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EVALUATION OF CHLOROPENTAFLUOROBENZENE AS AN INTAKE SIMULANT FOR CHEMICAL DEFENSE TRAINING

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

JAMES N. McDOUGAL, Lt Col, USAF, BSC
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13 ABSTRACT (Maximum 200 words)

For a number of years the U S. Air Force has been performing research to develop safe intake simulants for chemical warfare agents (CWA) to provide accurate and quantitative real-time assessment of troop proficiency and gear efficacy during chemical warfare (CW) field exercises. Chloropentafluorobenzene (CPFB) was identified and evaluated as a candidate inhalation simulant, and was determined to possess desirable physiochemical and toxicological properties. These include rapid uptake, low metabolism and toxicity, rapid and predictable clearance, real-time detectability by existing portable "breathalyzer" technology and by fielded CWA detectors, realistic canister breakthrough, and commercial availability. A physiologically based pharmacokinetic (PBPK) model for CPFB has been developed which accurately describes the timecourse of blood and exhaled air concentrations during and following inhalation exposures of rats and primates to CPFB. This model has been employed to predict human exhaled air concentrations for several hours following brief CPFB exposures, such as might be experienced in training exercises using CPFB as an intake simulant. These simulants could be used to determine the exhaled air concentrations at which personnel would have been incapacitated had the exposure been to a real agent. The PBPK model was also used to calculate internal dose measures for a quantitative assessment of safe exposure criteria for the use of CPFB in such exercises. To assure the safety of personnel it is recommended that field exercises be designed to avoid exposures greater than 30 parts per million (ppm), with the daily (8 h) time weighted average not to exceed 3 ppm. This exposure guideline should not impair use of CPFB since field analytical methods can measure CPFB at part per trillion levels.

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PREFACE

This is one of a series of reports describing the results of the experimental laboratory programs conducted by the Toxic Hazards Research Unit operated by ManTech Environmental Technology, Inc. This document serves as the final report on a risk assessment effort to define the maximum safe exposure level for the use of chloropentafluorobenzene as an inhalation simulant based on available physicochemical and toxicological data. The research described in this report began in October 1991 and was completed in October 1992 under Department of the Air Force Contract Number F33615-90-C-0532 (Study No. F13). Lt Col James N. McDougal served as Contract Technical Monitor for the Toxicology Division, Occupational and Environmental Health Directorate. Armstrong Laboratory, located at Wright-Patterson Air Force Base, OH.

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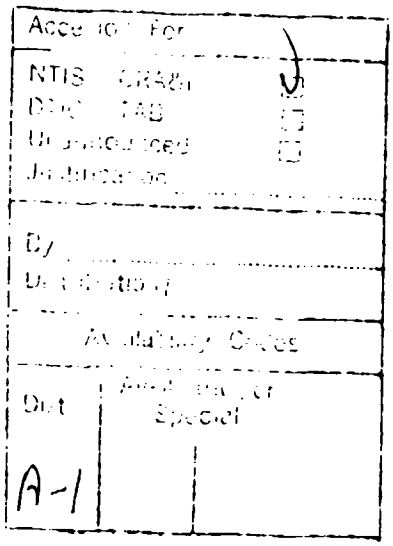

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ABBREVIATIONS

CHO	Chinese hamster ovary
CPFB	Chloropentafluorobenzene
CT	Concentration-time product
CW	Chemical warfare
DMMP	Dimethyl methylphosphonate
ECD	Electron capture detector
g	Gram
GST	Glutathione conjugation
h	Hour
HCB	Hexachlorobenzene
HGPRT	Hypoxanthine-guanine phosphoribosyl transferase
kg	Kilogram
L	Liter
mg	Milligram
mg/m^3	Milligram per cubic meter
min	Minute
NOAEL	No observed adverse effect level
PBPK	Physiologically based pharmacokinetics
ppm	Parts per million
ppt	Parts per trillion
RH	Relative humidity
SCE	Sister chromatid exchange
TWA	Time-weighted average

SECTION 1

INTRODUCTION

The U S Air Force and other NATO agencies have programs for the development of intake simulants of chemical warfare (CW) agents for use in CW training exercises. These intake simulants would allow quantitative assessment of troop proficiency and chemical defense gear efficacy. Inhalation simulants provide information on inhalation exposure, primarily assessing proficiency of mask use. Current intake simulants, such as methyl salicylate rely on troop feedback by description of the odor, and do not allow quantitative and objective exposure determination. For the past several years, the Air Force has been developing candidate uptake simulants that would allow objective quantitation of inhalation exposure, providing real-time feedback on decrement in performance had the exposure been to a live agent.

BACKGROUND

In a 1982 study funded by the Air Force, A. D. Little developed a list of candidate chemical simulants for the agents sarin, soman, and tabun (Little, 1982a). Vapor pressure was used as the initial screening criteria, with acceptable candidates designated as volatile (0.27 to 2.1 mmHg), intermediate (0 03 to 0.27), low (0.0001 to 0.03), or nonvolatile (less than 0.0001). From available sources, a list of 120 compounds falling into one of the four vapor pressure categories was compiled. These candidates were further screened through a literature search based on chemical properties, available toxicological data, and detection in body fluids. The list was narrowed to seven candidates: four volatile (dimethyl sulfoxide, dipentene, butanethiol, and hexanethiol) and three intermediate (methyl benzoate, benzyl alcohol, and octanoic acid). Although none of the compounds fully meet all Air Force-specified criteria, all had documented, approved human exposure. A more exhaustive search for compounds having low or intermediate vapor pressure yielded six chemicals that met a majority of physical criteria and had low toxicity: diethyl sebacate, dibenzyl ether, isoamyl benzoate, anisyl phenylacetate, *n*-octyldecanethiol, and phenylethyl phenylacetate (Little, 1982b).

During this period, the Air Force Toxic Hazards Division also evaluated the toxicological risk associated with dimethyl methylphosphonate (DMMP), which had been proposed as a general Air Force training simulant. Possessing similar physical characteristics to organophosphate nerve agents, detectability with agent field detectors, and having low acute toxicity, DMMP appeared to be an ideal agent simulant. However, toxic effects seen after longer-term exposure, including testicular atrophy in rodents (MacEwen and Vernot, 1985), precluded its use on troops. The compounds identified by A. D. Little as candidate simulants all failed to satisfy the minimal criteria for an acceptable uptake simulant when reevaluated by the Air Force. The primary deficits involved

detectability and biological inertness; due to extensive and often complex metabolism, it would not be possible to quantify exposure by measuring the compound or a single metabolite in a bodily fluid. Rather than continue to screen the literature for acceptable compounds, an alternate approach was developed: the requirements for a simulant would be defined, and a compound developed to meet these criteria (Jepson et al., 1985). In particular, selection was to be based on:

- resistance to biological metabolism;
- partitioning properties between air, blood, and tissues;
- physical characteristics (to generate realistic exposures); and
- detectability in low concentration.

INTAKE SIMULANT DEVELOPMENT

Perfluorocarbons were initially chosen as the class of compounds to be investigated based on their relative detectability and biological inertness. It was determined, however, that perfluorocarbons were not sufficiently soluble in biological tissues to serve as intake simulants, so compounds in which one or more of the fluorines was replaced by another halogen were also investigated (see Table 1). Replacement of a fluorine by bromine significantly increased tissue solubility, but also lead to rapid metabolism; substitution with chlorine gave compounds with intermediate properties. Of the seven commercially available fluorohalocarbons evaluated in the study (Jepson et al., 1985), chloropentafluorobenzene (CPFB) was identified as the most promising candidate, providing good detectability, desirable partitioning characteristics, relative biological inertness, and acceptable physical properties.

TABLE 1. PHYSICAL PROPERTIES OF CANDIDATE SIMULANTS

Compound	Formula	MW	BP °C	Density g/mL	Vap Press mmHg 25 °C	Blood:Air Partition
Perfluoropentane	C_5F_{12}	288	31	1.61	646.0	0.22
Perfluorohexane	C_6F_{14}	338	57	1.65	263.0	<0.1
Perfluoroheptane	C_7F_{16}	388	80-82	1.69	92.5	<0.1
Perfluorodecalin	$C_{10}F_{18}$	462	143	1.96	5.8	<0.1
Perfluorobenzene	C_6F_6	186	78	1.59	85.6	4.1
Bromopentafluorobenzene	C_6F_5Br	247	135	1.94	3.8	32.9
Chloropentafluorobenzene	C_6F_5Cl	202	117	1.66	14.1	13.5
1,3 Dichlorotetrafluorobenzene	$C_6F_4Cl_2$	219	156	1.66	3.0	35.3

(continued)

TABLE 1. Continued

Compound	Formula	MW	BP °C	Density g/mL	Vap Press mmHg 25 °C	Blood:Air Partition
Chlorofreon E-2	$C_8F_{17}ClO_2$	547	---	1.71	16.0	<0.1
Chlorofreon E-3	$C_{12}F_{19}ClO_3$	653	---	1.74	1.0	<0.5
1,1,2 Trichloroperfluorooctane	$C_8F_{15}Cl_3$	487	120	1.55	1.0	0.90
1,2 Dichloroperfluorostyrene	$C_8F_8Cl_2$	319	96	----	1.0	358.
4 Chlorobenzotrifluoride	$C_7H_4F_3Cl$	180	136	----	7.0	38.7
2,3 Dichloro-5-trifluoromethyl-pyridine	$C_6H_2F_3Cl_2N$	216	92	----	1.5	95.8
2,6 Dichloro-4-trifluoromethyl-pyridine	$C_6H_2F_3Cl_2N$	216	111	----	1.5	111.

Figure 1 shows the results of gas-uptake analysis of CPFB in rats. In the gas-uptake analysis, several animals are maintained in a closed chamber, and the air is continuously recirculated. Oxygen (O_2) is replenished and carbon dioxide is scrubbed as necessary to maintain stasis. A known amount of test chemical is then added to the chamber, and the concentration of the chemical in the chamber is monitored over time. The rapid initial decline in the chamber concentration of CPFB seen in Figure 1 is due to tissue uptake and demonstrates that CPFB is readily absorbed. Following the tissue-uptake phase, any further decline in chamber concentration would indicate loss of chemical because of metabolism. The fact that the concentration curve for CPFB reaches a plateau after the first few hours, suggests that CPFB is not extensively metabolized. By comparison, the chamber concentration of bromopentafluorobenzene decreased by more than 20% between Hours 3 and 6 under the same conditions. A physiologically based pharmacokinetic (PBPK) model for CPFB was developed, and the closed chamber data was analyzed to quantify the rate of metabolism. It was determined (Jepson et al., 1985) that metabolism was first-order, with a rate constant of 2/h (for a 1 kg animal, scaled by body weight to the -0.3 power), indicating that CPFB is poorly metabolized in comparison to other halogenated hydrocarbons.

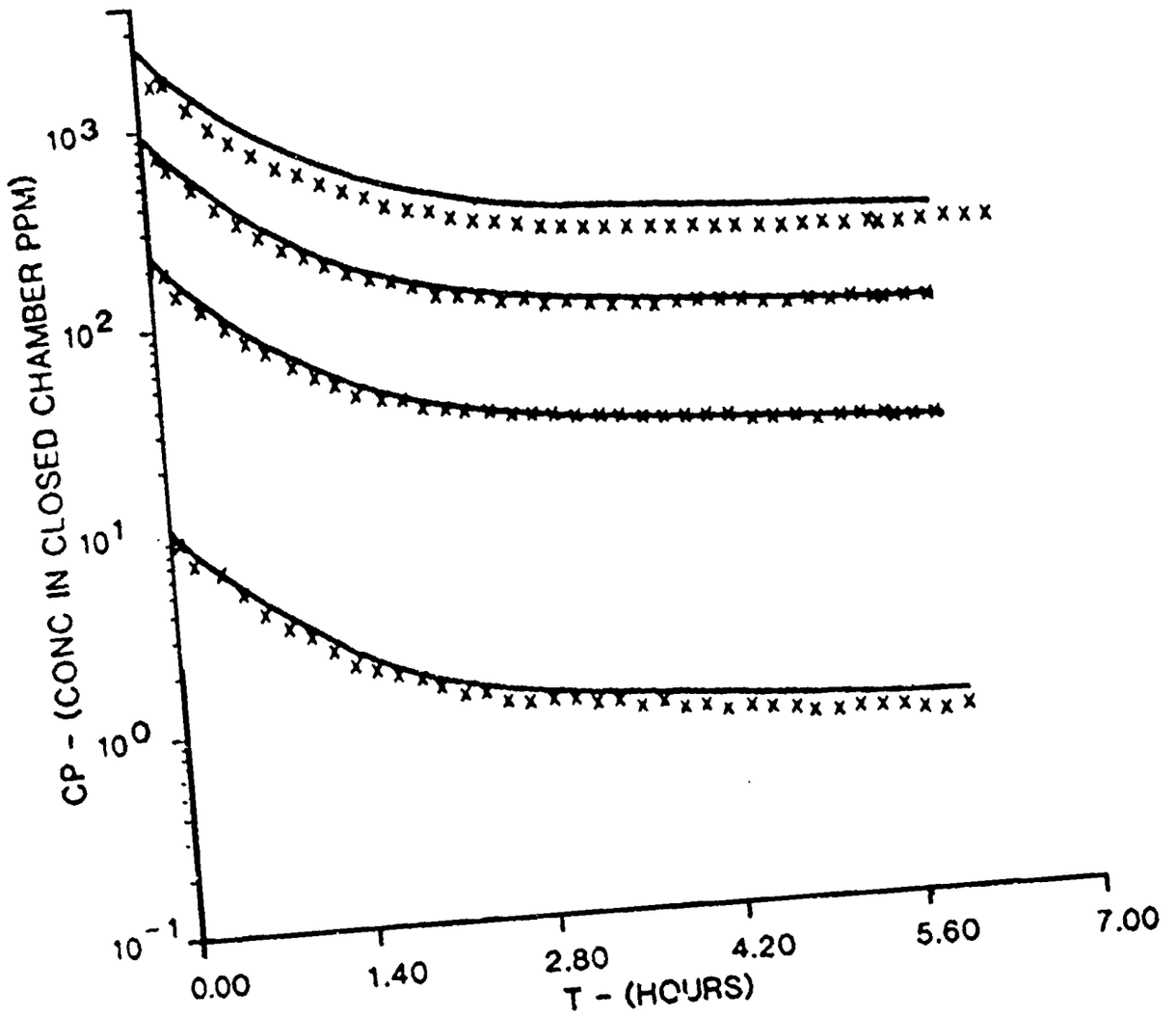

Figure 1. Computer Simulation (Solid Line) vs. Observed (x) Chamber Concentrations (ppm) Over Time (h) for Rats Exposed to Initial Concentrations of 10, 250, 1000, and 1800 ppm CPFB in a Closed, Recirculating Chamber System. (Adapted with permission from Jepson et al., 1985).

SECTION 2

SIMULANT EVALUATION: PHYSICAL PROPERTIES

As shown in Table 2, CPFB is a volatile, nonflammable liquid with a very high vapor density (which helps to prevent excessive vertical dispersion when released). It is unreactive and is compatible with essentially all materials; therefore, it does not present any unusual storage or handling difficulties.

AGENT MIMICRY

Chloropentafluorobenzene possesses physical properties appropriate for the generation and maintenance of a reasonable field exposure environment, and the simulation of a nonpersistent CW agent (see Table 2). Canister penetration studies (Figure 2) indicate that CPFB is readily adsorbed by a dynamically conditioned (80% relative humidity [RH]) carbon filter with a capacity of approximately 480,000 mg min/m^3. Using a 4000 mg/m^3 challenge and a 30 L/min 80% RH airstream, CPFB had a breakthrough time of 120 min. The penetration profile after breakthrough is fairly steep, and is consistent with the behavior of many other organic compounds with boiling points near 100 °C.

TABLE 2. PHYSICAL PROPERTIES OF CPFB

Chemical State (20 °C)	colorless liquid
CAS Registry Number	344-07-0
Chemical Formula	C_6F_5Cl
Molecular Weight	202.51
Boiling Point (°C)	102.0
Flash Point (°C)	not flammable
Liquid Density (g/mL)	1.66
Vapor Density (versus air)	7.0
Vapor Pressure (mmHg, 20 °C)	14.1
Volatility (mg/m^3)	1.53×10^5
Action on metals or other materials	Inert with most materials; liquid CPFB may dissolve some plastics (e.g., polycarbonate); fluorinated polymers (e.g., Teflon) may swell slightly

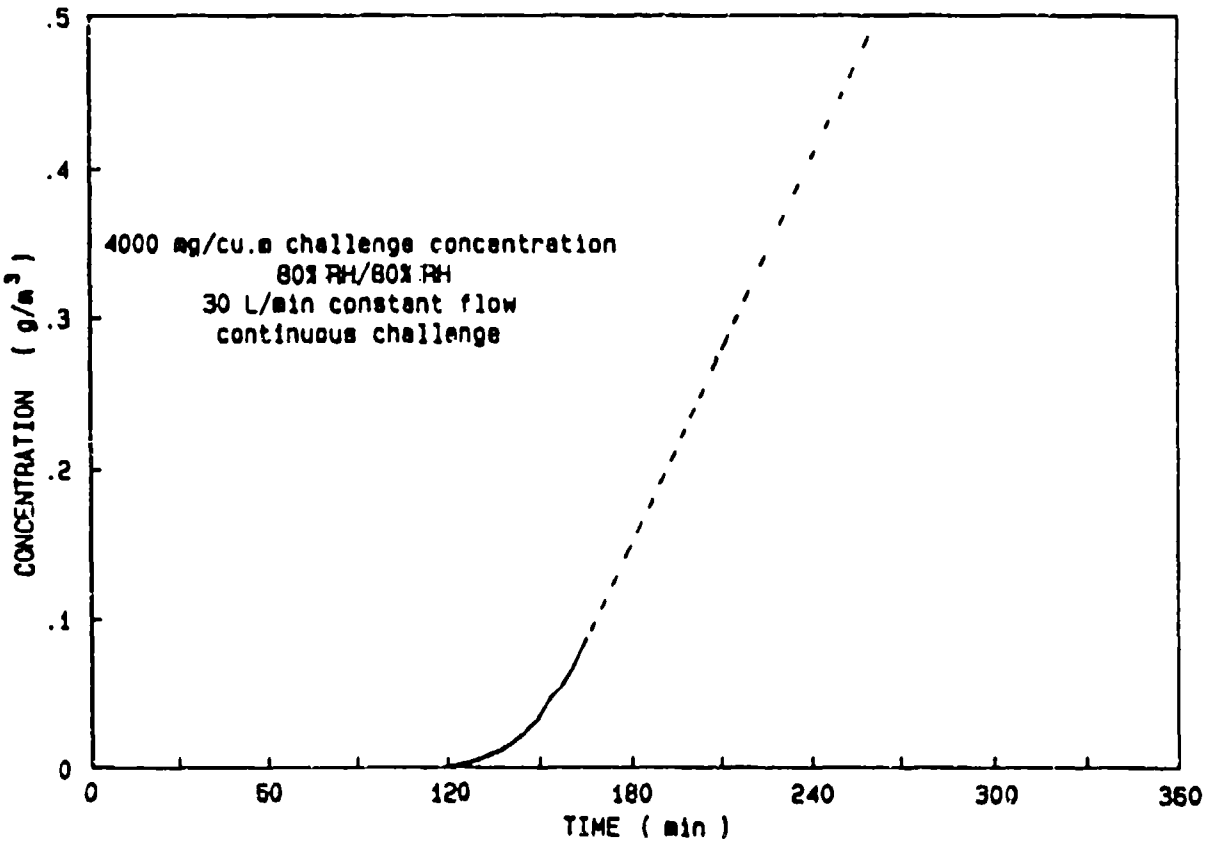

Figure 2. CPFB Penetration Curve for an ASC/T Carbon Filter Canister; 4000 mg/m^3 Challenge, 30 L/min Constant Air Flow (80% RH). Curve represents CPFB concentration (g/m^3) measured downstream of the canister over time (min) while a constant concentration is maintained upstream of the canister. (Courtesy of Dr. J. Pagatto, Defense Research Establishment Ottawa [DREO], Ottawa, Ontario, Canada).

EXHALED AIR ANALYSIS

To evaluate the possibility that direct measurement of CPFB in exhaled air could be used to determine total exposure, a study was conducted in which rats were exposed by inhalation for 1 h to CPFB at 300, 600, and 1200 ppm, and expired CPFB concentrations were monitored for 1 h postexposure (Vinegar et al., 1990). Exhaled breath concentrations 1 h postexposure were still greater than 1% of the exposure concentration. The PBPK model for CPFB was modified to utilize actual measured ventilation rate data, and was then used to demonstrate the ability to accurately estimate exposure concentration on the basis of postexposure exhaled breath analysis. As a further evaluation of the feasibility of breath analysis, inhalation exposures to CPFB were conducted on eight anesthetized rhesus monkeys (Crank and Vinegar, 1992). Chloropentafluorobenzene concentrations in expired breath were measured during and after 15-min exposures at 300 ppm. Exhaled air concentrations predicted by the PBPK model were compared with those observed (results shown in

Figure 3). The continued presence of significant concentrations of CPFB (greater than 1% of exposure concentration) in exhaled air more than 20 min following the exposure, and the ability of the model to relate exposure and exhaled air concentrations, demonstrate the feasibility of using breath analysis for exposure determination in field exercises.

The PBPK model described in the Appendix was used to predict human exhaled air concentrations following short-term exposures to low levels of CPFB. The predictions of the model for concentration-time products (CTs) of 3, 9, 30, and 90 ppm-minutes are shown in Figure 4. To illustrate the use of the model to assess personnel exposure, an exhaled breath measurement of 10 ppb obtained 2 h after a simulant release would indicate exposure of that individual to a CT of 9 ppm-minutes. The equivalent agent exposure corresponding to a particular simulant exposure, and thus the likelihood of impaired performance under actual CW conditions, could be calculated in advance from the ratio of the CPFB challenge used in the exercise to the agent challenge anticipated during warfare. Personnel with CTs above the level corresponding to agent incapacitation could then be identified as casualties for the remainder of the exercise.

FIELD ANALYSIS

Because CPFB is perhalogenated, it is well suited to real-time detection at low concentrations in the environment or in exhaled breath using a direct reading sensor or an electron capture detector (ECD). Figure 5 illustrates the linear response of a direct reading chlorohydrocarbon sensor (Transducer Research Inc, Naperville, IL) to 2 to 100 ppm CPFB. This sensor would be useful for field detection, providing suitable sensitivity and excellent selectivity without O_2 or water interference. With only minor modification, an off-the-shelf portable explosives vapor analyzer (Scintrex, Concord, Ontario, Canada) utilizing an ECD could serve as a portable CPFB breathalyzer, providing detection to one part per trillion by volume. Either instrument would provide a noninvasive, real-time assessment of troop exposure using exhaled breath without the need for sample preconcentration.

PRACTICALITY

Chloropentafluorobenzene is commercially available (Aldrich Chemicals, Milwaukee, WI) at reasonable cost in liter quantities. Larger volumes could be produced at significantly lower cost (Bristol Chemicals, U.K.). Because CPFB is a neutral, nonreactive and nonflammable halocarbon, it presents no problems in routine handling or transport.

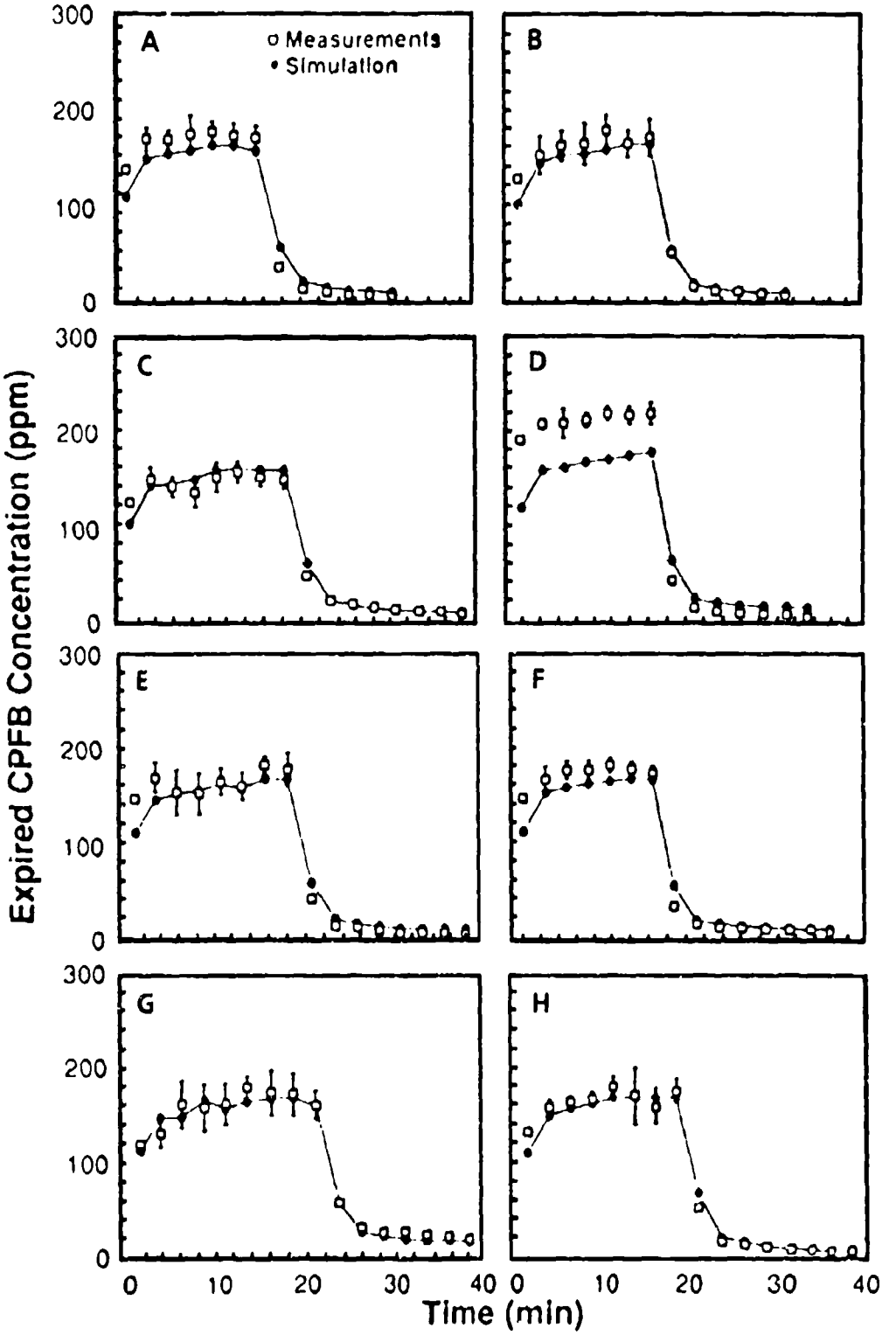

Figure 3. **Computer Simulation (Solid Line) vs. Observed Data (Bars, Representing Standard Error) for CPFB Concentration (ppm) in Expired Air of Eight Rhesus Monkeys During and After 20 min, 300 ppm CPFB Exposures.** (Reproduced from Crank and Vinegar, 1992).

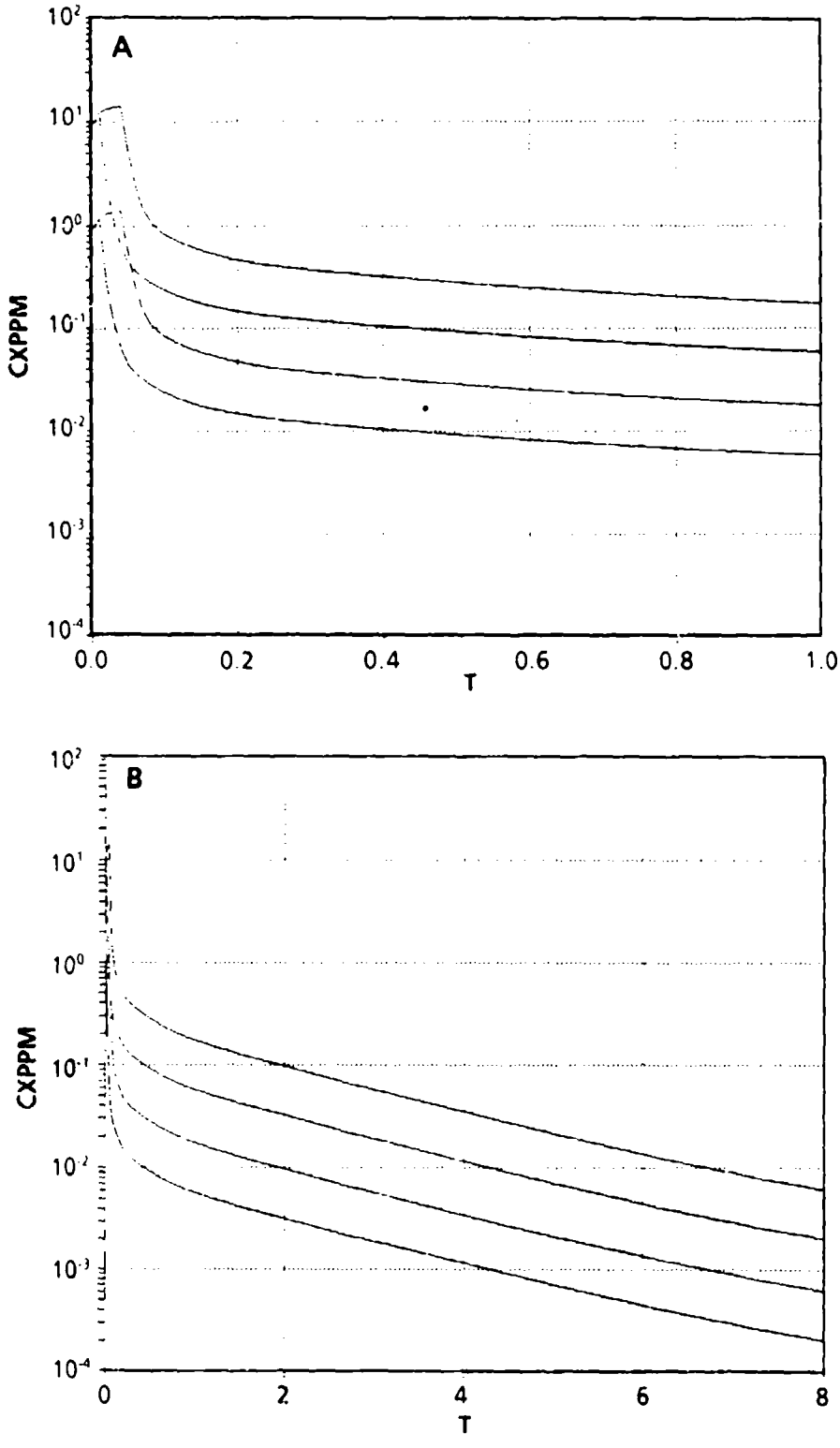

Figure 4. **Model-Predicted Exhaled Air Concentrations (ppm) Over Time (h) for Humans Exposed to 3 or 30 ppm CPFB for 1 or 3 min.**

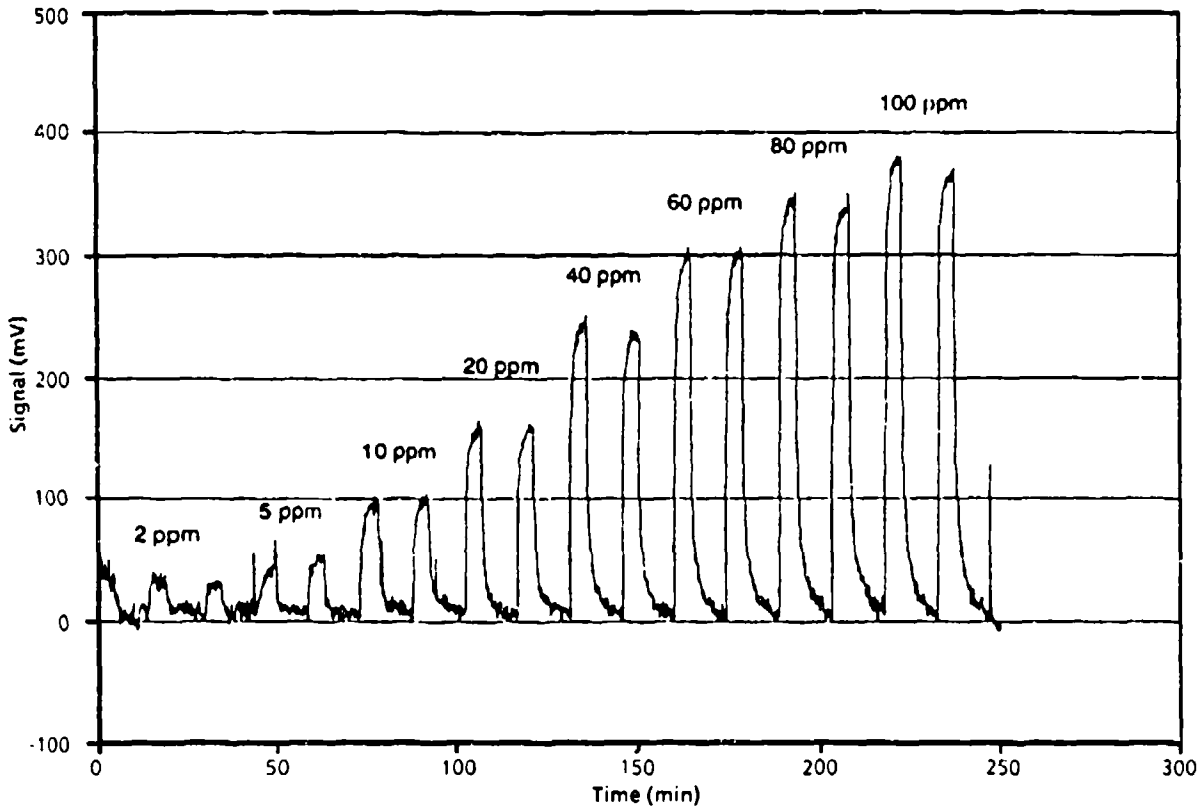

Figure 5 Direct-Reading Chlorohydrocarbon Sensor Response (mV) to 2 to 100 ppm CPFB Challenges in Air. (Courtesy of Transducer Research, Inc., Napierville, IL).

SECTION 3

SIMULANT EVALUATION: TOXICOLOGICAL PROPERTIES

In order to ensure that CPFB could be safely used as an intake simulant, a number of studies were performed to evaluate its potential toxicity. These studies were designed to elucidate any short-term or long-term effects, and to assess the likelihood that CPFB could be carcinogenic or teratogenic.

ACUTE TOXICITY

The primary irritation hazard, sensitization potential, and acute inhalation toxicity of CPFB were evaluated by Kinkead et al (1987). Chloropentafluorobenzene demonstrated no potential for skin sensitization in tests on guinea pigs, and was only a mild skin and eye irritant in rabbits. Short-term exposure to CPFB vapor was shown to pose no serious hazard by the inhalation route when all rats survived a 4-h exposure to an upper limit concentration of 4.84 mg/L (581 ppm), a concentration many orders of magnitude higher than that which is likely to be encountered in the field. Similarly, oral dosing indicates an LD_{50} of greater than 5 g/kg, which would classify CPFB as "practically nontoxic" (Kinkead et al., 1990a).

MUTAGENICITY/GENOTOXICITY

Chloropentafluorobenzene was tested for potential genotoxic activity by three different laboratories (Tu et al., 1986; Steele, 1987, Kutzman et al., 1990) using a battery of *in vitro* assays (Table 3). The first attempt to perform these assays (Tu et al., 1986) was compromised by experimental difficulties associated with the tendency of CPFB to precipitate out of solution and to dissolve the dishes. In the second study (Steele, 1987), it was again noted that CPFB dissolved the standard plastic dishes, so the study was performed in specially designed glass dishes. A third study (Kutzman et al., 1990) was performed by a reference laboratory because the results of the first two studies seemed to be somewhat equivocal.

Chloropentafluorobenzene does not appear to be mutagenic. The Ames Salmonella reverse mutation assay was uniformly negative in all studies, both with and without the addition of a rat liver S9 metabolic activation system. Similarly, all of the laboratories obtained negative results when CPFB was tested in mammalian cell culture for mutagenic activity at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in Chinese hamster ovary (CHO) cells.

The results of tests for genotoxicity were less consistent. There was some evidence of CPFB-induced sister chromatid exchange (SCE) and/or chromosomal aberration in the earlier studies, but the final study detected no increases in chromosomal aberrations and only observed SCE with the

addition of liver S9 metabolic activation (suggesting that generation of significant levels of metabolite may be required to observe this effect). In the case of the assay for unscheduled DNA repair synthesis in primary rat hepatocytes, the first study suggested that CPFB produced increased repair of DNA damage; however, both the second and third studies failed to confirm this finding. Cell transformation results were also variable, with only the second study showing any indication of an ability of CPFB to induce morphological transformation *in vitro* in BALB/c-3T3 cells.

TABLE 3. SUMMARY OF *IN VITRO* RESULTS FOR CPFB

In Vitro Assay	Tu et al.	Steele	Kutzman et al.
Ames Salmonella mutagenicity:			
-S9 activation	-	-	-
+ S9 activation	-	-	-
CHO/HGPRT gene mutation:			
-S9 activation	-	-	-
+ S9 activation	-	-	-
CHO sister chromatid exchange:			
-S9 activation	-	+ /-	-
+ S9 activation	-	+ /-	+
CHO chromosome aberration:			
-S9 activation	+ /-	+ /-	-
+ S9 activation	+ /-	+ /-	-
Primary rat hepatocyte DNA repair	+ /-	-	-
BALB/c-3T3 cell transformation:			
-S9 activation	-	+ /-	-
+ S9 activation		+	-

To resolve the question of whether CPFB could act as a genotoxic or cytotoxic agent under *in vivo* conditions, a 21-day exposure of mice to CPFB at 30, 100, and 300 ppm was performed (Kinkead et al., 1989). Under these conditions, CPFB did not induce an increase in SCE in the bone marrow of the exposed mice, and the rate of cellular proliferation in the bone marrow was not altered. Similarly, assessment of the micronucleated polychromatic and normochromatic erythrocyte populations during the exposures indicated a general absence of genotoxic activity. A PBPK model

for CPFB was used to assess the tissue exposure to CPFB during this study (Kinkead et al., 1990b. Based on the modeling, bone marrow tissue exposure to CPFB during the *in vivo* study was similar to or greater than the concentrations used in the *in vitro* assays.

The PBPK model described in the Appendix was used to reconfirm the results of this earlier analysis in the particular case of SCE. A dose-related increase in SCE was observed in 2-h *in vitro* exposures to CPFB ranging from 100 to 250 mg/L (area under the curve ranging from 200 to 500 mg/L-h) in the presence of metabolic activation. For the *in vivo* study, bone marrow exposure to CPFB (as estimated by the model described in the Appendix) averaged 288 mg/L during the daily 6-h inhalation exposures to 300 ppm CPFB, with a daily area under the curve of 2023 mg/L-h. The lack of *in vivo* response appears therefore to reflect differences between the *in vivo* and *in vitro* situation rather than failure to achieve sufficient tissue exposure levels. It is possible that the bone marrow does not possess sufficient metabolic activity, in comparison with the *in vitro* situation, to generate the active chemical species.

Full evaluation of the potential for CPFB to be carcinogenic would require a lifetime animal bioassay. However, a reasonable assessment of the likelihood that CPFB could act as a carcinogen can be made on the basis of the above results, taken together with the rather unremarkable results of the subchronic exposures. Chloropentafluorobenzene does not appear to be mutagenic, either in the presence or absence of metabolic activation, and the questionable *in vitro* suggestions of genotoxicity were not borne out by the *in vivo* studies. In addition, subchronic exposure (Kinkead et al., 1990a) did not produce any of the tissue changes, such as peroxisomal proliferation, which typically accompany promotional carcinogenesis in rodents. Therefore, it is not likely that CPFB would be carcinogenic, even under the conditions of a lifetime bioassay.

SUBACUTE AND SUBCHRONIC TOXICITY

Repeated exposure of rats to high concentrations of CPFB produced lethargy and incoordination (1000 ppm, 6 h/day, 4 days) or unresponsiveness (500 ppm, 6 h/day, 15 days), but no tissue pathology. No behavioral or histological effects were observed for exposure to 250 ppm, 6 h/day, for 15 days (Gage, 1970). (Note: Reference incorrectly shows the concentration of the lowest exposure level as 50 ppm; the original ICI report, TR/449, records the concentration as 250 ppm – J.C. Gage, personal communication.)

In a more recent study (Kinkead et al., 1989), 10 Fischer 344 rats and six B6C3F1 mice of each sex were exposed to 30, 100, and 300 ppm CPFB for 3 weeks (15 exposures). Exposure to the highest concentration caused a reduction in the growth rate of rats, but did not affect the growth rate of mice. Both rats and mice showed a dose-related increase in liver-to-body-weight ratios. Mice showed clear evidence of liver toxicity (hepatocytomegaly and hypertrophy) at the highest exposure

concentration. Another treatment-related change in the livers of male and female mice and female rats was an increase in the incidence of single-cell necrosis in all CPFB-exposed groups. The formation of hyaline droplets in the kidneys of male rats was also noted, but the severity of the lesion was minimal, and no other kidney effects were seen. Consistent with the earlier study, no behavioral effects were noted, even at the highest dose.

In order to better evaluate the impact of prolonged or repeated exposure to CPFB, as well as to determine a no-observable-adverse-effect level (NOAEL), a 13-week exposure of rats and mice was carried out at concentrations of 1.2, 6, and 30 ppm (Kinkead et al., 1990a; Kinkead et al., 1991). No treatment-related effects were observed at any concentration in either species. In particular, the single cell necrosis seen in the 3-week study at 30 ppm was not observed in the 13-week study at the same concentration. A review of the tissues from the earlier study confirmed the finding of an increase over control, but both the number and severity of the lesions were so slight that it was felt that the finding was biologically unimportant. Thus, the only adverse effects seen were those noted for the 300 ppm exposure concentration in the 3-week study. A concentration of 30 ppm was therefore recommended by the investigators as an NOAEL in humans to protect individuals subjected to repeated inhalation of CPFB for extended periods.

REPRODUCTIVE TOXICITY

To evaluate the teratogenic potential of CPFB, time-mated Sprague Dawley rats were dosed orally at 0.3, 1.05, and 3.0 g/kg/day on Days 6 through 15 of pregnancy (Cooper and Jarnot, 1992). There was a significant reduction in maternal body weight and a significant increase in maternal liver weight at the highest dose. The percentage of postimplantation fetal loss was also greater only at the highest dose. Fetal weight and length differed significantly from the controls at both the high and intermediate doses, indicating a slightly increased fetotoxicity compared to the dam. The number of malformations and variations observed at any of the dose levels did not differ from controls, suggesting that CPFB is not teratogenic.

METABOLISM

Studies of the uptake of CPFB in a closed, recirculated chamber were consistent with a slow rate of first order metabolism (Jepson et al., 1985). In the same studies, the rate of metabolism of the related compound, bromopentafluorobenzene, was unaffected by pretreatment with the potent P_{450} inhibitor, pyrazole, suggesting that metabolism of these two compounds is not associated with the mixed function oxidase system. This finding contrasts with the metabolism of the related compound, hexachlorobenzene (HCB), which is characterized by both an oxidative (P_{450}) pathway and a glutathione conjugation (GST) pathway (Renner, 1988). This apparent difference between CPFB and HCB is consistent with the results of a comparative study of a series of dihalomethanes

(Gargas et al., 1986), which also feature competitive P_{450} and GST metabolism. This study demonstrated that the fluorine-substituted congeners, CH_2F_2 and CH_2FCl, showed little evidence of P_{450} activity, whereas compounds containing chlorine and/or bromine, but not fluorine, were readily metabolized by both pathways. Of course, these results were observed in rodents, and the possibility of species differences in the metabolism of CPFB cannot be ruled out. Evaluation of CPFB metabolism in human tissues would be necessary to confirm the assumption of equivalent metabolism across species.

In the case of HCB, the GST pathway initially produces *N*-acetyl cysteine conjugates which cleave to form chlorothiophenols, which are in turn subject to further metabolism (Renner, 1988). It can therefore be hypothesized that the liver toxicity associated with repeated exposure to CPFB may result from the generation of the analogous metabolite, pentafluorothiophenol, a toxic compound with an LD_{50} of 56 mg/kg (NIOSH, 1992).

EXPOSURE GUIDELINE DETERMINATION

The following discussion documents the rationale used to develop exposure guidelines for safe use of CPFB as an intake simulant during chemical defense training exercises. The anticipated exposure duration is brief, because the exercises are conducted outdoors and the chemical will rapidly disperse. Frequency of exposure should be very low, perhaps only a few times in a career, due to the complexity of such an exercise. This scenario differs considerably from the usual occupational exposure paradigm of prolonged daily exposure, 5 days per week, for many years.

The critical effect for evaluation of safe exposure to CPFB is the liver toxicity associated with repeated exposure (Kinkead et al., 1990b). Specifically, hypertrophy and hepatocytomegaly were observed in mice following exposure to 300 ppm CPFB, 6 h/day, for 3 weeks, and the liver-to-body-weight ratio in rats and female mice was increased in a dose-related fashion. Increased single cell necrosis was also observed at 30 ppm and 100 ppm in the same study, but this effect was not considered toxicologically significant, and neither the necrosis nor the increased liver-to-body-weight ratio were reproduced in a subsequent study at 30 ppm for 13 weeks (Kinkead et al., 1991). Taking 30 ppm as an NOAEL, and dividing by a factor of 10 to provide a margin of safety, yields a recommended exposure guideline of 3 ppm for a daily (8-h) time-weighted average (TWA).

A traditional guideline calculation would probably use a safety factor of 100, with a factor of 10 to account for uncertainty in the extrapolation from animal to human, and another factor of 10 to account for human variability. The selection of 10 as the safety factor applied in this case results from several considerations. First, the factor of 10 usually applied for extrapolation from animals to humans reflects a conventional wisdom based primarily on experience with the more common exposure routes, oral and intravenous, for chemicals that are themselves toxic and are cleared by

processes that scale roughly with surface area rather than body weight. Under these conditions, pharmacokinetic and empirical allometric considerations justify such a factor based on the relationship between applied dose and tissue exposure (area under the concentration-time curve) as a function of body weight (National Research Council, 1986). However, for inhalation exposure to a volatile, poorly soluble chemical such as CPFB, these same principles lead to an expectation that across species there will be a similar area under the curve of both parent and metabolites for equivalent external concentration and exposure duration (that is, for equal TWA concentrations). In support of this argument, the model described in the Appendix was used to calculate the daily area under the curve in the liver for exposure of rats and humans to 30 ppm CPFB for 6 h. The area under the curve in the liver predicted for rats was 46 mg/L-h, whereas for humans, even under conditions of moderate exercise, it was 72 mg/L-h, a difference of less than a factor of two. Thus the usual animal-to-human extrapolation factor of 10 is not justified in this instance.

Second, the anticipated human exposures are brief and infrequent, associated with special training exercises which are not expected to be a common occurrence. Therefore, the 3-week and 13-week rodent studies represent much more prolonged exposures than the human exposure scenario, with less opportunity for recovery in between exposures. The area under the curve in the liver predicted for an 8-h TWA exposure at the recommended guideline of 3 ppm is 9.6 mg/L-h, roughly a factor of 5 below that at the rodent subchronic NOAEL. For the relatively infrequent human exposures anticipated, this margin of safety below the subchronic NOAEL appears adequate to protect exposed personnel from liver effects.

In addition to liver toxicity, there is limited evidence of behavioral effects at higher CPFB concentrations (500 to 1000 ppm) (Gage, 1970). Any behavioral deficit induced by CPFB could not only degrade performance during a training exercise, but could also increase the likelihood of subsequent exposure through improper use of protective gear. To avoid any behavioral effects potentially associated with higher exposure concentrations, and given the uncertainty associated with predicting the atmospheric dispersion of vapors, it is recommended that simulant dispersal operations be designed to limit short-term exposures to less than 30 ppm. This concentration is based on the NOAEL for behavioral effects, 300 ppm (Kinkead et al., 1991), again with a safety factor of 10. In the case of acute behavioral effects, toxicity generally appears to be correlated with concentration rather than area under the curve. The model-predicted blood concentrations in humans associated with exposure to the recommended ceiling of 30 ppm are on the order of 1.35 mg/L, as compared to 24.6 mg/L and 26.6 mg/L in rats and mice, respectively, at the acute NOAEL of 300 ppm, providing a margin of safety of approximately 20.

Finally, fetotoxic effects were observed in rats with a NOAEL of 300 mg/kg/day. This level of oral exposure can be compared with the inhalation guideline by estimating the peak blood

concentrations and area under the curve for CPFB in the rodent study and comparing them with those achieved during human inhalation exposures at 3 and 30 ppm. For an oral dose of 300 mg/kg in the rat, the model estimates a peak blood level of 123 mg/L and an area under the curve for blood of 109.2 mg/L-h. For human inhalation at 30 ppm, the peak blood level is predicted to be 1.35 mg/L, and the area under the curve for blood at 3 ppm for 8 h is 1.166 mg/L-h. Thus the inhalation guidelines are also consistent with the prevention of fetotoxic effects, with a margin of safety of roughly 100

SECTION 4

SUMMARY

Chloropentafluorobenzene possesses a remarkable combination of physicochemical and toxicologic properties, making it an attractive candidate for use as an intake simulant in chemical defense field training exercises. It is volatile and unreactive, simplifying dissemination, and it mimics the performance of typical vapor threats in terms of persistence and canister penetration. It does not appear that CPFB would present any significant health hazards to personnel under the envisioned use. A thorough toxicological evaluation indicates that CPFB is not acutely toxic or teratogenic and is not likely to be carcinogenic. Liver toxicity was observed only after prolonged exposure to high concentrations. To ensure personnel safety, it is recommended that field exercises be designed to avoid short-term exposures to concentrations greater than 30 ppm, with the daily (8-h) TWA not to exceed 3 ppm. Because field analytical methods can measure CPFB at part per trillion levels, this should not be an impediment to its use in training exercises.

SECTION 5

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APPENDIX A

DESCRIPTION OF PBPK MODEL OF CPFB

STRUCTURE

The structure of the model is shown in Figure A-1, and the assumptions underlying the mathematical description follow those of Ramsey and Andersen (1984) with the following exceptions:

1. The model of Ramsey and Andersen included only saturable metabolism. An additional pathway of metabolism has been added in this model which is linear in concentration. Thus the equation for the rate of change of amount of CPFB in the liver contains an additional term:

   - KFC * CL * VL / PL (where the parameters are defined below)

2. A GI tract compartment has been added. Oral absorption takes place into this compartment by a first order process: KA * AST (where AST represents the amount of CPFB remaining in the stomach). The liver receives the blood flow from this compartment (QG) as well as its own arterial supply (QL). Thus the equations for the rate of change in the amount of CPFB in the stomach (RAST), GI tract (RAG), and the liver (RAL) are:

   $$RAST = -KA * AST$$

   $$RAG = QG * (CA - CG / PG) + KA * AST$$

   $$RAL = QG * (CG / PG - CL / PL) + QL * (CA - CL / PL) - VMAXC * CL / PL / (KM + CL / PL) - KFC * CL * VL / PL$$

3. A bone marrow compartment has been added. The form of the equation for the rate of change in the amount of CPFB in the bone marrow (RAM) is identical to that of the other basic tissues in Ramsey and Andersen (e.g., fat, slow, rapid):

   $$RAM = QM * (CA - CM / PM)$$

4. In order to better simulate the measurements of exhaled breath in anesthetized monkeys, the description of gas exchange between the lung and the blood was modified to explicitly model an alveolar space in which inhaled air at concentration CI and air in equilibrium with the blood were mixed. In place of the steady-state assumption used in Ramsey and Andersen, the following rate equation for the amount of CPFB in the blood (ABL) was integrated along with the equations for the tissue compartments:

   $$RABL = QP * (CALV - CX) + QC * (CV - CA)$$

where.

$$CALV = ALVS * ABL / (VBL * PB) + (1 - ALVS) * CI$$

The measured exhaled air concentration in parts per million (CXPPM) was then described by the equation

$$CXPPM = [DS * CI + (1 - DS) * ABL / (VBL * PB)] * 24450 / 202.51$$

The predictions of the model are compared with experimental data for rats and monkeys in figures A-2 and A-3, respectively

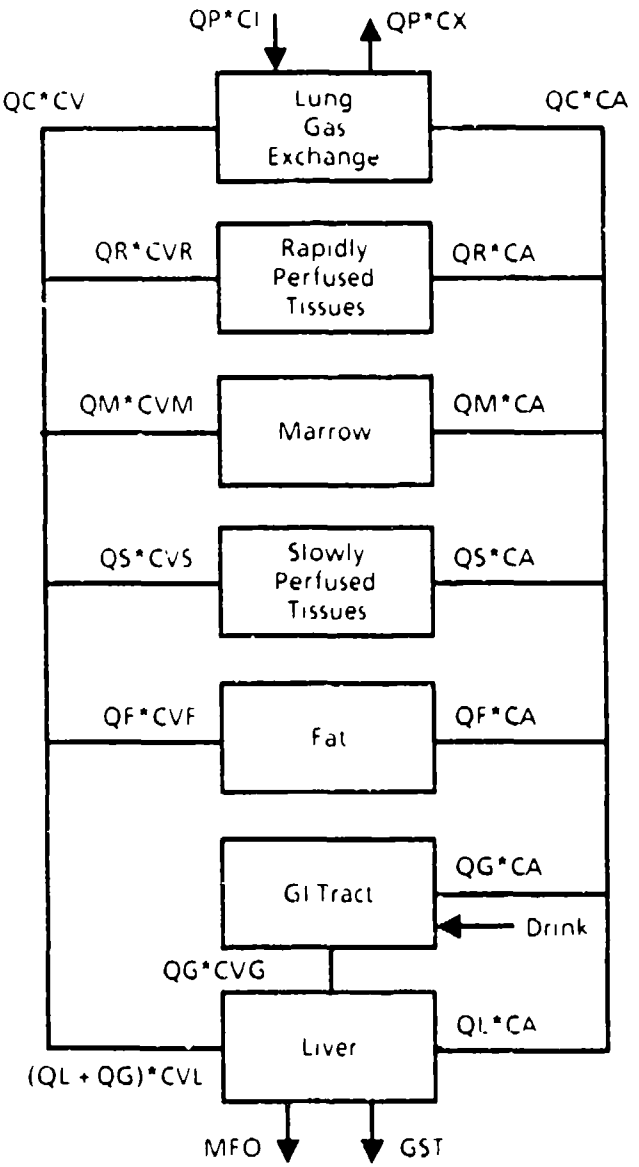

Figure A-1. Diagram of the PBPK Model of CPFB.

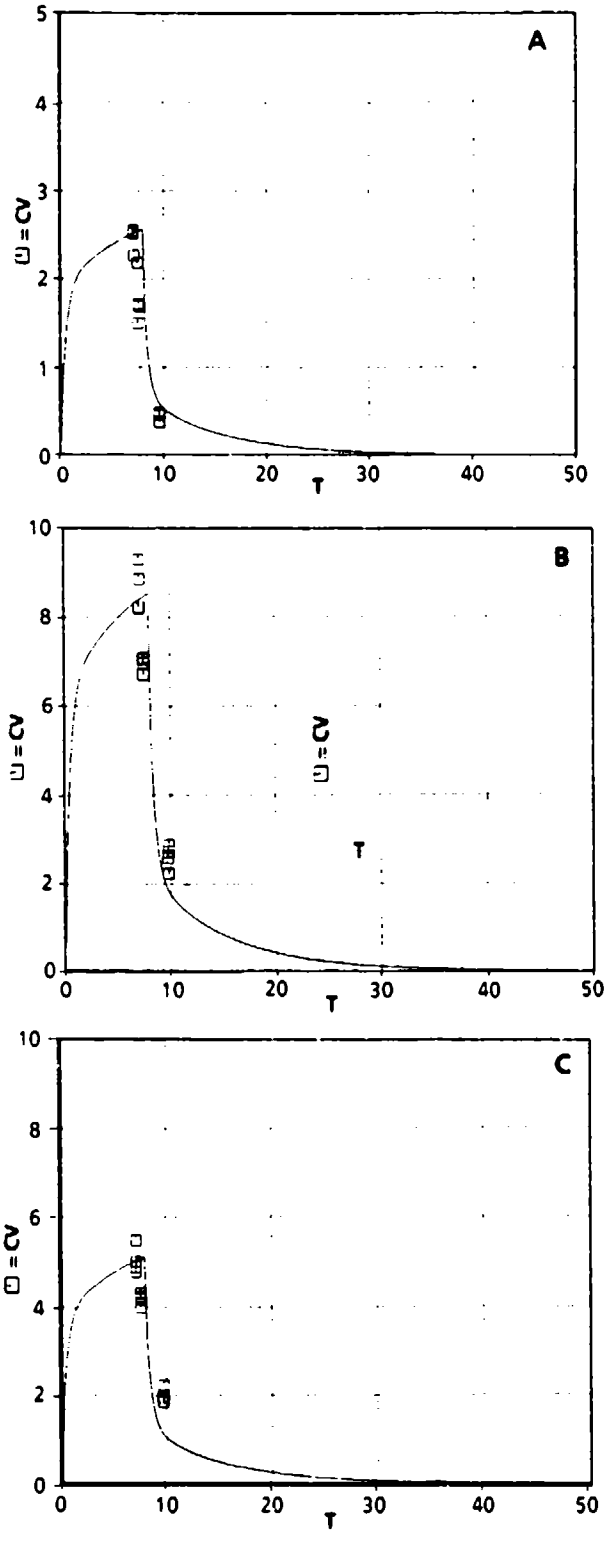

Figure A-2. Model-Predicted (Lines) and Measured (Boxes) Venous Blood Concentration on 11th Day After Exposure of Rats to CPFB for 6 h Per Day at 30 ppm (a); 100 ppm (b); and 300 ppm (c).

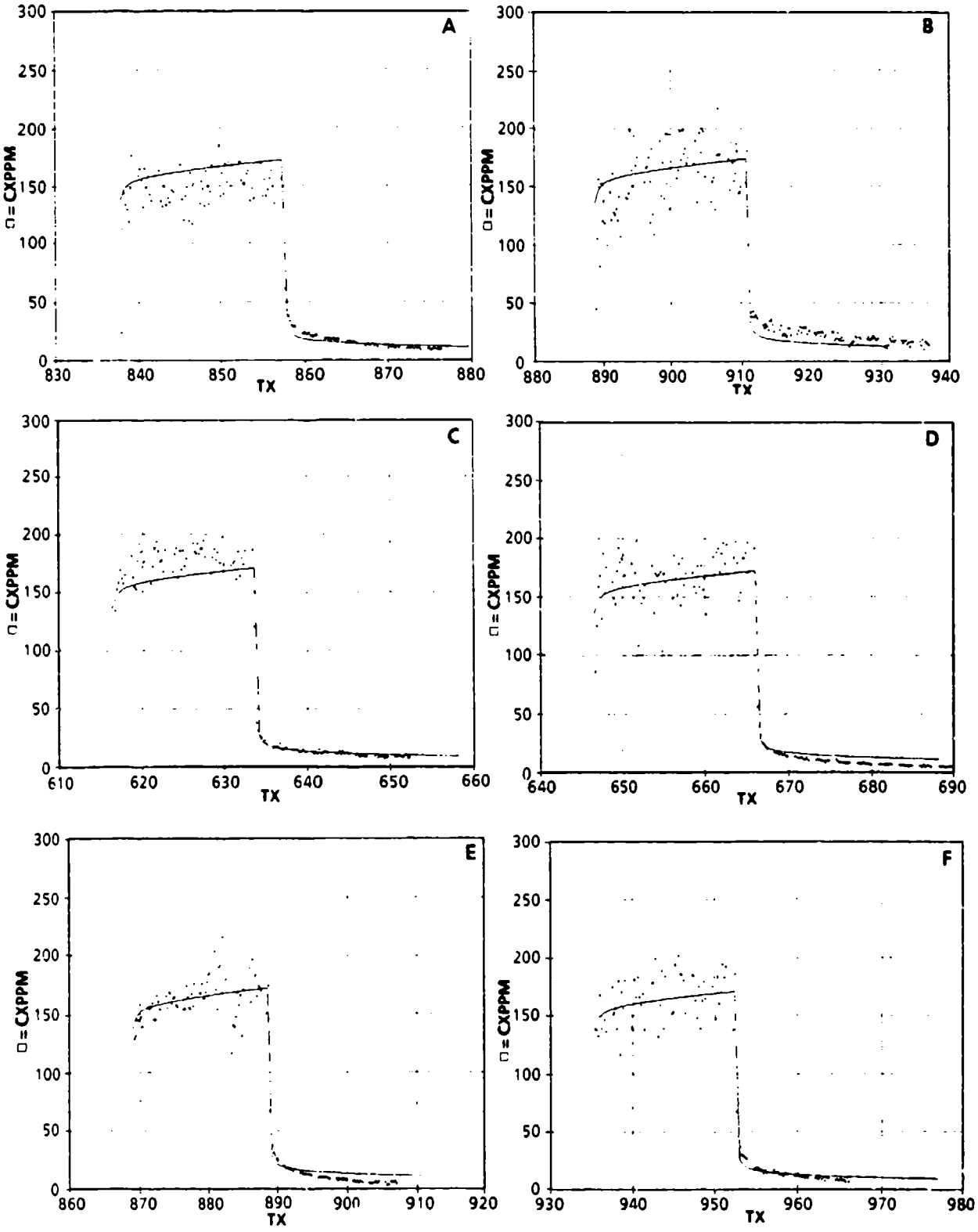

Figure A-3. Model-Predicted (Lines) and Measured (Points) Exhaled Air Concentrations on Eight Monkeys Exposed to 300 ppm CPFB for 17 to 20 min.

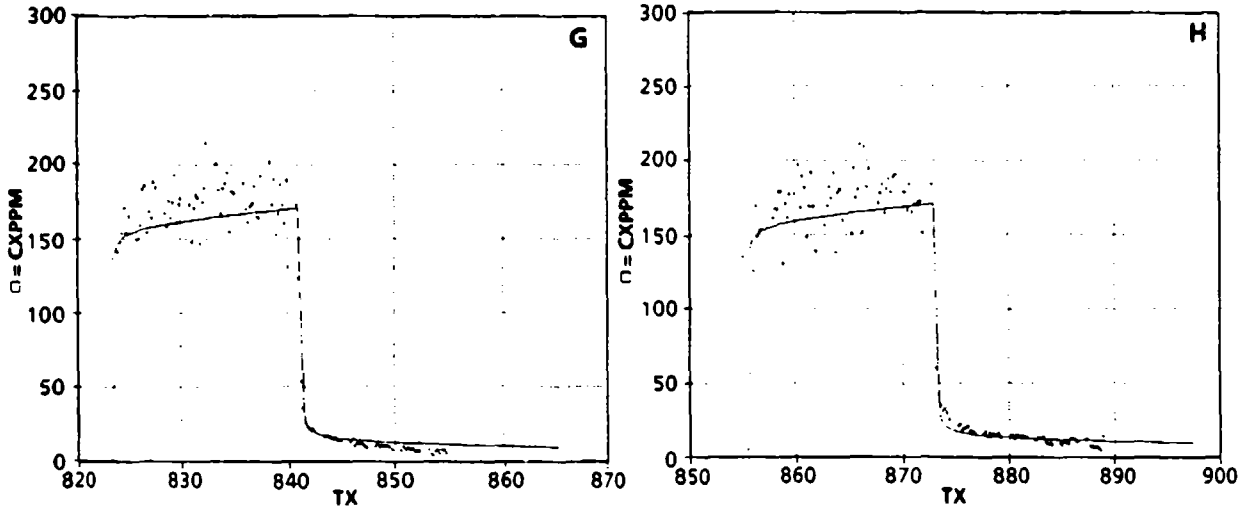

Figure A-3. Continued.

UNSCALED PARAMETERS

		Mouse	Rat	Monkey	Human
BW	Body Weight (kg)	.023	0.22	8.7	70.0
KA	Oral Uptake Rate (/h)	5.0	5.0	5.0	5.0
ALVS	Alveolar Dead Space (Fraction)	0.0	0.0	0.4	0.0
DS	Bronchiolar Dead Space (Fraction)	0.3	0.3	0.45	0.3
QCC	Cardiac Output (L/h, 1 kg animal)	16.5	11.6	12.0	18.0
QPC	Alveolar Ventilation (L/h, 1 kg animal)	29.0	21.2	17.0	35.0
Tissue Blood Flows (Fraction of Cardiac Output):					
QFC	Flow to Fat	.030	.058	.052	.052
QGC	Flow to GI Tract	.166	.183	.185	.185
QLC	Flow to Liver	.036	.032	.065	.065
QMC	Flow to Bone Marrow	.110	.110	.110	.110
QRC	Flow to Rapidly Perfused Tissues	.409	.362	.348	.348
QSC	Flow to Slowly Perfused Tissues	.249	.255	.240	.24

Tissue Volumes (Fraction of Body Weight):					
VBL	Volume of Blood	.070	.070	.070	.070
VFC	Volume of Fat	.100	.070	.190	.050
VGC	Volume of GI Tract	.033	.033	.045	.045
VLC	Volume of Liver	.050	.040	.027	.027
VMC	Volume of Bone Marrow	.030	.030	.020	.020
VRC	Volume of Rapidly Perfused Tissues	.041	.020	.026	.026
VSC	Volume of Slowly Perfused Tissues	.550	.600	.709	.56
Partition Coefficients:					
PB	Blood/Air	12.3	12.3	7.0	7.0
PF	Fat/Blood	75.0	75.0	93.0	93.0
PG	GI Tract/Blood	2.55	2.55	3.65	3.65
PL	Liver/Blood	2.77	2.77	8.0	8.0
PM	Bone Marrow/Blood	11.6	11.6	16.0	32.0
PR	Richly Perfused Tissue/Blood	2.55	2.55	3.65	3.65
PS	Slowly Perfused Tissue/Blood	1.07	1.07	2.1	2.1
Metabolic Parameters:					
KFC	Rate Constant for 1st Order Pathway (/h - 1 kg animal)	2.0	2.0	2.0	2.0
	KM Affinity of Saturable Pathway (mg/L)	0.4	0.4	0.4	0.4
	VMAXC Maximum Velocity of Saturable Pathway (mg/h, 1 kg animal)	0.	0.	0.	0.

SCALED PARAMETERS

```
QC = QCC*BW**0.75
QP = QPC*BW**0.75

QF = QFC*QC
QG = QGC*QC
QL = QLC*QC
QM = QMC*QC
QR = QRC*QC
QS = QSC*QC

VBL = VBLC * BW
VF = VFC*BW
VG = VGC*BW
VL = VLC*BW
VM = VMC*BW
VR = VRC*BW
VS = VSC*BW

KF = KFC/BW**.25
VMAX = VMAXC*BW**0.75
```

DOSE SURROGATES

Amet	Total amount metabolized per unit body weight (mg/kg)
AUCB	Area under the curve of arterial blood concentration of CPFB (mg/L-h)
AUCL	Area under the curve of liver concentration of CPFB (mg/L-h)
AUCM	Area under the curve of CPFB in the bone marrow (mg/L-h)
CA	Concentration of CPFB in the arterial blood (mg/L)
CL	Concentration of CPFB in the liver (mg/L)
CM	Concentration of CPFB in the bone marrow (mg/L)
CV	Mixed venous blood concentration of CPFB (mg/L)
Dose	Total amount inhaled during exposure (mg/kg) = integral of QP * (CALV - CX) / BW

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