AIR FORCE APPROACH TO TOXICOLOGY OF HALON REPLACEMENTS

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Candidates for the replacement of Halon 1211 as a firefighting agent were tested (by New Mexico Engineering Research Institute) and chosen (by Air Force Civil Engineering Support Agency) based on fire fighting ability, ozone depletion potential, compatibility with existing equipment, and available toxicity information. Now the Air Force health and safety team needs to more completely address the safety of these candidates for their intended use. Although all available toxicity information was considered when narrowing down the candidates to the current few, more toxicity testing is being completed by industry and an understanding of the mechanisms of toxicity needs to be gained in order to complete an accurate assessment of the human health effects. The Air Force approach is to accomplish research to provide sufficient understanding of the interaction of these chemicals with biological systems and the mechanism of toxicity so that a quantitative risk assessment can be accomplished. The goal is to provide the scientific information necessary to avoid some of the conservative "uncertainty factors" used by EPA in their risk assessments.

The sequence of events for replacement of Halon 1211 from the toxicology point of view is shown in Figure 1. A list of approximately 30 chemicals was chosen about 5 years ago to undergo testing and evaluation as a fire fighting agents. This list was narrowed by testing and four replacements (HCFC142b, HCFC-123, HCFC-124, and perfluorohexane) have been. recommended. Users have tentatively accepted these agents and Toxicology Division is now in the process of doing a chemical specific risk assessment. Regulatory approval is the final step in the sequence.

Traditionally, toxicology relates exposure concentrations in laboratory animals to lethal or deleterious effects of a chemical. These studies result in a "no observable adverse effect level" (NOAEL) or a "lowest observable adverse effect level" (LOAEL) which are used as a starting point for setting risk levels and exposure standards. This traditional risk assessment process assumes that the relationship between exposure concentration and toxicity is directly proportional and constant. All the evidence indicates that this is not true in most situations and risk assessments can

Sequence of Events for Replacing Halon 1211

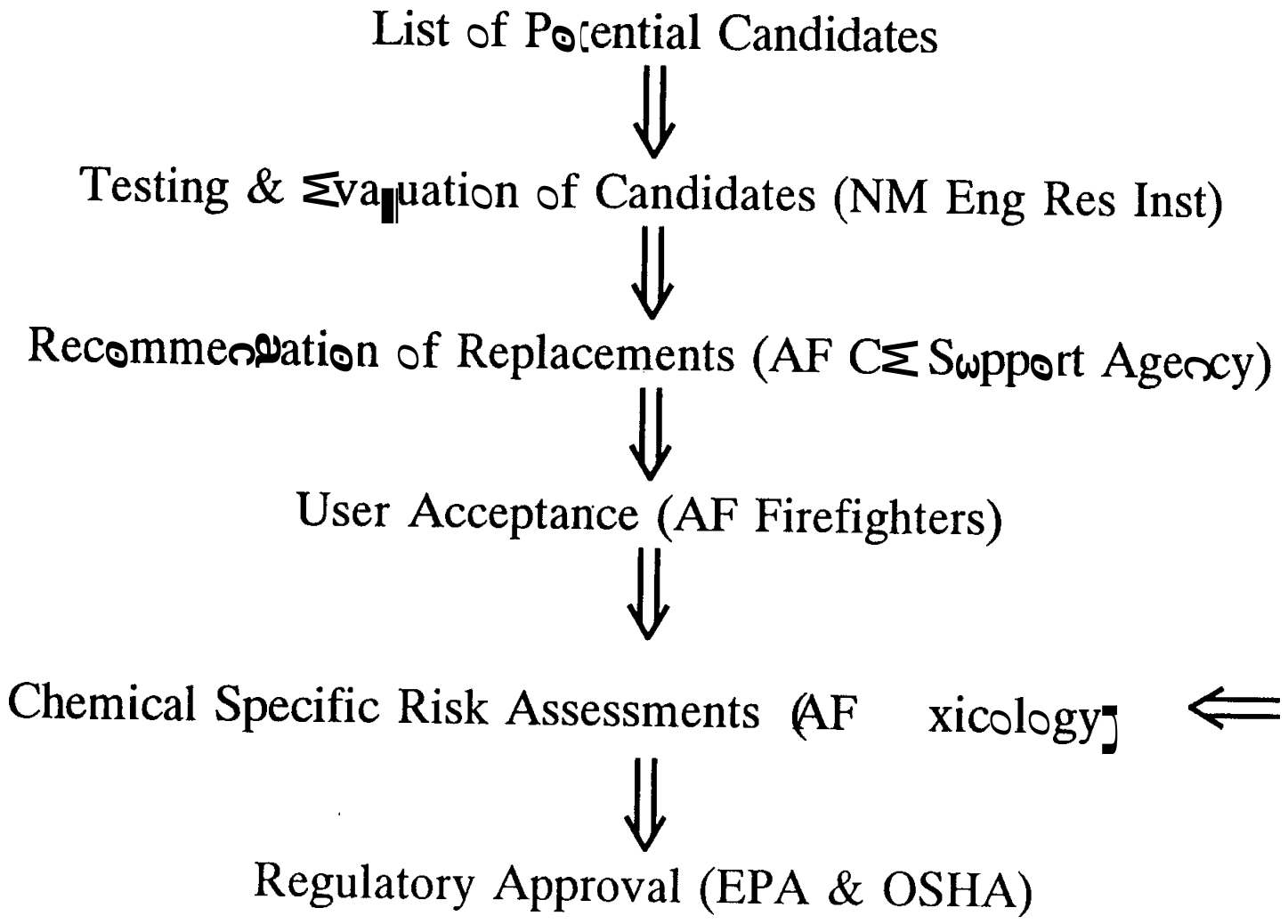


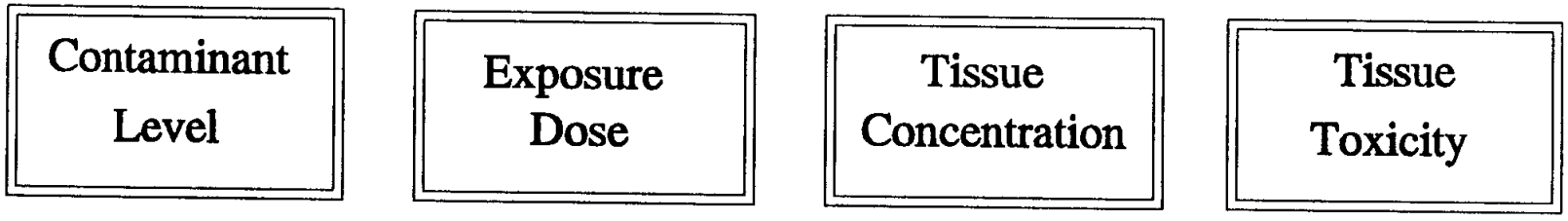
Figure 1

be greatly improved if a better understanding of the relationship between exposure concentration and toxicity can be gained for risk assessment purposes. Important parameters in the risk assessment process are shown in Figure 2. These parameters along the exposure pathway between exposure level and toxicity have been chosen because they can be measured or estimated to gain a better understanding of the process. The "Contaminant Level" is the amount of chemical in the workplace or the environment. Occupational exposures are generally due to breathing vapors or coming in contact with liquids. Environmental exposures are due to chemicals in the air, soil or water. The "Exposure Dose" is the total amount of chemical which enters the body. The "Tissue Concentration" is the amount of chemical in the tissue where the toxic event occurs. Depending on the mechanism of toxicity, it may be either the area under the curve or the peak concentration which is toxicologically significant. Also, either the parent or a metabolite or both may exert toxic effects. "Tissue Toxicity" is the acute or chronic effect of the chemical which can range from cell death to cancer.

The relationship between each of the parameters can be viewed as a transfer process where the relationship can be mathematically described (Figure 3). Exposure is the transfer between the amount of chemical in the workplace or environment and the amount of chemical which enters the body. The amount of chemical which gets transferred into the body during an exposure is affected by the protective equipment which is used, the care with which a chemical or chemical-containing media is handled, as well as, duration and frequency of exposure. Pharmacokinetics is the process of transfer within the body which will result in a certain tissue concentration. Absorption, distribution, metabolism and elimination affect the amount of chemical which actually gets to the target tissue and how long it remains. Pharmacodynamics is the relationship between tissue concentration and toxicity. Cellular turnover and repair processes affect the amount of damage which is actually caused by the chemical. These processes are not understood for most chemicals and as a result "uncertainty factors" are used by several government agencies to assure that the recommended levels are conservative enough. The EPA uses several types of 10 fold corrections to lower the acceptable exposure concentrations when the toxicity end point is other than cancer. These uncertainty factors are shown in Figure 4 next to the transfer processes that they affect. The Air Force approach is to provide quantitative information through laboratory research about the transfer processes so that the uncertainty factors can be avoided. This will be accomplished by appropriate physiologically-based pharmacokinetic modeling and *in vitro* studies.

Figure 5 shows the four chemicals which are being evaluated for their potential to produce toxicity. They are 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123), 2-chloro-1,1,1,2-tetrafluoroethane (HCFC-124), 1-chloro-1,1-difluoroethane (HCFC-142b), and perfluorohexane (PFH).

Important Parameters in the Risk Assessment Process



Workplace:
- Vapor
- Liquid

Environment:
- Air
- Water
- Soil

Total absorbed

AUC or peak:
- Parent
- Metabolite

Acute:
- Cell death
- Functional loss

Chronic:
- Cancer
- Functional loss

Figure 2

Transfer Functions in the Risk Assessment Process

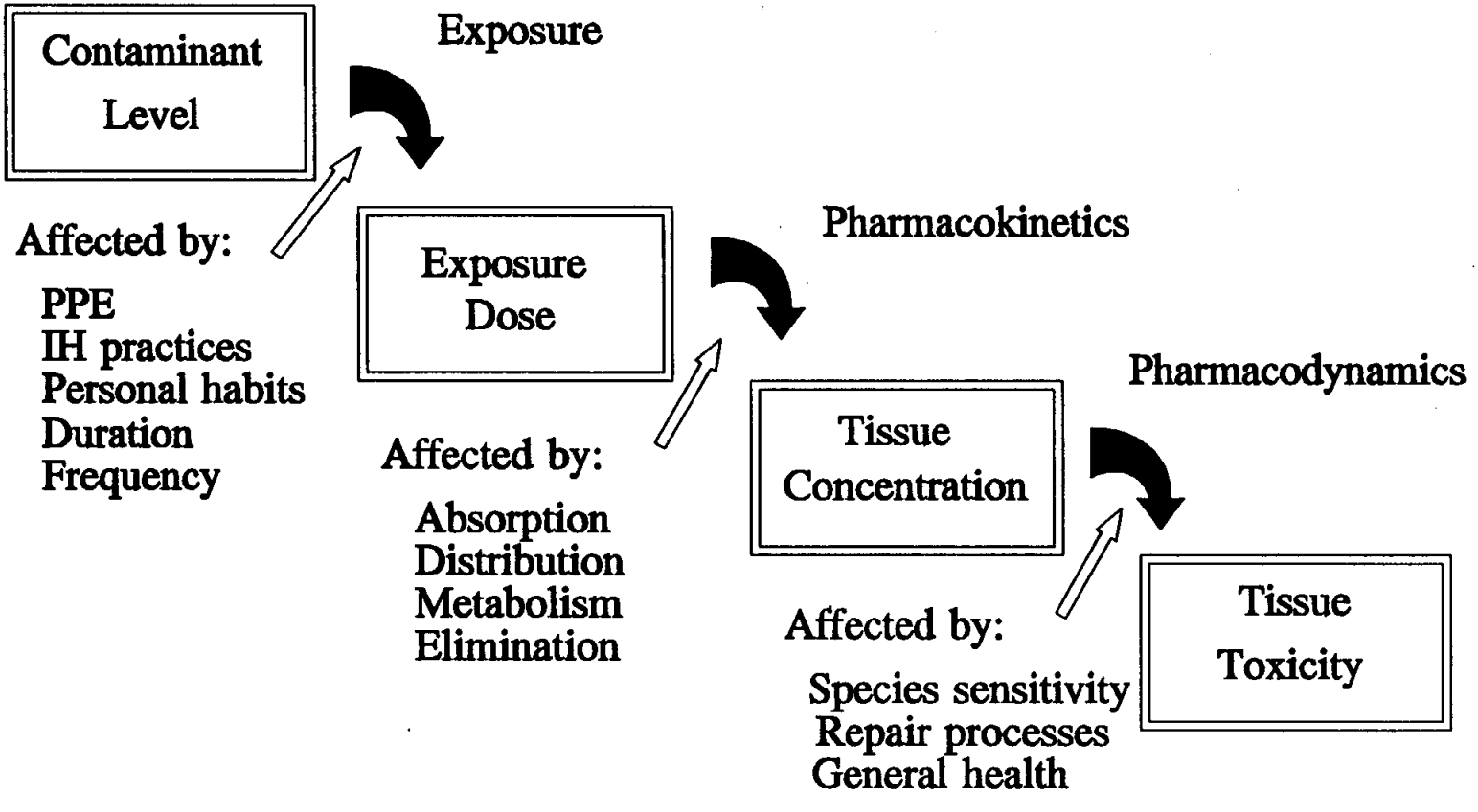


Figure 3

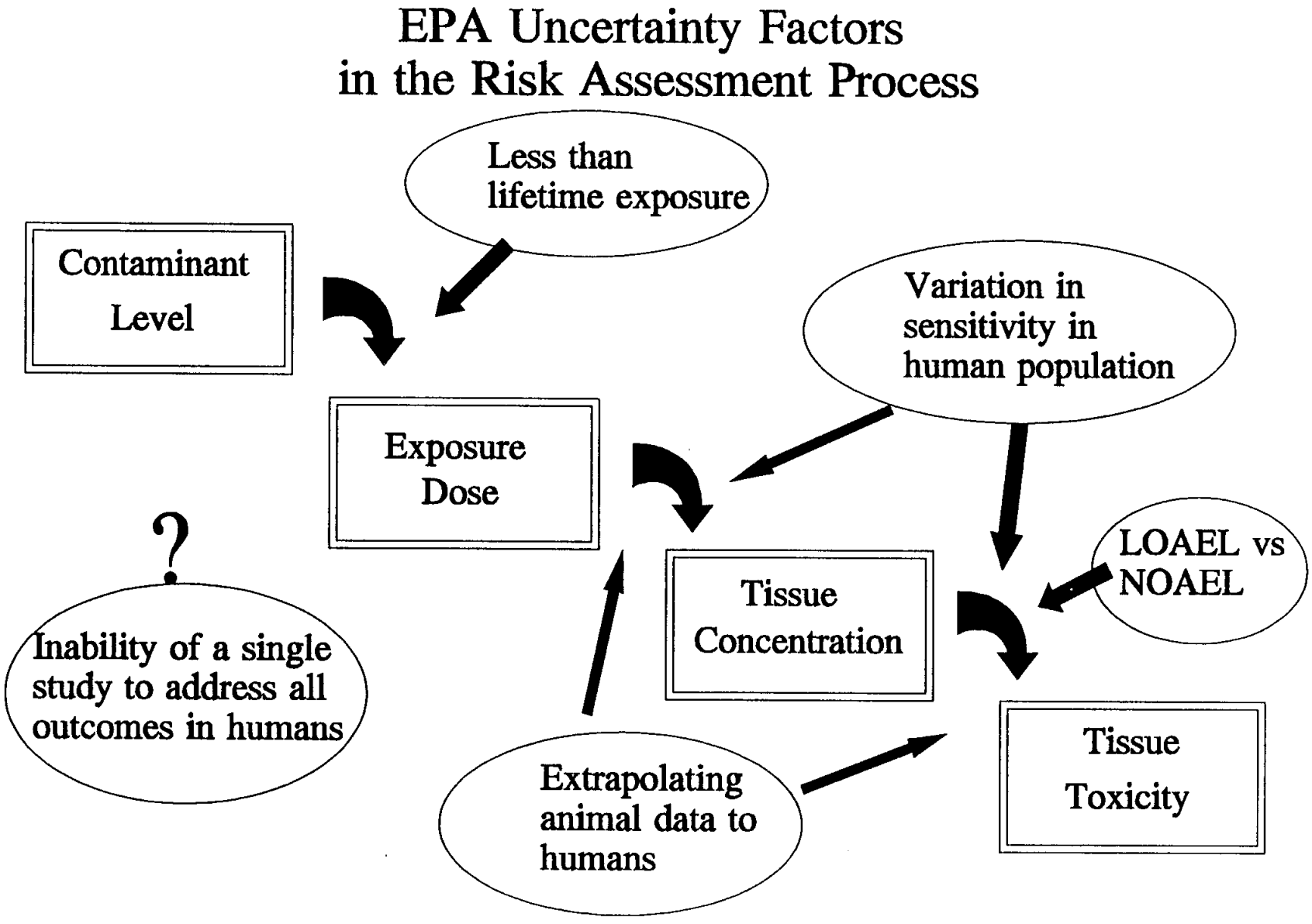

EPA Uncertainty Factors
in the Risk Assessment Process
Less than
lifetime exposure
Contaminant
Level
Variation in
sensitivity in
human population
Exposure
Dose
LOAEL vs
NOAEL
Tissue
Concentration
?
Inability of a single
study to address all
outcomes in humans
Extrapolating
animal data to
humans
Tissue
Toxicity

Figure 4

Halon Replacement Candidates

CANDIDATE	FORMULA	CHEMICAL PROPERTIES
HCFC-123	$CHCl_2CF_3$	Liquid B.P. 28°C
HCFC-124	$CHClFCF_3$	Gas B.P. -11°C
HCFC-142b	$CClF_2CF_3$	Gas B.P. -9°C
PFH (Perfluorohexane)	C_6F_{14}	Liquid B.P. 56°C

Figure 5

HCFC-123 and PFH are liquids at room temperature; HCFC-124 and HCFC-142b are gases. HCFC-123 and HCFC-124 possess geminal dihalomethyl groups (-CHX_2) and are similar structurally to the inhalation anesthetic, halothane (1-bromo-1-chloro-2,2,2-trifluoroethane).

To address the potential toxicological effects of these halon replacements, pertinent questions were asked. In general, this is the first step in a risk assessment process, to identify the health hazards. Are there acute health hazards with these chemical replacements? Is there cumulative toxicity with repeated exposure and, if so, what are the target organs of effect? Are there any noteworthy adverse effects in the areas of neurotoxicology, developmental toxicology, or reproductive toxicology? Is the test chemical mutagenic? Are these chemicals tumorigenic?

A literature search was performed on these four replacement candidates. Information was obtained from reports submitted to EPA by the Program for Alternative Fluorocarbon Toxicity Testing *(PAFT)* (EPA, 1990), personal communication with the industry (Pike and Pignato, 1991), and the open literature. The acute health hazards are summarized in Figure 6. There is a low order of toxicity in rodents. Inhalation LC_{50}s range from 32,000 ppm (HCFC-123) to 400,000 ppm (HCFC-142b), which is equivalent to 3.2 to 40 % v/v. For the liquid test chemicals, dermal or oral LD_{50}s are greater than the limit test dose of 5g/Kg. Clinical observations in rats exposed to high concentrations of HCFCs include unresponsiveness, hyperactivity, and irregular breathing. These signs are transient and disappear following exposure. Possible causes of death for rats exposed to high concentrations of HCFCs include asphyxiation (oxygen concentrations in the inhalation exposure chambers may not have been carefully monitored) or depression of the central respiratory center. In irritancy tests with rabbits, minimal to mild skin or eye irritation is observed.

Potential acute health hazards exist with these chemicals (Figure 7). These are only potential, because these effects have not been fully evaluated to state unequivocally that they are toxicologically important. HCFCs 123 and 124 are related to the inhalation anesthetic halothane. Clinical experience with halothane has led to the observation of a rare and unpredictable occurrence, halothane-induced hepatitis (Owen and Van Der Veen, 1986). One theory of the etiology of the hepatitis is an allergic reaction. Halothane-induced hepatitis is associated with the production of neoantigens formed by mfluoroacetylation of liver proteins. However, animal models to test this theory are inadequate. Anders and coworkers (Harris et al., 1991, and Martin et al., 1992) propose that HCFCs possessing geminal dihalomethyl groups, such as HCFC-123 and

Acute Health Hazards

- Low order of toxicity in rodents

  Inhalation LC_{50}s range from 32,000 to 400,000 ppm (3.2 - 40 % v/v)
  Dermal/oral LD_{50}s are > g/Kg

- Clinical observations in rats exposed to high concentrations of HCFCs

  Unresponsiveness, hypoactivity, irregular breathing

- Possible cause of death for rats exposed to high concentrations of HCFCs

  Asphyxiation
  Depression of respiratory center

- Minimal to mild irritation (rabbits)

  Skin
  Eye

Figure 6

tential Acute Health Hazards

- Immunologically mediated hepatitis with HCFCs having geminal dihalomethyl groups (HCFC-123 and HCFC-124)

  Proposed metabolic pathways of HCFC-123 and HCFC-124 involve formation of reactive trifluoroacetyl electrophiles which bind to protein

  Theory: Halothane-induced hepatitis is associated with the production of neoantigens formed by trifluoroacetylation of liver proteins

- Cardiac sensitization following high concentrations of halocarbons

  As a class, halocarbons are cardiotoxic and cause life threatening responses (cardiac arrhythmia, bronchoconstriction)

Figure 7

HCFC-124, form reactive trifluoroacetyl (TFA) electrophiles which bind to liver protein. These hepatic TFA proteins cross react with antibodies produced from patients with halothane-induced hepatitis.

Another potential acute health hazard is cardiac sensitization. **Cases** of teenagers who have abused fluorocarbon propellants **and** died suddenly are well known. Death is believed to be due to myocardial sensitization to endogenous epinephrine. **As** a class, halocarbons **are** cardiotoxic and cause life threatening responses, such **as** cardiac arrhythmia and bronchoconstriction (Aviado, **1975). HCFC-123, HCFC-124,** and **HCFC-142b** were tested for cardiac sensitization at Haskell Laboratory, E. I. Du Pont De Nemours **& Co.,** Inc., and all were positive at high concentrations **(>10000** ppm).

Another potential acute health hazard is thermal decomposition of perfluoro compounds to hydrogen fluoride (HF) and/or perfluoroisobutylene (PFIB) (Figure **8).** Several perfluoro chemicals **are** used for heat transfer, and thermal stability tests are often performed on them (Pike and Pignato, **1991).** HF and **PFIB** are highly toxic chemicals. In rats, the **1-hr** LC_{50} value for HF is **1276** ppm and for **PFIB,** the 10 min LC_{50} value is **17** ppm **(RTECS, 1981/82).**

A final consideration for potential health hazards is **an** impairment in performance and/or activity following **high** concentrations of halocarbons. Several halocarbons have anesthetic-like properties causing narcosis, unresponsiveness, ataxia, or loss of reflexes. This may be an important consideration when assessing emergency evacuation procedures during, for example, fire fighting activity.

For repeated exposures, a list of cumulative toxicity and target organs in rats is summarized in Figure **9.** In general, liver weight is mildly increased, and serum enzymes may be elevated. Liver histopathology is generally negative; positive histopathology is usually in the most sensitive species tested and at high doses. Focal necrosis and inflammatory cell infiltration describe the lesion. Kidney weights may also be mildly elevated, **but** histopathology is negative. A study involving rats exposed to **20,000** ppm **HCFC-123** for four weeks **(6** hr/day) indicated testicular degeneration and hypospermia (Kelly, **1989).** Serum chemistry alterations following **HCFC-123** exposure indicate alterations in lipid metabolism. Triglycerides and cholesterol levels were decreased (Malley, **1991).** Reactive metabolites may be involved with this finding. **HCFC-123** induces (mildly) peroxisome proliferation. A mild increase in hepatic beta-oxidation, but no increase in cell proliferation has been observed (Malley, **1991).** A variety of chemicals cause peroxisome proliferation. An association of peroxisome proliferation with hepatic tumor formation

Potential Acute Health Hazards (cont)

- Thermal decomposition of perfluoro compounds to hydrogen fluoride (HF) and perfluoroisobutylene (PFIB)

  HF and PFIB are highly toxic chemicals

HF	LC_{50}	1276 ppm	(1-hr, rat)
PFIB	LC_{50}	17 ppm	(10-min, rat)

- Impairment in performance and/or activity following high concentrations of halocarbons

  Several halocarbons have anesthetic-like properties causing narcosis, unresponsiveness, ataxia, or loss of reflexes

Figure 8

Cumulative Toxicity and Target Organs in Rats Exposed Repeated

- Liver weight increase (histopathology is generally negative)
- Kidney weight increase (negative histopathology)
- Testicular degeneration and hypospermia (HCFC-123)
- Serum chemistry alterations (HCFC-123)

  Alteration in lipid metabolism indicated by decreases in triglycerides and cholesterol

- Peroxisome proliferation induction (HCFC-123)

  Mild increase in hepatic beta-oxidation, no increase in cell proliferation

Figure 9

exists (Rao et al., 1988). However, a causal relationship between peroxisome proliferation and tumorigenesis has not been established. In the absence of mitogenesis, a correlation between peroxisome proliferation and carcinogenicity is weak (Marsman et al., 1988).

Except for assays for genotoxicity, tests for neurotoxicity, reproductive toxicity, or developmental toxicity have not been completed to fully evaluate the potential for these chemicals to induce these specific effects (Figure 10). HCFC-123 and HCFC-124 were negative in tests for mutagenicity. HCFC-142b was equivocal in some genotoxicity test systems, but an oncogenicity assay in animals was negative. PFH has not been tested for specific health hazards.

Results of tests for tumorigenicity are summarized in Figure 11. HCFC-124 and PFH have not been evaluated in a two-year rodent bioassay. HCFC-142b gas was tested in rats at concentrations of 0 (control), 1000, 10000, or 20000 ppm (Seckar, 1986). All endpoints measured were negative. The in-life phase of a two-year inhalation bioassay in rats with HCFC-123 was recently completed by the PAFT consomum. Exposure concentrations were 0 (control), 300, 1000, or 5000 ppm. The tissue histopathology has not been completed, but PAFT informed EPA (via a TSCA Section 8e) of an increase incidence in benign tumors in liver, pancreas, and the testes (Rusch, 1991). These tumors were not life threatening, meaning they did not shorten the time to death, and they developed late in life. A complete evaluation is underway including a thorough investigation of historical tumor data in naive rats and statistical analyses. PAFT members have revised downward their workplace exposure limits. For example, Allied-Signal, Inc. revised the Permissible Exposure Limit to 5 ppm for a 40-hr work week and 10 ppm for an 8-hr work day.

In summary, these chemical replacements for halons have a low order of acute toxicity, which may be the primary concern in the risk assessment process. There may be "potential" acute health effects at high concentrations. None of the agents discussed here have been fully tested and/or evaluated for their potential to cause toxicity. We need much more information to elucidate the mechanism(s) of toxicity of these chemicals. Metabolism studies may reveal toxicologically important metabolites formed from these agents. Factors, such as hypoxia or enzyme induction, may modify the formation of metabolites. Pharmacokinetic studies will help define the dosimetry for the risk assessment process. A understanding of the consequences of exposures to candidate Halon replacements will allow a more rational approach to risk assessment.

Noteworthy Adverse Effects

CANDIDATE	GENOTOXICITY	NEUROTOXICITY	REPRODUCTIVE OR DEVELOPMENTAL TOXICOLOGY
HCFC-123	Negative	not fully evaluated	not fully evaluated
HCFC-124	Negative	not fully evaluated	not fully evaluated
HCFC-142b	equivocal	not fully evaluated	not fully evaluated
PFH	not fully evaluated	not fully evaluated	not fully evaluated

Figure 10

Tumorigenicity

- HCFC-124 and PFH have not been evaluated in a 2-year rodent bioassay
- HCFC-142b

  2-year inhalation bioassay in rats: 0, 1000, 10000, and 20000 ppm

  All endpoints were negative

- HCFC-123

  2-year inhalation bioassay in rats: 0, 500, 1000, and 5000 ppm

  Histopathology has not been fully evaluated but PAFT informed EPA of increase incidence of benign tumors in liver, pancreas, and testes

  PAFT members revised downward their workplace exposure limits

Figure 11

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