MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

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INTEROFFICE COMMUNICATION

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TO: File for Perfluorobutylethylene (CAS #19430-93-4)

FROM: Brian J. Hughes, Toxics Unit, Air Quality Division

DATE: July 9, 2021

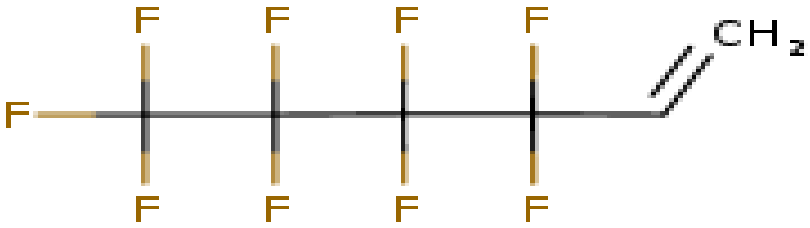
SUBJECT: Screening Level for Perfluorobutylethylene (CAS #19430-93-4)

Summary

The initial threshold screening level (ITSL) for Perfluorobutylethylene (PFBE) is 10,000 µg/m^3 based on an 8-hour averaging time. The ITSL for the annual averaging time is 2,600 µg/m^3.

Uses and Physical Chemical Properties

PFBE is part of a solvent mixture or spin agent that has been used in the production of polymers containing fluorine (PubChem 2021).

Table 1. Physical/Chemical Properties of Perfluorobutylethylene[1]	
Structure	
CAS Number	19430-93-4
Synonyms	3,3,4,4,5,5,6,6,6-Nonafluoro-1-hexene
Appearance/Odor	Clear colorless liquid with an ether-like odor
Molecular Weight	246.076 g/mol
Melting Point	<-20 ℃

[1] Information taken from ECHA (2021) dossier for Perfluorobutylethylene. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/5646/4/23.

Boiling Point	58℃ at 760 mmHg
Density	1400 g/L at 20℃
Vapor Pressure	167 mmHg at 20℃
log Pow	4.13
Water Solubility	15.6 mg/L at 20℃
Flash Point	-17℃
Auto flammability	402 ± 5℃
Log Koa[2]	1.6
Henry's Law	4.35 x 10^{-3} atm-m^3/mole

Literature Search

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold limit Values (TLVs). International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder, U.S. EPA ChemView, California Office of Environmental Health Hazard Assessment (OEHHA), and the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR).

Toxicokinetics

Information regarding the absorption, distribution, metabolism, and excretion was not found in the publicly available literature.

Genotoxicity

Study reports regarding the genotoxicity of PFBE were not directly available. However, EFSA noted the following information on their Scientific Opinion on the safety evaluation of the substance, (perfluorobutyl)ethylene (EFSA, 2021):

> "(Perfluorobutyl)ethylene was examined for its potential to induce reverse mutations in bacteria, forward mutations at the thymidine kinase (tk) locus in mouse lymphoma L5178Y cells, and structural chromosomal aberrations in Chinese Hamster Ovary (CHO) cells. Negative results were obtained in adequate studies, both in absence and presence of exogenous metabolic activation. Therefore, (perfluorobutyl)ethylene is considered non-genotoxic".

[2] Taken from EPA CompTox Chemicals Dashboard (2021). Available at: https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID6047575#properties.

Additionally, the genotoxicity of PFBE was evaluated using the Salmonella Typhimurium reverse mutation assay (Kennedy, 1990). PFBE was not mutagenic in the presence or absence of a metabolic activation system. Additional detail regarding strains, activation system, cytotoxicity, and details regarding the methodology were not given.

Studies

Acute:

An acute oral toxicity study was reported by ECHA (2021). The study was not conducted under any current guideline. In this study, Cr1:CD rats (10 males/group) were administered doses of PFBE in the range of 670-25000 mg/kg via oral gavage. The only adverse effect noted was congestion and weight loss in one out of 10 rats. No dose related adverse effects were noted. Therefore, the LD_{50} was >25000 mg/kg.

An acute inhalation toxicity study was reported by Kennedy (1990). No toxic effects were reported in mice exposed to 7178 ppm for one hour. No other details on the exposure conditions were presented. The same report noted a lack of skin irritation and a slight corneal clouding and mild conjunctivitis which was reversible 24 hours after exposure.

Repeat Dose:

In a 14-day subacute inhalation study (ECHA, 2021, study report dated 1981), Crl:CD rats (10 animals/sex/dose) were exposed to 500, 5,000, 50,000 ppm PFBE (purity 99%) for 6 hours per day for 5 days per week for two weeks via whole body, for a total of ten exposures. The analytical concentrations were 541, 4750 and 46,300 ppm for males and 473, 5140 and 46800 ppm for females. At the tenth exposure half of the rats were sacrificed and the others were sacrificed after a 14-day recovery period. The study was conducted in two different experiments one using male and the other using female rats under identical conditions.

Following 10 exposures, male rats exposed to 46,300 ppm PFBE tended to have significantly lower platelet counts and to excrete more fluoride in the urine than controls. Female rats exposed to 46,800 ppm PFBE tended to excrete more fluoride and urobilinogen in the urine than the controls. Females exposed to 5,140 or 46,800 ppm PFBE had significantly more monocytes in the blood than the controls. Organ/bodyweight ratios were significantly higher than controls following the tenth exposure for the kidney in male and female rats, and for the liver in males in the high-dose groups.

A No Observable Adverse Effect Concentration (NOAEC) of 473 ppm (4760 mg/m^3) was determined based on hematological effects on female rats.

In an OECD guideline 28-day subacute inhalation toxicity study (OECD 412) as reported in ECHA, 2021 (study report dated 2001). Male and female Wistar rats

(5/sex/dose) were exposed to 400, 2000, and 10,000 ppm (401, 2069, 9879 ppm analytical) of PFBE for 6 hours per day for 28 consecutive days via nose only exposure. Examinations included: clinical signs, mortality, body weight and body weight changes, food and water consumption, hematology, clinical biochemistry, organ weights (absolute and relative), and gross and histopathology.

In the high-dose group the treatment related histopathological findings were: 1) very slight focal to multifocal submucosal inflammatory cell infiltration in the larynx (1/5 males, 2/5 females), 2) very slight focal alveolar histiocytosis (1/5 males) and very slight focal interstitial inflammatory cell infiltration (1/5 females) in the lungs, and 3) very slight to slight fatty hepatocellular cytoplasmic vacuolation (4/5 males) and a slight focal (lobular) necrosis with a slight inflammatory cell infiltration (1/5 males).

Other treatment related effects included: body weight and body weight changes (data not shown), decreased mean serum partial thromboplastin time in high-dose group ($p < 0.01$), mildly increase serum cholinesterase levels and urea levels in males in the mid-dose group ($p = 0.05$), mean inorganic serum phosphate levels in females in the high-dose group ($p < 0.05$).

Based on the effects observed in the high dose of decreased mean serum partial thromboplastin time, histopathologic changes in larynx, lungs, and liver in high-dose groups in male and female rats, the Lowest Observed Adverse Effect Concentration (LOAEC) is 9,879 ppm. The NOAEC in this study is 2,069 ppm.

In an OECD guideline 90-day subchronic inhalation toxicity study (OECD 413), Wistar rats (10/sex/dose) were exposed to 0, 1,000, 3,000, and 10,000 ppm (1,000, 3040, and, and 10200 ppm analytical) of PFBE (purity >99.9%) for 6 hours per day and 5 day per week for 13 weeks via nose only.

The parameters evaluated were clinical signs, mortality, body weight and body weight changes, food consumption, ophthalmology, hematology, clinical biochemistry, organ weights (absolute and relative), and gross and histopathological examinations.

Slight reductions in group mean body weight gains compared to control values were evident for males exposed to PFBE. As these changes did not show a dose related response and a similar effect was not evident for females, this change was not considered to be adverse.

Reductions in white blood cell counts with associated changes in lymphocyte, monocyte and large unstained cell counts were evident for males and females exposed to PFBE. These changes did not show a dose-related response and may have been the result of higher control mean levels. In the absence of associated histopathological changes, these changes were not considered to be adverse.

Consequently, the NOAEC for PFBE in rats following 13-weeks exposure was considered by the authors to be 10200 ppm.

Reproductive/Developmental

In a guideline compliant developmental toxicity study, Sprague-Dawley rats (7 dams/dose group) were exposed to 1,000 and 70,000 ppm (10,000 and 711,337 mg/m^3) of PFBE for 6 hours per day for 10 days during gestation day 6 to gestation day 16 via whole-body exposure. The dams were sacrificed on day 21 and maternal and fetal examinations included: cage side observations, clinical observations, body weight, food consumption, and post-mortem examination of the uterus, ovaries, liver, examination of the ovaries and uterine content, and fetal soft tissue and skeletal examinations.

The maternal effects were limited in the high-dose group to a statistically significant reduction in body weight gain during GD 6 through GD 16 along with decrease food consumption during the same period. No other adverse effects were noted in the dams.

No treatment related fetal effects were recorded with regard to body weight, sex distribution, gross, skeletal or soft tissue examinations. The NOAEC for maternal, developmental and teratological effects was 70,700 ppm.

ITSL Derivation

Short-term (8-hour):

According to Rule 232 (1)(c) an occupational exposure level maybe used for the derivation of the ITSL where:

ITSL = OEL/100

The American Conference of Governmental Industrial Hygienists (ACGIH) derived a TWA for PFBE of 100 ppm based on hematological effects in 2001. Therefore, the following ITSL derivation is used.

Y µg/m3 = (100 ppm)(246.076)/(24.45) x 1000 ug/m3 = 1.0 x 10^6 µg/m^3 (rounded)

ITSL = 1,000,000/100 = 10,000 µg/m^3

Pursuant to Rule 232(2)(a), the ITSL is given an 8-hour averaging time.

This 8-hr ITSL also concurs with the Texas Effects Screening Level of 10,230 µg/m^3 for short-term exposures.[3]

Long-term (annual): Table 2. shows the LOAECs and NOAECs for repeated dose and developmental inhalation studies using PFBE.

[3] Available at: https://www.tceq.texas.gov/toxicology/database/tox.

Table 2. Summary of Effect Levels Identified in PFBE Inhalation Toxicity Studies								
Study	Guideline	Specie/Strain	DOSE (ppm)	Exposure	NOAEC (ppm)	LOAEC (ppm)	Basis for LOAEC/NOAEC	Reference
Sub-Acute	OECD 412 (equivalent)	Crl:CD rats (10 M and 10 F/dose)	M (541, 4750, 46,300 F (473, 5140, 46,000)	14-day (6 hours/day)	473	5140	Hematology	ECHA (2021) Study report dated 1981
Subacute	OECD 412	Rat/Wistar (5 M and 5 F/dose)	401, 2069, 9879	28-day (6 hours/day – Nose only)	2,069	9,879	Histopathologic changes in larynx, lungs, and liver in high-dose groups	ECHA (2021) Study report dated 2001
Sub Chronic	OECD 413	Rat/Wistar (10 M and 10 F/dose)	1,000, 3,040, 10,200	90-day (6 hours/day, 5 days/week for 13 weeks-Nose only)	10,200	None determined	Highest dose tested/ No treatment related effects	ECHA (2021) Study report dated 2017
Developmental	OECD 414 (equivalent)	Rat/Sprague-Dawley (7 F/dose)	1,050, 69,600	GD 6 to 15 (6 hours/day)	69,600	None determined	Highest dose tested/ No teratogenicity or embryotoxicity detected	ECHA (2021) Study report dated 1981
M = male, F = female								

None of the studies in Table 2 gave sufficient information for benchmark dose analysis. Although the 14-day subacute inhalation study had a lower NOAEC than the 28-day subacute study (473 ppm vs 2069 ppm, respectively), it also had a higher LOAEC (5140 ppm) than the NOAEL from the 28-day subacute study (2000 ppm); therefore, the 28-day subacute NOAEC was deemed more appropriate to use to derive the ITSL. Of the studies conducted on PFBE, the 28-day subacute study (ECHA 2021 study report dated 2001) gave the most information on dose-response from which a NOAEC could be derived for a point of departure. The ITSL according to Rule 232 (1) (d) is as follows:

$$\text{ITSL} = \frac{\text{NOAEC mg/m}^3 \times \text{Hours exposed per day}}{\text{Safety Factors} \quad 24 \text{ hours per day}}$$

Dosimetric adjustment and unit conversion to NOAEC:

NOAEC = 2069 ppm x 6 hours/24 hours = 517 ppm

PPM to µg/m^3:
Y µg/m^3 = (X ppm)(molecular weight)/24.45 x 1000 ug/mg
Y µg/m^3 = (517 ppm)(246.076 MW)/24.45 x 1000 ug/mg = 5.2 x 10^6 µg/m^3

ITSL:

ITSL = 5.2 x10^6 µg/m^3/(20)(100) = 2600 µg/m^3 (annual)

Safety factors:
Duration: 20x to account for the subacute to chronic adjustment factor
Interspecies factor: 10 to account for animal (rat) to man

Intraspecies factor: 10 to account for human variability

Based on Rule 232(2)(d) the ITSL is given annual averaging time.

The two ITSLs for PFBE are 2600 µg/m^3 with annual averaging time, and 10,000 µg/m^3 with 8-hour averaging time.

References

ECHA (European Chemical Authority). 2021. Dossier on Perfluorobutylethylene. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/5646

EFSA (European Food Safety Authority). 2011. Scientific Opinion on the safety evaluation of the substance, (perfluorobutyl)ethylene, CAS No. 19430-93-4, for use in food contact materials. EFSA Journal 9(2):1-11. Available at: j.efsa.2011.2000.pdf.

Kennedy, G.L. 1990. Toxicology of Fluorine-Containing Monomers. Critical Reviews in Toxicology. Vol 21(2): 149-170.

PubChem (2021). Perfluorobutyl ethylene. National Library of Medicine, National Center for Biotechnology Information. Available at: https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7917.