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REVIEW ARTICLE

PERFLUOROISOBUTENE: POISONOUS CHOKING GAS

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Summary

Perfluoroisobutene (PFIB) is a colorless toxic gas which can be absorbed into the body by inhalation. The substance irritates the respiratory tract and may be used as a potential chemical warfare agent. Inhalation exposure may cause severe symptoms of pulmonary edema associated with wheezing, difficulty in breathing and sputum expectoration. A bluish skin color is also observed. Initially, cough and chest pain may occur. However, severe symptoms of pulmonary edema may be delayed for several hours before a rapid deterioration of health occurs. Excessive exposure may cause death.

Key words: perfluoroisobutene; PFIB; irritant gas; acute lung injury; chemical warfare agent; toxicology

ABBREVIATIONS AND SYMBOLS

ALI	acute lung injury	NTP	National Toxicology Program
CUROSURF	natural porcine lung surfactant	PDIC	pyrrolidine dithiocarbamate
CWA	chemical warfare agents	PFIB	perhluoroisobutene
CWC	Chemical Weapons Convention	PTFE	polytetrafluoroethylene, Teflon
IGF-1	insulin-like growth factor	QNB	3-quinuclidinyl benzilate
LC_{50}	median lethal concentration	SP-B	surfactant protein B
NAC	N-acetylcysteine	SP-C	surfactant protein C

INTRODUCTION

Perfluoroisobutene (PFIB, C_4F_8, 1,1,1,3,3-penta fluoro-2-trifluoro methylpropene, CAS No. 3812-21-8) is a fluoro-olefin produced as a main by-product in large quantities by the fluoropolymer industry. For example in the manufacture of tetrafluoroethylene and hexafluoropropylene by pyrolysis of chlorodifluoromethane and tetrafluoroethylene. It is also used as etching material for semiconductor fabrication and synthesis of polymeric materials. PFIB is highly toxic colorless odorless gas, very dangerous even the case of brief inhalation. PFIB can result in acute lung injury (ALI), pulmonary edema and even death. Because of its high toxicity to humans, PFIB is designated by the Chemical Warfare Agents (CWA) and therefore is contained in Schedule 2A of Chemical Weapons Convention (CWC). The aim of the inclusion of chemicals, such as PFIB to Schedule 2 is to cover those

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chemicals, which would poses high risk to the human health (Bajgar et al., 2015). PFIB is also produced by thermal decomposition of polytetrafluoroethylene (PTFE, Teflon) (Zeifman et al., 1984). PFIB is also produced by PTFE overheating, which poses a serious health risk to human respiratory tract. PFIB is approximately ten times more toxic than phosgene (Oberdorster et al., 1994).

CHEMISTRY

PFIB is a colorless (Haynes, 2014) and odorless (Hoenig, 2007) hydrophobic reactive gas with boiling point 7 °C, melting point -130 °C (Haynes, 2014) and density 1.592 g/litre (Lewis, 2007). It is soluble in water, but it quickly decomposes forming various reactive intermediates and fluorophosgene, which then decomposes into carbon dioxide, a radical anion, and hydrogen fluoride (Lewis, 2004).

PFIB is highly electrophilic chemical (Zeifman et al., 1984). Its high electrophilicity is a result of the strong electron-attracting effects of the fluorine atoms of the trifluoromethyl groups and the conjugation of the fluorine's p electrons with the double bond of the vinyl group. PFIB is reactive towards nucleophilic reagents to yield substitution and addition radical byproducts. PFIB reacts with almost all known nucleophiles. Several reactive intermediates have been identified in the reaction of PFIB with nitron scavengers and nitroso spin. Some of the expected reactive nucleophiles include amines, alcohols, and especially thiols (Arroyo, 1997). PFIB can also be prepared by pyrolysis of perfluoropropylene (Young et al., 1967).

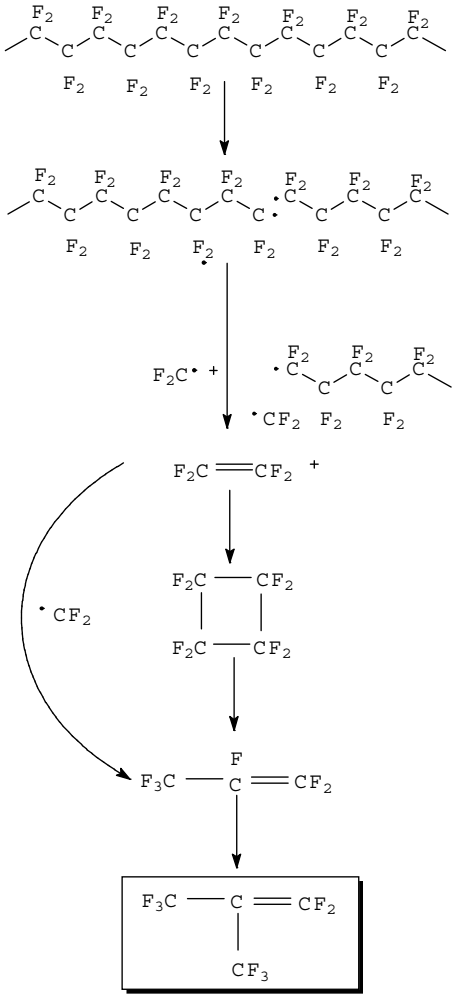

Figure 1. Pyrolysis of PTFE (Teflon)

PYROLYSIS OF PTFE

A significant source of PFIB is thermal degradation of PTFE (teflon). PTFE is a very thermally stable polymer, but when heated to 320 to 360 ° C, it degrades to release PFIB and other gaseous toxic substances such as C_2F_4, C_3F_6 and C_4F_8 (Coleman et al., 1968; Waritz, 1975) (Figure 1)). Such an event can occur very easily in the home when the Teflon pan or other Teflon non-stick surface foods overheat. In this case, the pan needs to be quickly removed from the fire, open the windows and leave the room. The threat in this case is not as human as pets, especially birds such as canaries or friends who are very sensitive to PFIB. Such an event can occur very easily in the home when the Teflon pan or other Teflon non-stick surface foods overheat. In this case, the pan needs to be quickly removed from the fire, open the windows and leave the room. In this case, humans are not endangered as pets, especially birds such as canaries or budgies who are very sensitive to PFIB (Griffith et al., 1973). A particularly dangerous situation may be the pyrolysis of the PTFE-based PFIB-release material and one cannot leave the contaminated area. Such a situation may occur, for example, on a spacecraft where a fire breaks out and astronauts are at risk of living with toxic gases (Ferin and Oberdorster, 1992; Perry, 2017).

ACUTE ANIMAL TOXICITY

The median lethal concentration (LC_{50}) was 0.5 ppm. Intoxicated animals either died with gross pathological signs of pulmonary congestion or recovered without apparent residual effects. The 15-second LC_{50} was 361 ppm and the 10-minute LC_{50} was 17 ppm (Smith et al., 1982). Similar results of acute toxicity after inhalation have been observed in other species. Two hour LC_{50} in mice has been either 1.6 ppm (Smith et al., 1982) or 0.98 ppm (Karpov, 1975), and the same toxicity value in rabbits either 4.3 ppm (Karpov, 1975) or 1.2 ppm (Paulet and Bernard, 1968), in guinea-pigs 1.05 ppm (Karpov, 1975) and in cats 3.1 ppm (Karpov, 1975). Lehnert et al. (1995) observed an unusually long latency time (about 8 hours) in rats that inhaled PFIB at a concentration of 12.2 ppm for 10 minutes.

REPEATED DOSE ANIMAL TOXICITY

Information on repeated doses of PFIB inhalation studies is available only to a limited extent (Clayton, 1977). Rats exposed to 0.1 ppm PFIB for six hours per day, five days per week and for two weeks showed no pathological changes and showed only mild respiratory damage and restlessness during exposure (Kennedy, 1990).

HUMAN TOXICITY

PFIB is irritating to the eyes, nose, skin, throat and lungs and is ten times more toxic than phosgene. It is extremely toxic gas that targets the lungs in inhalation. Inhalation exposure may cause severe symptoms. Low-level inhalation of the gas can lead to acute lung injury (ALI). ALI remains a significant source of morbidity and mortality in the critically ill patient population. Higher doses cause pulmonary edema with wheezing, difficulty in breathing, coughing up sputum and bluish discoloration of the skin (Brubaker, 1977; Zhang et al., 2017). PFIB toxicity is similar to that of other fluorolefins. Their toxicity is directly proportional to the reactivity of this olefin to nucleophiles (Cook and Pierce, 1973; Clayton, 1977). The higher the ractivity, the higher the toxicity. Data on the potential for PFIB to cause cancer, birth defects or reproductive effects in laboratory animals were not available. Also the potential for PFIB to cause cancer in humans has not been assessed by the U.S. National Toxicology Program 13th Report on Carcinogens (NTP, 2015).

Most often, poisoning occurs when inhaled PFIB released by pyrolysis of PTFE (above 300 ° C), for example overheating of Teflon dishes. This is called "polymer fever" and there are more such examples in medical literature (Harris, 1951; Williams et al., 1974; Silver and Young, 1993). Because PTFE or Teflon is a commonly used compound that can lead to polymeric smoke fever when heated under poorly ventilated conditions, these cases are quite common (Adams, 1963; Delgado and Waksman, 2004; Son et al., 2006; Toyama et al., 2006; Shimizu et al., 2012). These cases of PFIB poisoning in the household or industry rarely end with death (Temple et al., 1985), however in view of the increasing use of PTFE in commercial and industrial products, recognition of this subject is important for doctors in the field of emergency medicine and doctors in the field of occupational medicine (Tsai et l., 2000; Stenton, 2016).

A typical timing of PFIB poisoning according to the "polymer fume fever" scenario can be shown in case five workers accidentally exposed to a gas containing 2 percent PFIB. They all reported irritation of the respiratory tract within 24 hours of exposure and the lung irritation was manifested by cough in all cases. The patients developed headache, cough, substernal pain, dyspnoea and fever within the first hour following exposure. Their symptoms became worse at six to eight hours after exposure. The patients' condition improved on the fifth day and after two to three weeks they were expelled from the hospital. All the patients were shown to have pulmonary edema and this was confirmed at post mortem on two patients died. One died after 11 days after exposure, the other died after 13 days (Waritz and Kwon. 1968). The latency period for PFIB injury is one to four hours until pulmonary edema symptoms appear (Danishevskii and Kochanov, 1961).

Although it is known that Teflon a other similar fluorine-containing polymers are used in many cooking devices, it is less commonly known that it is also in the interior of many military vehicles, particularly armored vehicles. Because PFIB is produced off when Teflon burns, fires in these vehicles release PFIB. This can be deadly for the crew of vehicles, but also external vehicle fire observers should be carefully questioned about their exposure to smoke (USAMRICD, 2000). PFIB is human skin, eye, and mucous membrane irritant and human acute exposures causes marked irritation of conjunctivae, throat, and lungs (Lewis, 2004). Although the detection of PFIB in the air is possible, it is not very suitable for field use (Muir et al., 2005)

HISTOPATHOLOGY OF THE LUNG

The histopathology of rat lung has been studied by Brown and Rice (1991) after an acute exposure to PFIB at a concentration of 78 ppm for 1.5 min giving a Ct = 957 mg/m^3 for the first 24 hr following exposure. Within 5 minutes of exposure, changes in bronchioles and peribronchial alveoli were observed. Changes in ciliary structure and increased pinocytosis with occasional alveolar epithelial cell type I formation have been reported. Changes in ciliary structure and increased pinocytosis with occasional alveolar epithelial cell type I formation have been reported. This was followed by the progressive development of pulmonary edema, which was histologically visible 2-3 hours after exposure with a death occurring from 7 hours. Animals that were sacrificed 24 hours after exposure showed signs of enlarged pulmonary edema and alveolar interstitial infiltration of lymphoma nuclear cells and macrophages (Brown and Rice, 1991). In other experiments, PFIB induced pulmonary edema involving translocation of blood compartment proteins into the lung alveolar compartment. High performance capillary electrophoresis of rat lung lining proteins has shown that albumin, transferrin and IgG are the three major proteins transferred to the alveolar space (Gurley et al., 1991). In an earlier stage, increased permeability of the blood-air barrier after PFIB exposure is probably to result in injury to cellular tight junctions that act in conjunction with later changes in actin, resulting in increased permeability (Meng et al., 2011).

GENETIC TOXICITY AND CARCINOGENICITY

No information of either genetic toxicity or carcinogenicity was found. It is very tricky to predict the potential risk of PFIB genotoxicity or carcinogenicity based on experiments with other fluorocarbons (Longstaff et al., 1984, 1988; Consonni et al., 2013).

ENVIRONMENTAL TOXICITY

No officially available studies on the environmental effects of PFIB have been found. The concentration of PFIB 0.1 ppm in air is the maximum air concentration below which nearly all individuals could be exposed for up to one hour without serious adverse health effects or symptoms (Kennedy, 1990).

ANTIDOTE AND EMERGENCY TREATMENT

PFIB is a fluoroolefin that is ten times more toxic than phosgene (Patocka and Bajgar, 1998) but the mechanisms of ALI by PFIB inhalation remain unclear. Zhang et al. (2017) believe that oxidative injury and a secondary hyper-inflammatory response are recognized as the primary mechanisms of PFIB-induced ALI. No specific anti-PFIB drugs are currently available. Yang et al. (2017) showed that preventive application of peroraly used N-acetyl-cysteine (NAC) can significantly improve the survival of mice exposed to a lethal dose PFIB while NAC treatment

is ineffective (Lailey et al., 1991). A promising therapeutic approach in early-stage acute respiratory distress caused by PFIB, is a combined treatment by NAC and Curosurf (van Helden et al., 2004), natural surfactant, prepared from porcine lungs, containing almost exclusively polar lipids, in particular phosphatidylcholine, and about 1% of specific low molecular weight hydrophobic proteins SP-B and SP-C.

Oral NAC, which is comonly used as a mucolytic in chronic obstructive pulmonary disease, as well as in diseases which are complicated by the production of viscous mucus (Webb, 1962; Ziment, 1986), has shown protection against inhalation of PFIB in rats (Lailey, 1997). Protection from the lethal effect of inhaled PFIB was demonstrated when NAC was orally administered 4, 6 or 8 hours prior to gas exposure and the duration of protection was associated with the duration of elevated plasma cysteine, glutathione and NAC levels (Lailey, 1997).

The treatment of PFIB intoxication based on edema reduction by administration of diuretics was tested by Onyefuru et al. (1996). In experiments on rats, the diuretics furosemide and torasemide reduced the lung edema and the pattern and severity of the pathological changes associated with inhalation of PFIB and delayed the time to death (Onyefuru et al. 1996).

The results of Zhang et al. (2005) suggest that cholinolytics might have prophylactic and therapeutic roles in PFIB inhalation induced ALI. 3-quinuclidinyl benzilate (QNB) and anisodamine were used as model cholinolytics. Also pyrrolidine dithiocarbamate (PDTC) has a prophylactic role against PFIB inhalation-induced ALI (Zhao et al., 2007) as well as application of insulin-like growth factor (IGF-1) (Li et al., 2009). In any case, treatment with PFIB intoxications must be a complex procedure and, apart from antidote administration, must include other important factors, especially bed rest (Lehnert et al., 1995).

CONCLUSIONS

PFIB is a hydrophobic reactive gas which irritates the respiratory tract. Its inhalation can cause acute lung injury (ALI) or acute pulmonary edema with wheezing, difficulty in breathing, and death by overwhelming pulmonary oedema similar to that induced by phosgene inhalation. The mechnisms of ALI induced by PFIB remain largely unclear. PFIB is approximately ten times toxic as phosgene. PFIB is usually produced as a main by-product in large quantities by the fluoropolymer industry and is a hazard to human being in chemical industry accidents. Oral administration of N-acetylcysteine appears to be a good protective drug against the lethal effect of inhaled PFIB.

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Conflict of Interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

Adherence to Ethical Standards

This article does not contain any studies involving animals performed by any of the authors.

This article does not contain any studies involving human participants performed by any of the authors.

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