Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) Documents (1986)

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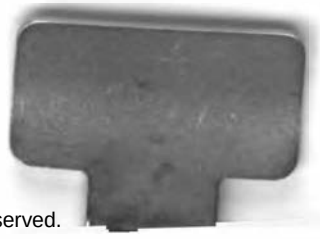

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Prepared by the
Committee on Toxicology

Board on Environmental Studies and Toxicology
Commission on Life Sciences
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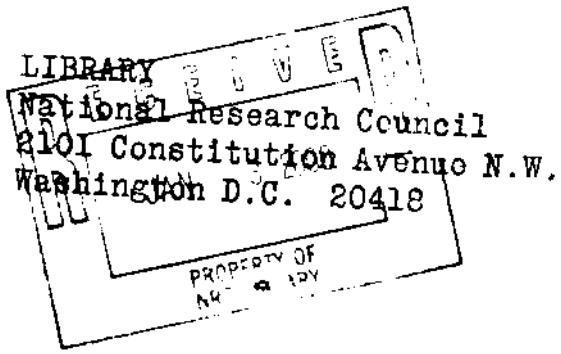

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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PREFACE

This document was prepared by the members of the Committee on Toxicology in the National Research Council's Board on Toxicology and Environmental Health Hazards (now the Board on Environmental Studies and Toxicology) for their use in developing emergency exposure guidance levels (EEGLs), continuous exposure guidance levels (CEGLs), and short-term public emergency guidance levels (SPEGLs) for chemicals of interest to the Department of Defense (DOD), the sponsor of the Committee on Toxicology. It is intended exclusively for use by the DOD for its particular exposure situations. The special needs and conditions of the DOD in its national defense role preclude direct application of these guidelines to community or work standards.

EEGLs, CEGLs and SPEGLs are not like standards issued by regulatory agencies and must not be so construed. Reports of the National Research Council contain only advisory information and recommendations. Federal and state agencies might use such advice from a National Research Council committee in establishing standards or advisories, but often incorporate other considerations--such as different population, technical feasibility, risk-benefit relationships, and additional safety aspects--in applying this advice.

INTRODUCTION

The possibility of sudden contamination of air during military and space operations has created the need for guidance regarding emergency exposure of groups of people to chemicals. Regulatory agencies, such as the Environmental Protection Agency and the Occupational Safety and Health Administration, are concerned with air pollutants--such as oxides of nitrogen and sulfur, oxidants, hydrocarbons, and carbon monoxide--for which community and workplace environmental exposure standards are set. But their interests explicitly exclude guidance for short-term unpredicted exposures to chemicals that might be encountered in military or space operations.

For the last 40 years, the National Research Council's Committee on Toxicology (COT) has, on request, recommended emergency exposure guidance levels (EEGLs) and continuous exposure guidance levels (CEGLs) for chemicals of concern to the Department of Defense (DOD). EEGLs are recommended for one purpose only: to provide guidelines for military personnel operating under emergency conditions whose circumstances are peculiar to military operations and for which regulatory agencies have not set relevant standards. CEGLs are recommended for normal long-lasting military operations. It must be emphasized that such guidance levels are not to be considered as standards like those issued by regulatory agencies for civilian populations. The process of setting EEGLs and CEGLs involves consideration of factors that are different from those related to the general population (age distribution, length of exposure, and susceptibility). In general, the personnel involved are expected to have appropriate protective equipment available and to have planned emergency escape routes, but EEGLs are not based on the availability of such equipment or routes. Because the military includes women, toxicities in women and fetuses are considered in developing some guidance levels. In addition, although it is assumed that the military population is healthy, relatively young, and uniform, allowance must still be made for inherent variability in sensitivity to chemicals. The Committee has recently published five volumes on guidance levels for emergency and continuous exposures to 35 chemicals (National Research Council, 1984a,b,c, 1985a,b). No formal procedure exists for modifying guidance levels other than a request for review by sponsors. At times, COT is asked by DOD to recommend an emergency exposure guidance level for the general public (a short-term public emergency guidance level, or SPEGL). Documents outlining the approach used by the committee in preparing guidance levels for the military have been described by COT (National Research Council, 1964, 1971, 1979). This document is an update of the earlier ones.

An EEGL is defined as a concentration of a substance in air (as a gas, vapor, or aerosol) that may be judged by DOD to be acceptable for the performance of specific tasks during rare emergency conditions lasting for periods of 1-24 h. Exposure at an EEGL might produce reversible effects that do not impair judgment and do not interfere with proper responses to the emergency. It must be noted, however, that EEGLs are not hygienic or safe. Such an exposure could result from a fire, from a spill, from a line break, or from any event that is unanticipated but nevertheless has a rate of occurrence that is predictable. The EEGL is a suggested peak level of exposure and is not to be regarded as a standard in any form or use.

CEGLs are ceiling concentrations intended to avoid adverse health effects, either immediate or delayed, and to avoid degradation in performance of military personnel after exposure for as long as 90 d. Accumulation, detoxification, and excretion are important in determining CEGLs. If a material is cumulative in its effects--i.e., not detoxified--its CEGL must be lowered to take that into account.

This document was prepared by the members of the Committee on Toxicology in the National Research Council's Board on Toxicology and Environmental Health Hazards (now the Board on Environmental Studies and Toxicology) for their use in developing emergency exposure guidance levels (EEGLs), continuous exposure guidance levels (CEGLs), and short-term public emergency guidance levels (SPEGLs) for chemicals of interest to the Department of Defense, the sponsor of the Committee on Toxicology. It is intended exclusively for use by the Department of Defense for its particular exposure situations. The special needs and conditions of the DOD in its national defense role preclude direct application of these guidelines to community or work standards.

EEGLs, CEGLs and SPEGLs are not like standards issued by regulatory agencies and must not be so construed. Reports of the National Research Council contain only advisory information and recommendations. Federal and state agencies might use such advice from a National Research Council committee in establishing standards or advisories, but often incorporate other considerations--such as different population, technical feasibility, risk-benefit relationships, and additional safety aspects--in applying this advice.

HISTORICAL DEVELOPMENT OF GUIDANCE RECOMMENDATIONS

In 1961, COT met to consider a request from the Air Force to recommend short-term exposure limits for several jet propellants. With the assistance of consultants and specially appointed members, COT recommended sets of short-term limits, which at that time were called emergency tolerance limits (National Research Council, 1961a,b). Exposures at the recommended levels were thought not to cause irreversible toxicity or significant loss of performance.

However, they were not considered innocuous, inasmuch as it was assumed that they could cause some intoxication.

After study of possible needs for such short-term limits, the American Industrial Hygiene Association (AIHA) Toxicology Committee (1964) concluded that the same type of emergency exposure limit was needed--that is, a limit that might be unhygienic, but would not result in irreversible toxicity or inability to perform emergency operations or self-rescue. The AIHA committee and the National Research Council's COT drew up sets of guiding principles in 1964, and these were shared and critically reviewed in free discussions. Several participants in the deliberations were members of both organizations. The resulting recommendations of the two groups, which used almost identical principles, included several important points:

o The emergency exposure limits should be used in planning only for emergencies; they should not be used in routine operations or when repeated exposures are anticipated.

o Planning for emergencies should be comprehensive and should incorporate information and principles in addition to the recommended limits, e.g., eddy diffusion equations, amounts of chemical substances that could be released, degree of volatilization or other generation in air, and descriptions of other hazards, such as fire and explosion.

o Traditionally, safety factors have been used to bridge the gap between what is known from experimental data and what is uncertain about human response. Safety factors should not be used routinely in developing emergency limits; however, they can be used if confidence in available data, their appropriateness, or other extrapolation is low. Such factors should be incorporated in final design criteria or emergency regulations that include exposure limits and other considerations. (During one of the deliberations, an analogy with civil-engineering design was offered. A designer of a bridge or a dam uses data on strength of materials, an incidence of one flood in 100 yr or other contingency estimates, and anticipated use of the bridge or dam and applies a safety factor before making the final design.)

DESCRIPTIONS OF GUIDANCE LEVELS

THE EMERGENCY EXPOSURE GUIDANCE LEVEL (EEGL)

The EEGL (previously known as emergency exposure limit, or EEL) is defined as a 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 a person. "Emergency" connotes a rare and unexpected situation with potential for significant loss of life, property, or mission accomplishment if not controlled. The EEGL, a single ceiling or upper number for a particular exposure period,

specifies and reflects the Committee's interpretation of available information in the context of an emergency.

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). Even in an emergency, exposure should be limited to a defined short period. Exposure at the EEGL might produce such effects as increased respiratory rate from increased carbon dioxide, headache or mild central nervous system effects from carbon monoxide, or respiratory tract or eye irritation from ammonia, phosgene, or sulfur dioxide. The EEGL is intended to prevent irreversible harm. While reduction in performance is permissible, it should not prevent proper responses to the emergency (such as shutting off a valve, closing a hatch, removing a source of heat or ignition, or using a fire extinguisher). For example, in normal work situations, a degree of upper respiratory tract irritation or eye irritation causing discomfort would not be considered acceptable; during an emergency, it would be acceptable, if it did not cause irreversible harm or affect judgment or performance seriously. The EEGL for a substance represents COT's judgment based on evaluation of experimental and epidemiologic data, mechanisms of injury, and, where possible, operating conditions in which emergency exposure might occur, as well as consideration of DOD goals and objectives.

Acute toxicity is the primary basis for establishing an EEGL. However, even brief exposure to some substances might have the potential to increase the risk of cancer or other delayed effects. If the substance under consideration is carcinogenic, a cancer risk assessment is performed with the aim of providing an estimate of the exposure that would not lead to an excess risk of cancer greater than 1 in 10,000 exposed persons. The acceptable risk selected for military exposures is based on considerations of policy and objectives of DOD.

In estimating the EEGL for a substance that has multiple biologic effects, all end points--including reproductive (in both sexes), developmental, carcinogenic, neurotoxic, respiratory, and other organ-related effects--are evaluated, and the most important is selected. If confidence in the available data is low or if important data are missing, appropriate safety factors are used and the rationale for their selection is stated. Generally, EEGLs have been developed for exposure to single substances, although emergency exposures often involve complex mixtures of substances and thus a potential for toxic synergism. In the absence of other information, guidance levels for complex mixtures can be developed from EEGLs by assuming as a first approximation that the toxic effects are simply additive--thus implying a proportional reduction in EEGLs for each of the constituents of a mixture.

EEGLs differ from STELs (short-term emergency exposure limits) recommended by the Occupational Safety and Health Administration

(OSHA) or the American Conference of Governmental Industrial Hygienists (ACGIH), in that STELs are generally 15-min limits to which workers may be exposed daily for many years.

THE SHORT-TERM PUBLIC EMERGENCY GUIDANCE LEVEL (SPEGL)

The SPEGL (previously known as short-term public emergency limit, or SPEL) is defined as a suitable concentration for unpredicted, single, short-term, emergency exposure of the general public. In contrast to the EEGL, the SPEGL takes into account the wide range of susceptibility of the general public. This includes sensitive populations--such as children, the aged, and persons with serious debilitating diseases. Effects of exposure on the fetus and on reproductive capacity of both men and women should also be considered.

THE CONTINUOUS EXPOSURE GUIDANCE LEVEL (CEGL)

CEGLs (formerly known as continuous exposure limits, or CELs) are ceiling concentrations designed to avoid adverse health effects, either immediate or delayed, of more prolonged exposures and to avoid degradation in crew performance that might endanger the objectives of a particular mission as a consequence of continuous exposure for up to 90 d. In contrast with EEGLs, which are intended to guide exposures during emergencies (exposures that, although not acceptable under normal operating conditions, should not cause serious or permanent effects), CEGLs are intended to provide guidance for operations lasting up to 90 d in an environment like that of a submarine.

PREPARATION OF EEGLs, CEGLs, AND SPEGLs

EEGLs and CEGLs are concentrations of airborne contaminants, usually expressed as parts per million in air (ppm) or as milligrams per cubic meter of air (mg/m^3). Substances with characteristic odors, colors, or irritancies sometimes provide a warning that could reduce exposure--useful information in this connection, although these are usually unreliable guides. The concentrations represented by EEGLs and CEGLs cannot be reliably detected by odor perception or smoke density for judging airborne concentrations. Sensory perception is not necessarily related to toxicity, and the ability to sense a given odor at a specific airborne concentration varies greatly.

Although EEGLs and CEGLs do not represent distinctions between safe and unsafe concentrations, it should be expected that some people will be adversely affected if an EEGL or CEGL is exceeded. Even if the EEGLs or CEGLs are not exceeded, however, some persons might be affected. If emergency exposure will last longer than 24 h, the EEGL no longer applies, and appropriate measures should be taken to comply with the concentration described by the corresponding CEGL.

EEGLs are based on the assumption that exposure will be followed by complete recovery. However, some contaminants might be carcinogens; in these cases, COT will provide guidance to interpret the relationship between exposure concentrations that result in a lifetime risk of cancer no greater than 1 in 10,000 exposed persons. The more often exposure to a given cancer-causing substance occurs, the more likely cancer is to develop; if exposure can be limited to once or a few times, cancer is less likely to develop.

Most military personnel will probably never be exposed to an EEGL, whereas a few will be exposed to one such event, and a low number might have more than one toxic exposure at an EEGL. In all cases of possible exposure to hazardous substances, the military is encouraged to have appropriate emergency protective equipment readily available, such as air-supplied respirators and protector clothing. Relevant emergency escape procedures should also be developed, and potential emissions should be monitored.

EEGL documents present information for the involved personnel to use in distinguishing health risks in a variety of emergency situations. Other elements in the process of making these distinctions are the potential volatility of released material, dispersion characteristics of vapors, monitoring devices (including those associated with olfactory evidence), and availability of specialized control personnel, relevant emergency protective equipment, and planned routes of escape. In general, EEGLs reflect experimental and clinical observations, epidemiologic data, and physiologic and toxicologic data on humans and animals, with special attention to possible field conditions of concern to DOD.

Both immediate and delayed health effects are considered in establishing an EEGL. Immediate effects, although often transitory, might well impede the performance of exposed persons. Immediate effects can also be long-lasting. Delayed effects, slower in onset, usually persist for long periods, but are difficult to predict from acute exposures.

Guidance level documents examine substances individually and present the rationale for recommendations. For substances that affect several organ systems or have multiple effects, the most important or most sensitive effects must receive the major attention. EEGLs have not yet been developed for mixtures, although it is recognized that most substances will be encountered as mixtures.

The first step in preparing an EEGL document is to review information provided by the requesting agency (see Appendix A). Next, COT reviews and evaluates prior EELs, threshold limit values (TLVs), or National Institute for Occupational Safety and Health (NIOSH) reports, as well as those from other regulatory agencies and literature supplied by COT staff.

The format for an EEGL document is shown in Appendix B. Appendix C is a reproduction of a completed document, which was published in 1984 (National Research Council, 1984b). Appendix D describes the method for extrapolating from oral animal data to human inhalation values. Appendix E contains useful conversion factors and reference values.

Development of an EEGL for different durations of exposure usually begins with the shortest exposure anticipated--i.e., 10-15 min--and works up to the longest, such as 24 h. Under the simplest framework, Haber's law is assumed to operate, with the product of concentration (C) and time (t) as a constant for all the short periods used. If Ct is 30 and t is 10, then C is 3; if Ct is 30 and t is 30, then C is 1. If detoxification or recovery occurs and data are available on 24-h exposures, this is taken into account in modifying Ct. In some instances, the Ct concept will be inappropriate, as for materials like ammonia that can be more toxic with high concentrations over short periods. Each material is considered in relation to the applicability of Haber's law.

As mentioned earlier, in estimating the EEGL for a substance that has multiple toxic effects, all the adverse effects--including reproductive and developmental effects, cancer, and neurotoxic, respiratory, and organ-specific effects--are evaluated, and the most seriously debilitating, work-limiting, or sensitive one is selected as the basis for guidance. This process is anticipated to produce a guidance level that should not lead to other toxic effects.

The question of birth defects or germline mutations (heritable effects) from chemical exposure is more difficult to cope with at this stage of knowledge. For some materials for which EEGLs have so far been developed, information on potential to cause birth defects or mutations has been lacking. Almost all toxicants examined so far have had multiple forms of toxicity. COT has based EEGLs on the most sensitive or most important health effects known. When available, data on structurally related substances are considered.

Several "default" assumptions are usually considered when the necessary detailed data are not available. For example, a material shown to be a germline mutagen might be a reproductive toxin, as well as a carcinogen. Materials shown to have reproductive toxicity in exposed females might also have reproductive toxicity in exposed males (e.g., damage to sperm), although there are differences in the biology of germ cell populations and in the capacity to repair damage.

As mentioned earlier, safety factors are used often, if not routinely. In the absence of better information, a safety factor of 10 is suggested for EEGLs--following recommendations of the National Research Council's Safe Drinking Water Committee (1977) if only animal data are available and extrapolation from animals to humans is necessary for acute, short-term effects or if the likely route of

human exposure differs from that of a relevant experiment. For carcinogens, if the computed risk is more than 1 in 10,000, the EEGL is lowered so that the anticipated risk is no more than 1 in 10,000.

SPEGLs are generally set at 0.1-0.5 times the EEGL. A safety factor of 2 is appropriate to protect more sensitive groups, such as children or the elderly; for fetuses or newborns, a safety factor of 10 is appropriate.

CEGLs are generally set at 0.01-0.1 times the 24-h EEGL (i.e., a safety factor of 10-100). Where there is evidence of substantial detoxification, a safety factor of 10 might be appropriate. If there is no evidence of detoxification or detoxification is slow, a safety factor of 100 might be more appropriate. If the substance in question accumulates in tissues, such as halogenated biphenyls and metals, even higher factors are used. The choice must be determined for each material separately. If data from chronic studies are available, they can be used to derive CEGLs--with additional safety factors if needed. COT does not propose CEGLs for carcinogenic substances.

To the best of COT's ability to predict the consequences of exposure at these guidance levels, only effects that are temporary and compatible with self-rescue are accepted. One exception applies to cancer. COT's recommendations are consistent with the prevailing scientific view that one exposure could contribute to cancer (refer to Office of Science and Technology Policy, 1985). The derivation of EEGLs for carcinogens is discussed in Appendix F.

GLOSSARY

Continuous exposure--Prolonged exposure to varying concentrations for up to 90 d.

Continuous exposure guidance level (CEGL)--Formerly continuous exposure limit (CEL); a ceiling concentration designed to avoid adverse health effects, either immediate or delayed, and to avoid degradation in crew performance that might endanger the objectives of a particular mission after exposure for up to 90 d (recommended by COT).

Committee on Toxicology (COT)--A committee in the National Research Council's Board on Environmental Studies and Toxicology. COT has been recommending formalized emergency and continuous exposure guidance levels to the Department of Defense since the 1960s.

Eddy diffusion--A current of air, water, etc., moving against the main current and with a circular motion.

Emergency--An unforeseen and unpredicted event requiring immediate response to preserve lives, vital equipment, or critical missions.

Emergency exposure guidance level (EEGL)--Formerly emergency exposure limit (EEL); an acceptable concentration for unpredicted, single, short-term, emergency exposure of a defined occupational group (recommended by COT).

Haber's law--The product of concentration and time is constant ($Ct = k$) for a given toxic effect.

Permissible exposure limit (PEL)--Acceptable concentration of airborne toxicants in the workplace for 8 h/d, 40 h/wk (promulgated by Occupational Safety and Health Administration).

Safety factor--Factor that allows for uncertainty in interpretation of experimental data in establishing standards, tolerances, and limits.

Short-term effects--Acute health effects lasting minutes to hours.

Short-term exposure--Single exposure, usually 1 h or less and not more than 24 h.

Short-term public emergency guidance level (SPEGL)--Fomerly short-term public emergency limit (SPEL); an acceptable concentration for unpredicted, single, short-term, emergency exposure of the general public (recommended by COT).

Virtually safe dose (VSD)--Dose at some acceptable level of low risk, e.g., excess risk of less than 1 cancer in 1,000,000 exposed persons.

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APPENDIX A

TYPES OF INFORMATION PROVIDED BY REQUESTING AGENCY

1. Names of material.

2. Concentrations and exposure times likely to be encountered.

3. Age, sex, and numbers that might be involved in each event.

4. Selection or exclusion of persons, for example, on the basis of medical examinations:

   a) Physical reasons. b) Mental reasons.

5. Population involved:

   a) Military. b) Civilian employees. c) General public.

6. Likelihood of event leading to exposure:

   a) Single or rare in lifetime. b) Occasional.

7. Likely concurrent exposures.

8. Degree of activity during exposure:

   a) Sedentary. b) Moderate. c) Vigorous.

9. Competence or level of performance required during exposures:

   a) Mental. b) Physical.

10. Location of activity:

    a) Aircraft. b) Naval vessel. c) Submarine.
    d) Open field. e) Other (e.g., tank).

11. Protective equipment that should be available:

    a) Respirator. b) Clothing. c) None. d) Other.

12. Likelihood that knowledgeable medical personnel would participate in a decision to authorize exposures or monitor responses under emergency conditions.

13. Description of hypothetical situation in which exposure guidance levels would be needed.

APPENDIX B

FORMAT FOR EEGL DOCUMENT

Background Information

- Physical and Chemical Properties
- Occurrence and Use

Summary of Toxicity Information

- Effects on Humans
- Effects on Animals
  - Acute, Subacute, and Chronic Exposures
  - Mutagenicity, Teratogenicity, and Carcinogenicity

Pharmacokinetics

- Absorption and Distribution
- Metabolism and Excretion

Inhalation Exposure Levels (from other sources, such as TLVs from ACGIH and Permissible Exposure Levels [PELs] from OSHA standards)

Committee Recommendations (emergency exposure guidance levels--current and prior COT recommendations and rationale for new numbers)

Recommendations for Future Research (when applicable)

Tables

References (and cutoff date for published papers).

APPENDIX C*

FLUOROCARBON 11

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical formula:	CCl_3F
Molecular weight:	137.38
Chemical names:	Trichlorofluoromethane, fluorotrichloromethane
Synonyms:	FC-11, Freon 11
CAS number:	75-69-4
Freezing point:	-111°C
Physical state:	Liquid below 23.7°C
Specific gravity:	1.494 (17.2°C)
Vapor density:	5.04 (air = 1)
Vapor pressure:	792 torr (25°C)
Solubility:	Insoluble in water; soluble in ethanol or alcohol
General characteristics:	At ordinary ambient temperatures, a colorless, nonflammable liquid or gas
Conversion factors:	1 ppm = 5.6 mg/m^3 1 mg/m^3 = 0.18 ppm

OCCURRENCE AND USE

Fluorocarbon 11 (FC-11) has been used primarily as an aerosol propellant, refrigerant, and blowing agent for polymeric foams. Its use is now banned because of its potential effects on the ozone layer.

It is prepared from carbon tetrachloride and antimony trifluoride (Stecher et al., 1968; ACGIH, 1980). FC-11 may be a contaminant of submarine atmospheres.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Inhalation of fluorocarbons during the years 1960-1970 was a prominent cause of abusive death among teen-agers. Severe cardiac arrhythmia--resulting from light plane anesthesia and intensified by

*This is a reproduction of a complete guidance document, which was published in 1984.

hypercapnia, stress, or activity--was suggested as an explanation for 110 cases of sudden sniffing death (Bass, 1970). Typically, a person would spray the Freon into a paper bag from a commercial aerosol product and inhale it; after a few breaths and a short excitement period, death might occur. Fluorocarbons are thought to sensitize the heart to asphyxia-induced sinus bradycardia, atrioventricular block, and ventricular T-wave depression (Haj et al., 1980).

Accidental ingestion of FC-11 occurred when a healthy man mistook a bottle in a refrigerator for a bottle of plain water. This resulted in freezing, tissue necrosis, and multiple perforations of the stomach. The patient recovered after surgery to remove the damaged tissue (Haj et al., 1980).

Labeled FC-11 administered to four healthy males by inhalation of a single breath held for 5 s was eliminated from the body rapidly. Results in humans appeared to parallel those in rats in more detailed studies (Williams et al., 1974). The investigators found rapid transfer of FC-11 to blood followed by distribution to fat, from which release was slow. Mergner et al. (1975) exposed a male and a female volunteer to radiolabeled FC-11 at 1,000 ppm for 7-17 min. Recovery of administered radioactivity in exhaled air was essentially complete (99% and 79%). Errors in collection of rapidly eliminated gases account for the differences from 100%. Only a very small fraction of the administered radioactivity (less than 0.2%) was exhaled as $^{14}CO_2$ or excreted as nonvolatile urinary activity. The impurities in FC-11--namely, chloroform and carbon tetrachloride--known to be metabolized could account for all the radioactivity found in urine and exhaled CO_2 after exposure to FC-11.

Cardiac effects have been studied in healthy subjects and patients with bronchopulmonary disease. None of the subjects exhibited cardiotoxic effects (Fabel et al., 1972).

Human volunteers were exposed to FC-113 (similar to FC-11) at 500 or 1,000 ppm for 6 h/d, 5 d/wk during a 2-wk period. No adverse changes were seen in performance of complex mental tasks, clinical status, or results of biochemical tests. Breath analysis did not reveal a significant buildup of FC-113 (Reinhardt et al., 1971).

EFFECTS ON ANIMALS

FC-11 has not shown appreciable oral toxicity in rats and dogs in either acute or chronic studies (Haskell Laboratory, 1970; NCI, 1978). The chronic investigations include 1-mo, 90-d, and 2-yr studies. FC-11 was tested on the intact skin of mice. It was well tolerated by the skin, but retarded the recovery of wounds and burns and regrowth of hair (Quevauviller, 1960; Quevauviller et al., 1963). Dermal application of FC-11 to rabbit skin did not produce any lesions (Scholz, 1962). Transient conjunctival irritation was observed after

application of FC-11 solution to the rabbit eye. No irreversible eye damage was seen (Haskell Laboratory, 1970; Kudo et al., 1971).

The LC_{50} of FC-11 for rats in a 4-h exposure is 26,200 ppm (Haskell Laboratory, 1970). A 30-min exposure of rats at 50,000 ppm caused no signs of intoxication. Similar exposure at higher concentrations caused clinical signs of central nervous system depression. Concentrations of 100,000 ppm or more were fatal after less than 30 min (Lester and Greenberg, 1950). Acute exposure of other species of laboratory animals produced similar effects (Caujolle, 1964; Haskell Laboratory, 1970; Nuckolls, 1933; Scholz, 1962).

Rats, guinea pigs, monkeys, and dogs were continuously (24 h/d) exposed to FC-11 at approximately 1,000 ppm for 90 d. One monkey died on day 78, but its death was not definitely linked to exposure to FC-11. No other animals were affected. No compound-related pathologic changes were observed. Another group of animals was exposed at 10,250 ppm, 8 h/d, 5 d/wk for 6 wk without adverse effects (Jenkins et al., 1970). In another study, dogs, cats, guinea pigs, and rats were exposed to FC-11 for 3.5 h/d, 5 d/wk for 4 wk; the dogs were exposed at 12,500 ppm, and the other animals at 25,000 ppm. No microscopic evidence of damage to the lungs, heart, spleen, liver, or kidneys was seen (Scholz, 1962).

Rats and mice exposed to FC-11 at 1,000 or 5,000 ppm for lifetime showed no evidence of carcinogenicity or other adverse health effects (C. Maltoni, unpublished).

FC-11, like other chlorofluorocarbons and hydrocarbons, was capable of sensitizing the beagle heart to exogenous epinephrine in standard 5-min cardiac-sensitization screening studies. A 5-min cardiac-sensitization screening test consists of a control intravenous injection of epinephrine at 8 μg/kg, followed later by a 5-min exposure to fluorocarbon and then a challenge with 8 μg/kg intravenously. Manifestation of arrhythmia (multiple consecutive ventricular beats), which is considered to pose a serious threat to life, or cardiac arrest (ventricular fibrillation) constitutes a positive test. The lowest concentration that elicited a marked response in exposed dogs was 5,000 ppm. A concentration of 1,000 ppm was ineffective. Dogs exposed while running on a treadmill (to increase their circulating epinephrine) were not sensitized at concentrations up to 10,000 ppm (Mullin et al., 1972).

Azar et al. (1973) studied nonanesthetized dogs and reported that the average blood concentrations of FC-11 associated with cardiac sensitization were 28.6 μg/L in arterial and 19.7 μg/L in venous blood.

Belej and Aviado (1975) studied cardiopulmonary toxicity of propellants in anesthetized dogs. They concluded that FC-11, unlike eight other halocarbon propellants studied, produced bronchodilation,

rather than bronchoconstriction. It also reduced pulmonary compliance and respiratory minute volume. FC-11 had the greatest tachycardiac effect of all compounds studied. Effects of FC-11 on the circulatory system were summarized by Aviado (1975, 1978).

In a bioassay supported by the National Cancer Institute (1978), oral FC-11 was not carcinogenic in rats or mice. No significant increase in tumor formation was seen in a study that used subcutaneous injection (Epstein et al., 1967). Additionally, FC-11 has not been shown to be mutagenic in the Salmonella typhimurium reverse-mutation bioassay (C.F. Reinhardt, Haskell Laboratory, personal communication). No embryotoxic, fetotoxic, or teratogenic effect of FC-11 was shown in a study with pregnant rats and rabbits; the animals were exposed for 2 h/d to a 200,000 ppm of a FC-11/FC-12 (1:9) mixture from day 4 to 16 of gestation for rats and from day 5 to 20 for rabbits (Paulet, 1976). Blake and Mergner (1974) studied the biotransformation of ^{14}C-labeled FC-11 (8,000-12,000 ppm) in male and female beagles after a short (6-20 min) inhalation. Essentially all the inhaled fluorocarbon was recovered in the exhaled air within 1 h. Only traces of radioactivity were found in urine or exhaled CO_2. The investigators concluded that FC-11 is relatively refractory to biotransformation after a short inhalation exposure and that it is rapidly exhaled chemically unaltered.

INHALATION EXPOSURE LIMITS

The American Conference of Governmental Industrial Hygienists (1980, 1983) recommended a ceiling of 1,000 ppm. The Occupational Safety and Health Administration's (1983) permissible exposure limit currently in effect for FC-11 is a ceiling of 1,000 ppm.

COMMITTEE RECOMMENDATIONS

The previous EELs and CEL were established by the Committee on Toxicology in 1966. No adverse effects have been observed in dogs, monkeys, guinea pigs, or rats continuously exposed to FC-11 at 1,000 ppm for 90 d or in a similar group repeatedly exposed at 10,250 ppm, 8 h/d, 5 d/wk for 6 wk (Jenkins et al., 1970). Dogs exposed at 12,500 ppm and cats, guinea pigs, and rats at 25,000 ppm for 4 wk were not affected (Scholz, 1962). Human exposure to FC-113 (a compound similar to FC-11) at 1,500 ppm produced no adverse effects after 2.75 h. Signs of central nervous system involvement were seen after exposure to FC-113 at 2,500 ppm for 30 min. These effects were reversible, and the volunteers appeared normal 15 min after cessation of the experiment (C.F. Reinhardt, Haskell Laboratory, personal communication). FC-11 can sensitize the mammalian heart to epinephrine and result in serious cardiac arrhythmia. However, the possible combined effects of excitement-stimulated epinephrine release and FC-11 on the heart are not easy to predict. It would therefore be prudent to take a more

cautious approach to EEL recommendations than was taken by the Committee in 1966, when it was not aware of the sudden-sniffing-death syndrome. The previous 60-min and 24-h EELs are too high, on the basis of experimental cardiac sensitization of dogs, which occurred when they were exposed at 5,000 ppm and given a large challenge injection of epinephrine. However, no sensitization occurred in resting dogs exposed at 1,000 ppm and given epinephrine or in exercising dogs exposed at 10,000 ppm (Mullin et al., 1972).

Based on the no-observed-adverse-effect concentration of FC-113 in humans (1,500 ppm for 2.5 h), the 10,000-ppm concentration (which did not cause cardiac arrhythmia in exercising dogs), and the results in standard 5-min cardiac-sensitization screening tests in dogs, the Committee recommends a 60-min EEL of 1,500 ppm. It bases its 24-h EEL on the finding in humans that repeated exposure to FC-113 at 500 or 1,000 ppm for 2 wk did not result in adverse effects. Finally, using the no-observed-effect concentration of 1,000 ppm in a continuous-exposure animal study and applying an uncertainty factor of 10, the Committee arrives at a recommended CEL of 100 ppm.

The present Committee's recommended EELs and CEL for FC-11 and the limits proposed in 1966 are shown below.

	1966	1984
60-min EEL	30,000	1,500 ppm
24-h EEL	20,000	500 ppm
90-d CEL	1,000	100 ppm

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APPENDIX D

EXTRAPOLATION OF DATA--ORAL TO INHALATION AND ANIMAL TO HUMAN

It is sometimes necessary to extrapolate data based on oral exposure of animals (such as rats), given in milligrams per kilogram (mg/kg), to inhalation exposure of humans, in milligrams per cubic meter of air (mg/m^3).

Two approaches are possible: one can extrapolate from rat oral data to human oral dose and then to human inhalation concentration; or one can extrapolate from rat oral data to rat inhalation concentration and then to human inhalation concentration. The first is more acceptable, because it does not rely on a similarity between rat and human breathing rates. A 70-kg man breathes 7-10 L/min at rest, 20 L/min when moderately active, and 40-60 L/min when engaged in heavy work. A resting 113-g (0.113-kg) rat breathes 75 ml/min (0.073 L/min)--almost 5 times as much as a human on a weight-for-weight basis.

FIRST APPROACH

Oral dose of 1 mg/kg per day in rat is assumed to be equal to oral dose of 1 mg/kg per day in human.

A 70-kg man at rest inhales 15 m^3 of air over a 24-h period. Dose inhaled by 70-kg man in 1 d = $[(1\ mg/kg)(70\ kg)]/(15\ m^3) = 4.7\ mg/m^3$.

If one considers a practical situation in which a 24-h period is involved and one wishes to estimate dose of a moderately active man, taking into account that he sleeps at night, the 24-h respiration volume changes from 15 m^3 to 20 m^3. The calculation, using this approach, is: $[(1\ mg/kg)(70\ kg)]/(20\ m^3) = 3.5\ mg/m^3$.

SECOND APPROACH

A 113-g rat at rest inhales 73 ml/min or 0.105 m^3 over a 24-h period.

Oral dose of 1 mg/kg in rat = inhalation dose in rat of $[(1\ mg/kg)(0.113\ kg)]/(0.105\ m^3) = 1.08\ mg/m^3$.

APPENDIX E

CONVERSION FACTORS

1. From gas in gas to ppm by volume, at 25°C and 760 mm Hg:

$$\frac{mg}{m^3} \times 10^{-3} = \frac{mg}{L}$$

$$\frac{mg}{m^3} \times \frac{24.450}{(mol.\ wt.)} = ppm$$

$$\frac{micromoles\ of\ gas}{mole\ of\ air} = ppm$$

$$\%\ by\ volume \times 10^{-4} = ppm$$

2. From gas, liquid, or solid in liquid to ppm by weight:

$$\frac{mg}{L} = ppm$$

$$\frac{mole}{L} \times mol.\ wt. \times 10^{3} = \frac{mg}{L}$$

3. From concentration in air to ingested dose:

$$\frac{mg}{m^3} \times volume\ of\ inspired\ air^*\ in\ m^3 \times \%\ retention/100 = mg$$

4. From concentration in diet to ingested dose:

$$ppb\ in\ diet \times 10^{3} = ppm\ in\ diet$$

$$ppm\ in\ diet = mg/kg\ in\ diet = \mu g/g\ in\ diet$$

$$mg/kg\ diet \times \frac{food\ intake,\ kg/d}{body\ weight,\ kg} = mg/kg\ per\ day$$

5. From percent to concentration:

$$w/w\ \% = 10^{-2}\ kg/kg$$
$$v/v\ \% = 10^{-2}\ L/L$$
$$w/v\ \% = 10^{-2}\ kg/L$$
$$g\ \% = g/100\ ml$$

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*COT assumes that a 70-kg man inhales 10 m^3 of air in an 8-h workday. Volume of inspired air = (minute volume) (time of exposure).

Reference values used by COT:

Daily water intake, adult human		2L			
Daily food intake, rat		20 g			
	Man	Woman	Child, 10 yr	Infant, 1 yr	Newborn
Body Weight, kg	70	58			
Blood volume, L	5.2	3.9			
Total blood weight, g	5,500	4,100			
Red-cell volume, L	2.2	1.35			
Red-cell weight, g	2,400	1,500			
Plasma volume, L	3.0	2.5			
Plasma weight, g	3,100	2,600			
Urine volume, L/d	1.4	1.0	1.0	0.45	
Surface area, cm^2	18,000	16,000			
Minute volume, resting, L/min	7.5	6.0	4.8	1.5	
Minute volume, light activity, L/min	20.0	19.0	13.0	4.2	1.5
Volume inspired air, 8-h workday, m^3	9.6	9.1			
Volume inspired air, rest all day, m^3	15				
Volume inspired air, moderate activity plus sleep, m^3	20				

APPENDIX F

EEGLS FOR CARCINOGENS

When a substance under evaluation is an animal or human carcinogen, a separate quantitative risk assessment is undertaken in recognition of the fact that even limited exposure to such agents can theoretically increase the risk of cancer (Office of Science and Technology Policy, 1985).

Estimating EEGLs for chemical carcinogens is complicated. Vainio et al. (1985) extracted data from the first 38 volumes of IARC Monographs on chemicals and exposures for which some data on carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals existed. In all, 288 chemicals, industrial processes and complex mixtures fulfilled these criteria. For 30 chemicals or mixtures of chemicals and nine industrial processes there was sufficient evidence of carcinogenicity in humans; and for 63 chemicals and mixtures of chemicals and for five industrial processes, there was evidence that these exposures were probably carcinogenic in humans. For 61 chemicals or groups of chemicals and six industrial processes or occupations, no evaluation of carcinogenicity in humans could be made. For 115 chemicals, there is sufficient evidence of carcinogenicity in experimental animals, but no epidemiologic data are available.

Many experimental investigations involve high-dosage, long-duration exposures to compensate for the small number of animals that are used. Data on short-term or single exposures are virtually nonexistent.

Substances that are carcinogenic in one mammalian species are often carcinogenic in another; species differences in metabolic capacities sometimes account for less than perfect correlations. Further studies are needed to establish which species most closely approximate humans. It would not be surprising to find that this is different for different chemical classes. Quantitative data from humans are sparse. In the absence of human data, it is usually assumed that carcinogenic risk derived from animal data is directly and quantitatively applicable to humans. Extrapolation from high-dose animal exposures to low-dose human exposures is often required, and this involves many uncertainties. The shape of the dose-response curve at low doses is generally unknown, especially below the 1% tumor-response range. Repair rates, possible nonlinearities, and other factors involved in low-dose studies are not available. Variations in personal habits, diet, other exposures, intercurrent disease, and age at first exposure

contribute additional uncertainties in predicting human effects. Mathematical models suggest greater precision than exists.

The role of short-term exposures in producing cancer is not clear. On the one hand, any exposure to a carcinogen has the potential to add to the probability of carcinogenic effects, and such exposure should be avoided or at least minimized. Nitrosoureas, for example, are carcinogenic after a single exposure, and hydrazines and other alkylating agents might also have this capacity. On the other hand, the effects of long or repeated exposures could greatly overshadow brief exposures (up to 24 h). Industrial accidents involving brief exposures to vinyl chloride or benzidine may be in that category. A familiar example of strong relation of cancer risk to duration of exposure is tobacco-smoking. Exposure to tobacco products for a day or less, although not carrying zero risk, carries much less risk than chronic smoking and will not be likely to add significantly to the risk of tobacco-related cancer.

The following mathematical approach is applicable for EEGL computations for carcinogens.

1. If there has been computed an exposure level d (usually in ppm in air), which after a lifetime of exposure is estimated to produce some "acceptable" level of excess risk of cancer--say, 1×10^{-6}--this has been called a "virtually safe dose" (VSD). Computation of the dose d, if not already done by a regulatory agency, will be computed by COT in accordance with generally accepted procedures used by the major regulatory agencies--i.e., using the multistage no-threshold models for carcinogenesis and the appropriate body weight/surface area adjustments when extrapolating from an animal species to humans.

2. If carcinogenic effect is assumed to be a linear function of the total (cumulative) dose, then for a single 1-d human exposure an acceptable dose (to yield the same total lifetime exposure) would be d x 25,600 (there being approximately 25,600 days in an average lifetime); the allowable 1-d (24-h) dose rate would be

$$d \times 25{,}600.$$

3. Because of uncertainties about which of several stages in the carcinogenic process a material may operate in, and because of the likely low age of military persons, it can be shown from data of Crump and Howe (1984) that the maximal additional risk that these considerations contribute is a factor of 2.8. As a conservative approach, the acceptable dose is divided by 2.8, i.e.,

$$\frac{d \times 25{,}600}{2.8}$$

If a lifetime excess risk, R, is established by DOD (for example, at 1×10^{-4}, as has been suggested by the International Council on Radiation Protection for nuclear power plant workers), then the appropriate extent of risk at the EEGL would be

$$\frac{d \times 25{,}600}{2.8} \times \frac{R}{\text{level of risk at } d} .$$

(In the example given here, the level of risk at d was no more than 1×10^{-6}.) If R is 1×10^{-4}, then R/risk at d = $10^{-4}/10^{-6}$ = 100.

4. If a further element of conservatism is required (for example, where animal data need to be translated to human risk), an additional safety factor can be used as a divisor.

The assumption that the carcinogenic response is directly proportional to total dose is likely not to hold for all materials and all tissues that these materials affect. Appropriate mathematical models need to be developed for materials that have other mechanisms for the induction or promotion of cancer. Thus, if a proto-oncogene needs to go through several mutations before it is "turned on" to produce frank cancer cells, the material that leads to the final mutation might show a higher-degree dose-response function than the material producing the first-stage mutation. Knowledge of mechanisms that produce different dose-response curves should, in the future, lead to better material/mechanism-specific risk assessment computations.

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