ≥ 20,000 ppm PFBI resulted in 100% mortality prior to the completion of the 4-hr exposure period. No rats died following the 10,000 ppm exposure. Signs of treatment during or immediately following exposure included secretory and respiratory responses (clear or red nasal discharge, chromodacryorrhea and labored breathing). Recovery from these effects was observed within two days post exposure. Surviving animals gained body weight normally, as compared to control animals, and there were no macroscopic abnormalities in tissues examined at necropsy. The 4-hr LC_{50} (95% confidence limits) for the combined sexes was 14,000 ppm (13,000 ppm – 16,000 ppm) (Dodd *et al.*, 2004).

Mean analytical concentrations for the 10-min exposures in the cardiac sensitization study were 900, 3,900 and 6,200 ppm PFBI. Individual responses to epinephrine alone were selected for each dog prior to the testing regimen for the purpose of establishing an epinephrine dose at which there was a clear but minimal effect on the electrocardiogram (ECG), ideally with a few ectopic beats. The range of iv doses used was 2 to 12 µg epinephrine per kg body weight. There were no indications of cardiac sensitization to epinephrine at 900 and 3,900 ppm PFBI.

At 6,200 ppm, two dogs responded positively. One dog responded with a burst of consecutive unifocal beats approximately three seconds after the second epinephrine challenge. A second dog responded with two bursts of unifocal ectopic activity. The first burst occurred approximately 14 seconds after the second challenge, and the second burst occurred six seconds later. Clinical signs observed in some dogs, but not all dogs exposed to PFBI included salivation, limb and/or muscle tension, and non-specific signs of agitation. These results indicate that the cardiac sensitization LOAEL for PFBI is 6,200 ppm and the NOAEL is 3,900 ppm (Dodd *et al.*, 2004).

Genotoxicity Results

In the preliminary toxicity test using four strains of *Salmonella typhimurium* (TA 98, TA 100, TA 1535 and TA 1537) and one strain of *Escherichia coli* (WP2 *uvr*A), PFBI was not toxic towards any tester strain. Thus 5000 µg PFBI/plate was chosen as the highest dose level for the mutation test. No substantial increases in revertant colony numbers of any of the bacterial strains were observed following PFBI treatment at any dose level, in the absence or presence of S-9 (prepared rat liver fraction of stimulated mixed function oxidase system). Concurrent positive control compounds demonstrated the sensitivity of the assay and the metabolizing activity of the S-9 preparations (Dodd *et al.*, 2004).

In the preliminary toxicity assessment using human lymphocytes, PFBI was highly toxic at concentrations ≥ 625 µg/mL in the absence of S-9. Dose levels of 39 to 200 µg/mL were selected for metaphase analysis where 39 µg/mL was the highest non-toxic concentration. In the presence of S-9, PFBI was highly toxic at 313 µg/mL. Dose levels of 78 to 263 µg/mL were selected for metaphase analysis in experiments using S-9. No statistically significant increases were observed in the proportion of aberrant cells treated with PFBI compared to the solvent control cultures in the absence or presence of S-9. Positive control compounds caused large statistically significant increases in the proportion of aberrant cells, demonstrating the efficacy of the S-9 fraction and the sensitivity of the test system (Dodd *et al.*, 2004).

Repeated Inhalation Toxicity Results

4-Week Inhalation Study

The mean analytical concentrations for the four PFBI exposure groups were 0 (control), 102, 997 and 10,000 ppm. There was no PFBI aerosol formation during PFBI exposures. There was no mortality during the four weeks of study, and the only clinical sign of treatment was reduced activity during exposure in rats of the 10,000 ppm group. Body weight gain was reduced significantly in male rats only of the 10,000 ppm group. Food consumption was not different between control and PFBI exposed groups (Dodd *et al.*, 2004).

Results of blood sampling indicated mean hematology values were similar between all study groups. Except for triglycerides and thyroxine (T_4) levels, all other serum chemistries were either similar for all study groups or the changes observed were not related to PFBI exposure in a dose-dependent manner. Serum triglycerides increased significantly in a concentration-related manner in male rats of the 1,000 and 10,000 ppm groups and in female rats of the 10,000 ppm group. The increase in triglycerides was approximately two-fold greater in rats of the 10,000 ppm group compared to control rats. Levels of total T_4 increased in PFBI-exposed

rats, but levels of thyroid stimulating hormone (TSH) and total triiodothyronine (T_3) in PFBI-exposed rats were not statistically significantly different from control values. The increase in serum T_4 was approximately three-fold greater in male rats of the 1,000 and 10,000 ppm groups compared to control males. In female rats of the 1,000 and 10,000 ppm groups, the increase in serum T_4 was approximately two-fold greater than control values (Dodd *et al.*, 2004).

Urine iodide levels were increased in male rats of the 1,000 ppm group and in male and female rats of the 10,000 ppm group. A large variation in urine iodide levels in some groups was attributed to one or two rats having high values, but all values measured were within an acceptable range per the laboratory's experience (Dodd *et al.*, 2004). Urinary iodide levels and thyroid hormone levels were consistent with iodine administration. Although PFBI was not measured in blood or urine, the increased iodide in the urine indicated that metabolism of PFBI occurred, resulting in a release of iodide.

Mean absolute organ weights were similar between control and PFBI-exposed rats, except for the 17% increase in liver weights of the 10,000 ppm female rats compared to liver weights of control females. There were no treatment related findings during gross necropsy. The only treatment related microscopic finding was hypertrophy/hyperplasia of goblet cells in the respiratory mucosa of the nasal septum (anterior region) in male and female rats of the 10,000 ppm PFBI group. The severity of this lesion was graded as minimal in all cases (Dodd *et al.*, 2004).

13-Week Inhalation Study Plus 4-Week Recovery Period

The experimental design of the 13-week inhalation study (6 hr/d, 5 d/wk for at least 65 exposures) included a 4-week recovery period (male rats only). The mean analytical concentrations for the four PFBI exposure groups were 0 (control), 500, 1,489 and 4,931 ppm. There was no PFBI aerosol formation during PFBI exposures. Except for an accidental death of one control male rat, there was no mortality during the 13 weeks of exposure and 4 weeks of recovery. The only clinical sign of treatment was an increase in ano-genital staining in rats of the 5,000 ppm group. Absolute body weight was reduced in male rats only of the 5,000 ppm group. Recovery of ano-genital staining and body weight reduction was observed in males of the 4-week recovery period. Food consumption was not different between control and PFBI exposed groups. There were no PFBI-related effects on functional observational battery parameters or on motor activity (Mattie *et al.*, 2006).

Slight, non-dose related differences in group means were observed for a few hematologic parameters, but these changes were not considered to be PFBI exposure related. Decreases (approximately 20%) in serum AST/ALT and/or ALKP were observed in all PFBI-exposed groups, and a 12% increase in serum phosphorus was observed in ≥ 500 ppm male rats and ≥ 1,500 ppm female rats. Other statistically significant differences in glucose, BUN, creatinine, and cholesterol were observed in one sex only and the magnitude of the changes were considered slight (Mattie *et al.*, 2006).

None of the observed statistically significant organ weight changes were associated with histopathological correlates; these included increased kidney weights in the ≥1500 females and decreased spleen weight in the 5000 ppm males. Increased adrenal weights at ≥1500 ppm (both sexes) with decreased thymic weight in the 5000 ppm males were indicative of stress while the effect on the accessory sex glands in males at 5000 ppm were considered secondary

to decreased body weight. Most or all of the above differences were not apparent at the end of the 4-week recovery period (only male rats evaluated) (Mattie *et al.*, 2006).

The primary tissue affected following 13 weeks of inhalation exposure of PFBI to rats was the thyroid. The findings consisted of a minimal thyroid follicular cell hypertrophy occasionally accompanied by hyperplasia but without an increase in thyroid weight in the 500, 1500 and 5000 ppm males; only one 5000 ppm female had similar histopathological thyroid changes. At ≥500 ppm, there were also increased TSH levels in female rats only and increased total T_3 and T_4 in animals of both sexes. All observed effects in the thyroid resolved following a 4-week recovery period (only male rats evaluated) (Narayanan and Mattie, 2006).

LOAEL/NOAEL for Repeated Exposure of PFBI

Results from the 4- and 13-week repeated exposure studies were evaluated in total to assess differences and similarities in exposure-response findings. For example, effects observed in the 4-week study at 10,000 ppm PFBI, but not observed in the 13-week study at 5,000 ppm (highest concentration tested) included the following: reduction in animal activity, an increase in serum triglycerides, an increase in liver weight (females only), and minimal hypertrophy/hyperplasia in respiratory mucosa of the nasal region. Thus, these effects appear to be dependent more on the concentration of PFBI and not duration of exposure. Effects observed in both the 4- and 13-week studies at the highest PFBI concentrations tested in each study were a reduction in body weight or body weight gain (male rats only in both studies) and an increase in T_4. Effects observed in the 13-week study, but not in the 4-week study, included the following: minimal thyroid follicular cell hypertrophy; increases in T_3, TSH (females only), phosphorus, adrenal weights and kidney weights (females only); decreases in AST, ALT and ALKP; and, in male rats only, decreases in the weights of spleen, thymus and accessory sex glands. However, all effects observed in the 13-week study resolved following a 4-week recovery period (male rats only were evaluated) (Mattie *et al.*, 2006).

In both repeated exposure studies, body weight reduction was observed in male rats exposed to ≥ 5,000 ppm PFBI. This finding, combined with other observed changes in biological endpoints (described above), suggest mild toxicity at ≥ 5,000 ppm PFBI. The observation of mild organ weight changes (adrenals and kidneys) in rats of the 1,500 ppm group of the 13-week study were indicative of stress over and beyond changes observed in the target tissue (thyroid). However, there was no histopathology observed in these tissues in rats exposed to either 1,500 ppm or 5,000 ppm. Further, the organ weight changes were not consistent for both sexes (kidney weights) and were reversible following 4 weeks recovery (male rats only were evaluated). At PFBI concentrations below 5,000 ppm, the only consistent changes of potential biological importance were those related to the thyroid. A specific effect of PFBI on the thyroid was anticipated, since the thyroid is sensitive to compounds that interfere with iodine absorption, distribution, metabolism and elimination (Mattie *et al.*, 2006).

There is considerable scientific debate on interpreting the biological impact of changes in circulating levels of TSH, T_4 and T_3. Furthermore, extrapolating thyroid hormone results in animal studies to adverse effects in humans is controversial. This debate has been especially active for the chemical perchlorate, an inhibitor of iodine uptake. It is interesting to note that an Expert Review Panel of the Perchlorate State of the Science Symposium 2003 considered,

> "…*developmental deficits or delays, and goiter and other effects of frank hypothyroid condition to be adverse effects. Subnormal concentrations of circulating thyroxin (T_4) and tri-iodothyronine (T_3) or supernormal concentrations of circulating thyrotropin (TSH)*

are considered to be adaptive. Iodide uptake inhibition and increased perchlorate excretion may be considered pre-adaptive." (University of Nebraska Medical Center, 2003)

At this time, the author's preliminary conclusion is that observed increases in serum thyroid hormones and in the incidence of minimal thyroid follicular cell hypertrophy (male rats only without an increase in thyroid weight) in PFBI-exposed rats are considered to be adaptive responses and not adverse effects. Thus, the NOAEL for PFBI was selected to be 1,500 ppm, since this was the highest concentration in the 13-week study that showed no adverse effects. This selection is further supported by the results of the 4-week study where 1,000 ppm PFBI was the highest concentration that showed no adverse effects.

PROPOSED OCCUPATIONAL EXPOSURE LEVEL (OEL)

The results of the PFBI studies summarized above indicate a low order of acute toxicity, as defined by EPA's Toxicity Categories (U.S. EPA, 1998) and the Department of Transportation's toxicity categories for assigning hazardous materials to hazard zones and packing groups (49 CFR 173.133, 2001). However, for chemicals that illicit cardiac sensitization, the results of the dog cardiac sensitization (to epinephrine) test become, in general, the most critical endpoint to consider for assessing acute health hazard. For PFBI, the LOAEL for cardiac sensitization was 6,200 ppm and the NOAEL was 3,900 ppm. Uncertainty factors (e.g., species extrapolation and sensitive populations) are not generally applied to results from the dog cardiac sensitization test, because of the conservative nature of the test by design (Snyder *et al.* 1997). Thus, the NOAEL value of 3,900 ppm may be considered a justifiable acute exposure limit concentration for PFBI.

The genotoxicity results observed following PFBI treatment indicated an absence of mutagenicity and clastogenicity. These results are only part of a battery of tests performed to evaluate a chemical's potential for tumorigenicity. Therefore, though inconclusive, these results provide confidence that PFBI is not tumorigenic by direct acting genotoxic mechanisms.

As discussed above, for repeated exposure, a NOAEL of 1,500 ppm PFBI was selected. This concentration was derived from the 13-week inhalation study with a 6 hr/day exposure design. A dosimetric adjustment for daily exposure time in an occupational setting (8 hr/day) was applied to yield an exposure adjusted NOAEL of 1,125 ppm. The following uncertainty factors (UFs) were considered: animal to human extrapolation, interhuman variability, subchronic to chronic duration, and strength of database.

Animal to human extrapolation

In general, a default factor of 10 is used to allow for uncertainty of animal to human extrapolation of biological effects. Further, the factor of 10 is divided into a toxicodynamic component (factor of 3) and a toxicokinetic component (factor of 3), such that the two combined approximates 10 ($3 \times 3 \approx 10$). A toxicodynamic factor of 3 was selected to account for differences in sensitivity between species. No information is available on the toxicokinetics of PFBI, but data are available for another similar perfluoroiodocarbon, trifluoroiodomethane (CF_3I). Results of kinetic studies with CF_3I (Williams *et al.*, 1994) showed that the human blood:air partition coefficient was smaller than the rat blood:air partition. This relationship is likely to be the same for PFBI, because of similar physico-chemical properties of these

chemicals. Thus, an uncertainty factor of 1 was selected for the toxicokinetics component of the animal to human extrapolation, resulting in a combined default factor of 3 (3 x 1 = 3).

Interhuman variability

Similar to the uncertainty of animal to human extrapolation, a default factor of 10 is used to allow for interhuman variability. A major component of the uncertainty associated within the human population is susceptibility, i.e., is the existing database robust enough to represent exposure-response relationships between all individuals? However, the occupational workforce is considered to be healthy and age-specific. This consideration eliminates the concerns of susceptibility due to illness, disease or age (e.g., children, elderly). Since specific relevant data are not available, a factor of 3 was selected to account for variations in sensitivity to PFBI within occupational workers.

Subchronic to chronic duration

Results of the 4-week and 13-week subchronic studies indicated that concentration of PFBI appeared to be more significant than duration of exposure for producing toxicity. Also, effects observed in the 13-week study were reversed within 4 weeks further suggesting that effects were concentration-dependent. Since information is not available on long-term toxicity studies with PFBI, a factor of 3 was selected to address this uncertainty.

Strength of database

To-date, the toxicity profile is lacking specific information on potential effects of PFBI on reproductive function and/or developmental biology. However, there were no lesions observed in reproductive organs of mature rats exposed to PFBI at concentrations of 5,000 ppm for 13-weeks or 10,000 ppm for 4-weeks. In addition, CF_3I, a similar chemical to PFBI, was not considered a reproductive toxicant. On the basis of this information, the strength of the database was considered satisfactory, and an additional uncertainty factor was not selected.

Application of uncertainty factors

Uncertainty factors for animal to human extrapolation (3), interhuman variability (3), and subchronic to chronic duration (3) were combined to given a total uncertainty factor of approximately 30. This factor was then applied to the NOAEL adjusted for daily exposure (1125 ppm) to derive an 8-hr time weighted average (TWA) of 40 ppm (rounded off). The recommended occupational exposure limit for repeated exposure to PFBI is 40 ppm.

COMPARISON OF PROPOSED OEL FOR PFBI WITH AEL OF TRIFLUOROIODOMETHANE

There are limited toxicity data on perfluoroiodocarbons, because they are not produced as commercial products. One fluoroiodocarbon for which published toxicity data exist is trifluoroiodomethane (CF_3I), a replacement candidate for CF_3Br (Halon 1301). Unlike PFBI, CF_3I has a boiling point of -22.5ºC and exists as a vapor at room temperature. Table 1 compares results of toxicity studies on PFBI reported here with results of toxicity studies reported by other investigators using CF_3I (Dodd and Vinegar, 1998; Dodd *et al.* 1997a, 1997b, 1999).

In rats, CF_3I was less toxic than PFBI following single 4-hr exposures, but was comparable with PFBI in producing cardiac sensitization in dogs. The criteria for LOAEL and NOAEL in the cardiac sensitization test were the same for both chemicals, and the tests were run in the same laboratory. Both CF_3I and PFBI were negative in mammalian cell genotoxicity screening assays, but CF_3I was positive in the Ames assay while PFBI was negative. One notable difference in methodology in the genotoxicity studies is that CF_3I was administered as a vapor, while PFBI was administered as a liquid.

In the 2-week inhalation study with CF_3I, four groups of five male rats each were exposed 2 hr/day, 5 days/wk to 0, 30,000, 60,000 or 120,000 ppm (Dodd *et al*. 1997b). No deaths were observed, though lethargy and slight lack of coordination were noted in rats of the 60,000 and 120,000 ppm groups at the conclusion of each daily exposure. Mean body weight gains were depressed in rats of the 60,000 and 120,000 ppm groups. Serum thyroglobulin and reverse T_3 were increased at all CF_3I exposure levels. At necropsy, no gross lesions or differences in absolute or relative organ weights were noted. Histopathologic examination of the thyroid and parathyroid glands indicated no morphological abnormalities in the CF_3I exposed rats. A LOAEL of 60,000 ppm was selected by the authors on the basis of clinical signs and depressed weight gains. The increases in serum thyroglobulin and reverse T_3 were not considered adverse effects, thus 30,000 ppm was selected by the authors as a NOAEL. When compared with the LOAEL and NOAEL of the 4-week inhalation study on PFBI reported here, the values are higher for CF_3I (Table 1). However, the CF_3I study exposed rats only 2 hr/day for 14 days, while the PFBI study exposed rats 6 hr/day for 20 days.

A 13-week inhalation study (Dodd *et al.* 1997b) and a reproductive inhalation toxicity screen (Dodd *et al.* 1999) were conducted with CF_3I at concentrations ranging from 2,000 to 80,000 ppm. Results indicated that the thyroid was the most sensitive target tissue following exposure, and that CF_3I was not a reproductive toxicant. Of interest, the EPA requested a health hazard assessment of the CF_3I toxicity database (Clewell and Lawrence, 1999) for the purpose of establishing acceptable exposure limits (AELs) in conjunction with EPA's SNAP program (Skaggs and Rubenstein, 1999). For acute exposure, a ceiling of 2,000 ppm CF_3I was proposed based on the cardiac sensitization potential of CF_3I. For repeated (occupational) exposure, an 8-hr TWA of 150 ppm CF_3I was proposed on the basis of potential systemic toxicity effects including thyroid hormone effects. In comparison, proposed ceiling and 8-hr TWA values for PFBI are 3,900 ppm and 40 ppm, respectively.

Table 1. Comparison of Toxicity Data of PFBI and CF_3I

Biological Endpoint	PFBI Results	CF_3I Results	Reference for CF_3I Results
Acute Inhalation Toxicity in Rats (4-hr LC_{50})	14,000 ppm	~160,000 ppm	ManTech Environmental, 1994
Cardiac Sensitization via Inhalation (LOAEL/NOAEL)	6,200 ppm/ 3,900 ppm	4,000 ppm/ 2,000 ppm	Dodd and Vinegar, 1998
Gentoxicity – Mutagenicity in Bacteria	Negative (5/5 strains)	Positive (4/5 strains)	Dodd *et al.*, 1997a
Genotoxicity – Clastogenicity in Mammalian Cells	Negative (human lymphocytes)	Negative (mouse lymphoma and mouse erythrocytes)	Dodd *et al.*, 1997a
Short-Term Repeated Inhalation Toxicity in Rats (LOAEL/NOAEL)*	10,000 ppm/ 1,000 ppm	60,000 ppm/ 30,000 ppm	Dodd *et al.*, 1997b
Subchronic Inhalation Toxicity in Rats (LOAEL/NOAEL)**	5,000 ppm/ 1,500 ppm	20,000 ppm/ 2,000 ppm	Dodd *et al.*, 1997b, 1999

*4-week nose-only inhalation study (twenty 6-hr exposures) for PFBI; 2-week nose-only inhalation study (fourteen 2-hr exposures) for CF_3I

**13-week nose-only inhalation study for PFBI; 13-week nose-only inhalation study and single generation whole-body reproductive toxicity study for CF_3I

CONCLUSIONS

- The NOAEL value of 3,900 ppm for cardiac sensitization may be considered a justifiable acute exposure limit concentration for PFBI
- Based on tests performed to evaluate a chemical's potential for tumorigenicity, PFBI does not appear to be tumorigenic by direct acting genotoxic mechanisms
- After a dosimetric adjustment for daily exposure time in an occupational setting (8 hr/day) the NOAEL for the13-week study was 1,125 ppm
- Uncertainty factors were developed for animal to human extrapolation (3), interhuman variability (3) and subchronic to chronic duration (3), for a combined value of 30
- The recommended occupational exposure limit for PFBI as an 8-hr time weighted average (TWA) is 40 ppm based on the NOAEL and uncertainty factors
- Comparing PFBI with trifluoroiodomethane supports that 40 ppm will be protective for occupational exposure

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