Possible lethal effects of CS tear gas on Branch Davidians during the FBI raid on the Mount Carmel compound near Waco, Texas April 19, 1993

Prepared for

The Office of Special Counsel
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by

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1. Introduction

1a. Questions of the OSC and author responsibility

The Office of Special Counsel retained me on December 2, 1999, to evaluate the toxicological effects of CS gas on individuals inside the Branch Davidian complex on April 19, 1993. Specifically, the Office of Special Counsel asked me to determine: (1) whether CS gas killed or contributed to the death of any Branch Davidians on April 19, 1993; and (2) whether the interaction of CS and methylene chloride (MC) gas killed or contributed to the death of any Branch Davidian on April 19, 1993.

I, Dr. Uwe Heinrich, Professor of Toxicology and Aerosol Research, Hannover Medical School, and Director of the Fraunhofer Institute of Toxicology and Aerosol Research, Hannover, Germany, compiled this report, acting as a private consultant to the Office of Special Counsel. The statements made here are my responsibility; no responsibility is therefore attached to the Fraunhofer Institute of Toxicology and Aerosol Research, to the Fraunhofer Society for the Advancement of Applied Research, or to the Hannover Medical School. My biographical resumé is appended.

1b. Background

On April 19, 1993, the FBI used the riot control agent CS (o-chlorobenzylidene malononitrile) to induce a group of Branch Davidians living near Waco, Texas to leave their residence. The CS tear gas was inserted into the building in 4 distinct phases in the time period from 6.00 a.m. until shortly after noon. CS was sprayed into the building through holes created by Government CEVs and by firing small non-explosive dart-like CS-containing projectiles into the windows and/or broken walls. Shortly after noon, a fire developed which ultimately destroyed the entire compound. Nine people escaped from the residence during the course of the fire, but more than 75 others, including 28 children, died inside the building.

1c. Summary Conclusions

o-chlorobenzylidene malononitrile (CS), a strong irritating riot control agent, was inserted into the Branch Davidian Mount Carmel compound near Waco, Texas, to induce the inhabitants to leave the building. The insertion of CS started at 6.00 a.m. on April 19, 1993. Shortly after noon fire broke out and destroyed the whole compound. Seventy-five Branch Davidians, including 28 children, died inside the building. The question arose whether CS gas or the interaction of CS and methylene chloride (MC) killed or contributed to the deaths of the Branch Davidians. I was asked by the OSC to answer this question and I prepared a report that tried to do so. My report is based on numerous documents and scientific literature provided to me by the OSC, on my own literature research, and on the report of Dr. Havens for the OSC on the CS and MC exposure scenario which might have occurred in the various rooms of the Mount Carmel building. The possible effects of methylene chloride on the group of Branch Davidians staying in the Mount Carmel compound on April 19, 1993, are dealt with in Dr. George Lucier's report to the OSC.

There are various preparations of CS and various techniques to make CS airborne in an inhalable form. In Waco, a solution of CS in MC, contained in non-explosive projectiles and CO_2 pressurized canisters, was used to insert the CS. Dispersed as droplets from this fluid, fine particles of crystalline CS emerged after instantaneous evaporation of MC.

Experimental animals were exposed to CS to get information on toxic and lethal effects of CS. Most of these experiments reported in the literature were already conducted 30 - 40 years ago when there were no OECD and Good Laboratory Practice guidelines for standardized toxicity tests in experimental animals. Furthermore, only one of these studies used MC/CS and the toxic potency of the various CS preparations (pulverized CS, molten CS, CS from thermal grenades) including CS dissolved in methylene chloride (MC/CS) was mostly different.

Even with the calculation of a human equivalent CS concentration to consider the species-specific differences in the anatomy and physiology of the respiratory tract, the toxic and lethal effects of inhaled CS reported from the various animal experiments are only of limited meaning for the evaluation of possible toxic and lethal effects in MC/CS-exposed humans. There are no reports on human death related to CS exposure.

In this report, the calculation of the possible lethal concentration of MC/CS for humans is namely based on the experiment with MC/CS and micropulverized CS in rodents and with micropulverized CS in monkeys. MC/CS and micropulverized CS appeared to have similar toxic potency in animal experiments.

Comparing the CS concentration that led to early mortality in experimental animals with one of the worst CS exposure scenarios calculated for the Mount Carmel compound shows that these concentrations differ only by a factor of 5 - 10 and for the most sensitive guinea pig even by a factor below 5. Because of the well-known reduction of the breathing volume of rodents exposed to irritating agents which was not considered when calculating the human equivalent concentration, these safety factors may be even lower. Due to the higher minute ventilation in relation to the lung size, the normalized CS deposition rate in children is higher than in adults, resulting in more pronounced toxicity in children compared to adults exposed to the same CS concentration. This means that children were at higher risk to experience lethal effects from the worst calculated CS exposure scenario which might have occurred in the Mount Carmel building.

Based on the available data on toxic and lethal effects of the CS and considering the worst exposure scenario at Waco, there is a distinct possibility that this kind of CS exposure can significantly contribute to or even cause lethal effects. This statement only holds true, however, if the inhabitants were not able to leave such a worst exposure scenario despite the very irritating and burning effects of CS or were not able to protect themselves sufficiently by wearing a gas mask. As death does not occur immediately after short-term CS

inhalation exposure in animal experiments but only after some time, it can be assumed that other factors (e.g. the fire) could have also contributed to the death of the Mount Carmel inhabitants.

2. o-chlorobenzylidene malononitrile (CS)

2a. Chemistry of CS

CS is the short name for o-chlorobenzylidene malononitrile, which was developed by Carson and Staughton in 1928. C and S are surname initials of Carson and Staughton. CS is the condensation product of chlorobenzaldehyde with malononitrile and its molecular weight is 188.6.

CS is a white crystalline product with a melting point of 94 ° Celsius and a boiling point of 310 - 315 ° Celsius. CS is soluble in organic solvents. In methylene chloride (MC) at room temperature, the solubility of CS is approximately 39 % by weight; in acetone, the solubility is approximately 42 % (Edgewood Arsenal Technical Report 4301, Weimer et al. 1969).

The solubility of CS in water, on the other hand, is very low (2×10^{-4} M). CS is hydrolyzed in water and the products of this hydrolysis are o-chlorobenzaldehyde and malononitrile. Hydrolysis means the cleavage of a molecule, in this case CS, by the addition of water. Hydrolysis is important in toxicology and is catalyzed by a large number of different hydrolytic enzymes. Because of this process, the amount of CS in water or water-containing fluids is reduced by 50 % within 14 minutes at pH 7.4 and 25 ° Celsius, or within 0.17 minutes at pH 11.4 and 25 ° Celsius. The time required to reduce the amount of a substance by 50 % is called the half-life of this substance. In acid solutions of pH 4 and below, CS is quite stable. The watery lining fluid of the respiratory tract has a pH value of approx. 7, but inside the organelles of the alveolar macrophages (cells that take up material deposited on the surface of the alveoli), the pH is between 4 and 5. The normal decomposition of CS produces CN, C_2H_2, HCl, NO_x, CO, $COCl_2$, and N_2O.

Preparations of CS used to generate CS-containing atmospheres are the following: (1) CS melted and sprayed in the molten form; (2) spraying of CS dissolved in methylene chloride (10 %) or in acetone (5 %); (3) dispersion of CS2 as dry powder [CS2 is a siliconized, micropulverized form of CS with improved flow properties and greater weather resistance (95 % micropulverized CS with silica (Cab-o-sil) treated with hexamethyldisilazone); this mixture prevents agglomeration, increases flowability and also markedly increases hydrophobicity]; and (4) dispersion of CS from thermal grenades by generation of hot gases. The particle size (mass median diameter) of the CS aerosol generated from MC/acetone solution, by spraying melted CS or firing thermal grenades is reported to be in the range of 0.5 - 2 µm. Particle size can vary depending on the generated droplet size of the dispersed fluid and in respect of powders on the micronization process used.

2b. Metabolites/reaction products of CS in the mammalian organism

When CS comes into contact with body fluids, it is quickly broken down. CS reacts very rapidly with plasma proteins and more slowly with water. CS is also metabolized in the organism. In toxicology, metabolization refers to the enzymatic transformation of xenobiotics (foreign substances), resulting in products that may be less toxic than the parent compound [this is the case for the CS metabolites except hydrogen cyanide (HCN)] or more toxic than the parent compound. CS is metabolized to o-chlorobenzyl malononitrile (CSH_2), o-chlorobenzaldehyde, o-chlorohippuric acid, and thiocyanate. Presence of these metabolites in the body is a strong indicator of CS exposure. Compared to CS, CSH_2 showed 60 % reduced toxicity and about 15-fold lower irritancy. Metabolites like CSH_2 were also found after inhalation exposure and not only after intravenous, intraperitoneal or intragastric application of CS. O-chlorobenz-aldehyde is further metabolized to o-chlorobenzoic acid. The major metabolite detectable in the rat is o-chlorohippuric acid. The less toxic thiocyanate is formed from cyanide derived from malononitrile (Stern et al. 1952). Thiocyanate was found in urine of exposed animals and man, also after inhalation exposure. CS also reacts quite rapidly with sulfhydryl groups (-SH), in cysteine, glutathione and in this way, enzymes in the body containing -SH

groups may be inhibited. Also, lipoic acid, important for the metabolism of the surface active agent (surfactant) covering the alveoli, reacts rapidly with CS. The half-life of CS and CSH_2 in blood is 5.5 and 9 seconds respectively, meaning that the time available to exert harmful systemic effects if rather short.

3. Toxicity of CS

3a. Animal experiments: general remarks

Most of the toxicity tests with experimental animals after intravenous, intraperitoneal, intragastric, inhalational and ocular application of CS were done 30 - 40 years ago and were not published in peer-reviewed scientific literature. These studies did not follow OECD guidelines for toxicity testing and were not conducted according to Good Laboratory Practice (GLP). Various animal species were exposed by inhalation to different preparations and concentrations of this strongly irritative CS agent to obtain information on dose levels at which toxicity effects may start to occur, how the dose-response curve may look, and what kind of toxic lesions may develop. Two of the more recent studies were published in 1983 by Marrs et al. and in 1990 by the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services. Both studies focus on repeated exposure and subchronic and chronic toxicity/carcinogenicity of CS in rodents after inhalation exposure.

These early animal and exposure data were used to evaluate the CS concentrations needed to effectively control riot activities without harming those exposed. Based on controlled human studies, the concentration of CS which is intolerable in one minute to 50 % of those exposed is in the range of 0.1 - 10 mg/m^3. This intolerability is caused by a strong irritation and burning sensation especially in the respiratory tract and eyes

Toxicity tests in experimental animals also include the application of doses that result in mortality in some of the exposed animals. Based on these data, the concentration or dose of the test substance that leads to 50 % mortality of the treated animals can be calculated. The LD50 (Lethal Dose 50 %) or LC50

(Lethal Concentration 50 %) is the dose in mg/kg b.w. or the concentration (mg/m^3) in inhalation experiments where 50 % of an exposed group of animals will die. LD50/LC50 is not a constant that indicates how toxic a substance is, it is merely a statistical expression that describes the lethal effect of a substance under certain experimental circumstances.

In general, it is difficult and rather uncertain to extrapolate the LD50/LC50 of a substance from one animal species to another. Extrapolation from one group to another of the same species is also difficult when the experimental conditions are not exactly the same.

3b. Toxicology of aerosol inhalation

This uncertainty with species extrapolation is especially high when the test substance is an aerosol (airborne particle or droplet) tested in inhalation studies because the amount of an aerosol deposited and retained in the respiratory tract after inhalation exposure is very different among various animal species and man. The dose of an inhaled aerosol that is responsible for a certain effect is not the inhaled aerosol concentration in µg/l or mg/m^3 but the amount of aerosol that remains in the respiratory tract after inhalation.

The deposition of an inhaled aerosol in the respiratory tract very much depends on the aerodynamic size of the aerosol and on the anatomy of the respiratory tract. For example, the length and diameter of the air-conducting structures significantly affects the type of air flow and the flow velocity of the inhaled air in these structures. It is no wonder that the deposition efficiency levels of aerosols in the respiratory tract are quite different for example in rodents than in dogs, monkeys, and humans. This means the inhalation exposure of different animal species to the same exposure concentrations of an aerosol in mg/m^3 may lead to different aerosol doses and toxic effects in the respiratory tract even if the sensitivity of the animals is assumed to be the same.

Furthermore, if the inhaled aerosol exerts only local effects in the respiratory tract, such as irritation, inflammation, and damage of the cell membranes, the

adequate dosimetry to compare rodents and man is aerosol mass per unit surface area of the lung. This is due to the different size of the lungs and breathing volumes between rodents and humans.

Early animal studies often used LC50 values from animal inhalation experiments with CS to extrapolate to humans to evaluate the safety margin between irritating and toxic effects in humans. For the reasons described above, this is an inappropriate extrapolation if species-specific and anatomic and physiologic data are not considered.

In this same respect, many, if not all, of the experts that have previously reviewed the CS gas exposure in the Branch Davidian complex have compared the lethal CS concentration found in the early animal experiments to the concentrations that could have occurred inside the complex. This comparison can only be done legitimately and with a certain reliability if the given animal experiment concentration leading to 50 % lethality will transform to the human equivalent concentration (HEC). This transformation or dosimetric conversion to an HEC must take into account the various species differences important for calculation of the species-specific dose in the respiratory tract.

The various species used in inhalation toxicology studies do not receive identical doses in comparable respiratory tract regions when exposed to the same external particle or gas concentration because the respiratory system of humans and various experimental animals differ in anatomy and physiology in many quantitative and qualitative ways. These variations affect air flow patterns in the respiratory tract and, in turn, the deposition of an inhaled agent as well as the retention of that agent in the system. The retained dose of an inhaled agent in the various regions of the respiratory tract (nose, mouth, nasopharynx, oropharynx, laryngeopharynx, larynx, trachea, bronchi, bronchioles, alveolar ducts, and alveoli) is not only governed by the exposure concentration and the physico-chemical properties of the test material, but also by the individual species anatomy (for example, airway size, airway branching pattern) and physiology (for example, breathing rate, clearance mechanism). The greater complexity of the nasal passages coupled with the obligate nasal

breathing of rodents results in greater deposition in this region of the respiratory tract in rodents than in humans.

The calculation of a human equivalent concentration (HEC) estimates from observed exposure effect levels in laboratory animals is based on model-derived adjustment factors considering species-specific dosimetry differences. For the calculation of the HEC of particles as described in the U.S. Environmental Protection Agency Report "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (EPA/600/8-90/066F, 1994), the regional deposition-dose ratio (RDDR) is needed.

$HEC\ (mg/m^3) = AEC\ (mg/m^3) \times RDDR$ [AEC = animal equivalent concentration]

RDDR is a multiplicatory factor used to adjust an observed inhalation particle exposure concentration of an experimental animal (A) to the predicted inhalation particulate exposure concentration for a human (H) that would be associated with the same dose delivered to a special region of the respiratory tract.

$$RDDR = \frac{\text{regional deposited dose (A)*}}{\text{regional deposited dose (H)*}}$$

* normalized to lung surface area.

The dose deposited in a special region of the respiratory tract RDD (mg/min) depends on the exposure concentration C (mg/m^3), the minute volume V (ml/min) and the fractional deposition in a special region of the respiratory tract F.

$$RDD = 10^{-6} \times C \times V \times F$$

The calculation of the RDDR or the HEC is based on the software available as a supplement to the aforementioned EPA report. For the calculation of the HEC estimate of CS exposure that would result in 50 % mortality, based on LCt50 values in rats, a polydisperse CS aerosol (Sigma g = 1.8; a monodisperse aerosol has a Sigma g of about 1.1; Sigma g is the geometric variance of the particle size) with a mass median aerodynamic particle diameter of 1.0 µm up to 5.0 µm was used. The body weight of the exposed rats and humans was assumed to be 200 g and 70 kg respectively. Based on these assumptions, the pulmonary (P) dose deposition ratio ($RDDR_P$) was 0.3 - 0.6 and the human equivalent LCt50 estimate is therefore, on average, about half the reported rat LCt50 values.

Particularly in aerosol inhalation toxicology, the inhaled dose retained in the respiratory tract not only depends on the exposure concentration of the aerosol, but also on the exposure time. The longer the constant exposure concentration, the higher the inhaled dose. Very often in the CS literature or reports, the dose term LCt50 can be found. This term gives the product of concentration multiplied by the time of exposure under conditions where 50 % of the exposed animals will probably die. This term refers to Haber, who for toxic gases found that the same response occurs at a constant value for concentration x time, that is the total dose inhaled. Haber discovered this relationship while experimenting with the war gas phosgene. This so-called "Haber's law" (c x t = k) was confirmed for other poisonous gases; but, Haber's law is only a rule and there are always exceptions to the rule. In these cases, the response is not constant but differs between high concentration with short exposure time and low concentration with long exposure time.

With CS there is a deviation from Haber's law. Higher CS exposure concentration for a shorter time seems to be less toxic than a lower concentration for a longer time. In rats, 4,000 mg/m^3 CS for 18 minutes (c x t = 70,000) caused 50 % lethality and with 40 mg/m^3 CS only 600 minutes (c x t = 24,000) and not 1,800 minutes (c x t = 72,000) were necessary to kill 50 % of the animals. Furthermore, the death rate in rats increased exponentially with linear increase of exposure time or inhaled dose. The death rate after

inhalation exposure to 4,000 mg/m^3 CS for 5, 10 and 20 minutes was 2/60, 16/60 and 50/60 respectively.

It is also important to notice that the LCt50 value describes only one point of the concentration-response curve and the path of the curve that is the alteration of the effects with increasing and decreasing exposure concentrations is not known. There are various factors that determine the path or slope of this curve. Individual sensitivity is one important factor in respect of the direct-acting irritating CS agent.

Proceeding from the assumption that Haber's law can be applied to CS although some experiments show that c x t does not seem to be constant, LCt50 values for CS were calculated in the literature from experiments employing various exposure times as well as various exposure concentrations and CS preparations. This procedure implies a great uncertainty, especially in respect of the extrapolation to CS-exposed humans.

3c. Animal experiments: toxicity data

The high toxicity and acute lethality of CS given intravenously or intraperitoneally is not seen after inhalation exposure. After short-term inhalation exposure, there is always some time lag between exposure and the time of death. This high toxicity associated with intravenous or intraperitoneal exposure is due to the rapid metabolism of CS which leads to high levels of hydrogen cyanide in the body (Jones & Israel 1970; Cucinell et al. 1971). Hydrogen cyanide, as the undissociated acid, prevents the use of oxygen by blocking the electron transfer from cytochrome a3 to molecular oxygen. That means, it blocks cell respiration or oxidative metabolism even if the partial pressure of oxygen in the tissue is normal. Cells of the brain, especially the brain stem, are very sensitive to the effects of HCN and a dysfunction in this area of the brain may lead to respiratory arrest. A blood cyanide level of greater than 0.2 µg/ml blood is considered toxic. Lethal cases have usually had levels above 1 µg/ml blood (Casarett and Doull's Toxicology, 1980).

HCN also stimulates the chemoreceptors of the carotid and aortic bodies. Hyperpnea, such as increased breathing, can occur, resulting in more of the poisonous CS atmosphere being inhaled. Cardiac irregularities and hypertension can also be caused by cyanide. The evidence for the endogenous release of cyanide in rats inhaling CS at 21,000 mg.min/m^3 is based on increased urinary excretion of thiocyanate (Frankenberg & Sorbo 1973). Other metabolites of CS (2-chlorobenzyl malononitrile, 2-chlorobenzaldehyde) were also found in the blood after inhalation exposure (Leadbetter 1973, Leadbetter et al. 1973).

Cyanide is detoxified in the liver by the mitochrondrial enzyme rhodanese, which catalyzes the transfer of sulfur from a sulfate donor to cyanide, forming less toxic thiocyanate. Thiocyanate is readily excreted in urine.

In contrast to intravenous or intraperitoneal exposure experiments, in inhalation experiments, only delayed deaths were observed after exposure to high concentrations of CS. This response indicates a different mechanism of action of CS depending on the type of exposure. After inhalation exposure, the toxic response focuses primarily on the lung, with direct effects on the mucous membrane and the epithelial cells. In addition to strong irritation at higher concentrations, inflammation and damage to the alveolar capillary membrane also occur followed by the development of edema, emphysema, hemorrhages, and atelectasis due to reduced synthesis and/or destruction of the surface-active material (surfactant) in the lung. These effects lead to compromised oxygen transfer from the lung to the blood capillaries and eventually, after some time, to death from suffocation. The effect of cyanide produced by the metabolism of CS may add to this suffocating situation.

High exposure concentrations of CS (2,850 mg/m^3 for 10 minutes) in monkeys caused severe lung damage (edema, emphysema, and bronchiolitis). Only coughing and nasal discharge, however, was observed in monkeys exposed to approximately 300 mg/m^3 CS for 5, 10 and 30 minutes. Dogs, as well, died after high doses of CS inhalation exposure, but only some hours later after they too had developed pulmonary edema, hemorrhages and atelectasis.

Slight differences in toxic potency were described, depending on whether the CS-containing atmosphere was generated pyrotechnically using thermal grenades or ammunition, sprayed as heated and molten CS forming a condensation aerosol, sprayed as a solution of CS in acetone or methylene chloride, forming crystalline CS particles after instantaneous evaporation of the organic solvent, or dispersed as micronized CS powder containing anticoagulation substances. At Waco, a solution of CS in methylene chloride was used.

There is no systematic toxicity study comparing the various CS aerosol preparations under similar experimental conditions, but there are some indications based on LCt50 values that CS aerosols from molten CS appear to be somewhat more toxic than micropulverized CS and clearly more toxic than CS from thermal grenades. Based on one inhalation experiment with CS dissolved in MC or acetone and sprayed for inhalation exposure to guinea pigs, organic solutions of CS, grenade-type CS and powdered CS2 appeared to have similar LCt50 values, but the LCt50 value for molten CS was 5 - 8 times lower (McNamara et al., 1969). At Waco, only MC/CS was used, but the toxic potency of thermal grenade CS and fine powdered CS (particle size ~ 1 µm) does not seem to be very different from the toxic potency of MC/CS inhaled as a fine dry CS crystal after evaporation of the organic solvent. In the following, the lowest c x t exposure values leading to mortality are listed:

a) Non-rodents

Species	Concentration (mg/m^3)	Time (minutes)	c x t ($mg.min/m^3$)
Monkey[1]	1,950	32	62,400
Monkey[2]	469	24	11,246
Monkey[3]	1,700	25	42,500
Dog[1]	2,595	5	12,975
Dog[2]	508	36	18,276
Dog[3]	2,400	28	67,200

[1] Thermal grenade; [2] Molten; [3] Powder

b) Rodents

Species	Concentration (mg/m^3)	Time (minutes)	c x t ($mg.min/m^3$)
Rat[1]	600	15	9,000
Rat[2]	560	25	14,000
Rat[3]	1,135	30	34,050
Guinea pig[1]	2,595	5	12,975
Guinea pig[1]	454	23	13,000
Guinea pig[2]	400	5	2,000
Guinea pig[3]	1,135	30	34,050
Mouse[2]	1,100	20	22,000

[1] Thermal grenade; [2] Molten; [3] Powder

Based on these early mortality data, rodents seem to be more sensitive (mortality starts at lower c x t values) than non-rodents, but based on the LCt50 values for molten and grenade CS, the opposite seems to be true, with non-rodents being more sensitive than rodents.

The LCt50 value for molten and grenade CS in rodents/non-rodents is 75,971/32,268 mg.min/m^3 and 79,080/35,559 mg.min/m^3 respectively. In respect of the concentration-response curve, this would mean that the slope of this curve that is determined by the minimum lethal concentration and the LCt50 point must be steeper in non-rodents than in rodents.

The slope of the log dose-response relationship is a measure for the variation in sensitivity within the group of animals or humans investigated. The smaller the variation, the steeper the curve.

The LCt50 of CS2 powder in non-rodents (dogs and monkeys) was 69,397 mg.min/m^3 and in rodents (rats and guinea pigs) was 56,792 mg.min/m^3. Data on the particle size of the powder CS were not reported.

With this comparison, one has to consider that the deposition efficiency of inhaled particles in the lung and therefore the CS dose in the lung may be different in the various animal species. The particle deposition patterns in the lung are similar for mice and rats on the one hand and for monkeys, dogs and humans on the other; the pattern for guinea pigs lies in-between. The differences are mainly the result of anatomical differences among these species. Furthermore, the rodents can reduce their breathing volume by 50 - 70 % when exposed to a sensory irritant. In this way, the rodents are able to lower the inhaled dose of the irritating agent.

The most sensitive animal species is the guinea pig. The LCt50 for sprayed molten CS was 8,410 mg.min/m^3(minimum lethal concentration 400 mg/m^3 for 5 minutes). For CS dispersed from thermal grenades, the LCt50 value was 36,439 mg.min/m^3 (minimum lethal concentration 454 mg/m^3 for 23 minutes) and for powdered CS2, the LCt50 value was 49,082 mg.min/m^3 (minimum lethal

concentration 1,135 mg.min/m^3 for 30 minutes). The guinea pig has abundant smooth bronchial musculature which makes this species more susceptible to inhaled irritants because it develops bronchioconstrictive and asthma-like responses more easily.

At Waco, only MC/CS was used. There is only one experiment mentioned in the available literature on inhalation toxicity testing with CS dissolved in methylene chloride (10 % solution), but no information is given on the droplet size generated by dispersion of this fluid. Large droplets would fall very rapidly to the ground and the size of the crystalline CS particles that are formed after evaporation of methylene chloride from the liquid aerosol very much depends on the amount of CS dissolved in the droplet.

Comparison of the guinea pigs exposed to CS2 powder and those exposed to CS dispersed from methylene chloride solution is quite similar: 49,082 and 45,838 mg.min/m^3 respectively. Early mortality in guinea pigs exposed to CS generated from methylene chloride solution occurred after 10 - 15 minutes of exposure to 800 - 1,000 mg/m^3 CS. CS powder caused early mortality after inhalation of 1,135 mg/m^3 for 30 minutes.

No increased mortality was reported in rats exposed to between 500 and 2,500 mg/m^3 of MC/CS for between 5 and 45 minutes, resulting in c x t values between 2,000 and 59,000 mg.min/m^3. With micronized CS powder, the LCt50 value for rats is reported to be 67,588 mg.min/m^3. There is no explanation other than the conduct of the rat experiment for the different effects between powder CS and MC/CS reported in rats but not in guinea pigs.

Also, no information was given on the concentration of methylene chloride in the exposure chamber. The combinatory effect of inhaled CS and methylene chloride has to be assumed. In particular, the effect of CO which is formed as a metabolite of methylene chloride in the organism has to be considered. CO binds to hemoglobin and in this way reduces the transport capacity of oxygen into the blood. Poor oxygen transfer into the lung due to CS-related lung

damage together with reduced hemoglobin-binding capacity for oxygen may increase the risk of asphyxiation.

These data point to a higher toxic potency of CS dispersed from methylene chloride solution compared to CS powder in guinea pigs, but no information was given on the characteristics of the aerosol generated. None of 18 monkeys with bacterial infection in the lung (which may have caused reduced breathing) died after exposure to 30,000 mg.min/m^3 CS dispersed from methylene chloride solution. The LCt50 value from monkeys exposed to powdered CS was 42,500 mg.min/m^3. With no other information available, it can be assumed that the LCt50 value for MC/CS in monkeys may not be very different to the LCt50 value of micronized powdered CS.

The respiratory tract of humans shows more similarities with the respiratory tract of monkeys than with that of rodents. This refers to the characteristics of the nasal cavity, the cellular composition of the bronchiolar epithelium, the presence of respiratory bronchioles in humans and monkeys, but mostly not in rodents, as well as similar minute volume per kg body weight and fractional pulmonary deposition (for 1, 2 and 5 µm particles) in humans and monkeys (CRC Handbook of Toxicology, 1995; Concepts in Inhalation Toxicology, 1989). On the other hand, for extrapolating toxicity data from animal experiments to humans, the most sensitive animal species is chosen if no data available demonstrating mechanistically or otherwise that the high sensitivity is a species-specific effect which will not occur in humans. For inhalation risk assessment, the most sensitive species is the species that shows an adverse effect level which, when dosimetrically adjusted, results in the lowest human equivalent exposure concentration.

Averaging all experimental animal data reported in the literature on LCt50 values, the U.S. military determined an LCt50 value of 52,000 mg.min/m^3 for molten CS, and 61,000 mg.min/m^3 for grenade CS, but these values cannot be extrapolated to humans without calculating a human equivalent concentration estimate or employing uncertainty factors for species-to-species extrapolation.

3d. Toxicity data in humans

CS is a peripheral sensory irritant and the exposure-related symptoms include eye irritation, excessive lacrimation, blepharospasm, burning sensation in the nose and throat, excessive salivation, constricting sensation in the chest, feeling of suffocation, sneezing and coughing, and stinging or burning sensation on the exposed skin. In higher concentrations, CS can also irritate the stomach, leading to vomiting and diarrhea. The detection limit of CS in humans by smelling is approximately 4 $\mu m/m^3$, the concentration of CS that causes people to leave is
0.5 mg/m^3. At 1 mg/m^3 lacrimation occurs and a concentration of 10 mg/m^3 will deter trained troops.

CS concentrations that may be injurious to the health of 50 % of the exposed humans are reported to be 10 - 20 $mg.min/m^3$. The irritating potency of CS varies among individuals and increased ambient temperature and humidity can also intensify the irritating effects.

Very often the ICt50 value is reported. This incapacitating concentration is the CS concentration that is intolerable to 50 % of the population exposed for 1 minute. The decision to tolerate the irritant is strongly influenced by the individual's will to resist.

Higher CS exposure can be tolerated when the concentration of CS is gradually increased. The range of the ICt50 value reported in the literature is 0.1 - 10 mg/m^3 for 1 minute. Smaller CS particles have a predominantly respiratory effect, whereas larger CS particles have predominantly ocular effects. This finding was reported using particles of different sizes (0.9 µm and 60 µm) generated by spraying a solution of 2 % CS in methylene chloride.

Humans can tolerate CS of 1.5 mg/m^3 for 90 minutes. When the concentration is built up over 30 minutes, an atmosphere of 6.6 mg/m^3 can be tolerated. The size of the CS aerosol dispersed in these controlled human exposures from a 10 % solution in methylene chloride or from molten CS was in the range of 0.5 -

1 µm. The following major symptoms in the respiratory tract were reported during controlled human exposure to CS (over 30 minutes), gradually attaining a concentration of 6.6 mg/m^3: slight burning, coughing, sneezing, eye irritation, burning became painful with constricting sensation in the chest, gasping when aerosol was inhaled, holding breath and slow and shallow breathing, and paroxysms of coughing that forced the individuals to leave the exposure chamber (Punte et al. 1963).

In the literature, the short accidental exposure of a previously healthy male subject of 43 years of age to high concentrations of CS caused inside a room by a smoke gas projectile containing 1 g of CS was reported. This subject developed a toxic pulmonary edema. He recovered after several weeks of medical treatment (Krapf & Thalmann 1981).

There are no reports on human death caused by CS. Therefore, CS concentration, or concentration times time value for lethal effects in humans, can only be derived from animal experiments.

4. CS concentration and exposure scenarios in the Mount Carmel compound, Waco

The CS agent was inserted into the building dissolved in methylene chloride using pressurized canisters (Model 5 Protectojet) containing 1070 g methylene chloride and 30 g CS as well as ferret rounds containing 33.25 g methylene chloride and 3.7 g CS. The solution of CS in methylene chloride was ejected from the canister through a small orifice and tube by means of CO_2 as propellant. The plastic ferret rounds burst after hitting the walls or windows of the building, distributing the methylene chloride/CS solution as liquid aerosol. Methylene chloride evaporates very rapidly from the small droplets generated by the delivery systems, leaving behind small solid CS particles that can easily be inhaled. Because of the evaporation of methylene chloride, the indoor air was not only contaminated with CS particles, but also with gaseous methylene chloride.

Based on information provided by the Office of Special Counsel (OSC), a total of 20 canisters and 386 ferret rounds were used in the Waco operation on April 19, 1993, starting at about 6 a.m. and ending shortly after noon. Dr. Jerry Havens prepared a report for the OSC where he calculated room concentrations of CS and methylene chloride in the Mount Carmel complex using the tear gas insertion log, put together by the OSC, and various environmental and building specifications also provided by the OSC (see also Report by Jerry Havens entitled "Analysis of Flammability Hazard Associated with the Use of Tear Gas at the Branch Davidian Compound, Waco, Texas, April 19, 1993" prepared for the Office of Special Counsel, John C. Danforth). This information and the COMIS computer model were used to estimate the concentration of CS and methylene chloride in the various rooms of the Mount Carmel complex, taking into account ventilation in the building.

Dr. Havens also calculated 15-second time interval series of CS and methylene chloride concentrations in each room and compartment in the Mount Carmel building using various tear gas insertion scenarios. The following list of rooms highlights the rooms that experienced the highest CS and MS concentrations under the most probable insertion scenario. These concentration predictions assume worst case matters including complete dispersion and all ferrets made it into the complex. These concentrations and concentration time values are used to answer the questions posed to me by the Office of Special Counsel, including whether CS exposure could have attributed or even caused the death of Branch Davidians living in the Mount Carmel compound on April 19, 1993:

1. <u>Room 27 (bunker)</u>

   Insertion of one canister at 11.50 a.m. resulted in an initial concentration of 318 mg/m^3 CS and 3,268 ppm methylene chloride in Room 27. After 30 minutes, the room concentration of CS and methylene chloride is still 215 mg/m^3 and 2,196 ppm respectively. The calculated c x t value is approximately 8000 $mg.min/m^3$ CS (see also Fig. 1: RM27/1). As described in Dr. Havens' report, this scenario is highly improbable given the depth of penetration of the CEV at 11.50, and the capabilities of the Model 5 Protectojet.

2. Room 27 (bunker)

   Insertion of half a canister at 11.50 a.m. resulted in an initial concentration of 160 mg/m^3 CS and 1,631 ppm methylene chloride in Room 27. After 30 minutes, the room concentration of CS and methylene chloride is still 119 mg/m^3 and 1,214 ppm respectively. The calculated c x t value is approximately 4,200 mg.min/m^3 CS (see also Fig. 2: RM27/0.5). As described in Dr. Havens' report, this is the most probable scenario within the Branch Davidian complex on April 19, 1993.

3. Room 19

   Various insertions of tear gas during the time period of 6.13 a.m. to 7.35 a.m.. The maximum concentration of CS and methylene chloride reached during this time was 768 mg/m^3 and 7,746 ppm respectively. The calculated c x t value is approximately 7,000 mg.min/m^3 CS (see also Fig. 5: RM19).

4. Room 5

   Insertion of tear gas at 6.05 a.m. resulted in an initial concentration of 1,108 mg/m^3 CS and 11,341 ppm methylene chloride. After 2 minutes, the concentrations of CS and methylene chloride drop to almost half the initial concentrations (661 mg/m^3 and 6,768 ppm respectively), and 20 minutes after starting the tear gas insertion the CS and methylene chloride concentrations are down to 16 mg/m^3 and 161 ppm respectively. The calculated c x t value is approximately 4,000 mg.min/m^3 CS (see also Fig. 3: RM5).

5. Room 7

   Tear gas insertion starts at 9.11 a.m. leading to an initial concentration of 1,178 mg/m^3 and 11,035 ppm methylene chloride. After 1 minute, the room concentrations of CS and methylene chloride are down to 6 mg/m^3 and 62 ppm respectively. The calculated c x t value is approximately 2,100 mg.min/m^3 CS (see also Fig. 4: RM7).

6. Room 30

   Insertion of 2 canisters within one minute between 11.49 a.m. and 11.52 a.m.. Two peak concentrations occurred: 334 mg/m^3 and 364 mg/m^3 for CS and 3,415 ppm and 3,726 ppm for methylene chloride. 2.5 minutes after starting the tear gas insertion, the concentrations are down to 10 mg/m^3 CS

and 106 ppm methylene chloride. The calculated c x t value is approximately 330 mg.min/m^3 CS (see also Fig.6: RM30).

5. Was there a higher risk of Branch Davidians to die because of the CS exposure?

5a. Adult exposure

In the monkey, which is the most adequate animal species in respect of anatomic and physiologic respiratory tract similarities to humans for making predictions of toxic effects in the respiratory tract of CS-exposed humans, only slight clinical symptoms such as coughing and nasal discharge were reported after exposure to approximately 300 mg/m^3 CS (molten and sprayed) for up to 30 minutes. On the other hand, early mortality occurred in monkeys after exposure to 469 mg/m^3 CS for 24 minutes and another non-rodent species, the dog, showed mortalities after exposure to 508 mg/m^3 CS for 36 minutes. The lowest c x t value indicating that mortality starts to occur was 11,246 mg.min/m^3 in monkeys and 12,975 mg.min/m^3 in dogs. With powdered CS, which seems to have a somewhat lower toxic potency than molten CS and which may be more similar to MC/CS used at Waco, the lowest c x t values for monkeys and dogs indicating early mortality were 42,500 mg.min/m^3 and 67,200 mg.min/m^3.

For the exposure scenario RM27/1, a CS concentration of 318 - 215 mg/m^3 for 30 minutes and a c x t value of approximately 8,000 mg.min/m^3 were calculated. Assuming that the fire in the Waco complex had destroyed this area at 12.15 p.m., the c x t value would be a little lower (see Fig. 1). There is not a big safety factor between the inhaled dose with early indication of mortality in monkeys and dogs exposed to molten CS and the CS dose inhaled theoretically by Branch Davidians in this exposure scenario or the one of RM19 with a c x t value of approximately 7,000 mg.min/m^3 dispersed from MC/CS solution. Even if only half a canister had been inserted into Room 27, the calculated c x t value is only 2 to 3 times lower than the c x t value that caused early mortality in dogs and monkeys exposed to molten CS. Also, the LCt50 value for CS (molten and grenade type) in non-rodents is only 5 to 6 times

higher than the c x t values calculated on the basis of the exposure scenarios of Room 27 and Room 19. Taking the value of early mortality in monkeys exposed to powdered CS (42,000 mg.min/m^3) which may be more similar to the MC/CS used at Waco than molten CS, there would be a safety factor of 10 if the exposure scenario of Room 27 filled with half a canister of MC/CS is used.

Provided the monkey is as sensitive to CS in the lung as the exposed humans, the comparison of the human situation especially to the monkey may be quite valid because the anatomy of the respiratory tract, including the nasal region, and the aerosol deposition efficiency of man and monkey are very similar.

Because only very few data from experiments with monkeys are available and the rodents seem to be more sensitive to CS exposure than monkeys, and because rodents, especially the rat, are the animal species most used for toxicity tests, the risk assessment of CS for humans should also consider the rodent data available. In rodents, mostly rats and guinea pigs, the inhaled doses (c x t values) of molten or thermal grenade CS that led to early mortality were in the range of 2,000 mg.min/m^3 (400 mg/m^3 for 5 minutes) up to 14,000 mg.min/m^3 (560 mg/m^3 for 25 minutes). The most sensitive rodent is the guinea pig with an LCt50 value for molten CS of only 8,410 mg.min/m^3. The LCt50 values of CS powder and CS dispersed from a solution in methylene chloride are quite similar, namely 49,082 and 45,838 mg.min/m^3 respectively. Taking the rodent species together, the LCt50 values for molten, grenade and powder CS are 75,971, 79,080 and 56,792 mg.min/m^3 respectively. Similar toxic potency of powdered CS and MC/CS used at Waco can be assumed.

These inhaled concentration levels lethal to rodents are far higher than those calculated for the various exposure scenarios in the Mount Carmel compound of the Branch Davidians. However, taking into account the differences between rodents and humans in respect of anatomy of the respiratory tract, breathing volume, lung surface, particle deposition efficiency in the respiratory tract, etc., the human equivalent concentration that would lead to the same effect in humans as observed in rodents (50 % mortality) has to be calculated before the animal exposure and effect data can be extrapolated to humans.

Using the approach to calculate the human equivalent concentration as published by the U.S. EPA in 1994 (EPA/600/8-90/066F), it turned out that the LCt50 values for rats and guinea pigs leading to 50 % mortality would be only roughly half the value as the human equivalent concentration. As the most harmful effects of inhaled CS occur in the alveolar region of the lung, only the fractional deposition for this part of the lung (pulmonary) was taken into account when calculating the human equivalent concentration.

Taking this human equivalent concentration into account and assuming that the rodent lung is as sensitive to CS as the human lung, then the human LCt50 values derived from rodent data would be in the range of 25,000 - 40,000 $mg.min/m^3$.

Based on the most sensitive rodent species, the guinea pig, the human equivalent LCt50 value for CS dispersed from a solution in methylene chloride would be roughly 23,000 $mg.min/m^3$. Another uncertainty not considered in this calculation is the reduced breathing volume in rodents exposed to sensory irritants. The CS dose actually retained in the rodent lung is clearly lower than the calculated dose because the normal and not the reduced respiratory frequency and breathing volume of the rodents were used for calculating the human equivalent concentration. This would lead to an even lower human equivalent LCt50 estimate.

Although the inhaled concentrations in animal experiments, including monkeys, that caused early deaths or even 50 % mortality are not too far from the inhaled concentration values calculated for Rooms 27 and 19 in the Mount Carmel building, one has to consider that the ICt50 value for humans, that is the CS concentration that forces 50 % of the exposed humans to leave the exposure situation, because of the strong irritating effects is at least a factor of 30 lower than these predicted room concentrations. This means that, only if the inhabitants of the Mount Carmel residence were not able to leave the rooms in which such high concentrations of CS occurred, would the CS exposure possibly contribute to the deaths of some of the Branch Davidians. If the

Branch Davidians were free to leave the rooms with high concentrations, CS would probably not have contributed to their death.

As death does not occur immediately after short-term CS exposure in animal experiments but only after some time, it can be assumed that other factors (e.g. the fire) could have also contributed to the death of the Mount Carmel inhabitants.

5b. Child exposure

The inhaled breathing volume per surface area in children up to 7 years of age is about 8 - 20 times greater than in adults (Barnes 1987, West 1987). The rate of aerosol deposition normalized to lung surface area is about 35 % greater in children (7 - 14 years of age) than in adolescents and adults for resting breathing and 2 µm particle size. The increase in normalized deposition rate in children is due to the higher minute ventilation in relation to the lung size (Bennett & Zemann 2000). This means that children exposed to the same CS aerosol atmosphere as adults will get higher doses of CS per lung surface area than adults and therefore the toxic effects of a certain CS exposure atmosphere can be more pronounced in children than in adults.

Furthermore, age-dependent model calculations based on the dimensions of airways and the geometry of branching airway networks within the lungs indicate that, for example, 1 µm particles will have a lung deposition of 24 % in an adult, but 33 % in a 22-month-old child; this is a relative increase of 38 % (Musante et al. 2000). Children, who were not able to leave the rooms exposed to high concentrations of CS (Room 27 and Room 19) or who were not otherwise protected from CS inhalation, would be at a higher risk for toxic effects of CS than adults exposed to the same CS concentration.

5c. Multiple chemical exposure

1. Methylene chloride (MC)

In addition to the exposure to CS, the inhabitants of the Mount Carmel residence also inhaled relatively high concentrations of methylene chloride. Methylene chloride can induce narcotic effects and unconsciousness in high concentrations (approximately ≥ 10,000 ppm). Concentrations of methylene chloride of up to almost 8,000 ppm could have occurred, though only for a short time, if the predicted exposure scenario of Room 19 is considered. MC is metabolized in the body partly to CO, which leads to the formation of CO hemoglobin and thus to the reduction in the oxygen transport capacity of the blood. Together with a CS-related lung injury leading to poor oxygen transfer from the alveolar space to the blood capillaries, the increased COHb values add to the danger of suffocation.

Possible effects of methylene chloride on the central nervous system are reported and discussed by Dr. George Lucier in his report to the OSC (Analysis of the Toxicity Hazards of Methylene Chloride Associated with the Use of Tear Gas at the Branch Davidian Compound at Waco, Texas, on April 19, 1993).

2. Effects of hydrogen cyanide (HCN)

Besides the direct toxic effect of high concentrations of CS on the lung, the formation of hydrogen cyanide (HCN) from malononitrile, a metabolite of CS, and its toxic effect, especially on the most sensitive brain cells, possibly leading to respiratory arrest, cannot be ignored when possible lethal effects of CS exposure are discussed. In animal experiments, a synergistic lethality induced by the combination of carbon monoxide and cyanide was reported. This effect could not be explained by altered carbon monoxide or cyanide blood concentrations (Norris et al. 1986).

With room concentrations of more than 100 mg/m^3 CS for about 30 minutes, as was predicted if half a CS-containing canister would have been inserted into Room 27 (bunker) and assuming the people in this room did not have gas masks and were not able to leave, more than 10 µmol or 270 µg cyanide per minute could be formed in the body. This calculation includes a 50 %

deposition efficiency of inhaled CS aerosol in the respiratory tract, a minute volume of the exposed person of 20 liters and the metabolic availability of both of the CN groups of the CS molecule. But toxification (formation of cyanide) as well as detoxification (formation of thiocyanate) kinetics are not known.

The blood cyanide level of Waco descendants reported in the "Forensic Pathology Evaluation of the 1993 Mount Carmel Deaths and Other Pertinent Issues" prepared for the OSC was, on average, 18.5 µmol/l or 0.5 mg/l.

In the literature, the mean blood cyanide level of 615 fire victims was 980 µg/l, ranging from 60 - 4,000 µg/l (Barrillo et al. 1994). Cyanide is produced from all material containing C and N heated to a certain temperature. Also, the fire in the Waco building, starting shortly after noon, may have produced hydrogen cyanide that could be inhaled by the Branch Davidians. This cyanide adds to that produced metabolically from CS in the body.

Lethal blood cyanide levels are usually greater than 1 mg/l and levels greater than 0.2 - 0.25 mg/l are considered toxic and dangerous (Silverman et al. 1988).

For comparison, cyanide concentration in mainstream cigarette smoke is reported to be in the range of 40 - 70 ppm (Yamanaka et al. 1991). This means one 30 ml puff of a cigarette may contain 0.04 - 0.08 µmol or 1 - 2 µg cyanide. After abstaining from smoking for at least 2 hours, the smoking of one cigarette resulted in a blood cyanide level of approximately 0.5 µmol/l or 13 µg/l (Lundqvist
et al. 1987). This is roughly a factor of 40 lower than the average blood cyanide level of the Waco descendants. Their cyanide levels are well in the toxic and dangerous range. However, it is well known that cyanide can be produced and degraded in blood and tissue, especially dependent on the surrounding temperature, making interpretation of blood levels rather difficult and uncertain (Barrillo et al. 1994, Seto 1996).

6. Conclusion

Based on the predicted CS exposure situation in the Mount Carmel compound and assuming the exposed people were not able to leave such worst exposure scenarios, despite the very irritating, burning effects of CS inducing heavy coughing, and considering the variation in sensitivity in humans, including children, there is a distinct possibility that this kind of CS exposure can significantly contribute to or even cause lethal effects. If, on the other hand, the exposed people were able to leave the rooms (CS-related toxicity in the respiratory tract needs some time to actually cause death), avoid the rooms, or were able to protect themselves sufficiently by wearing gas masks, the CS exposure experienced by Branch Davidians, while uncomfortable, would not have caused lethal effects.

Hannover, 28 September, 2000

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Prof. Dr. Uwe Heinrich

Biographical Resumé

Prof. Dr. Uwe Heinrich

Dr. Heinrich is Professor of Toxicology and Aerosol Research at the University Medical School, Hannover, Germany, and Director of the Fraunhofer Institute of Toxicology and Aerosol Research, *Drug Research and Clinical Inhalation.* He received his Diploma (M.S.) in Zoology (Endocrinology, Physiological Etiology, and Histology) and his Dr.rer.nat. (Ph.D.) in Biology (Zoology, Physiology, Biochemistry, and Pharmacology) from the Eberhard-Karls University, Tübingen, Germany.

Dr. Heinrich has been a lecturer in Toxicology and Experimental Oncology at the University Medical School, Hannover, since 1984 and received his Dr.rer.biol.hum.habil. (Habilitation) and venia legendi in Experimental Oncology from the same university in 1989.

Dr. Heinrich was a research fellow in General Toxicology, specializing in Inhalation Toxicology, at the Institute of Toxicology of Bayer AG, Wuppertal, Germany, and a research fellow in Environmental Hygiene and Experimental Oncology at the Medical Institute of Environmental Hygiene, Heinrich-Heine University, Düsseldorf, Germany.

Dr. Heinrich's research interests are in inhalation toxicology, environmental and occupational hygiene, risk assessment, and preclinical research. He has published his research results in more than100 scientific papers and in 1991 he received the Kenneth Morgareidge Award for outstanding research in the field of inhalation toxicology.

Dr. Heinrich is a Fellow of the Academy of Toxicological Sciences (U.S.) and also serves on various national and international committees related to his expertise. He is currently Vice President of the International Society of Environmental Medicine.

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Personal Data

Date of birth	December 15, 1948, Salzgitter, Germany
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Education

1955 - 1959	Elementary school in Salzgitter, Germany
1959 - 1969	Gymnasium in Salzgitter
1969 - 1973	Studies at Eberhard-Karls-Universität in Tübingen
1973	Diploma (M.S.) in Zoology (Endocrinology, Physiological Ethology, Histology)
1976	Dr. rer. nat. (Ph.D.) in Biology (Zoology, Physiology, Biochemistry, Pharmacology)
1984 - present	Lecturer (Toxicology, Experimental Oncology) at Hannover Medical School
1989	Habilitation and venia legendi 'Experimental Oncology' at Hannover Medical School, University Lecturer (Privatdozent)
1996	University Professor 'Toxicology and Aerosol Research', Medical School, Hannover

Profession

1976/1977	Research fellow in general toxicology and especially inhalation toxicology at the Instiute of Toxicology of Bayer Corporation, Wuppertal, Germany
1977/1978	Research fellow in environmental hygiene and experimental oncology at the Medical Institute of Environmental Hygiene at Heinrich-Heine-Universität Düsseldorf, Germany

1978/1981	Scientific member and group leader 'Inhalation Toxicology' at Fraunhofer Institute of Toxicology and Aerosol Research in Münster, Germany; responsible for long-term animal inhalation studies, clinical chemistry and hematology, lung function laboratory and animal house
1981 - 1996	Head, Department of Environmental Hygiene, Lung Funtion Laboratory and Animal House at the Fraunhofer Institute of Toxicology and Aerosol Research, Hannover, Germany
1988 - 1996	Deputy Director of the Fraunhofer Institute of Toxicology and Aerosol Research, Hannover, Germany
1996 - present	Director of the Fraunhofer Institute of Toxicology and Aerosol Research, Hannover, Germany

Award

1991	International Life Sciences Institute Kenneth Morgareidge Award

Editorial Responsibilities

- Editorial Board 'Inhalation Toxicology' (1989 - 1997)
- Editorial Board, 'Umweltmedizin in Forschung und Praxis' (1996 - present)
- Co-Editor, 'Gefährdungsabschätzung von Umweltschadstoffen' (Hazard Assessment of Environmental Pollutants) (1998 - present)

Reviewer

- Manuscripts from various journals (5/year)
- Research proposals (5/year)

Member

- Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. German Research Organisation (Deutsche Forschungsgemeinschaft)
- Advisory Committee Toxicology, Committee on Hazardous Substances, Ministry of Labour and Social Affairs (Bundesministerium für Arbeit und Sozialordnung)

- Scientific Advisory Committee, 'Programme for the Prevention of Health Hazards caused by Industrial Substances', Employment Accident Insurance Fund of the Chemical Industry (Berufsgenossenschaft der chemischen Industrie)

- Temporary Adviser, World Health Organization

- Temporary Member of the Group of National Experts on Classification and Labelling of Dangerous Substances, EWG, DGXI, Brussels

- Participant of IARC Working Group of Experts on the Evaluation of Carcinogenic Risks to Humans

Recently Organized/Chaired

- Joint Meeting of the European Commission and Health Effects Institute 'The Health Effects of Fine Particles: Key Questions and the 2003 Review', Brussels, January 1999

- International Inhalation Symposia, Hannover (1987, 1989, 1991, 1993, 1995, 1997, 1999, 2001)

- International Multidisciplinary Conference on Environmental Medicine, Graz, Austria, September 1999

- 7th International Symposium on Particle Toxicology, Maastricht, The Netherlands, October 1999

- International Congress on Environmental Health, October 2000, Hannover

Member of Scientific Societies

- Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie

- Deutsche Gesellschaft für Pneumologie

- International Society of Environmental Medicine (Vice President)

- EUROTOX

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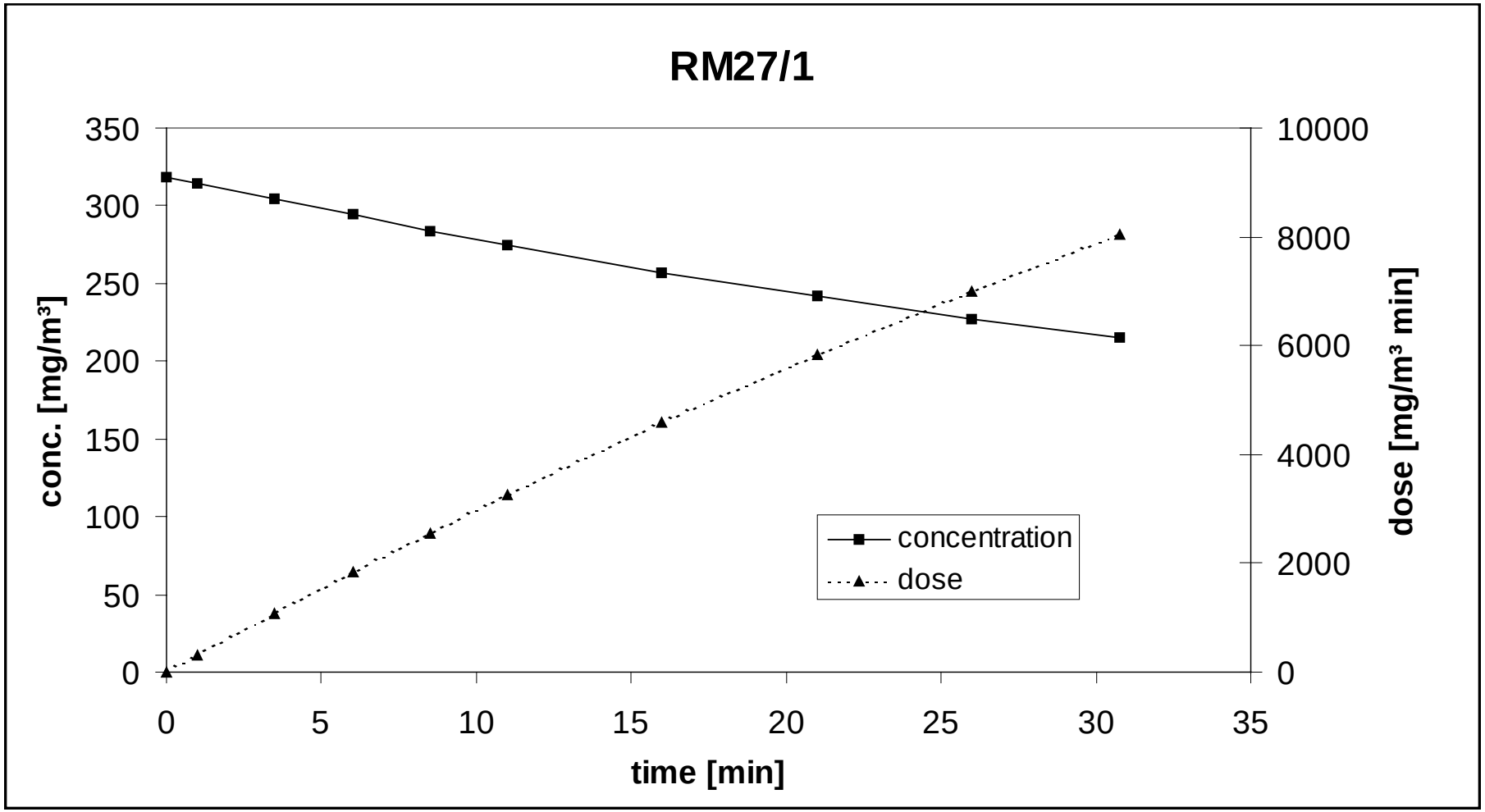
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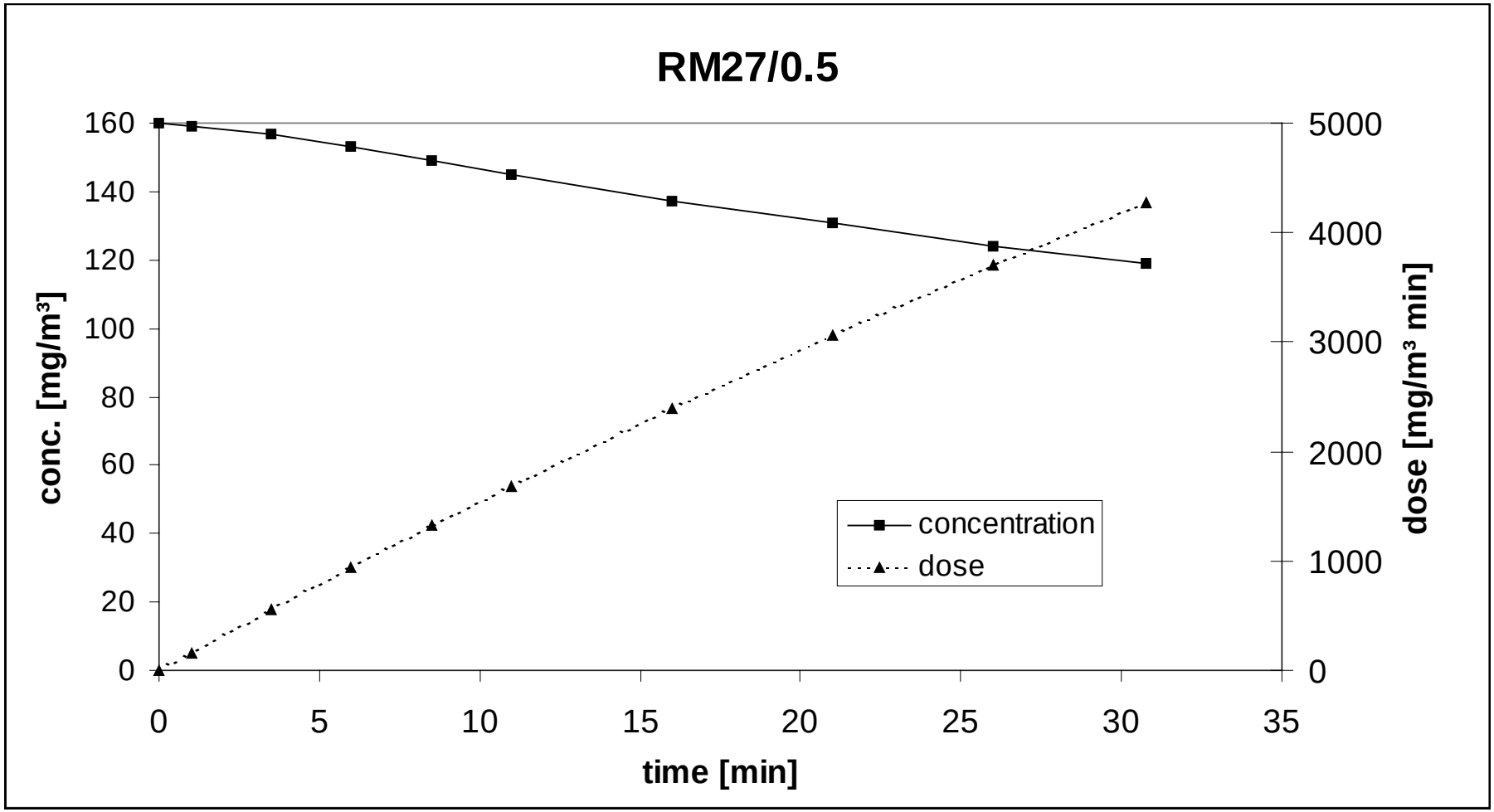
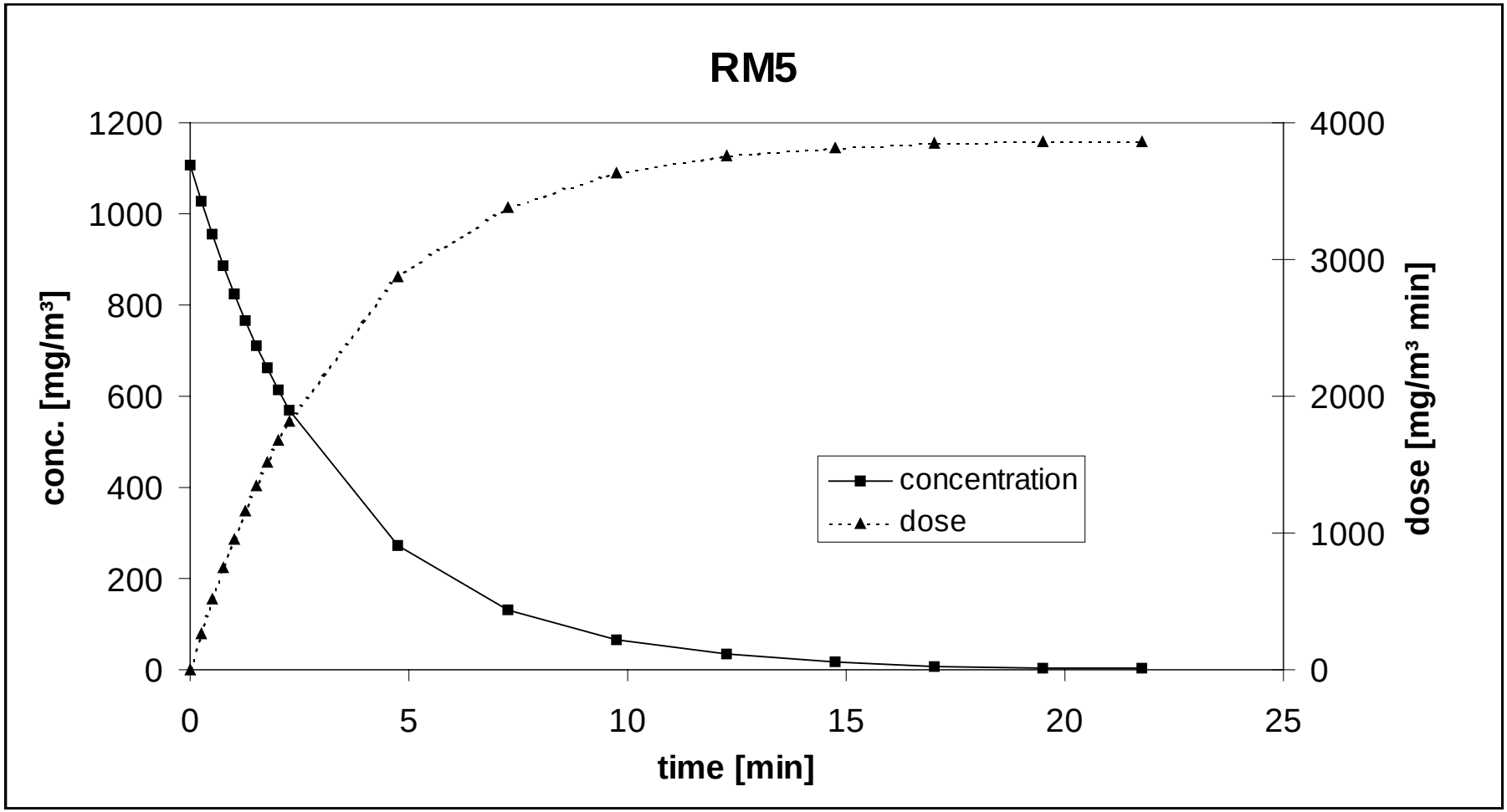
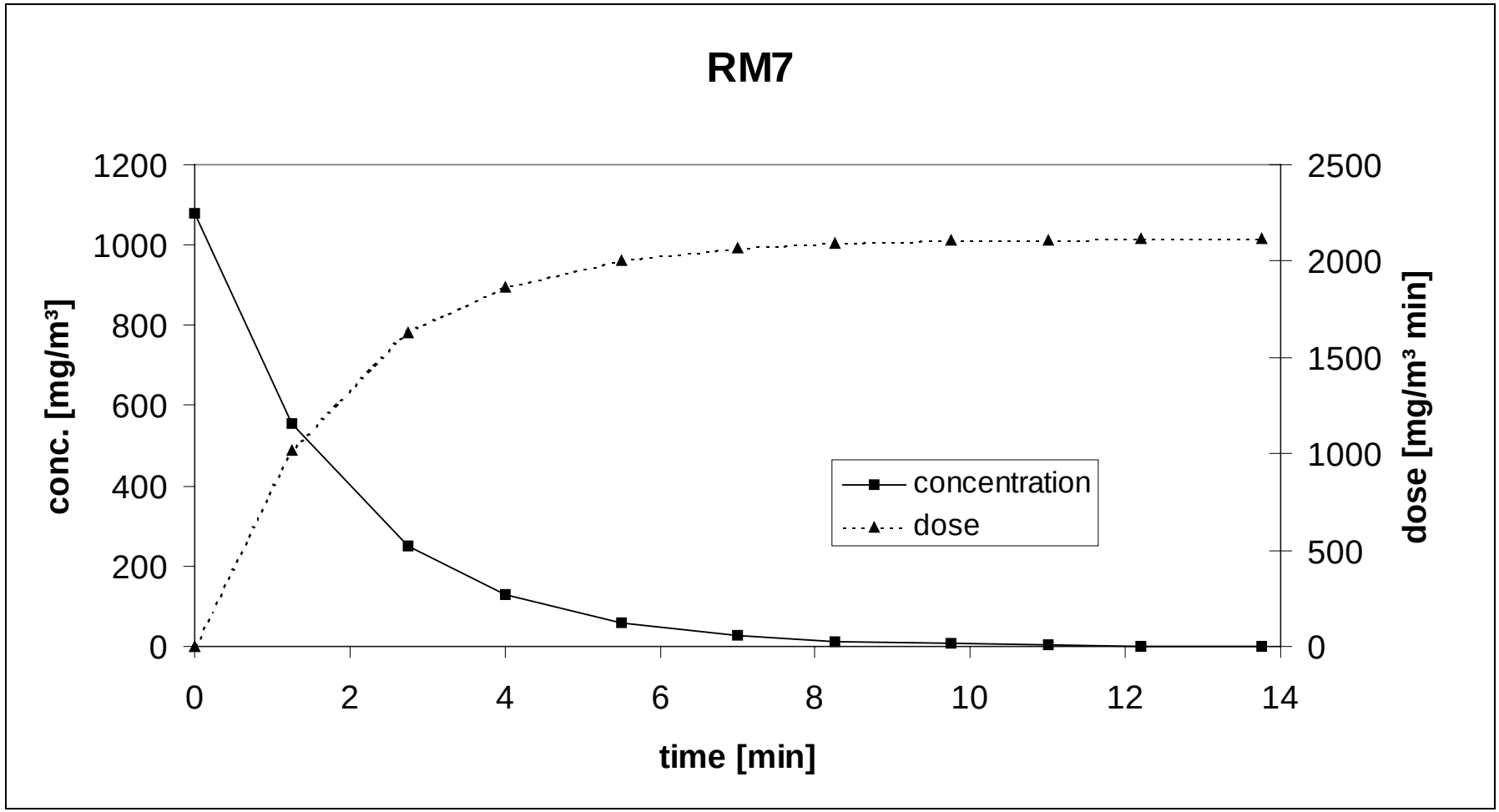
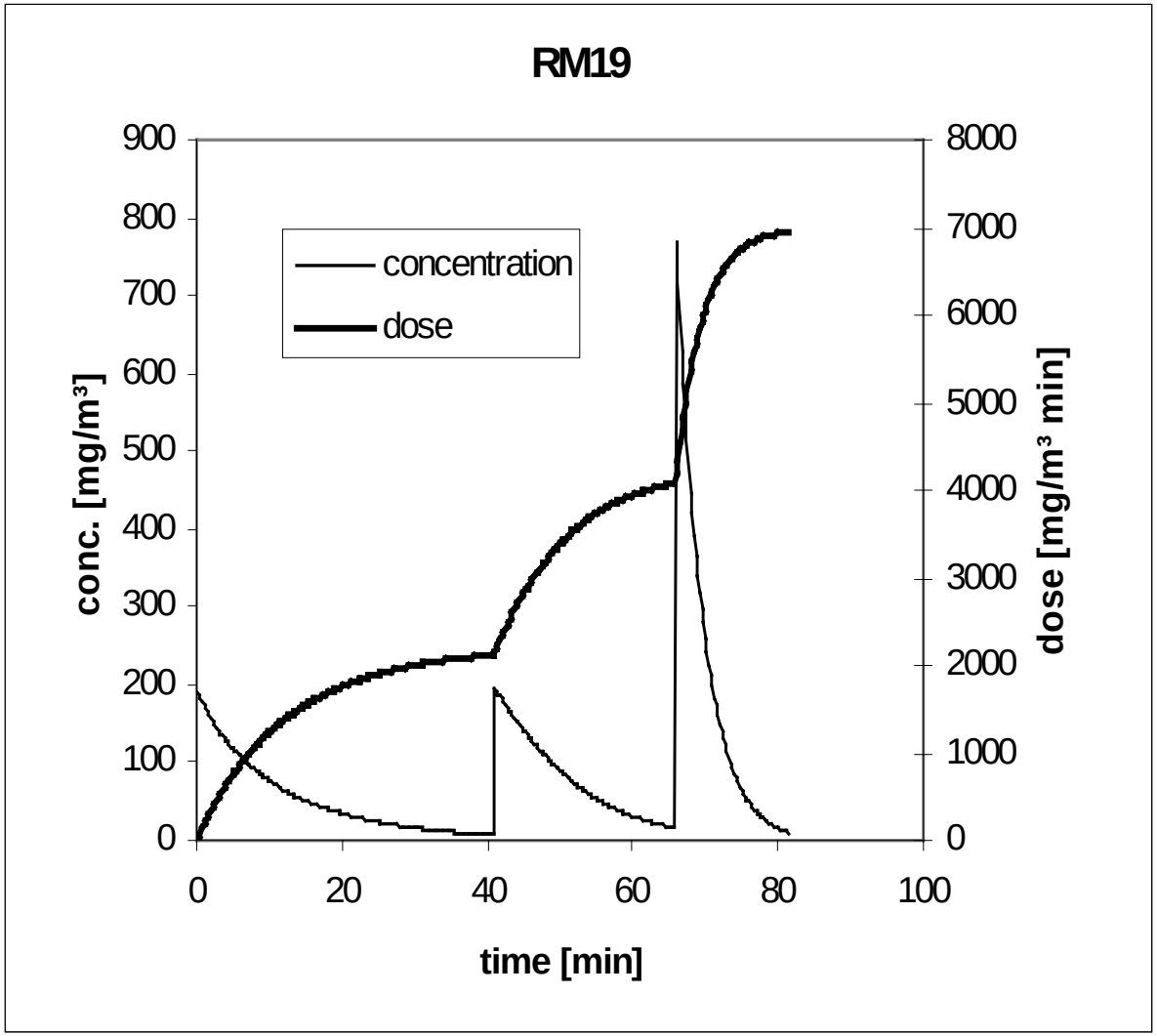
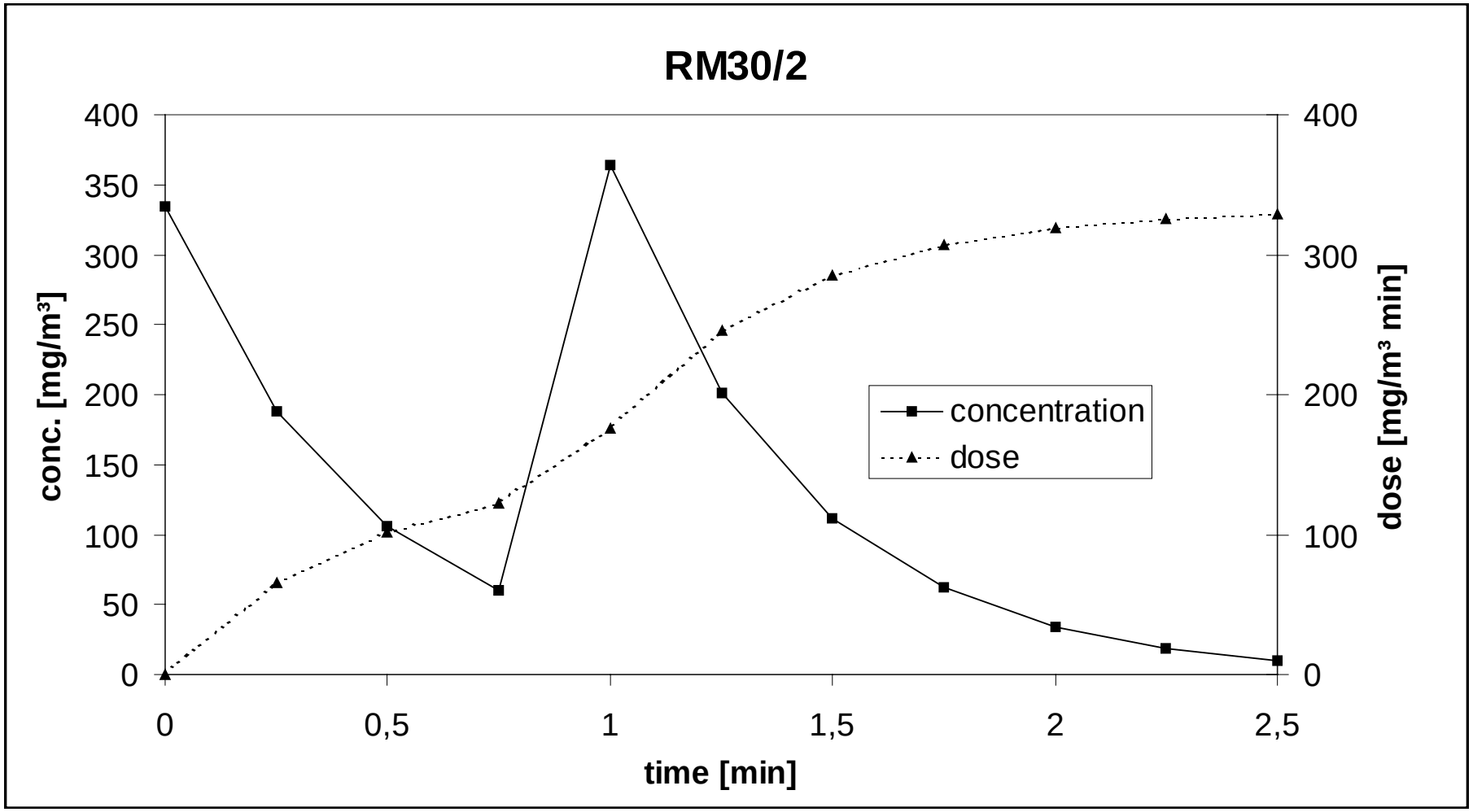
30
35


RM27/0.5
conc. [mg/m³]
dose [mg/m³ min]
time [min]
concentration
dose
0
20
40
60
80
100
120
140
160
0
1000
2000
3000
4000
5000
0
5
10
15
20
25
30
35


RM5
1200
1000
800
600
400
200
0
conc. [mg/m³]
4000
3000
2000
1000
0
dose [mg/m³ min]
0
5
10
15
20
25
time [min]
concentration
dose


RM7
1200
1000
800
600
400
200
0
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
conc. [mg/m³]
dose [mg/m³ min]
time [min]
concentration
dose


RM19
900
800
700
600
500
400
300
200
100
0
8000
7000
6000
5000
4000
3000
2000
1000
0
0
20
40
60
80
100
concentration
dose
conc. [mg/m³]
dose [mg/m³ min]
time [min]


RM30/2
400
350
300
250
200
150
100
50
0
conc. [mg/m³]
400
300
200
100
0
dose [mg/m³ min]
0
0,5
1
1,5
2
2,5
time [min]
concentration
dose