RECOMMENDING EXPOSURE LIMITS FOR HALON REPLACEMENTS

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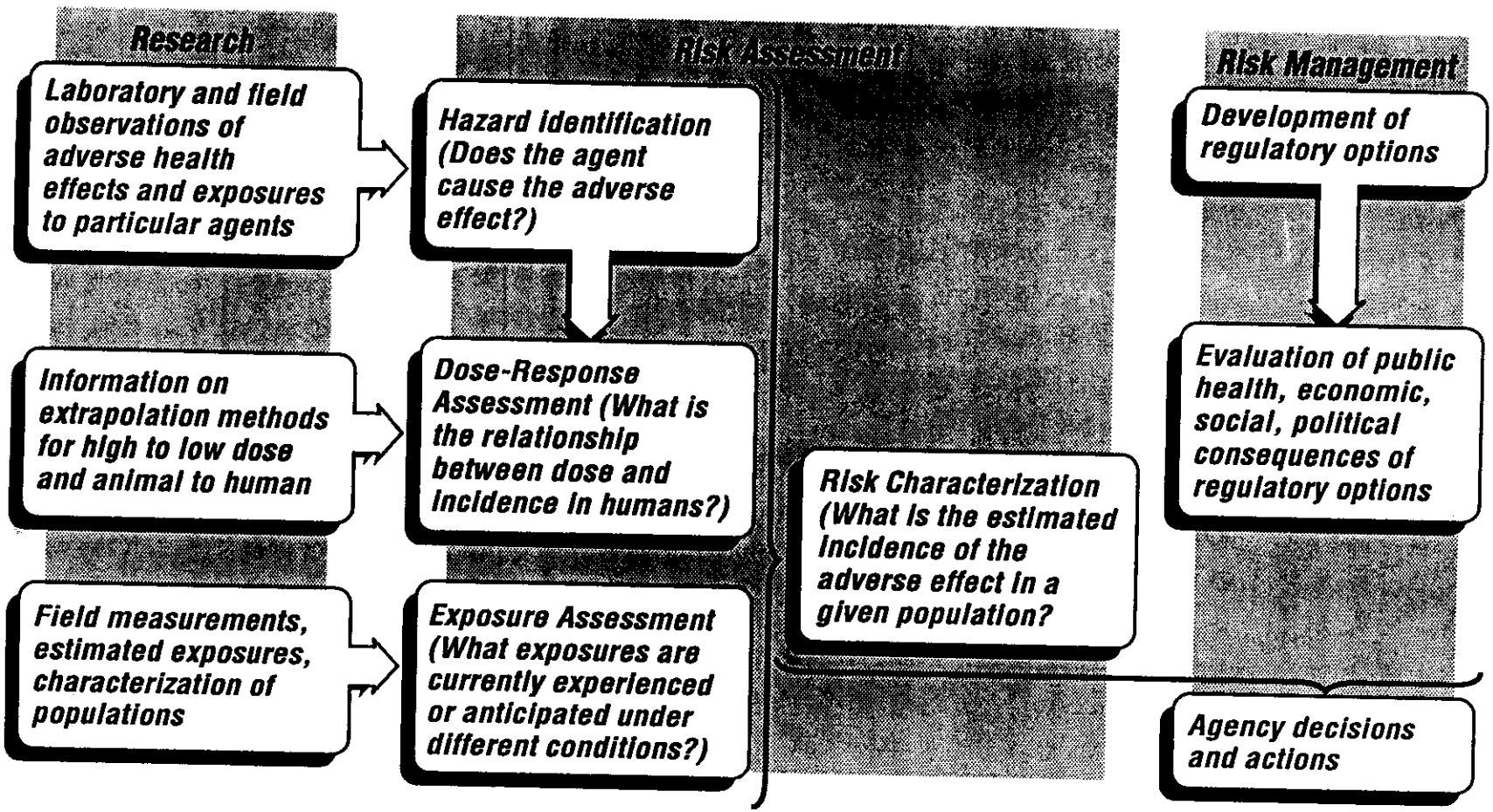
Safe use of replacements for halon fire-extinguishing agents requires that the potential human exposure scenario and toxicity in laboratory animals be assessed and compared. It is important to be able to recommend appropriate exposure levels to assure that the benefits of clean fire-extinguishing agents can be evaluated with the risks of their use. Regulatory agencies such as the Occupational Safety and Health Administration (OSHA) and the US Environmental Protection Agency (USEPA) will ultimately set occupational and environmental limits; however, it is essential in the interim, for the Air Force to apply its toxicology resources to recommend safe scenario specific risk management values and be involved in determining dose-response estimates. HCFC-123 has been a primary candidate for replacement of Halon 1211 as a "streaming" fire-fighting agent. The purpose of this document is to review the risk assessment process and then discuss the recommendation of an emergency exposure guidance level (EEGL), an occupational threshold limit value - time weighted average (TLV-TWA) and an environmental reference concentration (RfC) value based on state-of-the-art extrapolations from laboratory animal toxicity to human exposure scenarios.

Risk Assessment Process

Figure 1 shows the relationship between research and the regulatory processes of risk assessment and risk management' . According to this scheme, research, risk assessment and risk management are related but distinct processes. Risk assessment is the application of sound judgement to field and laboratory research with the intent of answering specific questions. Risk management includes the process of evaluating alternative regulatory decisions and deciding among them. Risk assessment can be divided into four separate steps: hazard identification, dose-response assessment, exposure assessment, risk characterization.

Elements of Risk Assessment and Risk Management



NAS (1983) framework for risk assessment and risk management.

Hazard identification is the process of determining whether an exposure to a chemical can deleteriously impact health. Human epidemiology studies are probably the best predictor for determining if there is a hazard with the use of a chemical. As a result. most hazard identification involves exposing laboratory animals to chemicals to determine if specific chemicals cause adverse effects. Exposures may be short term or long term. Studies on isolated cells may also be useful, particularly for mutagenicity testing. Structural relationships to chemicals which are known to be toxic may also be used to help identify a hazard.

Dose-response assessment is the process of determining the quantitative relationship between the health effect and the dose of the chemical. It answers tlie question about the relationship between exposure dose and health effect in humans. Since hazard identification is most frequently done in laboratory animals, the dose-response assessment involves extrapolation from laboratory animals to humans. Laboratory studies are often at higher doses, for longer durations and not necessarily the appropriate route for human exposures. It is almost always necessary to extrapolate the species, dose, route or duration to the human situation. The relationship between dose and response is frequently non-linear. The influence of pharmacokinetics and pharmacodynamics on the dose-response relationship is incorporated into this assessment.

Exposure assessment is the process of measuring or estimating the potential *or* actual duration, frequency and intensity of exposures to a chemical. Field or industrial hygiene measurements are required. Characterization of the population (average age, male/female mix, general health, and sensitive populations) potentially exposed is also important to fully assess the exposure.

Risk characterization is the final process of estimating the incidence of a health effect under the conditions of the exposure assessment. This step involves the integration of the dose-response assessment and the exposure assessment and requires a great deal of judgement due to uncertainties in the previous steps.

Risk Assessment for HCFC-123

HCFC-123 (2.2-dichloro-l ,1,1-trifluoroethane) is a candidate replacement for Halon 1211 for streaming agent applications. It is currently used as a foam blowing agent, refrigerant and cleaning solvent. HCFC-123 is structurally similar to halothane (1-bromo-1-chloro-2,2,2-trifluoroethane), a clinical anesthetic, and both chemicals appear to be metabolized by similar pathways[2]. Halothane has been used as an anesthetic for three decades and has recognizable but minimal toxicity. Due to lack of human information on HCFC-123, human toxicity information for halothane is used by analogy in the risk assessment process for HCFC-123.

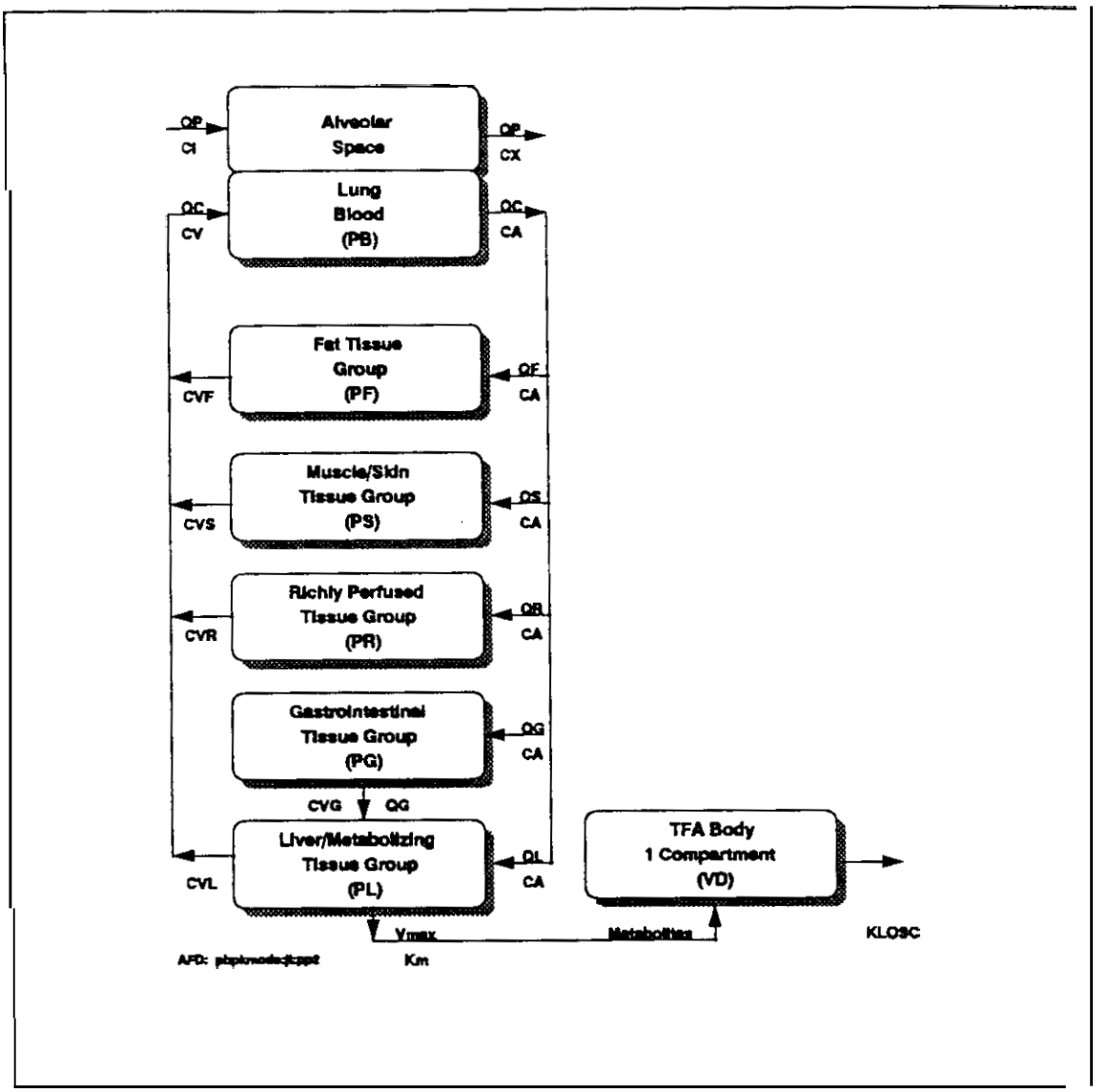
There is no human epidemiology information available for HCFC-123 and *in vitro* mutagenicity tests have been negative. In the laboratory, HCFC-123 is a mild anesthetic

which also may cause cardiac sensitization to epinephrine'. In longer term studies, liver enlargement and changes in circulating levels of cholesterol, triglycerides and glucose occur[4]. Toxicity is summarized below.

HAZARD IDENTIFICATION FOR HCFC-123

- No epidemiology
- *In vitro* tests
  - Ames test negative
- Acute toxicity
  - **4 hr** inhalation LC_{50} is 32,000 to 35,000 ppm (rats)
  - Dermal/oral LD_{50} is greater than 2 g/Kg (rats)
  - Cardiac sensitization at 19,000 ppm (dogs)
  - CNS depression at 5,000 ppm (rats)
  - Hepatic lesions at 20,000 pprn (guinea pigs)
- Subchronic toxicity (rats)
  - CNS depression at 5,000 ppm
  - Serum cholesterol, triglyceride and glucose changes

Halothane has more potent anesthetic effects than HCFC-123. There is epidemiological evidence of cardiac sensitization during anesthesia and halothane has been implicated in malignant hyperthermia and halothane-induced hepatotoxicity. Toxicity for halothane is summarized below.



The dose-response assessment for HCFC-123 is facilitated by the development and validation of a physiologically-based pharmacokinetic (PB-PK) model for the distribution, metabolism and elimination of HCFC-123 (Figure 2). When these types of models are properly validated they allow extrapolation even when the biological processes involved (e.g. enzyme activity) are non-linear. Lumped compartments are used to simplify the physiology into the important components. Each compartment receives a portion of total cardiac output and has an affinity (expressed as a partition coefficient) for HCFC-123. Metabolism occurs in the liver group and exhalation occurs in the lung. Simultaneous differential equations are used to keep track of the mass of chemical in the system. Using such a model allows prediction of

tissue doses of parent or metabolite for various exposure scenarios and fakes into account the non-linear processes involved.

PB-PK models are also used to handle the species extrapolation required to estimate the human health effects of HCFC-123. This is accomplished with a "parallelogram" approach with halothane (Figure 3). Since there are no human exposures available for HCFC-123 but there are with halothane, it is necessary to build and validate a human model for HCFC-123 by analogy. PB-PK models for the pharmacokinetics of halothane and HCFC-123 are developed and validated with laboratory experiments in the rat. The physiological parameters are changed to reflect human blood flows and ventilation rates and the model is validated using the human studies which are available for halothane. When the rat to human extrapolation is successful for halothane, it is assumed that the same procedures can be used for developing the HCFC-123 human model. Due to the structural and metabolic similarities between halothane and HCFC-123, this reasonable assumption provides a model for the human which can be used to estimate the dose-response effects.

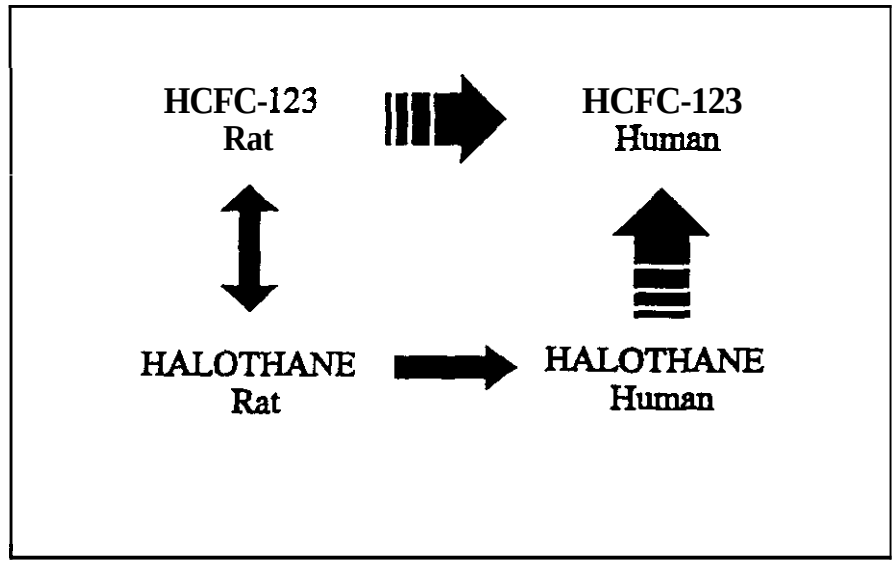


Figure 3 - Parallelogram approach for extrapolation between species and chemicals

Two studies[5,6] have measured the concentrations of HCFC-123 following release during simulated fire-fighting. See text box below:

EXPOSURE ASSESSMENT FOR HCFC-123

Fire fighter

- MRI monitoring of outdoor fire training exercises
  - 150 lb extinguisher used for either *3* minutes or 30 seconds
  - Breathing zone levels were 0.2 - **5.4** ppm
  - Ankle height concentrations were approximately 10 times higher
  - HCFC-123 concentrations in plume were 0.2 - 180 ppm
  - Downwind air samples were 0.2 - 129 ppm

- Meridian monitoring of HCFC-123 firefighting exercises in outdoor pit
  - 20 lb extinguisher discharge time was 2-3 seconds
  - 150 lb extinguisher discharge time was 11-37 seconds
  - Breathing zone samples from all tests ranged from 7 - 870 ppm

- Meridian monitoring of HCFC-123 firefighting exercises in aircraft hanger
  - 20 lb and 150 lb units were completely discharged
  - Breathing zone samples ranged from 5 - 300 ppni
  - Maximum concentration achieved at discharge point was 1,000 ppm

Appropriate information for an aircraft maintenance worker is not available. It would be desirable to have information about concentrations which might be found in a hanger throughout the day. Meridian Research Inc.[6] measured transient peak concentrations in a hanger after a discharge, see text box:

EXPOSURE ASSESSMENT FOR HCFC-123
Aircraft Maintenance Worker

- Meridian monitoring of HCFC-123 firefighting exercises in aircraft hanger
  - Concentrations at monitoring point, farthest away in hanger, were *2*
  - 650 ppni after discharge of 150 lb extinguisher

Appropriate information for the general public also is not available. Midwest Research Institute (MRI) measured concentrations immediately downwind from outdoor fire-training exercise (see text box). It would be useful to have measurements much farther downwind.

EXPOSURE ASSESSMENT FOR HCFC-123
General Public

- MRI monitoring of outdoor fire training exercises
  - **Air** concentrations immediately downwind were 0.17 to 129 ppm

Risk characterization for HCFC-123 involves combining exposure assessments for each scenario with the dose-response data to provide the scenario specific recommended level. The scenario which would have the highest allowable concentration would be the Emergency Exposure Guidance Level (EEGL) which is recommended by the Committee on Toxicology of the National Academy of Sciences (see text box). Our estimate of an appropriate level is 50,000 ppm as a one minute EEGL. One minute was chosen because nearly every extinguisher in the inventory that contains HCFC-123 can be emptied in less than one minute. The selection of 50,000 ppm is based on a duration adjustment from mild CNS depression which was found in rats exposed to 5,000 ppm for one hour which is sixty times the duration of the EEGL. Dogs exposed to 10,000 ppm for 5 minutes showed no CNS depression. According to the PB-PK model, less than one-fifth of the amount of the chemical which would be absorbed in five minutes would be absorbed in one minute, because of the

limited time for absorption. Cardiac sensitization would not be expected to be a problem since dogs challenged with epinephrine and exposed to 10,000 ppm for 5 minutes showed no marked arrhythmias.

EMERGENCY EXPOSURE GUIDANCE LEVEL (EEGL) DEFINITION

"The EEGL is defined as ceiling guidance level for single emergency exposure, usually lasting from 1 h to 24 h -- an occurrence expected to be infrequent in the lifetime of an individual."

"An EEGL is acceptable only in an emergency, when some risks or some discomfort must be endured to prevent greater risks (such as fire, explosion or massive release)."

" It is intended to prevent irreversible harm."

"EEGLs differ from Short-Term Exposure Limits (STEL) in that STELs are generally 15-min limits to which workers may be exposed daily for years."

The exposure limit which would apply to the workplace environment is the Threshold Limit Value-Time Weighted Average (TLV-TWA) which is enforced by OSHA and often established by the American Conference of Governmental Industrial Hygienists (ACGIH). The TLV is a number which should protect a normal worker from health effects due to the chemical (see text box). Our recommended TLV is 100 ppm based on a rat lifetime study for 6 hours/day, 5 days/week for two years which showed minimal, if any, toxic effects. There were changes in serum chemistry at all concentrations, but there was also a dose-related increase in survival. At 5,000 ppm, liver weights of the treated rats were higher than control.

THRESHOLD LIMIT VALUE (TLV-TWA) DEFINITION

"The time-weighted average concentration for a normal 8-hour work-day and a 40-hour workweek, *to* which nearly all workers may be repeatedly exposed, day after day, without adverse effect."

"(Hypersusceptible or otherwise unusually responsive)... workers may not be adequately protected from adverse health effects from certain chemicals at concentrations at or below these threshold limits."

The reference concentration (RfC) is intended to protect the general population including sensitive subgroups from non-cancer health effects due to lifetime daily inhalation exposure to HCFC-123. Determination of the RfC is in process at the **USEPA.** This level will be set using duration and dose adjustments with a PB-PK model. The concentration ultimately selected may be an order *of* magnitude lower than the recommended TLV.

REFERENCE CONCENTRATION (RfC) DEFINITION

"... an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure to the human population that is likely to be without appreciable risks of deleterious non-cancer effects during a lifetime."

In summary, the process *of* determining exposure limits for a new chemical is based on guidance provided by the National Research Council, but requires a great deal *of* judgement when making decisions about the health of workers and the general population. When uncertainty about :he extrapolation of laboratory information to the human situation is reduced, fewer conservative assumptions are made in the decision-making process. For short-term levels such as the EEGL, the duration adjustment is the most uncertain part of the extrapolation. For long-term levels such as the RfC, uncertainty lies predominantly in the species extrapolation. Improving certainty in the extrapolation process is the key to refining the process of determining safe levels.

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