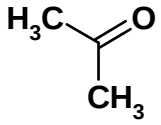
INTERIM 1: 07/2005

ACETONE
(CAS Reg. No. 67-64-1)



INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

For

NAS/COT Subcommittee for AEGLs

Juli 2005

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Acetone is a colorless volatile liquid with a sweetish, mildly pungent and fruity odor. The reported odor thresholds vary widely. In recent studies using standardized procedures and n-butanol as control substance, odor detection threshold ranged from 41-86 ppm.

Acetone is completely miscible with water and a number of organic solvents and most oils. Owing to its high volatility, low flash point, low autoignition temperature, and the wide range of explosive limits in air (lower: 2.6 %, upper: 12.8 % v/v), acetone poses an acute fire and explosion hazard.

Acetone is the most widely used ketone in industry. It is used primarily to synthesize methacrylates, bisphenol A, and methyl isobutyl ketone. Another important use is that as a solvent in paint, ink, resin, and varnish formulations. Acetone is also used as a process solvent in the manufacture of cellulose acetate yarn, smokeless gun powder, surface coatings, and various pharmaceutical and cosmetic products.

In humans and other mammalians, acetone is a minor metabolite of normal intermediary metabolism. Consequently, small quantities may occur in exhaled air. Endogenous acetone formation is closely linked with ketogenesis in the catabolism of body fat. Concentrations above normal levels in body tissues build up during fasting and especially in diabetic patients in ketoacidotic state.

The toxicity of acetone is low. Following exposure to acetone, the primary effects in humans are irritation and effects on the central nervous system (CNS). Data on inhalation exposure of humans are available from controlled clinical and from occupational studies, furthermore, some case reports of oral intoxications provide some data on effective blood concentrations.

Animal studies were mostly carried out with rats, but also with baboons, mice, guinea pigs and cats. As in humans, CNS effects are also observed in animals following acute inhalation exposure. Genotoxicity was not observed *in vitro* and *in vivo*. Carcinogenicity studies are lacking. In developmental toxicity studies with repeated exposure, reduced maternal and fetal weight was observed but the incidence of malformations was not significantly increased.

The level of distinct odor awareness (LOA) for acetone is 160 ppm. The LOA derivation follows the guidance as described (van Doorn et al. 2001a). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

The AEGL-1 derivation is based on observations in four studies with human volunteers exposed for 3-5 minutes (Nelson et al. 1943), 2 hours (Ernstgard et al. 1999), 6 hours (Matsushita et al. 1969a) and 7.5 hours (Stewart et al. 1975). At 200 ppm, subjective symptoms (eye/throat irritation) were not reported more often than in controls (Stewart et al. 1975). At 250 ppm, no irritative symptoms on mucous membranes or effects on the central nervous system (headache, fatigue, feeling of sickness, dizziness, intoxication) were observed in one study (Ernstgard et al. 1999); in a second study, slight irritation and few complaints about subjective discomfort (feeling of tension, general weakness, heavy eyes, lacking in energy) were reported at 250 ppm, and these subjective symptoms were felt by most volunteers at 500 ppm and 1000 ppm (Matsushita et al. 1969a). Slight irritation at 300 ppm and subjective irritation in the majority of exposed volunteers at 500 ppm were reported in a further study (Nelson et al. 1943). Therefore, 200 ppm were selected to derive AEGL-1. Because this concentration represents a NOAEL for local effects and effects at higher concentrations were weak, an intraspecies factor of 1 is applied. The value of 200 ppm was used for all timepoints since accommodation to slight irritation occurs

and the complaints about subjective discomfort at higher concentrations were reported not to increase during 6 hour or 7.5 hour exposure.

The AEGL-2 is based on the NOAEL for ataxia in rats following exposure to 6000 ppm acetone for 4 hours (Goldberg et al. 1964). At the next higher concentration of 12,000 ppm, reversible ataxia was observed. Reversible ataxia also was observed in another study at exposure of rats to 12,600 ppm for 3 hours, but a no-effect level was not determined in that study (Bruckner and Peterson 1981a). Toxikokinetic studies show that following inhalation the concentration of acetone in blood is similar or lower in humans than in rats. Furthermore, with respect to toxicodynamics, effects of substances such as acetone that are non-specific acute CNS-depressants in general do not show much variation between species. Finally, an interspecies factor of 3 which is often used in the derivation AEGL for CNS-depressant volatile solvents like acetone would (together with an intraspecies factor of 4.2, see below) have resulted in AEGL-2 of 480 ppm for 4 hours and of 320 ppm for 8 hours. These values are not supported by data from controlled human studies in which exposures up to 1000 - 1200 ppm for up to 7.5 hours resulted in irritation and slight headaches but no more severe effects. Furthermore, available toxikokinetic data for humans show that an exposure to 480 ppm for 4 hours or 320 ppm for 8 hours would lead to acetone concentration in blood below 50 mg/L. Such concentrations are still in the physiological range which can be observed in healthy fasting humans. Therefore, an interspecies factor of 1 was used. A substance specific intraspecies uncertainty factor of 4.2 (see derivation of AEGL-3 below) was applied to account for sensitive individuals. The experimentally derived exposure values were scaled to AEGL time frames using the equation $c^n \times t = k$ with n = 1.7 as outlined below for AEGL-3.

The AEGL-3 is based on a study in rats in which no deaths of animals occurred at exposure to 12,600 ppm for 3 hours (Bruckner and Peterson 1981a). In that study, also no deaths were observed in animals exposed to 19,000 and 25,300 ppm, but since 1 of 6 animals died at 16,000 ppm in another study (Smyth et al. 1962), the findings at 12,600 ppm exposure for 3 hours were taken as basis for the derivation of AEGL-3. An interspecies uncertainty factor of 1 was applied because the same toxic effects (CNS-depression) which are relevant for AEGL-2 are also relevant in case of AEGL-3. Also, an interspecies factor of 3 (together with an intraspecies factor of 4.2, see below) would result in AEGL-3 of 840 ppm for 4 hours and 560 ppm for 8 hours. These values are not supported by data from a controlled human study in which no life-threatening effects were observed at exposures up to 2110 ppm for 8 hours and a number of other studies in which no severe effects on the central nervous system were observed at exposures up to 1000 - 1200 ppm for 6 - 7.5 hours. With respect to an intraspecies factor, it is observed in humans that newborns consistently are the most sensitive age group for volatile anesthetics in general (NRC 2001). No human data for acetone were available allowing for the derivation of a substance-specific intraspecies factor. However, in a study with rats of different ages it was observed that the lethal dose ($LD_{50\ oral}$) of acetone was 4.2-fold lower in newborns than in adults (Kimura et al. 1971). It is assumed that intraspecies differences between humans are also covered by this range. Therefore, an intraspecies uncertainty factor of 4.2 was applied to account for sensitive individuals. The experimentally derived exposure values were scaled to AEGL time frames using the equation $c^n \times t = k$ with a value of n = 1.7 that was derived by extrapolation from 4-hour and 8-hour LC_{50} data (Pozzani et al. 1959).

The derived AEGL values are listed in the table.

SUMMARY TABLE OF AEGL VALUES FOR ACETONE [a]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	200 ppm (470 mg/m³)	200 ppm (470 mg/m³)	200 ppm (470 mg/m³)	200 ppm (470 mg/m³)	200 ppm (470 mg/m³)	NOAEL for slight irritation (Ernstgard et al. 1999; Matsushita et al., 1969a; Nelson et al. 1943; Stewart et al. 1975)
AEGL-2 (Disabling)	9,300 ppm* (22,000 mg/m³)	4,900 ppm* (11,000 mg/m³)	3,200 ppm* (7700 mg/m³)	1,400 ppm (3400 mg/m³)	950 ppm (2300 mg/m³)	Ataxia in rats (Bruckner and Petersen 1981a; Goldberg et al. 1964)
AEGL-3 (Lethality)	see below #	8,600 ppm* (20,000 mg/m³)	5,700 ppm* (14,000 mg/m³)	2500 ppm (6000 mg/m³)	1,700 ppm (4000 mg/m³)	No lethality in rats (Bruckner and Petersen 1981a; Smyth et al. 1962)

a: Cutaneous absorption of liquid acetone may occur. Since liquid acetone is an eye irritant, eye contact must be avoided.
#: The lower explosive limit (LEL) of acetone in air is 2.6 % (26,000 ppm). The AEGL-3 value of 16,000 ppm (39,000 mg/m³) for 10 minutes is higher than 50 % of the LEL. Therefore, extreme safety considerations against hazard of explosion must be taken into account.
*: Concentrations are higher than 1/10 of the lower explosive limit of acetone in air. Therefore, safety considerations against hazard of explosion must be taken into account.

References

Bruckner, J.V. and R.G. Peterson. 1981a. Evaluation of toluene and acetone inhalant abuse. I. Pharmacology and pharmacodynamics. *Toxicology and Applied Pharmacology* 61: 27-38.

Ernstgard, L., E. Gullstrand, G. Johanson, and A. Lof. 1999. Toxicokinetic interactions between orally ingested chlorzoxazone and inhaled acetone or toluene in male volunteers. *Toxicological Sciences* 48: 189-196.

Goldberg, M.E., H.E. Johnson, D.C. Pozzani, and H.F.Jr. Smyth. 1964. Effect of repeated inhalation of vapors of industrial solvents on animal behavior. I. Evaluation of nine solvents vapors on pole-climb performance in rats. *American Industrial Hygiene Assocation Journal* 25: 369-375.

Kimura, E.T., D.M. Ebert, and P.W. Dodge. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. *Toxicology and Applied Pharmacology* 19: 699-704.

Matsushita, T., A. Yoshimune, T. Inoue, S. Yamaka, and H. Suzuki. 1969a. [Experimental studies for determining the MAC value of acetone. I. Biological reactions in the "one-day exposure" to acetone.]. *Sangyo Igaku* 11: 477-485. (Japanese, English summary).

Nelson, K.W., J.F. Ege, M. Ross, L.E. Woodman, and L. Silverman. 1943. Sensory response to certain industrial solvent vapors. *Journal of Industrial Hygiene and Toxicology* 25: 282-285.

NRC. 2001. Standing Operating Procedure for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. National Research Council (NRC), Committee on Toxicology. National Academy of Science, National Academy Press, Washington, D.C. http://www.nap.edu/catalog/10122.html.

Pozzani, D.C., C.S. Weil, and C.P. Carpenter. 1959. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. *American Industrial Hygiene Assocation Journal* 20: 364-369.

Smyth, H.F.Jr., C.P. Carpenter, C.S. Weil, D.C. Pozzani, and J.A. Striegel. 1962. Range-Finding Toxicity Data: List VI. *American Industrial Hygiene Assocation Journal* 23: 95-107.

Stewart, R.D., C.L. Hake, A. Wu, S. Graff, D.G. Graham, H.V. Forster, W.H. Keeler, A.J. Lebrun, P.E. Newton, and R.J. Soto. 1975. Acetone: Development of a Biologic Standard for the Industrial Worker by Breath Analysis. NTIS PB82172917. The Medical College of Wisconsin Department of Environmental Medicine, Milwaukee, Wisconsin.

van Doorn, R., M.W. Ruijten, and C.J. van Leeuwen. 2001. Guidance for the Development of a Level of Odor Annoyance as a Endpoint for AEGL-1 and ERPG-1. Presented at the NAC/AEGL-meetings.

1 INTRODUCTION

Acetone is a colorless liquid with a sweetish, mildly pungent and fruity odor. Commercially, most acetone (about 96 %) is produced by peroxidation of cumene with subsequent cleavage of cumene hydroperoxide to acetone and phenol. Smaller amounts are derived from catalytic dehydrogenation of isopropanol (about 4 % of total production), the microbial fermentation of carbohydrates, and as a by-product from the synthesis of other chemicals. In 1994, worldwide production capacity was about 3.8 million tonnes (WHO 1998).

Industrially produced acetone is normally 99.5 % pure, with water being the major contaminant. Acetone is completely miscible with water and a number of organic solvents and most oils. Owing to its high volatility, low flash point, low autoignition temperature, and the wide range of explosive limits in air (lower: 2.6 %, upper: 12.8 % v/v; ATSDR 1994), acetone poses an acute fire and explosion hazard. Chemical and physical properties of acetone are presented in Table 1.

TABLE 1: CHEMICAL AND PHYSICAL PROPERTIES

Parameter	Data	Reference
Synonyms	Dimethyl ketone; methyl ketone; 2-propanone; propanone; beta-ketopropane; pyroacetic ether	ATSDR 1994
Chemical formula	C_3H_6O	
Molecular weight	58.08 g/mol	Weast 1973
CAS Reg. No.	67-64-1	ATSDR 1994
Physical state	Liquid at room temperature	
Solubility	Completely miscible with water, ethanol, benzene, ether	Weast 1973
Vapor pressure	181.72 mm at 20 °C	ATSDR 1994
Vapor density (air = 1)	2.0	
Liquid density (g/cm³)	0,7899 (at 20 °C)	Weast 1973
Melting point	-95.35 °C	Weast 1973
Boiling point	56.2 °C (at 1013 hPa)	Weast 1973
Explosive limits in air	2.6 – 12.8 % (v/v)	ATSDR 1994
Flash point (closed cup)	-20 °C	ATSDR 1994
Autoignition temperature	465 °C	ATSDR 1994
Conversion factors (at 25 °C)	1 ppm = 2.374 mg/m³ 1 mg/m³ = 0.421 ppm	Calculated according to NRC 2001

Acetone is the most widely used ketone in industry. It is used primarily to synthesize methacrylates, bisphenol A, and methyl isobutyl ketone. Another important use is that as a solvent in paint, ink, resin, and varnish formulations. Acetone is also used as a process solvent in the manufacture of cellulose acetate yarn, smokeless gun powder, surface coatings, and various pharmaceutical and cosmetic products (Morgott 1993; ATSDR 1994).

Due to the considerable volatility of acetone the greatest potential of exposure is usually through inhalation. In addition, dermal exposure may result from skin contact with consumer products containing acetone, e.g. nail polish (ATSDR 1994).

Acetone is a minor metabolite of normal intermediary metabolism in mammals including humans. Consequently, small quantities may occur in exhaled air. Endogenous acetone formation is closely linked with ketogenesis in the catabolism of body fat, and therefore, the concentration of acetone in body tissues may vary widely, depending on a number of factors such as nutritional state. Concentrations above normal levels in body tissues and in exhaled air develop during fasting and especially in diabetic patients in ketoacidotic state.

2 HUMAN TOXICITY DATA

2.1 Acute Lethality

In the 1996-2001 annual reports of the American Association of Poison Control Centers (APCC) Toxic Exposure Surveillance System (TESS), among 8,208 registered numbers of exposures to acetone only one case with lethal outcome was reported (Litovitz et al. 1997; 1998; 1999; 2000; 2001; 2002). In this case, a 30-year-old person committed suicide by inhaling a paint thinner containing acetone. Cardiac or respiratory arrest occurred before arrival at hospital, further data are not available (Litovitz et al. 2001). Furthermore, in the same report period as noted above, among 20,502 registered cases of exposure to nail polish remover containing acetone, one case of death was reported in a 4-year-old child who had ingested an unknown amount of remover. At arrival at hospital, she was unresponsive and seizing and received phenobarbital. Later on, hypotension, severe metabolic acidosis, and ketonuria were noted as well as fixed and dilated pupils. The seizures resolved, but she remained unresponsive and the electroencephalogram recorded no brain wave activity. She was pronounced dead three days after ingestion from presumed anoxic brain injury (Litovitz et al. 1999).

2.2 Nonlethal Toxicity

Compared to other industrial solvents acetone is of relatively low toxicity. Generally, mild respiratory tract and eye irritation can be considered the most sensitive indicator of acute exposure to acetone vapor. In addition, slight and reversible alterations in individual parameters of standardized neurobehavioral tests have been described in humans at acetone concentrations as low as 250 ppm. Severe transient effects, including vomiting and unconsciousness, were reported for workers who were exposed to acetone concentrations exceeding 12,000 ppm for about 4 hours. In between, less severe symptoms of CNS effects were observed including lightheadedness and headache. In general, signs and symptoms of acetone intoxication are nonspecific. Since increased levels of acetone are rapidly cleared from the body by metabolism and excretion, effects observed after chronic exposure in general agree with those following acute exposure.

2.2.1 Case Reports

The relatively low toxicity potential of acetone is reflected by the annual APCC TESS reports (see 2.1). E.g., in 2001, of the 1244 registered incidents of exposure to acetone, 387 were treated in health care facilities. Among these, 79 outcomes were regarded as a “moderate” and seven as a “major” medical problem that was not further described. None of these cases was fatal (Litovitz et al. 2002).

During the course of a controlled human study on the effects of acetone (Stewart et al. 1975, see 2.2.2), the senior investigator noted sudden onset of vertigo with nystagmus after 40 minutes of exposure to 1000 ppm acetone. This 48-year old man had a diagnosis of paroxysmal vertigo that had been made after a similar episode several years ago. Two further episodes had occurred since diagnosis, each associated with high exposure to a (not named) ketone, while exposure to different chlorinated solvents had not triggered the vertigo.

Accidental occupational exposure

A 29 years old worker had several slight acetone intoxications during the three years he worked in the acetone recovery department of a synthetic fiber company, but had to be hospitalized after an incident of acute inhalation exposure while cleaning a kettle containing acetone (Sack 1941). The subject wore a respirator which, however, did not fit properly. No air concentrations were reported, but the blood levels of acetone reported indicate a severe overexposure to acetone. The worker had become unconscious

while inside the kettle. At arrival in the hospital, he was in coma, but agitated, his breath showed a strong odor of acetone; he vomited several times and showed marked salivation and hyperreactivity. The patient awoke after revival with a CNS stimulant (Coramin®: Nikethamid), but excitability, nausea and salivation continued for a few hours. Blood levels of acetone were 436 and 302 mg/L at 8 and 10 hours after the accident, respectively, and 180 mg/L on the following day. No acetone was found in the blood three and four days after the accident. Acetone was also detected in the urine until the morning after admittance to the clinic. Urobilin, red and white blood cells and some albumin in the urine, together with an increase in serum glucose and bilirubin levels suggested that a slight and reversible liver and kidney damage had occurred. The patient was without symptoms after 8 days and therefore discharged.

Two cases of acute acetone intoxication were reported in a raincoat manufacturing plant, where workers coated the seems with a resin that was dissolved in either acetone (1st step of operation) or methyl ethyl ketone MEK (2nd step) (Smith and Mayers 1944). Two female workers suffered episodes of CNS depression with loss of consciousness, but quick recovery after hospitalisation. According to the authors these incidents were ascribed to the additive effects of both solvents, and exposure concentrations assumed to have been higher than the total ketone concentrations (1000 ppm, i.e. 330 and 495 ppm acetone plus 398-561 ppm MEK) measured in workroom air samples.

Symptoms of dizziness, leg weakness, confusion, headache, throat and eye irritation were experienced by seven workers exposed to high acetone concentrations while cleaning a pit containing aqueous acetone that had escaped from nearby holding tanks (Ross 1973). The acetone vapor concentration in the pit was reported to be greater than 12,000 ppm. Apart from acetone up to 50 ppm of trichloroethane were detected in the pit. While few symptoms were reported during 4 hours of work in the pit in the morning, workers suffered from symptoms within about 2 minutes when they reentered the pit after lunch break. Ross (1973) speculated that higher concentrations had built up following the agitation of the aqueous acetone during cleaning. One worker who became unconscious could be discharged from hospital after 4 days.

In an attempt to commit suicide, an employee inhaled vapor from a cylinder of acetylene gas (Note: Acetylene is stored in pressurized gas cylinders as acetonic solution in diatomaceous earth) (Foley 1985). He developed signs and symptoms of acetone intoxication including coma, hyperglycemia and acetonuria, and acetone was detected in the urine three days after the incident. No measurements as to the exposure concentrations were reported.

Single accidental exposure in hospitals

Several cases of acute acetone poisoning were reported which generally involved hospital patients with broken hips or legs who received large hip, leg or body casts. The plaster substitute used at that time contained a large amount of acetone, which was used as a setting fluid (for review, see Morgott 1993). The patients were typically exposed to acetone vapor, but concomitant dermal exposure was also considered in some cases. Generally, the first symptoms occurred within 1 - 12 hours of exposure and included initial lethargy and drowsiness, followed by nausea and vomiting later on. Many patients became unconscious, and some attending physicians mistakenly diagnosed a diabetic coma. Other clinical sings and symptoms included glycosuria, acetonuria, ketosis, hematemesis, labored breathing, tachycardia, and throat irritation. The onset of symptoms was reported to be between one and less than 24 hours. In general the patients recovered within one to four days. No measurements of acetone concentrations in the room air were made in all these cases, and a lack of blood analysis for acetone precludes any quantitative estimates of the exposure. However, the breath of the patients strongly smelled of acetone and qualitative or semi-quantitative tests for acetone in urine were always positive if done (Chatterton and Elliott 1946; Cossmann 1903; Fitzpatrick et al. 1947; Hift and Patel 1961; Pomerantz 1950; Renshaw and Mitchell 1956; Strong 1944).

Non-inhalation exposure

Several case reports were described in which individuals had ingested larger amounts of acetone, but some of these cases are confounded by co-exposure to other possible narcotic agents (Morgott 1993; WHO 1998).

An extremely high acetone blood level was found in a 30-month old child who had ingested most of a 180 ml bottle (6 ounce) of nail polish remover containing 65 % acetone and 10 % isopropanol (no data on the remaining 25 %) (Gamis and Wasserman 1988). Acetone blood levels at 1, 18, 48, an 72 hours after the onset of symptoms were 4450, 2650, 420, and 40 mg/L, respectively. At transfer to hospital, the patient developed tonic-clonic seizures which were aborted by phenobarbital. At hospital, the following signs were noted: unconsciousness, no arousal to pain, reflexes nonelicitable. Clinical examination revealed acetonuria, acetonemia, metabolic acidosis, respiratory depression (with cessation of spontaneous respiration requiring intubation and mechanical ventilation), hyperglycemia, ketonemia, and hypothermia. The patient received intensive medical care and could be discharged on the 4th day after a neurological examination showed no abnormalities. A 6-month follow-up examination also showed no signs of neurodevelopmental complications.

A woman who had ingested nail polish remover was lethargic but conscious upon admission to hospital; neurological examination showed no abnormal response. The ingested dose was not known, but extremely high acetone blood levels (2500 mg/L) were found. No hyperglycemia or glucosuria were reported. The woman was a known alcoholic with a long-lasting history of chronic alcohol abuse with neuropathy and was under medication to control for seizures and with diuretics for blood pressure control (Ramu et al. 1978).

In an attempt to commit suicide, an 42-year-old man swallowed 800 ml of acetone. After an unknown period of time, he was found unconscious at 5.00 a.m. On admission to hospital his breath smelled strongly of acetone, and because of progressing respiratory insufficiency he was intubated and ventilated. The patient was carefully hyperventilated, received bicarbonate infusion, haemofiltration was performed over 16 hours and forced diuresis with high fluid intake was undertaken. His condition quickly improved and he was extubated after 14 hours. He was conscious and stable next morning. The serum acetone concentration was 2000 mg/L on the first day (exact time not stated), about 400 mg/L one day later and below 100 mg/L another day later. There was no subsequent evidence of organ damage (Zettinig et al. 1997).

In a further case of attempted suicide, an adult man who consumed about 200 ml of pure acetone (about 2241 mg/kg b.w.) fell into coma (Gitelson et al. 1966). He reacted positively to treatment. However, leg pain and marked disturbance of gait was still noted on day 6 and on day 13 when the patient was discharged. Hyperglycemia lasted unusually long and was evident even 4 weeks after the incident, but returned to normal after 2 months of dietary restriction.

2.2.2 Experimental Studies

In a clinical study on the metabolism of “ketone bodies”, volunteers received an infusion of 10 g of acetone in 200 ml of saline by means of a pump at a constant rate over 2 hours (83 mg acetone/minute). It was reported that a slight drop in blood pressure and a slight transient drowsiness were frequently observed (no further details). No such effects occurred in similar experiments with acetoacetate. The average concentration of acetone in blood of 12 healthy volunteers reached 100 mg/L after one hour and 140 mg/L at the end of the acetone infusion, respectively; the concentration in organs were not measured. In a second series of experiments with 19 non-diabetic subjects and 12 subjects with

partially controlled diabetes, the average acetone concentration at the end of infusion reached about 195 mg/L and 230 mg/L, respectively (Koehler et al. 1941).

The findings of clinical volunteer studies with controlled inhalation exposure to acetone are summarized in **TABLE 2**. In these laboratory studies, mostly the irritative effects on eyes and mucous membranes and the acute effect on the central nervous system (CNS) were investigated.

An average number of 10 subjects (both genders) were exposed to nominal vapor concentrations of 200, 300 or 500 ppm of acetone for 3 - 5 minutes (Nelson et al. 1943). The volunteer status of the experimental subjects was not reported. In a post-exposure self-classification, the subjects rated the subjective effect of exposure on eyes, nose and throat. While the “highest concentration which [the] majority of subjects estimated satisfactory for 8-hour exposure” was 200 ppm, slight irritation was noted at 300 ppm. 500 ppm was irritating in most subjects and judged objectionable for an 8-hour exposure, although this exposure level was said to be tolerated by most subjects.

Ten male volunteers (age 24-49 years) were exposed to 250 ppm (measured concentration: 231 ppm and 238 ppm acetone in 2 sets of experiments) for 2 hours (Ernstgard et al. 1999). Immediately before, during and up to 350 minutes after exposure, the subjects rated irritative symptoms (eyes, nose, and throat or airways), effects on the central nervous system (headache, fatigue, feeling of sickness, dizziness, intoxication), and smell on an analogue scale reaching from “not at all” to almost unbearable”. Except for the smell, no increased ratings were noted.

Nine male volunteers (age: 22-62 years) were exposed to analytically controlled acetone concentrations of either 100 or 500 ppm for 2 hours (DiVincenzo et al. 1973). No untoward effects on hematology and serum biochemistry including hepatic and renal parameters were noted, neither were subjective symptoms (not otherwise specified) reported. The only effect was an awareness of odor noted at 500 ppm. The main purpose of this study was related to pharmacokinetics (see section 4.1.1).

Two male and two female student volunteers were exposed to chamber concentrations of either 170-450 ppm or 450-690 ppm for four hours (Nakaaki 1974). The exposure concentrations were described as fluctuating; no constant exposure levels could be achieved. In neurobehavioral tests, a tendency of prolongation of estimated time (i.e. passage of time for periods lasting from 5-30 sec.) was noted. However, the data varied widely and no statistically significant differences were reported between either of the exposure ranges and "control values". The latter were reportedly obtained from "whole experimental value". It should be noted that the design and validity of the control conditions is not clear.

Groups of 5 healthy male university students aged about 22 years were exposed to acetone vapor for 6 hours (with a 45 minutes break after 3 hours) during one day (Matsushita et al. 1969a). At exposure concentrations of 100 or 250 ppm, very slight mucous membrane irritation (scores: 1-2 on a scale of 0-10, recorded at 10, 30 and 90 min. of A.M. and P.M. exposure each) and unpleasant odor (scores: 1-2 at 100 ppm; 1-4 at 250 ppm) were noted. In addition, on the morning after exposure the subjects of the 250 ppm group complained about feeling of tension, heavy eyes, lack of energy (score: 2), while no such effects were reported from the 100 ppm group. All these effects, which were based on subjective ranking of up to seven symptoms by the subjects, were more pronounced at 500 or 1000 ppm (scores: 4-10). The score for unpleasant odor (4-10 at 10 min.) decreased with increasing exposure time (2 at 90 min.) indicating adaptation. In addition, temporary decrease in phagocytic activity of neutrophils (at 500 and 1000 ppm) and a slight increase in eosinophil (+50 % at 500 and +80 % at 1000 ppm) and leucocyte counts in peripheral blood was noted at 3 and 7 hours post-exposure possibly indicating an inflammatory reaction caused by the irritating effects of acetone vapor. All values were at normal after 32-48 hours.

In principle, the above findings were confirmed in a multiple-day study with exposures to either 250 (resting or exercising) or 500 ppm for 6 hours/day (with a 45 minutes break after 3 hours) and 6 days (Matsushita et al. 1969b). In this experiments, increased activity through physical exercises did not enhance the scores for subjective complaints of mucous membrane irritation and unpleasant odor. In the 500 ppm group, irritation was felt to be strongest immediately after entering the exposure chamber in the morning and afternoon sessions. Accommodation was noted with increasing exposure time on each day, but no day-to-day adaptation occurred. In addition to the protocol followed in the previously reported experiment, neurobehavioral tests were conducted. Reaction time to a visual stimulus was found to be longer at the first two exposure days both at resting and exercising. However, the non-pooled absolute values were not statistically significant from controls. It should also be noted that the performance parameters obtained for the controls overlapped with those of the exposed subjects during a two-day post-exposure period.

In a double blind study, groups of 11 male and 11 female volunteers ranging in age from 18 - 32 years were exposed to 250 ppm acetone for 4 hours (Dick et al. 1988; Dick et al. 1989). Control groups included a chemical-placebo group (11 males, 10 females), a 95 % ethanol group (9 males, 11 females; 0.84 ml/kg as a positive control) and an ethanol-placebo group (11 males, 11 females). The computerized testing regimen consisted of 2-hour sessions on each of three days: a practice session on day 1; tests prior to exposure, during exposure (two testing sessions) and postexposure on day 2, and a postexposure session on day 3. During each 2-hour test session four psychomotor tests (choice reaction time, visual vigilance, dual task, and short-term memory scanning), a neurophysiological test (eye blink reflex), and one sensorimotor test (postural sway) were administered to the test subjects. A profile of mood states (POMS) psychological test was administered following exposure and on the following day. The authors did not report the occurrence of any irritation nor did they explicitly state the absence of such effects. Exposure to 250 ppm of acetone vapor produced small, but statistically significant effects in (i) the dual auditory tone discrimination compensatory tracking test (increase in response time and false alarm percent rate), (ii) the POMS test. As the latter result was statistically significant only in males on the anger-hostility scale with no consistent trend, it was probably due to chance. For comparison, ethanol, at a measured blood alcohol content of 0.7-0.8 ‰, produced pronounced performance decrements in several tests.

Several neurophysiological tests were performed on two groups of male university students exposed to acetone vapor concentrations of either 250-270 ppm (n = 8) or 500-750 ppm (n = 9) for 6 hours with a 1-hour break after 3 hours (Suzuki 1973). Statistically nonsignificant tendencies in 4 of 5 neurophysiological tests were noted, i.e., (i) decrease in spontaneous galvanic skin response (GSR) and increase in the evoked GSR at 250-270 ppm; (ii) decrease in evoked vasoconstriction activity in both groups; (iii) decrease in mean time interval for 10 heart beats at the high exposure concentration; and (iv) increase in cerebral activity. It should be noted that the positive correlation of temperature increase in the exposure chamber with several of the observed responses precludes a clear interpretation of the study results, although the degree of this correlation was reportedly affected by acetone exposure.

Dalton et al. (1997a) found an association between perceived irritation or annoyance and perceived odor of acetone. As further described below, a group of 27 workers perceived the intensity of the acetone odor to a much lesser degree than a control group of 27 subjects who had no history of occupational exposure to chemicals. Likewise, after 20-minute exposure to 800 ppm of acetone the workers with a history of repetitive exposure reported significantly less irritation and health symptoms (e.g. lightheadedness, headache) than non-occupationally exposed subjects. Parallel tests with phenylethyl alcohol (PEA) used as control odorant, which is considered to be a pure non-irritating olfactory stimulus, revealed that response bias play a large role in the subjective rating of perceived irritation from acetone, particularly in subjects who have no history of previous (repetitive) exposure to acetone.

The influence of cognitive bias on the perceived irritation and health symptoms from acetone exposure was confirmed by another investigation of the same study group (Dalton et al. 1997b). 90 volunteers with no history of occupational exposure to solvents were exposed to 800 ppm of acetone or 200 ppm PEA for 20 minutes. The subjects were assigned to three groups (n = 30 per group) that received different characterizing information about the nature and consequence of long-term exposure to the odorants used in the study. It was told to the “neutral” group that the substance is approved for and commonly used in olfactory research as a standard, to the “positive bias” group that the odor was from natural extracts used in aroma therapy, and to the “negative bias” group that the substance was an industrial chemical used as solvent that is reported to cause adverse health effects following long-term exposure. All groups showed a similar pattern of decrease in the perceived odor intensity across the first 10 minutes of the exposure session. However, in the second half the ratings differed as a function of bias condition. The positive bias group showed the most adaptation to the perceived odor intensity of acetone. They also reported significantly less irritation during the 20-minute exposure than subjects from the “neutral” and “negative bias” group and reported the fewest health symptoms (lightheadedness, drowsiness, nausea, headache) following exposure. The “negative bias” group rated higher levels of odor intensity and, on average, reported the most overall irritation and more health symptoms than the other groups. However, the “neutral” group responded quite similar to the “negative bias” group. Interestingly, neither the mean nor the median detection thresholds for acetone (see below) varied as a function of bias condition. The overall pattern of results of this and similar studies including other substances (Dalton 1999; Dalton et al. 2000) suggest that many of the health-related effects of exposure to odorants are mediated not by a direct agency of odors but by cognitive variables, such as mental models of the relationship between environmental odors and health.

The same research group applied the so-called intranasal lateralization method to determine an objective measure of sensory irritation (Wysocki et al. 1997). This is based on the fact that, when a volatile compound is inhaled into one nostril and air into the other, the stimulated side can be determined, i.e. lateralized, only after the concentration reaches a level that stimulates the trigeminal nerve, which is the pathway for irritation. Compounds stimulating the olfactory nerve alone cannot be lateralized. It should be noted that only "sniffs" of acetone were inhaled by the volunteers in this lateralization method. Such extremely short exposure durations do not reflect real exposure situations.

Tests with the two groups of volunteers described above (Dalton et al. 1997a) revealed that thresholds for objective sensory irritation as measured with this lateralization technique were far higher than the levels reported to be associated with subjective, i.e., perceived irritation. For the group of occupationally exposed subjects a chemesthetic lateralization (irritation) threshold of 36,669 ppm (median) was found. The fact that the unexposed control subjects had a significantly lower threshold, i.e. 15,758 ppm (median), could indicate an exposure-induced adaptation. However, in a further study of this research group using the same methodology (Dalton et al. 2000), the median lateralization threshold of 36,608 ppm (geometric mean 21,176 ppm) for a group of 40 non-exposed volunteers was almost identical to the median for occupationally exposed determined in the previous study.

Two groups of each 16 male healthy subjects (average age 25.4 or 26.6 years) were exposed to an acetone concentration of 1000 ppm for 4 or 8 hours, respectively (Seeber et al. 1992b; Seeber et al. 1992a; Seeber and Kiesswetter 1991). In neurobehavioral tests which were similar to those used by Dick et al. (1988; 1989), no significant effects were observed. Compared to the exposure sessions in filtered room air an increased number of subjective complaints of mucosal irritation on eyes, mouth and throat and annoyance was noted in both acetone exposure groups. In the 8-hour exposure group, the subjective irritation effects slightly decreased after 4 hours indicating a limited adaptation. These experimental results were in principle confirmed by field studies with acetone workers (Seeber et al. 1991).

In their studies, Seeber et al. (1992b) also investigated the relationship between an individual's subjective response to a solvent exposure and his or her inherent "susceptibility" which was defined as the general tendency to minor subjective disturbances measured by a questionnaire, but independent of any experience with solvents. The hypothesis was that subjects showing higher susceptibility (or "multiple chemical sensitivity" MCS) would report stronger subjective response to solvent exposure. No correlations between acetone exposure (1000 ppm for 4 or 8 hours) and psychologic-neurological symptoms, such as state of well-being, tiredness, complaints and annoyance, and were found.

Healthy adult volunteers of both genders were exposed to acetone vapor in a controlled-environment chamber applying exposure schemes that should simulate typical occupational exposure (Stewart et al. 1975). In the first series, 4 male subjects (age 22-27 years; some drop-outs from week 3) were exposed for either 3 or 7.5 hours/day, each 4 days/week, to progressively higher acetone concentrations, i.e., 0 (week 1), 200 (week 2), 1000 (week 3), 1250 (week 4), 0 (week 5), 750-1250 (fluctuating; average: 1000 ppm; week 6). The first day of each week was an additional control exposure to 0 ppm. All subjects were given a complete medical and physical examination at the beginning and end of study. Blood count and 23-element clinical chemistry were done weekly. Blood pressure, temperature, subjective responses, clinical signs and symptoms, and urinalysis were recorded daily. Alveolar breath analysis was performed at 0, 0.25, 0.5, 1, 2, and 3 hours following exposures. Cardiopulmonary testing was done shortly before ending each weekly exposure session. A battery of neurophysiological and neurobehavioral tests was performed at various times throughout the exposures. The only clearly exposure-related measured effect observed was an increase in visual evoked response (VER) at 1250 ppm (7.5 hours) in 3 of 4 subjects. The following number of subjects reported subjective symptoms in the groups exposed at 0, 200, 1000 (week 3), 1250 and 1000 ppm (week 6): complaints of eye irritation 2/2/3/3/0; throat irritation 1/0/3/3/0; headache 1/1/0/0/0, dizziness 0/2/0/0/0, and tiredness 0/2/3/0/0.

In groups of 2, 4 and 4 female subjects (age 18-25 years) exposed to 1000 ppm of acetone for either 1, 3 or 7.5 hours/day, respectively, for 4 days, premature menstrual cycle was noted in 3 of 4 subjects 4 days after the 7.5 hours exposure. Otherwise the same examinations and tests were performed as with the male volunteers, but no other effects were observed (Stewart et al. 1975).

In experiments conducted by Haggard et al. (1994) there were no indications of intoxication following an 8-hour exposure to monitored acetone concentrations of up to 2105 ppm (5000 mg/m³). At 2105 ppm, the blood acetone level was 165 mg/L for subjects at rest and 330 mg/L at moderate exercise. However, the relevance of these results is limited because no information was given as to the number and volunteer status of the subjects studied and because the determination of signs and symptoms was not clearly reported. It should be noted that these experiments were part of an investigation into the toxicokinetics of acetone in rats and humans (see section 4.1) and the authors extrapolated from the effects observed in rat studies to humans based on acetone levels in the blood. Accordingly, "intoxication" (probably loss of judgment and coordination, but not exactly specified) was assumed to develop at approximately 84,000 ppm (200,000 mg/m³) of acetone in air within 1 hour exposure or at approximately 10,500 ppm (25,000 mg/m³) after 8 hours.

In several self-exposure trials (Kagan 1924), acetone was inhaled out of wash bottles through mouth respiration. Inhalation of the vapor of a 10 % acetone solution, which corresponds to a vapor concentration of about 9300 ppm, could not be tolerated for longer than 5 minutes because of strong throat irritation (intense feeling of heat), while 4600 ppm could not be tolerated for longer than 15 minutes. However, this was also attributed to the physical resistance of the wash bottle fluid.

TABLE 2: SUMMARY OF ACUTE NON-LETHAL EFFECTS IN CONTROLLED HUMANS STUDIES FOLLOWING INHALATION OF ACETONE

Exposure duration	Concentration ppm (mg/m³)	No. of subjects, effects and remarks	Reference
2 hours 2 hours	100 500	9 male subjects No effects on hematology and serum biochemistry; no subjective symptoms (not otherwise specified) NOAEL for above signs and symptoms; only effect: odor awareness	DiVincenzo et al. 1973
3-5 minutes 3-5 minutes 3-5 minutes	200 300 500	10 subjects of both genders Judged satisfactory for 8-hour exposure Slight irritation (not further specified) Irritating to eyes, nose and throat in most subjects; judged objectionable for 8-hour exposure	Nelson et al. 1943
2 hours	250 (measured 2-hour mean: 231-238)	10 male subjects No increased ratings of discomfort, i.e. of irritative symptoms in eyes or airways or effects on the CNS such as headache, fatigue, feeling of sickness, dizziness	Ernstgard et al. 1999
4 hours (with 2-hour break after 2 hours)	170-440 or 470-690 (fluctuating chamber concentrations)	2 male and 2 female subjects; neurobehavioral time estimation test; tendency of prolongation of estimated time, but no statistically significant differences between either of the exposure ranges and control values	Nakaaki 1974
6 hours (45 min. break after 3 hours) 6 hours (45 min. break after 3 hours)	100 or 250 500 or 1000	5 male subjects (i) Slight mucous membrane irritation; (ii) unpleasant odor; (iii) morning after complaints: feeling of tension, heavy eyes, lack of energy at 250 ppm; none at 100 ppm Above signs and symptoms more pronounced; in addition (only determined at these concentrations), temporary decrease in phagocytic activity of neutrophils; increase in eosinophil and leucocyte counts; all values at normal after 48 hours	Matsushita et al. 1969a
6 days; 6 hours/day (45 min. break after 3 hours) 6 days; 6 hours/day (45 min. break after 3 hours)	250 (resting); 250 (exercising) 500	5 or 6 male subjects (i) Slight mucous membrane irritation and unpleasant odor similar to single-day exposure irrespective of work load (ii) Reaction time to a visual stimulus longer at first two exposure days both at resting and exercising (non-pooled absolute values not statistically significant from controls) (i) Severity of mucous membrane irritation and unpleasant odor similar to single-day exposure; (ii) Reaction time to a visual stimulus longer on each of the six exposure days (non-pooled absolute values not statistically significant from controls; no consistent dose- or time-related trends in magnitude of response)	Matsushita et al. 1969b

TABLE 2: SUMMARY OF ACUTE NON-LETHAL EFFECTS IN CONTROLLED HUMANS STUDIES FOLLOWING INHALATION OF ACETONE

Exposure duration	Concentration ppm (mg/m³)	No. of subjects, effects and remarks	Reference
4 hours	250 (measured 4-hour mean: 237.4)	11 male and 11 female subjects; Small, but statistically significant effects in (i) the dual auditory tone discrimination compensatory tracking test (increase in response time and false alarm percent rate), (ii) the profile of moods states test (statistically significant only in males on the anger-hostility scale; no consistent trend; probably due to chance) No significant difference in psychomotor tests of choice reaction time, postural sway, visual vigilance, and memory scanning.	Dick et al. 1988; 1989
2x3 hours with 1 hour break	250-270 500-750	8 or 9 male subjects; statistically nonsignificant tendencies in 4/5 neurophysiological tests, but interference by temperature increase	Suzuki 1973
20 min.	800	27 workers rated odor of acetone as weak-to-moderate, 32 non-occupationally exposed subjects as strong-to-very strong; decreasing odor intensity with time; perceived irritation intensity correlated with corresponding odor results	Dalton et al. 1997a
20 min.	800	90 subjects with no history of occupational exposure to solvents Positive bias resulted in lower levels of perceived odor intensity, irritation and health symptoms	Dalton et al. 1997b
4 hours	1000	16 male subjects; subjective mucosal irritation on eyes, mouth and throat; subjective symptoms of complaints and annoyance; no significant effects on behavioral parameters	Seeber et al. 1992b
4 hours; 8 hours (30 min. break after 4 hours + 2 x 10-min. physical exercise)	1000	2 x 16 male subjects; subjective mucosal irritation (continuously decreasing with 8 hours exposure); no significant effects on behavioral parameters	Seeber and Kiesswetter 1991
3 or 7.5 hours (4 days/ week; 0 ppm at day 1 of week)	0 (week 1), 200 (week 2), 1000 (week 3), 1250 (week 4), 0 (week 5), 1000 (750-1250 ppm, week 6)	4 male subjects; increase in visual evoked response at 1250 ppm (7.5 hours); slightly more complaints of eye and throat irritation and tiredness at 1000 and 1250 ppm as compared to control sessions	Stewart et al. 1975
1, 3 or 7.5 hours (4 days/ week; 0 ppm at day 1 of week)	1000 (week 1), 0 (week 2)	2 (1 hour) to 4 (3 or 7.5 hours) female subjects; examinations and tests as with males Premature menstrual cycle in 3 of 4 subjects 4 days after exposure (7.5 hours); no effects with regard to above parameters	Stewart et al. 1975
8 hours	2110 (at rest and moderate exercise)	Subjects not otherwise specified; no indication of "intoxication"	Haggard et al. 1944
15 min.	4600 (11000)	1 subject; concentrations not tolerable longer due to throat irritation, but effect also attributed to the physical resistance of the wash bottle fluid	Kagan 1924
5 min.	9300 (22000)		

Odor perception

The odor of acetone has been described as sweet and pungent (Leonardos et al. 1969) or minty chemical, sweet (Ruth 1986) and refreshing (Lehmann and Flury 1938). A wide range of odor thresholds is reported in the literature. This wide range may be due to different degrees of purities of the test substances used, different methodology used, different bases used (median, mean, range), individual variability or an adaptation to odor perception following repetitive exposure.

Odor thresholds ranging from 20 - 680 ppm (47 mg/m³ to 1613.86 mg/m³) for acetone were reported in a compilation of data from the industrial hygiene literature (Ruth 1986).

In a critical overview of several chemicals, the range of odor detection thresholds for acceptable vs. all referenced values was reported as 3.6 - 653 ppm and 0.4 - 800 ppm of acetone, respectively, with a geometric mean of 62 ppm (AIHA 1997). The mean recognition concentration was reported as 130 ppm with acceptable values ranging from 33 - 699 ppm.

Based on 20 original literature references which were not explicitly reported, a geometric mean odor threshold of 13 ppm acetone (standard error 1.6 ppm) was reported (Amoore and Hautala 1983).

The lowest odor perception thresholds experimentally determined for acetone was reported ranging from 0.5 - 2.1 ppm (1.1 - 5 mg/m³) (Ryazanow 1962).

The odor recognition threshold was determined for 53 odorant chemicals including acetone under controlled laboratory conditions using a standardized and defined procedure (Leonardos et al. 1969). The odor threshold represents that concentration at which all four trained panelists could positively recognize the odor. For acetone of the highest purity commercially available from large scale production a threshold of 100 ppm was determined.

The relevance of adaptive change with regard to the perceived intensity of acetone's odor was investigated (Dalton et al. 1997a) and these results are of relevance for the interpretation of perceived irritating effects (see above). Using an up/down staircase method, the odor detection threshold for acetone (purity >99.5 %) was estimated for two groups of volunteers immediately before and after 20-minute chamber exposures to 800 ppm. In the group of 27 workers who had worked in an acetone-exposed occupational environment of a cellulose fiber production plant for at least 12 months (median 10 years), the median odor detection threshold was 86 ppm in the pre-exposure test series (mean 362 ppm) and 89 ppm in the post-exposure test series (mean 1,960 ppm). In a control group of 27 subjects who had no history of occupational exposure to chemicals, the odor detection thresholds did not differ significantly from the workers group, although the 20-minute exposure caused a greater shift in sensitivity to acetone from a median odor detection threshold of 84 ppm before to 278 ppm after the short-term exposure, but this was not statistically significant. Neither smoking status, age, gender nor exposure history was related to threshold sensitivity for acetone. However, with regard to the perceived odor intensity striking differences were noted between the workers and the control subjects. On average, the workers rated the odor of acetone as weak to moderate, whereas the control subjects perceived the odor as strong to very strong. The 20-minute exposure to 800 ppm of acetone resulted in an adaptation in both groups, i.e. a 46 % reduction in average perceived intensity for the controls and a 28 % reduction for the workers.

In another study of this research group using the same methodology, the median odor detection threshold was 41 ppm (mean 247 ppm, geometric mean 50 ppm) in a control group of 32 unexposed subjects, but 855 ppm in a group of 32 acetone-exposed workers (mean 1,016 ppm, geometric mean 414 ppm) (Wysocki et al. 1997). The authors give no explanation for the relatively high odor threshold in the latter group relative to the one reported in their other study (Dalton et al. 1997a). Possibly the subjects

had a relatively high and/or long exposure to acetone at the workshift before they were selected for testing. There is evidence that sensitivity returns to levels comparable to that of unexposed control subjects after exposed workers have been removed from the workplace for an extended period of time (Dalton and Wysocki 1996).

In a further study of this research group using the same methodology, the median odor detection threshold was 44 ppm (geometric mean 25 ppm) in a group of 40 previously unexposed volunteers (Dalton et al. 2000).

In the investigation of the influence of cognitive bias (see above), there were no significant differences in the odor detection thresholds of subjects with no history of occupational acetone exposure at the different bias conditions. The median odor detection threshold was between 54 - 136 ppm (mean 264 - 395 ppm) before a 20-minute exposure to 800 ppm of acetone and between 124 and 278 ppm (mean 498 - 553 ppm) after exposure (Dalton et al. 1997b).

2.2.3 Occupational / Epidemiologic Studies

In a cross-sectional study, 110 male (age range 18.7 - 56.8 years) acetone-exposed workers and 67 male (age range 20.7 - 57.5 years) non-exposed workers were monitored (Satoh et al. 1996). Acetone exposure levels at the end of the workshift as measured through personal samplers was on average 364 ppm (864 mg/m³) with a range of 19.6 - 1088 ppm (46.5 - 2583 mg/m³). These levels are quite consistent with the acetone levels measured in alveolar air ranging from 5.9 - 1002 mg/m³ (2.5 - 422 ppm) with a mean of 231 mg/m³ (97.3 ppm) which is about 26 % of the acetone level in the breathing zone. Biological monitoring revealed 4 - 220 mg/L (mean 66.8 mg/L) in blood and 0.75 - 170 mg/L (mean 37.8 mg/L) in urine. Symptoms at the end of the workshift that were recorded in exposed workers with higher frequency than in control workers included eye irritation, tear production and complaints of acetone odor. These symptoms also were reported to show good exposure-response relationships, but no detailed dose-response data were presented. Some neurobehavioral parameters (simple reaction time; digit span scores) were significantly lower in the 30 - 44 year range of acetone exposed workers, but with no clear exposure-response relationship. Neuropsychologic parameters did not show any differences between exposed and non-exposed groups, neither did ECG, hematological examinations and liver function tests.

Eye and throat irritation were reported in occupational health surveys on workers of a cellulose fiber facility (Raleigh and McGee 1972). In 1968, nine employees were monitored for seven 8-hour workdays and were asked to rate their experienced symptoms of sensory irritation. Analysis of breathing zone samples revealed a mean daily time-weighted average (TWA) exposure of 1006 ppm (range 950 - 1060 ppm; maximum 5500 ppm). Eye, throat and nasal irritation was noted by seven, four and three of the nine employees, respectively, and headache and lightheadedness was experienced by three. Generally, these symptoms were intermittent, transient, and occurred at concentrations well above 1000 ppm. Individual reactivity varied widely between the same individual and other persons. For instance, no eye irritation was reported at a concentration as high as 6053 ppm, while this individual had complained about eye irritation at much lower exposure levels before. At no time was objective evidence of eye irritation noted by physical examination. There were no complaints of nausea and the physical (objective) examinations were essentially normal for all individuals, except for a slight redness in the nasal mucosa of one person and slight congestion in the nose and throat of another. No effects on the CNS system were noted either as determined by lack of disturbance in the gait, no alterations in the finger-to-nose test, and normal Romberg sign.

In a second survey conducted in 1969, two of four filter press operators were monitored for three 8-hour work shifts and two for two 8-hour shifts (Raleigh and McGee 1972). TWA exposure was measured to be 2070 ppm (range 155 - 6596 ppm) during the 3-hour monitoring period. Complaints of

eye, throat and nasal irritation were reported by two, one and three employees, respectively. Physical examinations were negative.

Neurobehavioral tests were performed on five employees who worked on a production line using acetone based glue (Israeli et al. 1977). The workplace concentration was reported to be about 200 ppm as measured with Draeger tubes. Before and at the end of 8-hour shifts the reaction time to a light and sound stimulus was measured and compared to control values that were obtained on the same employees when not exposed to acetone for at least 48 hours. A statistically significant prolongation of the reaction time was found, but only when the mean values for each individual were averaged for the five subjects. It should be noted that the high variability of repeated test results were not taken into consideration. In addition, the data show that both the pre-shift and the post-shift response-time measurements were increased relative to the control sessions indicating that the effect reported was not exposure related.

In a more recent study (Seeber et al. 1993), eight employees exposed to acetone in the cellulose acetate production underwent neurobehavioral testing during a period of three weeks on three working days each week. The overall 4-hour TWA exposure concentration as measured with personal samplers was 938 ppm (range 164 - 5097 ppm). In the neurobehavioral tests that were similar to those used in their laboratory studies (see above; Seeber et al. 1992b; Seeber et al. 1992a; Seeber and Kiesswetter 1991), no significant exposure-related effects were observed, i.e. performance parameters, reaction time and vigilance, measured before, during and at the end of the shifts did not significantly differ from those of eight unexposed control persons. This is in accordance with the experimental studies described above. On the other hand, a clear exposure-related increase in the scores of subjective complaints of irritation and annoyance was noted and this was more striking than at the comparable 1000 ppm exposure in the laboratory study despite of similar internal exposure as determined through the rate of acetone excretion in the urine (see above; Seeber et al. 1992b; Seeber et al. 1992a; Seeber and Kiesswetter 1991).

In earlier investigations, more severe signs and symptoms were noted than reported in the above studies. However, either no or only limited details were given in the reports described below, e.g. regarding the monitoring methods, number of employees, physical status of other employees not exposed to acetone, and possible multiple exposure to other substances. Thus, the relevance of these findings remains unclear.

Vigliani and Zurlo (1955) presented a general overview of investigations in Italian factories with acetone exposure. Chronic inflammation of the airways, stomach and duodenum were noted in all employees exposed to 1000 ppm acetone for 3 hours daily over 7 - 15 years. Intermittent dizziness and asthenia was also noted. Measurements of acetone in the expired air at the end of the work shifts were reported to be 200 mg/m³ (ca. 84 ppm). This would indicate that the exposure concentrations were around 500 ppm, if based on the findings of DiVincenzo et al. (1973) or Seeber et al. (1992b), i.e. acetone concentration in expired air is approximately 20 % of room air acetone concentration. However, not enough information is given by the authors (Vigliani and Zurlo 1955) to permit drawing conclusions from this report.

In a retrospective mortality study of 948 workers (697 men, 251 women) who had been employed for at least three months to 23 years at a cellulose fiber plant where acetone was used as the only solvent, no significant excess risk of death from any causes was found as compared to rates for the general population in the USA (Ott et al. 1983a; Ott et al. 1983b). According to industrial hygiene surveys the mean TWA acetone concentrations were given as 380, 770 and 1070 ppm (902, 1678 and 2540 mg/m³) based on job categories. All hematological and clinical blood chemistry parameters were within normal limits.

2.3 Developmental/Reproductive Toxicity

In a controlled human study (see 2.2.2), in groups of 2, 4 and 4 female subjects (age 18-25 years) exposed to 1000 ppm of acetone for either 1, 3 or 7.5 hours/day, respectively, for 4 days, premature menstrual cycle (one week or more early) was noted in 3 of 4 subjects 4 days after the 7.5 hours exposure (Stewart et al. 1975).

No statistically significant differences in the incidence of miscarriage, perinatal death rate, or malformations could be observed in a group of 556 female laboratory workers exposed to a variety of solvents, including acetone (Axelsson et al. 1984).

Studies on reproductive function and development of fetuses and newborns carried out in the former Soviet Union have been summarized (Germanova 1986). In a group of 114 female workers exposed to about 33.3-200 mg/m³ acetone (14-84 ppm) in an acetate chemical fibre plant, rates of complications during pregnancy periods and at childbirth were reported to be higher than in the control group of 54 non-exposed females. In subgroups, profuse and prolonged menstruations, anovular cycles and a higher level of gonadotropic hormones in workers employed at least three years were described. Other studies on female workers of an acetate and PVC-fibre production plant (acetone concentration about 14-126 ppm) revealed more complications during pregnancy, higher weight and greater body length of newborn infants, and an increased number of developmental effects such as intrauterine hypothrophy and infants born in asphyxia in the group from acetone-exposed mothers compared to non-exposed controls. Since important parameters (description of exposed and control group with respect to age distribution, smoking history, alcohol consumption, exposure to other chemicals; monitoring of acetone concentrations at work, statistical evaluation methods) are lacking or not described in sufficient detail, no evaluation of the results is possible.

2.4 Genotoxicity

No signs of DNA-damage were observed in an alkaline single-cell gel electrophoresis (Comet) assay in cryopreserved peripheral blood mononuclear leukocytes from 34 female shoe workers exposed to organic solvents including acetone (Pitarque et al. 1999).

No further studies were located regarding genotoxic effects of acetone in humans *in vivo* (for *in vitro* data on mammalian including human cells see 3.4).

2.5 Carcinogenicity

No studies were located regarding cancer in humans after inhalation, oral or dermal exposure except for one retrospective mortality study described above (Ott et al. 1983a; Ott et al. 1983b). It must be stressed that the main topic of this study was on the cardiovascular effects of methylene chloride and the cohort of workers exposed to acetone served as the referent cohort. The incidence of deaths in this referent cohort was compared with expected deaths rates calculated from U.S. population subgroups. The acetone-exposed cohort consisted of 948 workers of a cellulose fiber plant who were exposed to acetone as the only solvent used in cellulose diacetate production. Median TWA acetone concentrations were given as 380, 770 and 1070 ppm (902, 1678 and 2540 mg/m³) based on job categories. No excess risk of death from any cause, including malignant neoplasms, was found.

2.6 Summary

The acute toxicity of acetone is low and no reports were located in which exposure of humans to acetone resulted in death. Acetone has a sweetish, mildly pungent and fruity odor. A wide range of odor

detection thresholds has been reported. More recent studies in which n-butanol was used as a control substance (Dalton et al. 1997a; 1997b; Wysocki et al. 1997), median odor detection thresholds of 41-84 ppm were determined in previously unexposed subjects.

At 200 ppm, subjective symptoms of eye and throat irritation were not reported more frequently than in nonexposed controls (Stewart et al. 1975). At 250 ppm, no increased ratings with respect to irritative symptoms and effects on the CNS were noted in one study (Ernstgard et al. 1999), slight irritation during exposure and some complaints about heavy eyes, lack of energy, and feeling of tension the morning after exposure were noted in a second study, and these subjective symptoms were felt by most volunteers at 500 ppm and 1000 ppm (Matsushita et al. 1969). In further study, slight irritation was reported at 300 ppm, and 500 ppm led to eye, nose and throat irritation in the majority of exposed (Nelson et al. 1943). Subjective signs of irritation were clearly notable in a number of controlled studies at exposure to 800-1000 ppm (Dalton et al. 1997a,b; Seeber et al. 1992 a,b; Seeber and Kieswetter 1991). "Objective" measures of sensory irritation by intranasal lateralization revealed far higher median irritation thresholds of 15,758 ppm and 36,608 ppm (Dalton et al. 1997a; 2000). Therefore, it has been suggested (Dalton 1999; Dalton et al. 2000) that many of the health-related effects of exposure to odorants are mediated not by a direct agency of odors but by cognitive variables, such as mental models of the relationship between environmental odors and health .

Neurological tests in a group of volunteers exposed to 250 ppm for 4 hours revealed a questionable change in a profile of mood state psychological test and statistically significant but small effects in a standardized auditory discrimination test (Dick et al. 1988; 1989). In another study, exposure to 1200 ppm for 7.5 hours caused an increase in visual evoked response in the EEG but no other significant neurological effects were observed at 250-1200 ppm (Stewart et al. 1975)

Central nervous system depression with loss of consciousness occurred in workers exposed to 330-495 ppm acetone for unknown exposure duration, but dermal exposure was likely and the workers were additionally exposed to about 400-600 ppm butanone (Smith and Mayers 1944). At exposure to acetone concentrations greater than 12,000 ppm that lasted from 2 minutes to 4 hours, workers suffered from irritation and CNS-depression with loss of consciousness (Ross 1973).

Due to limitations in the description of the studies, no conclusions can be drawn from the description of reproductive and developmental toxicity studies (Germanova 1986). No signs of DNA-damage were observed in a Comet assay in blood mononuclear leukocytes from workers exposed to organic solvents including acetone (Pitarque et al. 1999). No further studies were located regarding genotoxic effects of acetone in humans *in vivo*. Limited data from a retrospective mortality study provide no evidence of carcinogenicity in workers exposed to acetone (Ott et al. 1983 a,b).

3 ANIMAL TOXICITY DATA

3.1 Acute Lethality

Data on acute lethality after inhalation exposure to acetone are available for rats, mice, guinea pigs and cats (**TABLE 3**). Studies with non-inhalation exposure include rats, mice, rabbits, and guinea pigs. No data were available for nonhuman primates and dogs.

3.1.1 Rats

The LC_{50} values was determined for a number of solvents in female Carworth Farms-Nelson rats (Pozzani et al. 1959). Groups of six rats were exposed by whole body exposure to nominal vapor concentrations of acetone for either 4 or 8 hours. The LC_{50} values were calculated by the method of

moving averages. The 4-hour LC_{50} for acetone was 76.0 mg/L (31,996 ppm; 95 % confidence intervals 27,400 - 37,200 ppm), the 8-hour LC_{50} was 50,1 mg/L (21,091 ppm; 95 % C.I. 17,900 - 24,800 ppm). No data were given as to any clinical or necropsy observations.

In another study of the same research group, female Carworth-Wistar rats (n = 6 per group) were exposed by whole body exposure to nominal acetone vapor concentrations for four hours. One of six rats died at 16,000 ppm and all six rats died at 32,000 ppm (Smyth et al. 1962).

Groups of five male ARS/Sprague Dawley rats were exposed to nominal, but analytically confirmed, acetone concentrations of 12,600, 19,000, 25,300 or 50,600 ppm for three hours (Bruckner and Peterson 1981a). The highest concentration was lethal within two hours. A calculated 3-hour LC_{50} value of 55,700 ppm (95 % C.I. 54,000-57,400 ppm) was reported but it was also reported that the highest applied concentration was already lethal within two hours. Nonlethal effects are described in section 3.2.2.

TABLE 3: SUMMARY OF LETHAL EFFECTS IN ANIMALS AFTER ACUTE INHALATION EXPOSURE TO ACETONE

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat	16,000	4 hours	Death in 1/6 animals	Smyth et al. 1962
Rat	32,000	4 hours	LC_{100} (death in 6/6 animals)	Smyth et al. 1962
Rat	21,092	8 hours	LC_{50}	Pozzani et al. 1959
Rat	31,996	4 hours	LC_{50}	Pozzani et al. 1959
Rat	50,600	2 hours	Lethal after 2 hours (5 rats exposed, no.of deaths not reported)	Bruckner and Peterson 1981a
Rat	55,700	3 hours	LC_{50}	Bruckner and Peterson 1981a
Mouse	46,310 54,730	1 hour 0.7 hours	Deep narcosis; death in 2/3 animals after 6-10 minutes deep narcosis, no deaths	Flury and Wirth 1934
Mouse	63,150	2 hours	LC_{50} (no details reported)	Izmerov et al. 1982
Guinea pig	10,000	47-48 hours	Death in 5/8 animals; spleen and lung congestion, fatty liver, renal tubluar distension	Specht et al. 1939
Guinea pig	20,000	22-26 hours	Death in 8/9 animals; congestion and hemorrhage of spleen and lung	Specht et al. 1939
Guinea pig	21,800	22.3-23.4 hours	Death in 7/10 animals; narcosis, paralysis	Specht et al. 1939
Guinea pig	50,000	3-4 hours	Death in 8/8 animals; pulmonary congestion, edema, glomerular distension	Specht et al. 1939
Cat	21,260 26,944	3 hours 4 hours	Death in 1/1 animals Death in 1/1 animals	Kagan 1924
Cat	74,938	1.1 hours	No deaths (for non-lethal effects see **TABLE 4**)	Flury and Wirth 1934

Studies with non-inhalation exposure

Kimura et al. (1971) examined the oral toxicity of acetone to Sprague-Dawley rats at different stages of maturity. Acetone was given orally via straight needle in indiluted form in nonfasted rats, a microsyringe was used in case of the newborn animals. The animals were observed for one week following treatment. The following results were obtaine (data in the original reference presented as mL/kg were converted to mg/kg):

	oral LD_{50} in g/kg b.w.	(95 % confidence limit)
newborn (24-48 hours old, 5-8 g, ♂ & ♀)	1.7	(1.3-3.0)
immature (14 days old, 16-50 g b.w., ♂ & ♀)	4.4	(3.1-6.3)
young adult (80-160 g b.w., ♂)	7.2	(5.4-9.6)
old adult (300-470 g b.w., ♂)	6.7	(6.2-7.3)

Although no statistical analysis was presented for the comparison between the group of newborns and the groups at other ages, newborn rats seem to be more susceptible than rats at other ages (note that the confidence limits do not overlap). The differences between the LD_{50} of immature, young and old adult rats were statistically not significant.

A similar LD_{50} of 5800 mg/kg b.w. for Sprague-Dawley rats was determined (Freeman and Hayes 1985). LD_{50} of 9883 mg/kg b.w. and of 8450 mg/kg b.w. were reported for female Carworth Farms-Nelson rats and Wistar rats, respectively (Pozzani et al. 1959; Smyth et al. 1962).

3.1.2 Mice

Of 23 mice exposed to acetone vapor concentrations between 8420 ppm for 7.8 hours to 54,730 ppm for 0.7 hour (see section 3.2.3) two died after exposure to 46,310 ppm for 1 hour (Flury and Wirth 1934).

Without any details, a 2-hour LC_{50} of 150,000 mg/m³ (63,150 ppm) for mice was reported (Izmerov et al. 1982). Furthermore, a ten minute exposure to 20,600 ppm was reported to be lethal for an unspecified number of mice (no further details reported; Flury and Zernik 1931).

Studies with non-inhalation exposure

Tanii et al. (1986) reported an oral LD_{50} value of 5250 mg/kg b.w. for male ddY mice.

3.1.3 Guinea pigs

The study of Specht et al. (1939) showed that the lethality is dependent upon both the length and magnitude of exposure. Death rates in female guinea pigs were 8/8 animals at 50,000 for 3 - 4 hours, 8/9 animals at 20,000 ppm for 22 - 26 hours, and 5/8 animals with an exposure to 10,000 ppm. The animals that died were autopsied and examined for gross abnormalities. In varying degrees, pulmonary congestion and edema, splenic congestion and hemorrhage, renal congestion, and glomerular distension was found.

Studies with non-inhalation exposure

An LD_{50} value of 5250 mg/kg b.w. was reported for male guinea pigs (ATSDR 1994).

3.1.4 Rabbits

No data on acute lethality after inhalation exposure were available for rabbits.

Studies with non-inhalation exposure

A LD_{50} value of 5300 mg/kg b.w. was reported (Krasavage et al. 1982).

3.1.5 Cats

In experiments with individual cats, two animals died at exposures to 21,260 ppm (3 hours) and 26,944 ppm (4 hours), respectively (Kagan 1924; see also section 3.2.5).

On the other hand, no deaths occurred in a group of 3 cats exposed to 74,938 ppm for 1.1 hour (Flury and Wirth 1934; see also section 3.2.5). The authors explained the lower effect as compared to the experiments of Kagan (1924) with either intraspecies variability or methodological differences.

3.2 Nonlethal Toxicity

The available acute inhalation studies are summarized in **TABLE 4**. These include studies with repeated short-term exposure to acetone which resulted in acute effects.

3.2.1 Nonhuman primates

Studies with repeated inhalation exposure

Behavioral studies

A group of four male juvenile baboons (*Papio anubis*) was exposed to 500 ppm of acetone vapor continuously (24 hours/day) for seven days and complex operant discrimination performance was examined (Geller et al. 1979a). In relation to control sessions there was no change in the number of correct responses to a stimulus-induced discrimination task that was reinforced by a food reward. The number of extra incorrect responses highly varied, and response time was consistently higher relative to control values in two of four animals. Since the two other baboons showed a decrease in the response time, the neurobehavioral effects do not seem exposure-related.

3.2.2 Rats

Effects on the CNS

Haggard et al. (1944) exposed rats to analytically measured acetone concentrations of 2105, 4210, 10,225, 21,050, 42,100, 84,200, 126,300 ppm (5000 - 300,000 mg/m³) for up to 8 hours. Blood analysis (see 4.1.2) revealed that the onset and severity of narcotic effects is correlated with acetone blood levels. With increasing body burden the following distinct phases appeared: drowsiness and evidence of some loss of gross coordination at blood levels of 1000 - 2000 mg/L, loss of autonomic reflexes at a median blood level of 3000 mg/L (range 2910 - 3150 mg/L), unconsciousness, and respiratory failure at 9190 mg/L (range 9100 - 9300 mg/L). Exposure to 2105 or 4210 ppm of acetone was without effect during the entire 8-hour exposure duration. Acetone blood levels leading to first signs of intoxication (incoordination) were reached after ca. 7 minutes exposure to 126,300 ppm. At exposure levels of 10,525 ppm and higher, the above stages of intoxication were observed depending on the product of concentration and duration of exposure. Although this study seems to be a well-conducted study and included analytical monitoring of the exposure concentrations, it should be noted that there is a paucity of some relevant information, e.g. on strain, gender and number of animals.

TABLE 4: SUMMARY OF ACUTE NON-LETHAL EFFECTS IN ANIMALS AFTER INHALATION EXPOSURE TO ACETONE

Species (strain, sex, no./ group)[a]	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat (SD, 1-5[b])	25-200	3 hours	No clear exposure-related effects on operant behavior	Garcia et al. 1978
Rat (SD, m, 3)	150	30 minutes 1, 2 or 4 hours	None no clear exposure-related effects on operant behavior	Geller et al. 1979b
Rat (n.o.s.)	2105 4210 10,525 21,050 42,100 42,100 84,200 84,200 126,300 126,300	8 hours 8 hours 1.7-4.2 hours 2.2-2.7 hours 1.75-1.9 hours 4.5-5.5 hours 0.35-0.83 hours 2.5-3 hours 0.17-0.42 hours 1.75-2.25 hours	None none incoordination loss of righting reflex loss of corneal reflex respiratory failure loss of corneal and righting reflex respiratory failure loss of corneal and righting reflex respiratory failure	Haggard et al. 1944
Rat (CFE, f, 8-10)	3000 6000 12,000 or 16,000	4 hours/day; 10 days 4 hours/day; 10 days 4 hours/day; 10 days	None no ataxia; avoidance response inhibited after day 1 and 2 ataxia after day 1 only; avoidance response inhibited after day 1 - 10, escape response after day 1	Goldberg et al. 1964
Rat (SD, m, 5)	12,600 19,000 25,300	3 hours 3 hours 3 hours	Definite ataxia with impaired locomotion[c] animals immobile in absence of stimulation[c], recovery after 9 hours hypnosis with arousal difficult[c]	Bruckner and Peterson 1981a
Mouse (CD-1, m, 12)	<1000 3200 10,694 (±2738) 30,000 56,000	30 minutes 30 minutes 30 minutes 30 minutes 30 minutes	None EC_{10}: decreased response in operant behavioral test EC_{50}: decreased response in operant behavioral test responding ceased in most mice responding ceased in all mice	Glowa and Dews 1987
Mouse (Swiss, m, 6)	2032 2580 2800	4 hours 4 hours 4 hours	None 39 % decrease in duration of immobility in behavioral despair swimming test ID_{50}: 50 % decrease in immobility	de Ceaurriz et al. 1984

TABLE 4: SUMMARY OF ACUTE NON-LETHAL EFFECTS IN ANIMALS AFTER INHALATION EXPOSURE TO ACETONE

Species (strain, sex, no./ group)[a]	Concentration (ppm)	Exposure Duration	Effect	Reference
Mouse (white, 2-4)	8420 20,208 54,730	7.8 hours 1.6 hours 0.7 hours	Ataxia after 1.6-2.3 hours; drowsiness after 3.9-7.7 hours deep narcosis in 3/4 animals after 0.7-1.2 hours deep narcosis in 4/4 animals after <0.7 hours	Flury and Wirth 1934)
Mouse (CD-1; f; 32)	11,000 6,600	6 hours 6 hours/day; 12 days	Severe narcosis, no deaths No overt signs of toxicity	NTP 1988
Mouse (Swiss, m, 6)	77,516	10 minutes	RC_{50} for sensory irritation	Kane et al. 1980
Guinea pig (f, 10)	21,800	0.4 hours 4 hours 8.4 hours 9 hours 14.4 hours	Slight lacrimation ataxia drowsiness (8), no auditory reflex (2), narcosis (2) narcosis (9), no auditory reflex (2), poor righting reflex narcosis (10), no auditory or corneal reflex (2), no righting reflex (9)	Specht et al. 1939
Cat (n.o.s., 1)	1055 or 2442 3747 5094 7620 13,472; 21,892; 52,625	5 hours 4.5 hours 4 hours 4.5 hours 3.5; 3.7; 1.3 hours	Slight lacrimation and salivation slight drowsiness and stupor drowsiness, ataxia narcosis with clonic convulsions deep narcosis with clonic convulsions	Kagan 1924
Cat (f+m, 2-3)	16,840 48,468 74,938	3.75-4 hours 1.8 hours 1.1 hours	Eye irritation; ataxia after 1.5 hours; drowsiness after 3.7 hours narcosis narcosis with clonic convulsions	Flury and Wirth 1934)

[a] CFE = Carworth Farms Elias; SD = Sprague-Dawley; f = female; m = male; n.o.s. = not otherwise specified
[b] 8 rats were tested at 1 - 2 different concentrations
[c] as determined at the end of 3-hour exposure period

In the study on Sprague-Dawley rats (Bruckner and Peterson 1981a; see also section 3.1.1), the degree of narcosis was determined at regular intervals during and after exposure by means of a battery of tests of unconditioned performance and reflexes. The manifestations of CNS depression observed showed a dose-related increase in rats exposed to 12,600, 19,000 or 25,300 ppm of acetone for 3 hours (see **TABLE 4**). The pattern of animal performance or reflexes was similar in all exposure groups, with a progressive decrease of the scores measured with increasing exposure duration and a complete recovery of the animals after cessation of inhalation. Performance of animals exposed to 19,000 ppm was comparable to controls 9 hours after cessation of exposure, but complete recovery after 25,300 ppm was not reached until 21 hours. Recovery of the lowest exposure group was not monitored.

In a behavioral study (Goldberg et al. 1964; see below), several rats showed ataxia after a single 4-hour exposure to a measured acetone concentrations of 12,000 or 16,000 ppm. Due to a rapid adaptation, no such effects were observed on the subsequent nine days of further exposure. Exposure to 3000 and 6000 ppm was without effect in this respect.

The effect of solvents on the inihibition of propagation and maintenance of the electrically evoked seizure discharge was studied in in male Wistar rats (4/group) (Frantik et al. 1994). Three concentrations of solvent were selected in the linear part of the concentration-response curve (between 25 and 75 % of maximum effect, if possible). Exposure concentrations were measured by gas chromatography, but the exact concentrations used were not reported. Measurements were carried out within 1 min after removal of the animals from the exposure chamber. All data were processed using linear regression analysis to estimate the concentration of solvent in air evoking 37 % of the maximum possible effect. In case of acetone, a concentration of 3500 ppm (one-sided 90 % confidence intervall 370 ppm) and a slope of regression of 0.015 %/ppm were calculated. The lowest effect concentration which for most solvents could be proven statistically was 10 %. For acetone, the EC_{10} can be calculated as follows: $EC_{10,\ 4\ h,\ rat}$: = 3500 ppm – 27 % ÷ (0.015 %/ppm) = 1700 ppm.

In a further study of the same research group, solvent blood concentrations and subnarcotic effects (inhibition of electrically evoked seizures) were measured. A 4 hour exposure of resting rats to acetone at a concentration of 1680 and 4210 ppm (4 and 10 mg/L), respectively, led to blood levels of 183 and 520 mg/L of acetone: seizure inhibition amounted to 10 % and 50 %, respectively ($EC_{10,\ 4\ h,\ rat}$: 1680 ppm). Blood level and effect attained 1/2 of the final values after 80 min and 120 min of exposure to 4210 ppm acetone, respectively, and dropped to 1/2 more than 4 hours after exposure cessation (Frantik et al. 1996).

Behavioral studies

The effects of a very low concentration of acetone were investigated on the operant behavior of three male Sprague-Dawley rats which were trained to press a lever for a food reward on a a multiple fixed ratio (FR), fixed interval (FI) schedule of reinforcement (Geller et al. 1979b). A measured exposure chamber concentration of 150 ppm was maintained for 30 minutes, 1, 2 or 4 hours. The results were highly variable, i.e., no effects during the 30-minutes exposure relative to pre-exposure control sessions, increase in FR and FI values during 1-hour exposure, decrease in both values during 2-hour exposure, and inconsistent changes during 4-hour exposure. It should be noted that the small number of animals precludes meaningful statistical analysis.

High variation of the test results occurred also in a study with eight rats exposed to acetone concentrations ranging from 25 - 200 ppm for three hours (Garcia et al. 1978). There was no clear exposure-related effect on the lever-pressing behavior. It should be noted that only one rat was tested at 25 ppm and only two at 25 and 100 ppm, and all but one animals were used for two exposure levels.

The avoidance and escape behavior was studied in female Carworth Farms Elias rats aged 30-40 days which were exposed to acetone vapors for 10 days at 4 hours/day (Goldberg et al. 1964). Actual vapor concentrations as determined during exposure were within 10 % of the nominal concentration. 8 - 10 rats were used in both control and experimental groups with different chemicals, including acetone. Groups of animals were trained to escape (escape response, unconditioned response) an electric shock stimulus that was immediately terminated when the rat successfully climbed a pole as escape area. Concurrent with the shock a buzzer was activated; thus, the animals learned to climb the pole in response to the buzzer alone (avoidance response, conditioned response). Responses of each animal were determined on days 1, 2, 3, 4, 5 and 10 before, during, and 2 hours after removal from exposure. No effects of acetone were seen at 3000 ppm on all exposure days. At 6000 ppm, avoidance response (but not

escape response) was inhibited in 38 % and 25 % of animals after day 1 and 2, respectively. At 12,000 ppm, inhibition of both avoidance (50 %) and escape (37 %) response was noted after day 1, whereas after day 2 and 3 only avoidance response was inhibited (37 % and 25 %, respectively). After two or three days, normal responses were obtained in these exposure groups indicating development of adaptation and tolerance on repeated exposure to acetone. This was also true for the 16,000 ppm exposure group with regard to escape response (25 % after day 1; 0 % thereafter), whereas the avoidance response was inhibited throughout the entire study with a decreasing tendency in 62 % of the animals after day 1 - 25 % after day 4 - 10.

Studies with repeated inhalation exposure

Two groups of male Sprague-Dawley rats (6/group) were exposed to an acetone concentration of 19,000 ppm for 3 hours/day, 5 days/week, for 8 weeks, or left untreated (Bruckner and Peterson 1981b). The acetone concentration in the exposure chamber was monitored by gas chromatography. Serum GOT were slightly (non significantly) elevated in treated animals after 2, 4, and 8 weeks of exposure, serum LDH, BUN and liver triglyceride concentration were not altered at any time. Kidney weights of the treated animals were significantly lower than in controls after 4 weeks but not after 8 weeks. There was no effect on liver weight and no microscopic lesions were observed in liver, brain, heart and kidney.

Exposure of 50 male and 50 female rats to an acetone concentration of 3,000 ppm for 8 hours/day, 5 days/week for 20 months was reported not to lead to pathological changes in clinical chemical (BUN, GPT) or histological parameters or changes in relative weight of liver and kidney (Zeller et al. 1964).

3.2.3 Mice

Severe narcosis, but no deaths occurred in female CD-1 mice at exposure to 11,000 ppm acetone for 6 hours; no overt signs of toxicity were observed at 6,600 ppm (NTP 1988).

Sensory irritation

Sensory irritation was studied in groups of four male Swiss-Webster mice exposed to various acetone vapor concentrations between approximately 8500 and 183,000 ppm for 10 minutes (Kane et al. 1980). The RD_{50} value was 77,516 ppm (95 % confidence interval 59,004 - 115,366 ppm). The decrease in respiratory rate was observed within a few seconds; with acetone a complete fade of this response occurred after a few minutes.

A lower RD_{50} value (23,480 ppm, no confidence limits given) was reported for male Swiss OF_1 mice (n = 6) exposed to measured acetone vapor concentrations for 5 minutes (de Ceaurriz et al. 1981). Acetone was the least irritating of 22 solvents tested, although the RD_{50} value was only a third of the above value obtained by Kane et al. (1980) possibly due to different strain sensitivity or methodological variations.

Effects on the CNS

The inihibition of propagation and maintenance of the electrically evoked seizure discharge was studied in female H-strain mice (8/group) (Frantik et al. 1994). Concentration-effect regressions were determined for 48 common solvents including acetone. Three concentrations of solvent were selected in the linear part of the concentration-response curve (between 25 and 75 % of maximum effect, if possible. For some not explicitly named solvents the concentrations had to be lowered to avoid respiratory tract

irritancy). Exposure concentrations were measured by gas chromatography, but the exact concentrations used were not reported. Measurements were carried within 1 min after removal of the animals from the exposure chamber. All data were processed using linear regression analysis to estimate the concentration of solvent in air evoking 30 % of the maximum possible effect. In case of acetone, a concentration of 5000 ppm (one-sided 90 % confidence intervall 980 ppm) and a slope of regression of 0.006 %/ppm were calculated. The lowest effect concentration which for most solvents could be proven statistically was 10 %. For acetone, the EC_{10} can be calculated as follows: $EC_{10,\ 4\ h,\ mouse}$: = 5000 ppm – 20 % ÷ (0.006 %/ppm) = 1670 ppm.

Behavioral studies

Male Swiss mice were exposed to nominal, but monitored, acetone concentrations ranging from approximaetly 2000 - 3000 ppm for four hours (de Ceaurriz et al. 1984). In subsequent 3-hour behavioral despair swimming tests, the duration of immobility and initiation of swimming was measured after placing the animals in a container of water. Exposure to 2032 ppm of acetone caused no differences compared to a control group. Following exposure to 2580, 2858, and 3021 ppm the swimming lag time decreased by 39, 53 and 59 %, respectively. The median active level for this neurobehavioral effect (IL_{50}) was calculated as 2800 ppm.

The effects of five solvents including acetone on schedule-controlled operant behavior of 12 male CD-1 mice were studied in subsequent test series that also included pre-exposure tests serving as controls (Glowa and Dews 1987). The response rate (interruption of a photocell beam located behind a nose-poke hole) was measured under the fixed interval 60-second schedule of food reward. No effect of acetone exposure was seen at concentrations less than 1000 ppm, whereas 30,000 ppm abolished responding in most and 56,000 ppm abolished responding in all mice. The calculated EC_{50} for decreased responding was 10,964 ± 2738 (S.D.) ppm. 30 minutes after exposure was discontinued, responding recovered completely in all animals.

3.2.4 Guinea pigs

Exposure of female guinea pigs to acetone vapor concentrations between 10,000 and 50,000 ppm were lethal in some or all animals (see section 3.1.3) (Specht et al. 1939). For the exposure situation 21,800 ppm (measured), the signs and symptoms observed in 10 guinea pigs were reported in detail depending on the duration of exposure. As shown in **TABLE 4**, first signs of narcosis appeared after 4 hours, whereas after 8.4 hours two animals were already unconscious. After 9 hours, all but one animal were in coma. Exposure duration from about 22 hours resulted in death.

3.2.5 Cats

In experiments conducted by Kagan (1924), low degree lacrimation and salivation was noted in individual cats (sex and stain not reported) exposed to either 1055 or 2442 ppm for 5 hours. Drowsiness and ataxia occurred at 3747 and 5094 ppm, respectively, while a cat exposed to 7620 ppm showed signs of narcosis with clonic convulsions after 3.5 hours. At higher concentrations, deep narcosis was noted. Two deaths occurred at 21,260 or 26,944 ppm, but the cat exposed to 52,625 ppm survived. The reliability of these study results is limited due to the low number of animals per exposure level tested.

In the experiments conducted by Flury and Wirth (1934), narcosis occurred at much higher vapor concentrations, i.e., at 48,468 ppm for 1.8 hours or above. The authors assume that the weaker effects as compared to the experiments of Kagan (1924) are due to either intraspecies variability or methodological differences.

3.3 Developmental/Reproductive Toxicity

3.3.1 Rats

No studies were available in which animals were exposed only once.

Studies with repeated inhalation exposure

Sprague-Dawley rats were exposed to 0, 440, 2,200 or 11,000 ppm acetone for 6 hours/day, 7 days/week on days 6-19 of gestation (Mast et al. 1988; NTP 1988) Each group consisted of 10 virgin females (for comparison) and 26-29 mated females. There were no maternal deaths. In the 11,000 ppm group, body weight, weight gain, uterine weight and extragestational weight were significantly reduced in pregnant rats (in virgin females, body weight was also but non-significantly reduced). The mean pregnancy rates were at least 93 % in all groups, and their was no effect on the number of implantations, the mean percentage of live pups and of resorptions per litter, or the sex-ratio. The fetal body weight was significantly reduced at 11,000 ppm. The percent of litters with at least one pup exhibiting malformations and the diversity of malformations were increased at 11,000 ppm compared to 0 ppm (3.8 %), but the incidence of fetal malformations was not significantly increased. The incidence of fetal variations was not increased.

Studies with non-inhalation exposure

A group of 10 male Wistar rats were exposed to 0.5 % acetone in drinking water for 8 weeks. In the 6^{th} week, males were mated with untreated females. No effects were observed on the number of pregnancies, the number of fetuses/litter and on the weight and histology of the testes (Larsen et al. 1991).

In a subchronic study, F344 rats received 0; 2,500; 500; 10,000; 20,000; or 50,000 ppm acetone in drinking water for 13 weeks. In males, at the highest concentration (corresponding to 3,400 mg/kg b.w. d) relative (but not absolute) testes weight was increased, caudal and right epididymal weight were decreased, sperm motility was lower and the incidence of abnormal sperm was higher than in the control group (Dietz 1991; Dietz et al. 1991; NTP 1991).

3.3.2 Mice

No studies were available in which animals were exposed only once.

Studies with repeated inhalation exposure

Swiss CD-1 mice were exposed to 0, 440, 2,200 or 6,600 ppm (11,000 ppm on the first day) of acetone for 6 hours/day, 7 days/week on days 6-17 of gestation (Mast et al. 1988; NTP 1988). Each group consisted of 10 virgin females (for comparison) and 28-31 mated females. Since 11,000 ppm led to severe narcosis, the concentration was reduced to 6,600 ppm after one day. There were no other overt signs of toxicity, no maternal deaths, and no treatment-related effects on body weight, uterine weight or extragestational weight. The only significant effect was an increase in the relative liver weight in the 6,600 ppm group compared to controls. The mean pregnancy rates were at least 85 % in all groups, and their was no effect on the number of implantations, on any other reproductive indices, and on the sex-ratio. At 6,600 ppm, fetal weight was significantly lower and the incidence of late resorptions was slightly higher than in the control group. However, the mean number of live fetuses per litter was not decreased. The incidence of fetal malformations or variations was not altered at any acetone exposure concentration.

Studies with non-inhalation exposure

In a screening test, groups of 50 mated CD-1 mice received 0 or 3500 mg/kg b.w. acetone in water by gavage on days 6-15 of gestation. Two treated dams showed clinical signs of toxicity and died, no clinical signs or effects on body weight were observed on the surviving dams. Effects attributed to acetone were decreased reproductive index, increased gestational length, lower birth weight, decreased neonatal survival and increased neonatal weight gain (EHRT 1987).

3.3.3 Rabbits

No developmental/reproductive toxicity studies were located in which rabbits were exposed to acetone.

3.4 Genotoxicity

Genotoxicity studies were reviewed (IOMC 2000; WHO 1998): In procaryotes, acetone did not show mutagenic activity in several strains (TA92, TA94, TA97, TA98, TA100, TA1535, TA1537) of *Salmonella typhimurium* in the absence or presence of metabolic activation system and did not induce DNA-cell binding in *Escherichia coli*. Acetone was not mutagenic in *Schizosaccharomyces pombe*. Aneuploidy was observed in one, but not in a further test, with *Saccharomyces cerevisiae*. In *in vitro* studies with animal and human cells, acetone did not induce mutations in the TK locus in mouse lymphoma cells or sister chromatid exchange and chromosome aberrations in Chinese hamster ovary cells and human lymphocytes. *In vivo*, acetone did not induce micronuclei in bone marrow assays in mice and Chinese hamsters. There was no evidence of cell transformation in Fischer rat embryo cells and Chinese hamster cells cultured *in vitro* in the presence of acetone.

In a recent *in vitro* study, acetone caused no significant increase in the number of micronuclei in binucleated human lymphocytes in the absence or presence of external metabolic activation (Zarani et al. 1999).

3.5 Carcinogenicity

No studies were located in the literature regarding the carcinogenicity of acetone in animals.

Acetone has often been used as solvent vehicle in dermal toxicity studies in which generally mice were treated once or twice a week for up to two years. In these studies, there was no evidence that acetone will cause or promote skin tumors at the application site, but there was no naïve control in addition to acetone vehicle control (US EPA 2001; WHO 1998). In a more recent dermal study, female and male Tg.AC transgenic mice were treated with 200 µl of acetone daily for 20 weeks, received phorbol ester in acetone twice a week (positive cntrol) or were left untreated. Acetone caused no increase in the number of skin papillomas as compared to untreated controls (Holden et al. 1998).

An inhalation carcinogenicity study in F344 rats and CD-1 mice was carried out with isopropanol which is metabolized primarily to acetone. Following exposure to up to 5,000 ppm isopropanol vapor for 6 hours/day, 5 days/week for up to 78 weeks (mice) and 104 weeks (rats), the only neoplastic lesion showing an increased incidence was insterstitial (leydig) cell adenomas in rats. Because of the occurrence in control rats, these adenomas were not considered treatment related by the authors of the study (Burleigh-Flayer et al. 1997).

3.6 Summary

Lethality data were available for rats, mice, guinea pigs and cats, but original studies with LC_{50} values were located only for rats. These values ranged from 3-hour LC_{50} of 55,700 ppm (Bruckner and Peterson 1981a) to a 4-hour LC_{50} of 31,996 ppm and an 8-hour LC_{50} of 21,092 ppm (Pozzani et al. 1959). However, death of all animals (LC_{100}) following a 4-hour exposure to 32,000 ppm also was reported (Smyth et al. 1962). 16,000 ppm for 4 hours was the lowest concentration at which death in rats was observed (Smyth et al. 1962).

No death of rats was reported after single 3-hour exposures to 12,600 – 25,300 ppm (Bruckner and Peterseon 1981a), daily 4-hour exposures to 12,000 ppm for up to 10 days (Goldberg et al., 1964), 6-hour exposures to 11,000 ppm for 14 days (NTP 1988), and 3-hour exposures to 19,000 ppm for 8 weeks (Bruckner and Peterson 1981b).

In mice, deep narcosis and death occurred at 46,310 ppm after one hour of exposure (Flury and Wirth 1934).

At non-lethal concentrations, acute effects on the nervous system including alterations in neurobehavioral tests were observed.

In rats, signs of CNS-depression (ataxia) occurred at exposure to 12,600 ppm for 3 hours (Bruckner and Peterson 1981a) and to 12,000 ppm for 4 hours (Goldberg et al. 1964). Slight alterations of behavioral response (inhibition of avoidance response, but not of escape response) were described following a single 4-hour exposure at 6000 ppm (Goldberg et al. 1964). No consistent exposure related effects could be observed on operant behavior of rats exposed up to 4 hours to 25-200 ppm (Garcia et al. 1978; Geller et al. 1979b).

In mice, deep but reversible narcosis occurred at exposure to 56,000 ppm for 30 minutes (Glowa and Dews 1987) and, similarly, 54,730 ppm for 40 minutes (Flury and Wirth 1934). Deep narcosis also was observed after a single 6-hour exposure to 11,000 ppm, but not at 6,600 ppm (NTP 1988). Subtle changes in neurobehavioral tests were reported at 3200 ppm (Glowa and Dews 1987) and 2580 ppm (de Ceaurriz et al 1983).

In the only behavioral study located that used nonhuman primates, no consistent effects were observed in baboons during continuous exposure 24 hours a day for seven days to 500 ppm (Geller et al. 1979a): An increase in response time relative to control was observed in two but a decrease in the other two of the four animals exposed.

In a developmental/reproductive toxicity study with mice and rats, no maternal or fetal toxicity was observed at 2000 ppm. At 6,600 ppm in mice and 11,000 ppm in rats, maternal and fetal weight were reduced and the incidence of late resorptions in mice was increased. In rats exposed to 11,000 ppm, the percent of litters with at least one pup exhibiting malformations and the diversity of malformations was higher compared to controls, but the incidence of fetal malformations was not significantly increased.

Acetone was not mutagenic in tests with procaryote cells. Aneuploidy was observed in one study in yeast, but there was no evidence of genotoxicity in mammalian cells *in vitro* and *in vivo*. No evidence of cell transformation was observed in rat embryo and Syrian hamster cells *in vitro* cultured in the presence of acetone. No studies involving carcinogenicity of acetone were located in the literature.

4 SPECIAL CONSIDERATIONS

4.1 Metabolism and Disposition

Toxicokinetics and metabolism of acetone have been extensively examined in both humans and laboratory animals. In this Technical Support Document, mainly data on short-term exposure and inhalation are addressed.

Acetone is one of the three so-called "ketone bodies" (acetoacetate, ß-hydroxybutyrate, and acetone) that are synthesized in the body by ketogenesis (mostly) from fatty acids. Levels of ketone bodies are influenced by diurnal variation, person's age, physical activity, pregnancy and lactation, and especially by nutritional status. For healthy non-fasting humans that were not exposed to exogenous acetone, mean concentrations of acetone in blood of 0.84 mg/L (range 0.19-3.03 mg/L) (Wang et al. 1994) and 2.0 mg/L (Dick et al. 1988) were reported. Similarly, a median acetone concentration of 3100 ppb (ca. 2.4 mg/L) was measured in blood of a non-occupationally exposed reference group of the US population (Ashley et al. 1994). Fasting and clinical states like diabetes (**TABLE 6**), trauma and alcoholism can result in marked acetonemia and acetonuria (ATSDR 1994; WHO 1998). Acetone is normally eliminated mainly by enzymatic metabolism (70-80 % of the total body burden) or excreted *via* urine or exhaled. In breath of unexposed healthy humans, mean acetone concentrations of 0.3-0.4 ppm were measured (Dick et al. 1988). Far higher acetone concentrations of up to 161 µg/l (67.8 ppm) were measured in expired breath of humans that had fasted for six days (Göschke and Lauffenburger 1975).

Overall, no major differences are evident in toxicokinetics and metabolism between humans and animals. Acetone is rapidly absorbed *via* the respiratory tract after inhalation. In controlled studies on humans, a relative retention of ca. 50 % was observed independent of exposure concentration and physical activity. The total respiratory uptake is directly related to the pulmonary ventilation and increases with increasing work load. In controlled studies on humans, a steady state plateau of the acetone concentration in blood was not reached. Data on distribution are scarce, but due to its high water solubility acetone is expected to be widespread to tissues with high water content.

The metabolic pathways of acetone seem to be similar in humans and laboratory animals. The primary site of metabolism of acetone is the liver. The first step includes the oxidation to acetol by acetone monooxygenase, associated with cytochrome P450IIE1. This step is followed by two different pathways that both lead to the formation of pyruvate which – as a key product of intermediary metabolism – can enter various pathways, e.g. gluconeogenesis or the citric acid cycle.

Acetone is excreted mainly *via* the lung both unchanged and, following metabolism, as carbon dioxide. The fraction of unchanged acetone found in expired breath increases with elevated exposure concentrations due to the saturation of metabolic pathways. In humans, the maximum metabolic elimination rate was not determined. However, in humans and rats similar metabolic rates were observed at blood acetone levels of about 500 mg/L, and in rats, the metabolic rate at this blood level was close to the maximum metabolic elimination rate measured at blood acetone concentrations > 1000 mg/L. At higher blood levels the metabolic elimination approaches zero order kinetics and the respiratory tract is the main route of elimination via exhalation of unchanged acetone. Excretion *via* urine is only a minor route of elimination.

4.1.1 Human data

Absorption

Human data indicate a rapid, passive absorption of acetone from the lung and subsequent uptake into the blood. One of the main factors governing pulmonary uptake and distribution of the chemical in the body (see below) is the solubility of the gas in blood and tissues. The solubility is defined by the tissue/air partition coefficients. For acetone high tissue/air partition coefficients have been reported. Dills et al. (1994) measured *in vitro* the blood/air partition coefficient in samples of 73 human subjects. They calculated a mean value of 301 (± 22). No differences between men and women were observed. Similar *in vitro* experiments with blood samples of five volunteers resulted in a blood/air partition coefficient of 196 (± 31); acetone tended to be more soluble in plasma than in erythrocytes (Fiserova-Bergerova and Diaz 1986). Further literature data on the blood/air partition coefficient are in the same range: 167-330 (WHO 1998; Haggard et al. 1944).

In controlled studies on volunteers, acetone could be detected in the blood within the first minutes of inhalation exposure. A retention of ca. 50 % was observed independent of exposure concentration (range 84-550 ppm) and physical activity.

The total uptake in male subjects (n= 4-8 per group) exposed through mouthpiece (no dermal exposure) to 700 or 1300 mg/m³ (295-550 ppm) for 2 hours increased with increasing concentration and work load. However, the retention remained constant and was about 45 % of the amount administered (individual range 39-52 %). The alveolar acetone concentration in expired air increased within the first minutes of exposure from the endogenous concentration to 30-40 % of the concentration in inspired air (Wigaeus et al. 1981).

These results were confirmed in another study (Jakubowski and Wieczorek 1988). The mean retention in male volunteers (n= 5 per group, 200 mg/m³ [84 ppm] for 2 hours, exposure via face mask) was relatively stable and ranged between 40-44 % despite of increasing pulmonary ventilation. The total uptake was directly related to the pulmonary ventilation and increased from 34 mg/h at rest to 159 mg/h at 75W.

Similar results were observed in volunteers (5 per group) exposed in a chamber (no further data) to acetone concentrations of 56-500 mg/m³ (24-210 ppm) for 2-4 hours (Pezzagno et al. 1986). The mean retention was about 54 ± 4 % at rest and 53 ± 6 % at light exercise (50 W).

In a further study (Nomiyama and Nomiyama 1974b) Japanese students (n=5 per gender) were exposed for 4 hours to 127-131 ppm in an exposure room. The uptake of acetone was lower than in the preceding studies, i.e. 31 ± 7 %. There was also a significant difference between men (35 %) and women (26 %). The respiratory retention decreased within the first two hours of exposure until it reached a constant level of 18 % in men and 11 % in women (difference statistically significant). In a study conducted by Brown et al. (1987) there was no statistically significant gender-specific difference at a 4-hour exposure to 250 ppm, but a significant trend to lower blood concentrations in women exposed to 125 ppm. In the high dose group (250 ppm), the blood concentration in both genders reached ca. 15 mg/L; the steady state was not reached (Brown et al. 1987).

The pulmonary absorption is lower than expected based on the high blood/gas partition coefficient (see above). This effect could be due to the lower fat affinity of acetone compared with other organic solvents (fat-gas partition coefficient of 86; see section distribution) which may affect the passage through the alveolar membranes (Wigaeus et al. 1981) Another reason could be the evaporation of acetone from the mucous membranes of the conducting airways during expiration (Wigaeus et al. 1981; Pezzagno

et al. 1986), a “wash-out effect” which was found in short-term experiments (Schrikker et al. 1985; Schrikker et al. 1989).

In the study of Wigaeus et al. (1981; see above), also the concentration of acetone in the venous blood was measured. It increased continuously with increased total uptake during the exposure period of 2 hours and reached 10 mg/kg at rest at an exposure to 1300 mg/m³ (550 ppm); at 740 mg/m³ (310 ppm) but with exercise up to 150 W on a bicycle it reached 22 mg/kg. No tendency towards equilibrium was observed. Changes in acetone blood levels could be detected within the first minutes of exposure. Similar results were presented by DiVincenzo et al. (1973).

In male Japanese volunteers (n=5 per group) exposed for 6 hours to 100-1000 ppm with a 45 minutes break after 3.5 hours, the acetone concentration in blood reached maximum values at the end of the exposure period. In the high dose group, the blood concentration was 60 mg/L (Matsushita et al. 1969a).

Haggard et al. (1944) exposed male subjects (1 per experiment) to 1000, 3000, or 5000 mg/m³ (420, 1260, 2105 ppm) for 8 hours and measured the end-exposure blood concentrations (blood samples obtained by skin puncture). The maximum concentrations (after 8 hours exposure) in resting subjects were 30, 99, and 165 mg/L, respectively. Higher blood levels were detected in men who performed moderate exercise (steady walking at a brisk pace), i.e. 62 mg/L (420 ppm) and 330 mg/L (2105 ppm), repsectively. The authors calculated that an acetone concentration in the air of 3000 mg/m³ (1260 ppm) would result in a blood concentration of ca. 700 mg/L at equilibrium if humans are at rest (no data about exposure duration). The authors compared these data with results obtained from animal studies (see below) and concluded that data from caged rats may be applied with no great error to men performing moderate exercise.

There are no controlled studies available investigating the exposure durations at which a steady state plateau of the acetone concentration in blood is reached. The blood/air distribution coefficient of acetone is high indicating that a long time is required to reach this equilibrium. The steady state plateau has been demonstrated in laboratory animals (see below).

The high volatility of acetone limits the uptake after dermal exposure. However, in volunteers dermal absorption after semiocclusive application was reported (WHO 1998).

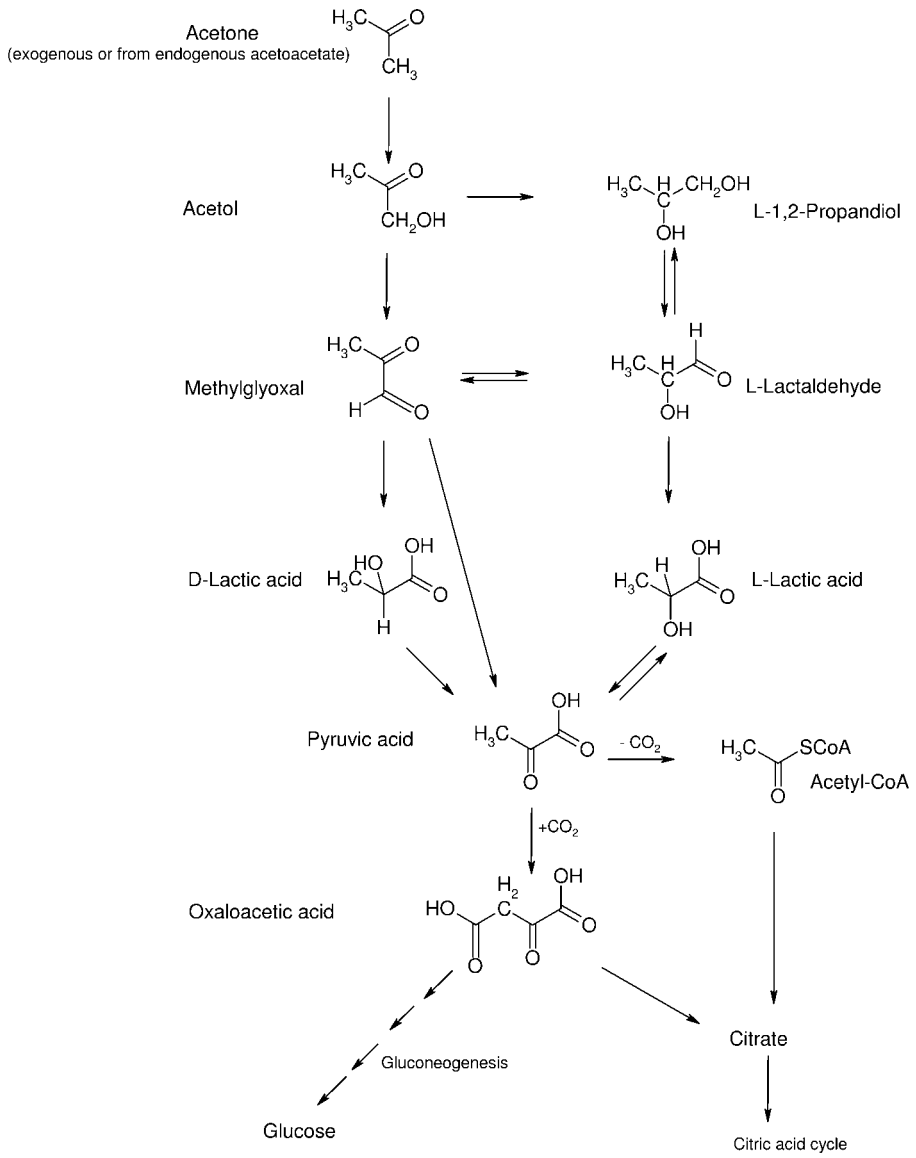
Distribution

Data on the distribution of acetone in humans are scarce. Tissue-gas partition coefficients using human autopsy material were determined *in vitro* (Fiserova-Bergerova and Diaz 1986). Samples of muscle, kidney, lung and brain revealed tissue-air partition coefficients between 121 and 160, which were little lower than the coefficient for blood (196), but clearly higher than the fat-gas partition coefficient of 86 (blood samples from 5 volunteers). These data indicate a nearly uniform distribution of acetone among the tissues with high water content, which was confirmed in experimental studies with rats and mice.

In vivo experiments with three human subjects (Haggard et al. 1944) revealed an average tissue-to-blood distribution factor of 0.82 (comparable to ethanol) also confirming that the distribution is dependent on the water content of the various tissues.

Metabolism

The metabolism of acetone has been extensively examined in laboratory animals, while only few data are available on humans. However, the metabolic pathways shown in figure 1 seem to be similar



in humans and laboratory animals. Since there is evidence that the metabolites do not affect the acute toxicity of acetone (WHO 1998), only a short description will be given.

FIGURE 1: PATHWAYS FOR THE METABOLISM OF ACETONE (AFTER Kalapos 1999, SIMPLIFIED)

The primary site of metabolism of acetone is the liver. The first step includes the oxidation to acetol by acetone monooxygenase, associated with cytochrome P450IIE1. This step is followed by two different pathways: (i) oxidation to methylglyoxal (also associated with P450IIE1) and (ii) probably

extrahepatic conversion to L-1,2-propandiol. Methylglyoxal is converted *via* D-lactate or directly to pyruvate. 1,2-Propandiol is also converted to pyruvate *via* L-lactate. Pyruvate is a main product of interediary metabolism that may enter e.g. the citric acid cycle or the gluconeogenic pathway. Consequently, in studies with ^{14}C-labelled acetone, ^{14}C-activity was also detected in other products and substrates of the intermediary metabolism and in carbon dioxide. The pattern of acetone metabolism can be altered by variations in the physiological status (WHO 1998; ATSDR 1994; Kalapos 1999).

Elimination

Acetone is excreted mainly *via* the lung both unchanged and, following metabolism, mainly as carbon dioxide. The fraction of unchanged acetone found in expired breath increases with elevated exposure concentrations due to the saturation of metabolic pathways. Excretion *via* urine is only a minor route of elimination. The metabolic elimination follows saturation kinetics. Data on elimination kinetics in intoxicated humans are limited to a few case studies. There is evidence that excretion of acetone after inhalation exposure is similar in humans and animals.

In the controlled study with Japanese students (Nomiyama and Nomiyama 1974a; Nomiyama and Nomiyama 1974b), relative respiratory excretion of 18 and 15 % was found for male and female subjects. In contrast to other organic solvents the concentration of acetone in the expired air decreased slowly.

In another study (Brown et al. 1987; Dick et al. 1988; see section Distribution), the blood levels (corrected for endogenous levels) declined from ca. 15 mg/L at the end of the 4-hour exposure period (250 ppm) to ca. 12 mg/L 1.5 hours after exposure and reached 1.5 mg/L (about baseline level) 20 hours after exposure. Assuming 1st-order kinetics the estimated half-life was 3.9 hours.

In the study of DiVincenzo et al. (1973), respiratory excretion of acetone was increased with increasing exposure concentration, duration, and physical activity (excretion doubled). In the high dose group (500 ppm for 2 hours at rest) the expired breath concentration declined slowly (after rapid decrease within the first min) from ca. 20 ppm to less than 5 ppm (7 hours post exposure). During exposure the concentration of acetone in venous blood increased to ca. 10 mg/L (corrected for endogenous level) in the high dose group (500 ppm for 2 h) and decreased in the post exposure observation period to 5 mg/L after ca. 3 hours. Similar results were reported for the low dose group (100 ppm for 2 hours).

In workers (n=22) of a plastics factory exposed to a mean occupational exposure concentration of 336 mg/m³ (142 ppm), a mean concentration of 23 mg/L acetone in the blood was measured at the end of the shift. Based on measurements at the end and 16 hours after the shift, the calculated half-life of acetone in blood was 5.8 hours (Wang et al. 1994).

In the study conducted by Matsushita et al. (1969a; see above for exposure data) the acetone concentration in the blood reached 60 mg/L in the high dose group (1000 ppm for 6 h) and declined to endogenous levels 48 hours after the end of exposure.

Haggard et al. (1944) measured the decline in blood concentration in a male subject at rest starting with a blood concentration of 72 mg/L. After ca. 11 hours a blood concentration of 36 mg/L was reached. Endogenous blood levels were observed after 27 hours. In further experiments with one male subject, metabolic elimination and excretion *via* exhaled air and urine was determined over a period of 24 hours in 4 hours intervals. The initial blood concentration of 73 mg/L decreased to 2 mg/L after 24 hours. Excretion of acetone via urine was small (< 2.5 %). Ca. 34 % were excreted *via* exhalation during the 1st interval (blood concentration decreased from 73 - 57 mg/L) and 6 % during the last interval (8-2 mg/L). The metabolic elimination increased with decreasing blood concentrations: 64 % of the total loss at high

blood concentrations in the first interval to 93 % in the last interval. The authors calculated a rate of metabolism of ca. 2 mg/kg b.w. and h. Similar results were found in experiments with a 2nd male subject at rest (initial blood concentration 70 mg/L). However, the metabolism rate rose to 6 mg/kg b.w. hour when the subject was under exercise (average blood concentration 36 mg/L). Comparing these results with other studies on humans or data on rats (see below) it can be concluded that a saturation of metabolic elimination was not reached at the documented blood acetone concentrations in humans.

In 9 patients with ketoacidosis plasma acetone concentrations varied between 90 and 517 mg/L. In these patients there was a positive linear relationship between plasma concentrations and excretion of acetone in breath. At low acetone plasma concentrations (ca. 100 mg/L) approximately 20 % of the acetone production was excreted in the breath and at high acetone plasma concentration this value increased to 80 %. At low plasma concentrations, about 75 % of the acetone was metabolised. This value decreased to 20 % at high plasma concentrations. At a plasma concentration of about 500 mg/L, the rate of acetone metabolism was about 11 mg/kg b.w. hour (data estimated from a graph). A similar rate of 10 mg/kg b.w. hour was observed in rats (**TABLE 5**) (Haggard et al. 1944).

The urinary excretion in humans shows a linear relationship to the corresponding time-weighted average concentration of acetone in the air(Pezzagno et al. 1986). Therefore, urinary excretion of acetone is used for biomonitoring of acetone exposure at the workplace (Schaller and Triebig 1996).

Few data are available on elimination of acetone at much higher blood levels. After ingestion of nail polish remover by a 53-year-old woman a blood acetone level of 2500 mg/L was determined upon the first admission to the hospital (effects: lethargy, broad-based gait). The authors calculated a half-life of 28 hours based on only a few data points. One month later the woman was again brought to the hospital. The examinations revealed a blood acetone concentration of 2500 mg/L. The blood level declined to about 600 mg/L ca. 84 hours after admission. The authors reported a half-life of 31 hours. The data in these 2 cases appeared to be log-linear and consistent with a first-order elimination process (Ramu et al. 1978).

In another case, in which a 42-year-old man had ingested 800 ml of acetone, a serum level of 2000 mg/L was determined (effect: unconsciousness). Repeated measurements of acetone in blood and urine indicated an elimination half-life of 11 hours. Elimination was accelarated by forced hyperventilation, haemofiltration, and forced diuresis with high fluid intake (Zettinig et al. 1997).

A half-life of 19 hours was reported in a 30-month-old child. The serum acetone level was 4450 mg/L about one hour after ingestion of nail polish remover (effects: unconsciousness, respiratory depression) and declined to 2650 mg/L at 17 h, to 420 mg/L at 48 h, and to 40 mg/L at 72 hours (Gamis and Wasserman 1988).

4.1.2 Laboratory animal data

Absorption

In 6 rats exposed to 355 mg/m³ (150 ppm) for up to 4 hours blood levels steadily increased for 2 hours and than remained constant for the next 2 hours at a blood concentration of 12 mg/L (Geller et al. 1979). In mice exposed to 1200 mg/m³ (506 ppm) acetone for up to 24 hours, the increase of acetone in the tissues (several organs including blood) levelled off to a steady state plateau after 3-6 hours (max. blood concentration ca. 100 mg/L) indicating that equilibrium was reached at this exposure concentration (Wigaeus et al. 1982).

The following maximum blood levels in rats exposed to 0, 1000, 2500, 5000, 10000, 15000 ppm were measured at the end of the 4-hour exposure period: 0, 91, 312, 727, 2114, 3263 mg/L, respectively (Charbonneau et al. 1986).

Rats were exposed to acetone concentrations of 5,000, 25,000, 50,000, 100,000, 200,000 or 300,000 mg/m³ (2,110, 10,550, 21,100, 42,200, 84,400, 127,000 ppm) for up to 8 hours; at doses >100,000 mg/m³ (42,200 ppm) the exposure duration was limited by severe toxic effects (see 3.2.2 and **TABLE 7**). At 2,110 ppm, the blood concentration reached 420 mg/L after 8 hours. At 10,550 ppm, a blood concentration of ca. 2000 mg/L was measured after 5 hours; first effects on the gross coordination were noted at blood concentrations of at least 1000 mg/L. 5-hour exposure to 21,100 ppm resulted in a blood concentration of ca. 4300 mg/L, which is clearly higher than the concentration leading to the loss of the righting reflex (ED_{50} = 3014 mg/L); after only one hour exposure, ca. 2000 mg/L blood acetone concentration was detected. Within 100 minutes of exposure to 42,200 ppm the acetone blood concentration reached a level of ca. 5000 mg/L, a blood level at which the loss of the corneal reflex was observed (ED_{50}= 5174 mg/L). Similar blood concentrations was measured in rats exposed to 84,400 ppm for 45-50 minutes or to 127,000 ppm for 22-25 minutes. Acetone blood levels leading to first signs of intoxication (effects on coordination) were reached after ca. 7 minutes exposure to 127,000 ppm (Haggard et al. 1944).

In a further study, a 4 hour exposure of resting rats to acetone at a concentration of 1680 and 4210 ppm, respectively, led to blood levels of 183 and 520 mg/L of acetone. At 4210 ppm, the level in blood attained 1/2 of the final value after 80 min (Frantik et al. 1996).

Distribution

In studies on the inhalation toxicokinetics of acetone in rats (Hallier et al. 1981) the calculated coefficient of distribution between organism and gas phase was 220 indicating that acetone is mainly distributed within the body water compartment.

In mice exposed to 1200 mg/m³ (506 ppm) of 2-^{14}C-acetone for up to 24 hours, acetone was rather evenly distributed in all highly perfused non-adipose tissues and reached a plateau after 6 hours of exposure. In the adipose tissue the maximum concentration was 1/3 of that in non-adipose tissues. In the liver and the brown adipose tissue the radioactivity (including the metabolites) increased during exposures up to 24 hours (Wigaeus et al. 1982).

Since the acetone concentration plays a relevant role in narcotic effects, Bruckner et al. (1981a) determined the concentration of acetone in rat brain after 3 hours exposure to 19000 ppm that led to CNS depression. The concentrations in brain, liver, and blood were 2.7 mg/g, 2.5 mg/g and 3.3 mg/ml, respectively. This is in accordance with *in vitro* findings of the tissue/gas partition coefficients in human tissues.

Metabolism

Extensive investigations have been performed in different species, mainly in rats, and with different routes of exposure. The metabolic pathways of acetone are illustrated in figure 1.

The pathways of acetone metabolism in rats were studied after i.v. infusion (3 hours duration) of trace amounts of 2-^{14}C-acetone or a dose of 1.6 mmol 2-^{14}C-acetone (314-387 mg/kg b.w.). The low dose resulted in incorporation of ^{14}C mainly into the carbon numbers 1, 2, 5, 6 of glucose whereas ^{14}C was incorporated in carbon numbers 3 and 4 at the higher dose. These results indicated that the conversion to C_2-intermediates predominates at high concentrations of acetone in the venous blood plasma (at

least 230 mg/L), while at low acetone plasma concentrations (1.2-17 mg/L), the incorporation of C_3-intermediates into glucose predominates (Kosugi et al. 1986).

In studies with rats, incorporation of C_1-fragments into serine (Sakami 1950) and excretion of formate were observed (Hallier et al. 1981), but to date, no enzyme systems have been identified that mediate the formation of formate from acetone (Kalapos 1999).

Elimination

Rats exposed for to 0, 1000, 2500, 5000, 10,000 or 15,000 ppm showed maximum blood acetone concentration of 0, 91, 312, 727, 2114, and 3263 mg/L, respectively, at the end of the 4-hour exposure period (Charbonneau et al. 1986). In the 2 high dose groups, elimination curves of the acetone concentration in blood showed a biphasic pattern and a slow rate of clearance during the first 10 hours post exposure (no further data). The authors postulated a saturation of the acetone clearance. Up to 5000 ppm the blood concentration reached endogenous levels 17-25 hours after exposure.

Toxicokinetics of acetone in male rats was studied in closed-recirculating exposure chambers at initial concentrations of up to 62,000 ppm (Hallier et al. 1981). The rate of acetone loss from the chamber was measured for up to 30 hours. After the initial equilibrium period of 8 hours the rate of metabolic elimination was dose dependent and showed saturation at higher concentrations. At chamber concentrations of 100 ppm or less, the metabolic elimination exhibited apparent first-order kinetics and followed Michaelis-Menten kinetics. The authors calculated a Michaelis constant of 160 ppm. The maximum velocity for this process was 18.6 mg/kg hours (cf data in Haggard et al. 1944).

The decrease in acetone blood concentration was studied in rats (Haggard et al. 1944). Initial high blood concentrations of ca. 2300 mg/L declined to endogenous acetone levels after ca. 45 hours; a concentration of 1200 mg/L was reached after ca. 11 hours. In further studies, the relative loss of acetone from blood by either excretion (via the lung and urine) or metabolism was studied (**TABLE 5**).

TABLE 5: EXCRETION AND METABOLIC ELIMINATION OF ACETONE IN RELATION TO THE BLOOD CONCENTRATION IN THE RATS (DATA FROM HAGGARD ET AL. 1944)

Observation period (hours)	Initial/ final blood concentration at end of observation period (mg/L)	Total loss of acetone, in mg/kg b.w. hour	Loss of acetone by excretion, in mg/kg b.w. hour	Loss of acetone by metabolism, in mg/kg b.w. hour	Loss by excretion in %	Loss by metabolism in %
4	2310 / 1840	96.4	83.5	12.9	87	13
6	2250 / 1570	92.7	79.3	13.4	86	14
4	1070 / 780	59.5	47.4	12.1	80	20
4	984 / 728	52.3	40.7	11.6	79	21
6	570 / 310	35.5	25.5	10.0	72	28
4	133 / 67	13.5	8.3	5.2	62	38
4	128 / 60	13.9	8.9	5.0	64	36
4	84 / 48	7.4	3.3	4.1	45	55
4	70 / 36	6.9	3.0	3.9	43	57

4	25 / 8	3.5	0.6	2.9	17	83
4	23 / 8	3.1	0.5	2.6	16	84

These studies confirmed the findings in humans that acetone is mainly eliminated by excretion at high blood concentrations, whereas metabolic elimination predominates at low blood concentrations. The metabolic elimination is influenced by the nutritional status: fasted rats showed a 30 % higher rate of metabolism than fed rats (Haggard et al. 1944).

In mice exposed to 1200 mg/m³ (506 ppm) of 2-^{14}C-acetone for 6 hours, unmetabolized acetone accounted for about 52 % of the expired radioactivity 0-12 hours after termination of exposure and 48 % was excreted in the form of carbon dioxide. The elimination of radioactivity was fast in blood, kidney, lungs, brain, and muscle with half-times of about 2-3 hours. The slowest elimination was seen in the subcutaneous adipose tissue with a half-time of ca. 5 hours. The acetone concentration reached endogenous levels 24 hours after exposure (Wigaeus et al. 1982).

4.2 Mechanism of Toxicity

At low blood acetone concentrations (< 100 mg/L), the main route of elimination is the metabolism by intrahepatic and extrahepatic pathways. The metabolites of acetone include glucose and the corresponding intermediates. It does not appear that any of these metabolites affect the toxicity of acetone (WHO 1998). With higher exposure concentrations the metabolic elimination becomes saturated and the increasing concentration of acetone in the blood results in systemic effects.

Possible signs of subtle altered performance in neurobehavioural tests have been described in human volunteers at acetone concentrations of 250 ppm. CNS-effects in humans at increasing acetone concentrations are headache and CNS depression including unconsciousness. The mechanisms by which acetone produces these effects remains unclear. However, as a lipophilic solvent acetone may interfere with the cellular membranes of neurones, altering the permeability to ions (ATSDR 1994).

While acetone itself is only moderately toxic, it may potentiate the toxicity of other chemicals, e.g. halogenated alkanes and alkenes, benzene, halogenated aromatics, nitrosamines, 2,5-hexanedione, and ethanol. Most animal experiments were done with single and repeated oral or parenteral administration of acetone but also with short-term inhalation this potentiation was observed. For example, the liver toxicity of carbon tetrachloride was enhanced after rats were exposed to acetone concentrations of 2500 ppm for 4 hours, no effects were observed after 1000 ppm (Charbonneau et al. 1986).

Postulated mechanisms for the potentiation of toxic effects of different chemicals are beyond the scope of this document. A summary of the three general mechanisms is presented below. Discussion of these mechanisms is available in ATSDR (1994) and WHO (1998):

(i) Increased activity of microsomal enzymes, particularly cytochrome P450IIE1 and associated enzyme activities (e.g. increased activity of these enzymes by acetone treatment enhanced the metabolism of carbon tetrachloride or chloroform to reactive hepatotoxic intermediates);

(ii) interference with uptake and/or elimination;

(iii) interactions at the target site or receptor protein.

4.2.1 Structure Activity Relationships

Aliphatic ketones such as acetone, methyl ethyl ketone, and methyl isobutyl ketone are generally of low acute toxicity. Ketones and other compounds metabolized to 2,5-hexanedione (e.g. hexane or methyl n-butyl ketone) cause peripheral neuropathies. Acetone is not metabolized to 2,5-hexanedione but may potentiate the toxicity of that compound (ATSDR 1994).

4.3 Other relevant information

4.3.1 Species variability

The data on lethal and CNS-effects of acetone in rats, mice, guinea pigs and cats provide no evidence for marked species differences. Furthermore, comparison of exposure data, corresponding concentrations of acetone in blood and effects noted in humans and rats at reported blood concentrations (**TABLE 6**; **TABLE 7**; **FIGURE 2**) do not provide evidence of marked species differences between rats and humans.

4.3.2 Susceptible Populations

No human data were located that provide evidence for a higher susceptibility of specific population subgroups. The primary effect of sufficiently high concentrations of acetone is central nervous system depression. The susceptibility of the general population to volatile central nervous system anesthetics as indicated by the minimum alveolar concentration (MAC) varies by no more than 2- to 3-fold (NRC 2001).

It may be speculated that diabetic persons suffering from diabetic ketoacidosis might be more susceptible to acetone exposure since their internal acetone burden may be far higher than in healthy individuals (**TABLE 6**). However, diabetic ketoacidosis in itself is a severe and potentially life-threatening metabolic disorder that requires hospitalization and intense medical treatment. Therefore, it is unlikely that those persons will be exposed to higher concentrations of acetone in the environment that may be reached e.g. at accidental releases.

There are no animal data from inhalation exposure studies with respect to an age-dependent sensitivity. However, an oral study with rats (Kimura et al. 1971) indicates that newborn rats seem to be more susceptible than older animals since the LD_{50} for newborn animals was 4.2-fold lower than that for young adult rats. No statistical comparison was performed with the data for newborn animals, but the 95 % confidence limit for the LD_{50} did not overlap with those of the other age groups.

TABLE 6: EXPOSURE, BLOOD LEVEL AND EFFECTS OF ACETONE IN HUMANS				
Expo-sure time	**Concen-tration in air (ppm)**	**Concentration in venous blood (mg/L) [a]**	**Effects/Remarks**	**Reference**
		< 10 100 - 700	Upper limit in non-fasting healthy individuals range in ketoacidotic diabetics	IOMC 2000
		44 (27 - 84) 17 (11 - 27) 80 (60 - 98)	Mean value (range) in 6 non-obese and in 6 obese humans after 3 days of fasting; mean value (range) in 3 obese humans after 21 days of fasting	Reichard et al. 1979
0 hours 2 hours 4 hours 4 hours	-- 125 125 125	ca. 2.0 6.2 10.4 ca. 12	Pre-exposure level No effect in neurological tests; Males Females	Brown et al. 1987; Dick et al. 1988
2 hours 4 hours	250 250	9.0 15.3	Slight and questionable effects on few parameters in neurological tests	Brown et al. 1987; Dick et al. 1988
2 hours	100 500	ca. 2 ca. 10	No subjective symptomes noted	Di Vincenzo et al. 1973
2 hours	250	16.8	Value at light exercise (50 W); no subjective symptoms noted	Ernstgard et al. 1999
0.5 hours 0.5 hours 2 hours	300 550 550	3.6 4.3 9.9	Values for resting subjects	Wigaeus et al 1981
6 hours	250 500 1000	ca. 20 ca. 48 60	Subjective symptoms next morning: slight feeling of tension, heavy eyes, lack of energy	Matsushita et al. 1969a
2 hours		ca. 140 (i) ca. 195 (ii) ca. 230 (iii)	Mean values for 7 (i) or 19 (ii) healthy or 12 (iii) diabetic volunteers after intra-venous infusion of 10 g acetone in 200 ml saline at a constant rate over 2 hours (83 mg/minute); slight drop in blood pressure and slight temporary drowsiness (no details given)	Koehler et al. 1941
8 hours	420 1260 2105	30 99 162	Resting subjects; no signs of intoxication noted	Haggard et al. 1944
8 hours	420 2105	62 330	At moderate exercise, no signs of intoxication noted	Haggard et al. 1944
		ca. 70 (2 hours after intake)	Oral intake of ca. 80 mg/kg b.w. by volunteer; no adverse effects reported	Haggard et al. 1944
		436 (8 hours after accident) 302 (10 hours) 180 (next day)	Accidental inhalation at work, man hospitalized unconscious, medical treatment, recovery	Sack 1941
		2000 (several hours after	Oral intoxication (pure acetone), man	Zettinig et

TABLE 6: EXPOSURE, BLOOD LEVEL AND EFFECTS OF ACETONE IN HUMANS				
Expo-sure time	**Concen-tration in air (ppm)**	**Concentration in venous blood (mg/L) [a]**	**Effects/Remarks**	**Reference**
		intake) 400 (one day later)	hospitalized unconscious, progressing respiratory insufficieny, medical treatment, recovery	al. 1997
		2500 (at admission to hospital)	Oral intoxication, woman hospitalized in lethargic, minimally responsive state; medical treatment, recovery	Ramu et al. 1978
		4450 (1 hour after onset of symptoms) 2650 (18 hours) 420 (48 hours) 40 (72 hours)	Oral intoxication (mixture of 65 % acetone and 10 % isopropanol), 2½ year old child, effects: seizure, unconscious-ness, no arousal to pain, respiratory depression, acidosis; medical treatment, recovery	Gamis and Wasserman 1988

a: at end of exposure time, if not otherwise stated.

TABLE 7: EXPOSURE, BLOOD LEVEL AND EFFECTS OF ACETONE IN RATS				
Expo-sure time	**Concen-tration in air (ppm)**	**Concentration in blood (mg/L) [a]**	**Effects/Remarks**	**Reference**
4 hours	150	12	No effect	Geller et al. 1979
4 hours	1,000	91	Effects of acetone not reported [b]	Charbonneau et al. 1986
4 hours	1680	183	EC_{10} for subnarcotic effects (inhibition of electrically evoked seizures)	Frantik et al. 1996
4 hours	2,500	312	Effects of acetone not reported [b]	Charbonneau et al. 1986
8 hours	2,100	420	No signs of "intoxication" (i.e., loss of gross coordination)	Haggard et al 1944
4 hours	4210	520	EC_{50} for subnarcotic effects (inhibition of electrically evoked seizures)	Frantik et al. 1996
4 hours	5,000	727	Effects of acetone not reported [b]	Charbonneau et al. 1986
8 hours	4210	1040		Haggard et al 1944
		1000	First effects on gross coordination	Haggard et al 1944
		1,000 – 2,000	Slight incoordination	Haggard et al 1944
1 hour	21,100	2000		Haggard et al 1944
5 hours	10,550	2000		Haggard et al 1944
4 hours	10,000	2114	Effects of acetone not reported [b]	Charbonneau et al. 1986
		3014	ED_{50} for loss of righting reflex	Haggard et al 1944
4 hours	15,000	3263	Effects of acetone not reported [b]	Charbonneau et al. 1986
3 hours	19,000	3300 (brain: 2700 mg/kg)	Loss of righting reflex	Bruckner and Peterson 1981a
5 hours	21,100	4300		Haggard et al 1944
		5174	ED_{50} for loss of corneal reflex	Haggard et al 1944
1.7 hours	42,200	5000		Haggard et al 1944
.75 hours	84,400	ca. 5000		Haggard et al 1944
0.4 hours	127,000	ca. 5000		Haggard et al 1944
		9185	ED_{50} for respiratory failure, unconsciousness,	Haggard et al 1944

a: at end of exposure time, if not otherwise stated; b: Study was conducted to investigate interaction of acetone with CCl_4 hepatotoxicity.

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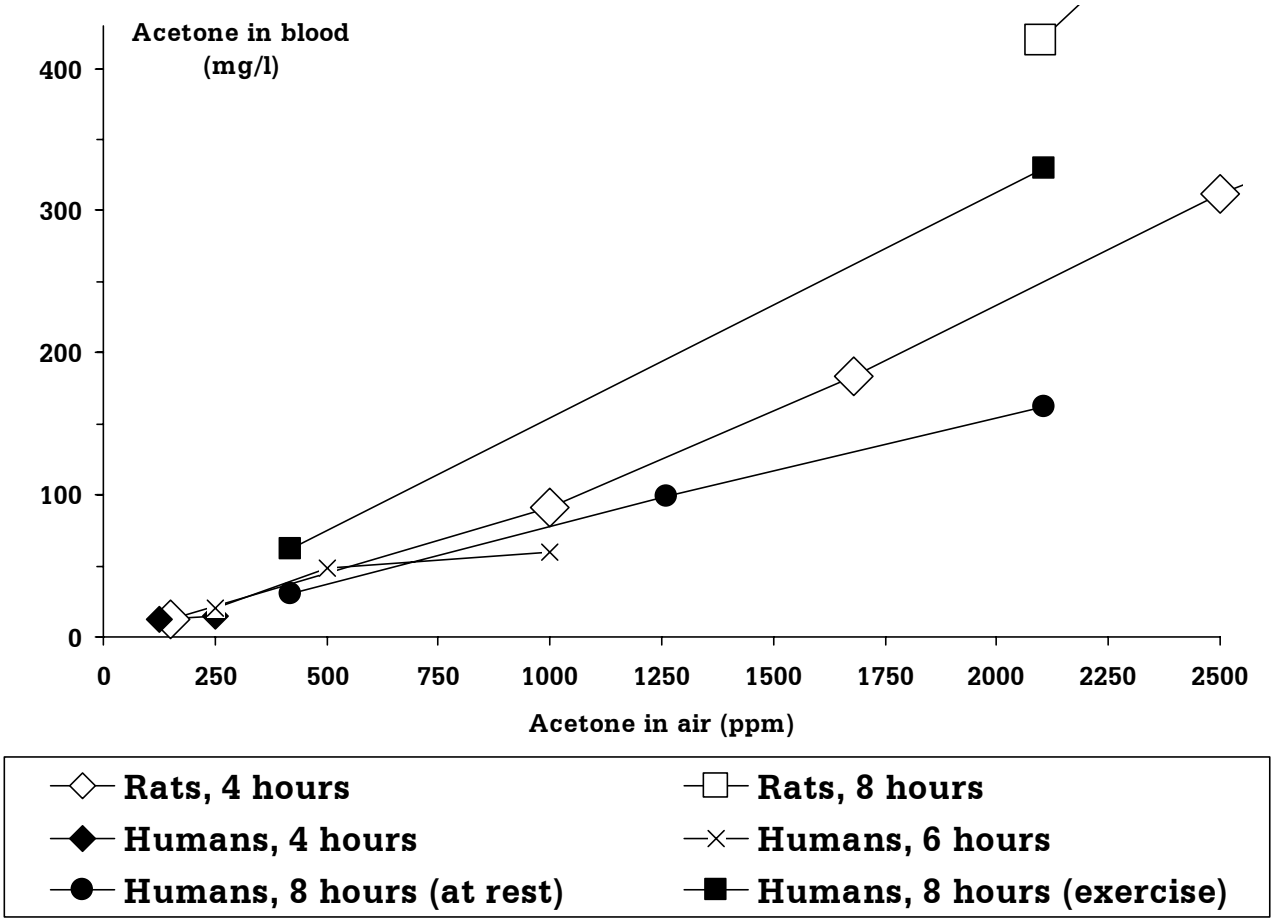


2 **FIGURE 2: COMPARISON OF ACETONE CONCENTRATION IN BLOOD OF HUMANS AND**
3 **RATS FOLLOWING INHALATION (DATA FROM HAGGARD ET AL. 1944).**

4 (Data at concentrations exceeding 2500 ppm in air were also available for rats but were omitted from the
5 graph.)

5 DATA ANALYSIS FOR AEGL-1

5.1 Summary of Human Data Relevant to AEGL-1

At 200 ppm, subjective symptoms of eye and throat irritation were not reported more frequently than in nonexposed controls (Stewart et al. 1975). At 250 ppm, no increased ratings with respect to irritative symptoms and effects on the CNS were noted in one study (Ernstgard et al. 1999); in a second study, slight irritation during exposure and some complaints about heavy eyes, lack of energy, and feeling of tension the morning after exposure were described, and these subjective symptoms were felt by most volunteers at 500 ppm and 1000 ppm (Matsushita et al. 1969a). At 300 ppm, slight irritation was reported, and 500 ppm led to eye, nose and throat irritation in the majority of exposed (Nelson et al. 1943). Subjective signs of irritation were clearly notable in a number of controlled studies at exposure to 800-1000 ppm (Dalton et al. 1997a,b; Seeber et al. 1992 a,b; Seeber and Kieswetter 1991). Results from the studies of Dalton indicate that health-related effects of exposure to odorants are mediated not by a direct agency of odors but by cognitive variables, such as mental models of the relationship between environmental odors and health. “Objective” measures of sensory irritation by intranasal lateralization (irritation of thr trigeminal nerve) revealed far higher median irritation thresholds of 15,758 ppm and 36,608 ppm (Dalton et al. 1997a; 2000).

Neurological tests in a group of volunteers exposed to 250 ppm for 4 hours revealed a questionable change in a profile of mood state psychological test and statistically significant but small effects in a standardized auditory discrimination test (Dick et al. 1988; 1989). In another study, exposure to 1200 ppm for 7.5 hours caused an increase in visual evoked response in the EEG but no other significant neurological effects were observed at 250-1200 ppm (Stewart et al. 1975).

5.2 Summary of Animal Data Relevant to AEGL-1

No exposure-related effects were noted in a neurobehavioral study with baboons and rats exposed to 500 ppm or 25-200 ppm, respectively (Garcia et al. 1978; Geller et al 1978a,b). A 4-hour exposure of rats to 1680 ppm led to a 10 % inhibition of electrically evoked seizures (Frantik et al. 1994; 1996), but no signs of intoxication (i.e. some loss of gross coordination) were observed in rats exposed to 2105 ppm for 8 hours (Haggard et al 1944).

5.3 Derivation of AEGL-1

Four studies with human volunteers including exposures to 200 – 500 ppm for 5 minutes to 7.5 hours were used to derive AEGL-1. At 200 ppm, subjective symptoms (eye/throat irritation) were not reported more often than in controls (Stewart et al. 1975). At 250 ppm, no increased ratings with respect to irritative symptoms and effects on the CNS were noted in one study (Ernstgard et al. 1999), while in another study slight irritation and few complaints about subjective discomfort were reported (Matsushita et al. 1969a). Slight irritation at 300 ppm and subjective irritation in the majority of exposed volunteers at 500 ppm were reported in a further study (Nelson et al. 1943).

Therefore, 200 ppm were selected to derive AEGL-1. Because this concentration represents a NOAEL for local effects and effects at higher concentrations were weak, an intraspecies factor of 1 is applied. The value of 200 ppm was used for all timepoints since accomodation to slight irritation occurs and the complaints about subjective discomfort were reported not to increase during 6 hour or 7.5 hour exposure.

The derived values are listed below.

TABLE 8: AEGL-1 VALUES FOR ACETONE					
AEGL Level	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm

The level of distinct odor awareness (LOA) for acetone is 160 ppm. The LOA derivation follows the guidance as described (van Doorn et al. 2001b). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The derived LOA is considered to have warning properties, but it must be noted that accomodation to odor usually occurs within minutes.

6 DATA ANALYSIS FOR AEGL-2

6.1 Summary of Human Data Relevant to AEGL-2

At exposure to acetone concentrations greater than 12,000 ppm that lasted from 2 minutes to 4 hours, workers suffered from irritation and effects on the CNS including loss of consciousness (Ross 1973).

From several toxikokinetic studies, clinical observations and case reports, data for acetone concentration in air, corresponding concentration in blood, and effects observed in humans are summarized in **TABLE 6**.

Effects below the AEGL-2, i.e. subjective signs of irritation were described in a number of controlled studies at exposure to 800-1000 ppm (Dalton et al. 1997a,b; Seeber et al. 1992 a,b; Seeber and Kieswetter 1991). Neurological tests in a group of volunteers exposed to 250 ppm for 4 hours revealed a questionable change in a profile of mood state psychological test and statistically significant but small effects in a standardized auditory discrimination test (Dick et al. 1988; 1989). In another study, exposure to 1200 ppm for 7.5 hours caused an increase in visual evoked response in the EEG but no other significant neurological effects were observed at 250-1200 ppm (Stewart et al. 1975). These effects are below the AEGL-2 level since they will not impair the ability to escape.

6.2 Summary of Animal Data Relevant to AEGL-2

No death of rats was reported after single 3-hour exposures to 12,600 – 25,300 ppm (Bruckner and Peterson 1981a), daily 4-hour exposures to 12,000 ppm for up to 10 days (Goldberg et al., 1964), 6-hour exposures to 11,000 ppm for 14 days (NTP 1988), and exposures for 3 hours/day, 5 days/week to 19,000 ppm for 8 weeks (Bruckner and Peterson 1981b).

At non-lethal concentrations, acute effects on the nervous system including alterations in neurobehavioral tests were observed. From several toxicity and toxikokinetic studies, data for acetone concentration in air, corresponding concentration in blood, and CNS-effects observed in rats are summarized in **TABLE 7**.

In rats, neurotoxic effects (ataxia) occurred at exposure to 12,600 ppm for 3 hours (Bruckner and Peterson 1981a) and to 12,000 ppm for 4 hours (Goldberg et al. 1964). Slight alterations of behavioral response (inhibition of avoidance response, but not of escape response) were described following a single 4-hour exposure at 6000 ppm (Goldberg et al. 1964).

In mice, deep but reversible narcosis occurred at exposure to 56,000 ppm for 30 minutes (Glowa and Dews 1987) and, similarly, 54,730 ppm for 40 minutes (Flury and Wirth 1934). Deep narcosis also was observed after a single 6-hour exposure to 11,000 ppm, but not at 6,600 ppm (NTP 1988). Subtle changes in neurobehavioral tests were reported at 3200 ppm (Glowa and Dews 1987) and 2580 ppm (de Ceaurriz et al 1983).

No exposure related effects could be observed in a behavioral study with nonhuman primates (baboons) at continuous exposure 24 hours a day for seven days to 500 ppm (Geller et al. 1979a).

In a developmental toxicity study in which mice and rats were exposed from day 6-17 or 6-19 of gestation, respectively, no maternal or fetal toxicity was observed at 2000 ppm. At 6,600 ppm in mice and 11,000 ppm in rats, maternal and fetal weight were reduced and the incidence of late resorptions in mice was increased. In rats exposed to 11,000 ppm, the percent of litters with at least one pup exhibiting malformations and the diversity of malformations was higher compared to controls, but the incidence of fetal malformations was not significantly increased. The relevance of an exposure duration of about half the gestation period in rodents to a less than one day exposure in humans is questionable. Therefore, these results will not be used for the derivation of AEGL-2.

6.3 Derivation of AEGL-2

In recent years, PPBK models have been developed which describe the kinetics of isopropanol and/or acetone in rats and humans (Clewell et al. 2001). These models may provide useful information on acetone kinetics in humans at lower concentrations (up to about 500 ppm) of acetone in air but they are not validated at the high levels which are relevant in the derivation of AEGL-2 and AEGL-3. Furthermore, even if PBPK models would be shown to adequately describe the kinetics of acetone in humans, an intraspecies factor still would be required in the derivation of AEGL-2 and -3 levels to protect sensitive subgroups.

The AEGL-2 is based on the NOAEL for ataxia in rats following exposure to 6000 ppm acetone for 4 hours (Goldberg et al. 1964). At the next higher concentration of 12,000 ppm, reversible ataxia was observed. Reversible ataxia also was observed in another study at exposure of rats to 12,600 ppm for 3 hours, but a no-effect level was not determined in that study (Bruckner and Peterson 1981a).

For volatile solvents like acetone, an interspecies uncertainty factor of 3 has been applied in the derivation of AEGL for several substances (e.g. tetrachloroethene). This is based on the similarity of effects manifested in rodents compared to humans. However, an interspecies factor of 3 (and an intraspecies factor of 4.2, see below) would have resulted in AEGL-2 of 480 ppm for 4 hours and of 320 ppm for 8 hours. These values contrast with observations made in a number of controlled human studies in which exposures up to 1000 - 1200 ppm resulted in irritation and headaches but no more severe effects (Matsushita et al. 1969a; Dalton et al 1997a,b; Seeber et al., 1992a,b; Stewart et al. 1975). Furthermore, form the data presented in **TABLE 6**, it can be estimated that exposure to 480 ppm for 4 hours or 320 ppm for 8 hours would lead to acetone concentration in blood below 50 mg/L. Such concentrations are still in the physiological range which can be observed in fasting humans.

Therefore, the interspecies uncertainty factor was reduced to 1.

With respect to an intraspecies factor, it is observed in humans that newborns consistently are the most sensitive age group for volatile anesthetics in general (NRC 2001). No human data for acetone were available allowing for the derivation of a substance-specific intraspecies factor. However, in a study with rats of different ages it was observed that the lethal dose ($LD_{50\ oral}$) of acetone was 4.2-fold lower in newborns than in adults (Kimura et al. 1971). It is assumed that intraspecies differences between humans are also covered by this range. Therefore, an intraspecies uncertainty factor of 4.2 was applied to account for sensitive individuals.

The experimentally derived exposure values were scaled to AEGL time frames using the equation $c^n \times t = k$ (Ten Berge et al. 1986). An exponent of n = 1.7 that was used for extrapolation to all time points was derived from the 4-hour and 8-hour LC_{50} for rats obtained by Pozzani et al. (1959) (see Appendix B).

The derived values are listed below.

TABLE 9: AEGL-2 VALUES FOR ACETONE

AEGL Level	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	9300 ppm*	4900 ppm*	3200 ppm*	1400 ppm	950 ppm

* Concentrations are higher than 1/10 of the lower explosive limit of acetone in air (2.6 % = 26,000 ppm). Therefore, safety considerations against hazard of explosion must be taken into account.

These values are supported by observations from a controlled human study (Stewart et al. 1975) in which volunteers were repeatedly exposed to 1200 ppm for 7.5 hours/day. Volunteers reported slight irritation, but no effects on the CNS (apart from an increase in visual revoked response) was observed.

7 DATA ANALYSIS FOR AEGL-3

7.1 Summary of Human Data Relevant to AEGL-3

The acute toxicity of acetone is low and no reports were located in which exposure of humans resulted in death.

A case report described that workers exposed to acetone concentrations greater than 12,000 ppm suffered from from irritation and CNS depression, which, depending on the duration of exposure (2 minutes to 4 hours) progressed to loss of consciousness (Ross 1973). In several nonfatal cases of severe intoxication with CNS-depression following oral intake of acetone, blood levels of 2000 4450 mg/L were measured several hours after intake (**TABLE 6**).

There are a number of poisoning cases following oral ingestion of acetone are described in the literature (see 2.2.1). The effects seen in theses cases are clearly above AEGL-2 level but the victims seemed to fully recovered and none of them died. These case reports show that very high blood levels of acetone (2000 mg/L or more) may be survived without obvious late sequelae. However, it must be noted that all patients were admitted to hospital and received intensive medical care. Therefore, it cannot be assumed that patients would have survived without such treatment. This consideration is stressed by two data: Firstly, in one of the reports (Zettinig et a., 1997) the authors state that the lethal level of acetone in humans is “not precisely defined” in the literature but clinical chemistry compilations refer that lethal outcomes may occur at blood levels exceeding 550 mg/L. Secondly, in another case, a neonate child with a combined level of acetone and isopropanol similar to the acetone blood level observed by Zettinig et al.

(1997) but receiving no medication or special intense medical care died after inhalation of isopropanol (which is metabolized to acetone) (Vicas and Beck 1993). Further factors must be taken into account: E.g., in the report of Ramu et al. (1978), the patient had a long-lasting history of chronic alcohol abuse with neuropathy and was under medication with drugs to control for seizures and with diuretics for blood pressure control. It is known that chronic alcoholic often tolerate higher levels of alcohol than non-alcoholics and this may also be true for other solvents such as acetone with similar CNS-effects. At the same time, medication against seizures may have suppressed CNS-effects of acetone poisoning. These factors severely limit the usefulness of the data. Also, if data from such cases were used for the derivation of AEGL-3, an route-to-route extrapolation from oral to inhalation uptake would have to be performed which would add further uncertainty. Therefore, data from case reports are not regarded as suitable for the derivation of AEGL.

7.2 Summary of Animal Data Relevant to AEGL-3

These LC_{50} values for rats ranged from 55,700 ppm (3 hour; Bruckner and Peterson 1981a) to a 4-hour LC_{50} of 31,996 ppm and an 8-hour LC_{50} of 21,092 ppm (Pozzani et al. 1959). However, death of all animals (LC_{100}) following a 4-hour exposure to 32,000 ppm also was reported (Smyth et al. 1962). 16,000 ppm for 4 hours was the lowest concentration at which death in rats was observed (Smyth et al. 1962).

No death of rats was reported after single 3-hour exposures to 12,600; 19,000 and 25,300 ppm (Bruckner and Peterseon 1981a), daily 4-hour exposures to 12,000 ppm for up to 10 days (Goldberg et al., 1964), 6-hour exposures to 11,000 ppm for 14 days (NTP 1988), and 3-hour exposures to 19,000 ppm for 8 weeks (Bruckner and Peterson 1981b).

In mice, deep narcosis and death occurred at 46,310 ppm after one hour of exposure (Flury and Wirth 1934). Deep but reversible narcosis occurred at exposure to 56,000 ppm for 30 minutes (Glowa and Dews 1987) and, similarly, 54,730 ppm for 40 minutes (Flury and Wirth 1934). Deep narcosis also was observed after a single 6-hour exposure to 11,000 ppm, but not at 6,600 ppm (NTP 1988).

Data from an oral study with rats (Kimura et al. 1971) indicate that newborn rats seem to be more susceptible than older animals since the LD_{50} for newborn animals was 4.2-fold lower than that for young adult rats.

In a developmental/reproductive toxicity study with mice exposed from day 6-17 of gestation, the incidence of late resorptions was increased at 6,600 ppm. The relevance of an exposure duration of about half the gestation period in rodents to a less than one day exposure in humans is questionable. Therefore, these results will not be used for the derivation of AEGL-3.

7.3 Derivation of AEGL-3

No death occurred in rats exposed to 12,600 ppm for 3 hours (Bruckner and Peterson 1981a). In that study, also no deaths were observed in animals exposed to 19,000 and 25,300 ppm, but in another study, 1 of 6 animals died at 16,000 ppm (Smyth et al. 1962). This second study was a study with nominal but not analytically confirmed concentrations. However, the data from this study are taken into account based on the fact that acetone is a highly volatile but non-reactive chemical and therefore gross deviations between nominal and analytical concentrations are regarded unlikely. Therefore, the derivation of AEGL-3 is based on a non-lethal concentration of 12,600 ppm after a 3-hour exposure of rats.

As for AEGL-2, an interspecies uncertainty factor of 1 was applied because the same toxic effects (CNS-depression) which are relevant for AEGL-2 are also relevant in case of AEGL-3. Additional-

ly, comparison of blood levels correlated with effects in humans and rats (**TABLE 6**; **TABLE 7**; **FIGURE 2**) do provide evidence of no marked species differences between rats and humans. Also, an interspecies factor of 3 (together with an intraspecies factor of 4.2) would result in AEGL-3 of 840 ppm for 4 hours and of 560 ppm for 8 hours which are contradicted by data from a controlled human study in which no life-threatening effects were observed at exposures up to 2110 ppm for 8 hours (Haggard et al. 1944) and a number of other studies in which no severe CNS-effects were observed at exposures up to 1000 - 1200 ppm for 6 - 7.5 hours (Matsushita et al. 1969a; Dalton et al 1997a,b; Seeber et al., 1992a,b; Stewart et al. 1975).

With respect to an intraspecies factor, it is observed in humans that newborns consistently are the most sensitive age group for volatile anesthetics in general (NRC 2001). No human data for acetone were available allowing for the derivation of a substance-specific intraspecies factor. However, in a study with rats of different ages it was observed that the lethal dose ($LD_{50\ oral}$) of acetone was 4.2-fold lower in newborns than in adults (Kimura et al. 1971). It is assumed that intraspecies differences between humans are also covered by this range. Therefore, an intraspecies uncertainty factor of 4.2 was applied to account for sensitive individuals.

The experimentally derived exposure values were scaled to AEGL time frames using the equation $c^n \times t = k$ (Ten Berge et al. 1986). An exponent of n = 1.7 that was used for extrapolation to all time points was derived from the 4-hour and 8-hour LC_{50} for rats obtained by Pozzani et al. (1959) (see Appendix B).

The derived values are listed below.

TABLE 10: AEGL-3 VALUES FOR ACETONE

AEGL Level	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3	see below #	8600 ppm*	5700 ppm*	2500 ppm*	1700 ppm

#: The lower explosive limit (LEL) of acetone in air is 2.6 % (26,000 ppm). The AEGL-3 value of 16,000 ppm (39,000 mg/m³) for 10 minutes is higher than 50 % of the LEL. Therefore, extreme safety considerations against hazard of explosion must be taken into account.

*: Concentrations are higher than 1/10 of the lower explosive limit of acetone in air. Therefore, safety considerations against hazard of explosion must be taken into account.

8 SUMMARY OF AEGLs

8.1 AEGL Values and Toxicity Endpoints

TABLE 11: SUMMARY/RELATIONSHIP OF AEGL VALUES [a]					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm
AEGL-2 (Disabling)	9300 ppm*	4900 ppm*	3200 ppm*	1400 ppm	950 ppm
AEGL-3 (Lethal)	see below [#]	8600 ppm*	5700 ppm*	2500 ppm*	1700 ppm

a: Cutaneous absorption of liquid acetone may occur. Since liquid acetone is an eye irritant, eye contat must be avoided

#: The lower explosive limit (LEL) of acetone in air is 2.6 % (26,000 ppm). The AEGL-3 value of 16,000 ppm (39,000 mg/m³) for 10 minutes is higher than 50 % of the LEL. Therefore, extreme safety considerations against hazard of explosion must be taken into account.

*: Concentrations are higher than 1/10 of the lower explosive limit of acetone in air. Therefore, safety considerations against hazard of explosion must be taken into account.

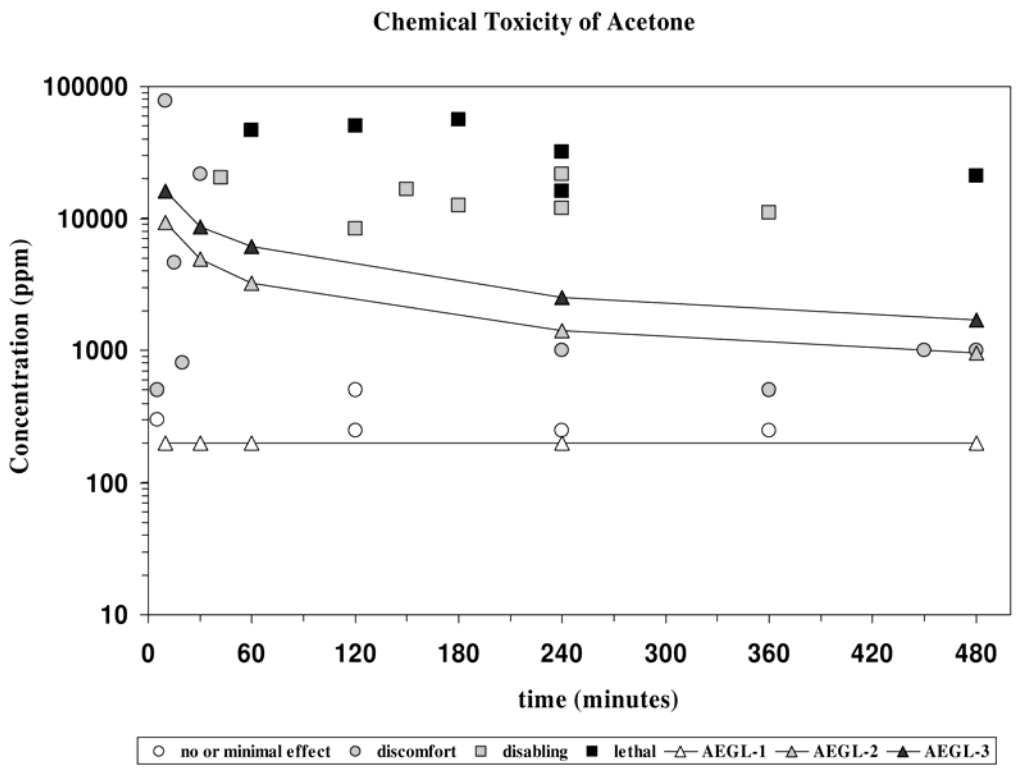


FIGURE 3: CATEGORICAL REPRESENTATION OF ACETONE INHALATION DATA

8.2 Comparison with Other Standards and Guidelines

Other standard and guidance levels for workplace and community are listed in **TABLE 12**.

TABLE 12: EXTANT STANDARDS AND GUIDELINES FOR ACETONE

Guideline	Exposure duration					
	10 min	**30 min**	**1 h**	**4 h**	**8 h**	**24 h**
AEGL-1	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm	
AEGL-2	9300 ppm*	4900 ppm*	3200 ppm*	1400 ppm	950 ppm	
AEGL-3	see below #	8600 ppm*	5700 ppm*	2500 ppm	1700 ppm	
TEEL-0 (US DoE 2002)[a]		1000 ppm				
TEEL-1 (US DoE 2002)[a]		1000 ppm				
TEEL-2 (US DoE 2002)[a]		8500 ppm				
TEEL-3 (US DoE 2002)[a]		8500 ppm				
IDLH (NIOSH 1996)[b]		[2500 ppm] [b]				
EEL (NRC 1984)[c]			8500 ppm			1000 ppm
Spacecraft MAC (NRC 2000)[d]			500 ppm			200 ppm
PEL-TWA (OSHA)[e]					750 ppm	
Acceptable peak (OSHA)[f]		1000 ppm				
REL-TWA (NIOSH)[g]					250 ppm	
TLV-TWA (ACGIH)[h]					750 ppm	
TRGS 900 (Germany)[i]					500 ppm	
TRGS 900 (Germany) Spitzenbegrenzung[j]	1000 ppm					
MAK (DFG 2000, Germany)[k]					500 ppm	
MAK (DFG, Germany) Kurzzeitkategorie[l]	1000 ppm					
Einsatztoleranzwert[m]				500 ppm		

#: The lower explosive limit (LEL) of acetone in air is 2.6 % (26,000 ppm). The AEGL-3 value of 16,000 ppm (39,000 mg/m³) for 10 minutes is higher than 50 % of the LEL. Therefore, extreme safety considerations against hazard of explosion must be taken into account.
*: Concentrations are higher than 1/10 of the lower explosive limit of acetone in air. Therefore, safety considerations against hazard of explosion must be taken into account.

a: **TEEL** (Temporary Emergency Exposure Limits; U.S. Department of Energy)

TEEL-0: The threshold concentration below which most people will experience no appreciable risk of health effects;

TEEL-1 The maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odor;
TEEL-2 The maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing or developing irreversible or other serious health effects or symptoms that could impair their abilities to take protective action;
TEEL-3 The maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing or developing life-threatening health effects.

It is recommended that, for application of TEELs, the concentration at the receptor point of interest be calculated as the peak 15-minute time-weighted average concentration. TEELs are published only for chemicals for which no ERPG has been derived. It should be emphasized that TEELs are default values, following the published methodology explicitly (US DoE 2002).

b: **IDLH** (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)

Basis for revised IDLH: Based on health considerations and acute inhalation toxicity data in humans (Haggard et al. 1944; Raleigh and McGee 1972) and animals (Flury and Wirth 1934; Pozzani et al. 1959), a value of about 5,000 ppm would have been appropriate for acetone. However, the revised IDLH for acetone is 2,500 ppm based strictly on safety considerations (i.e., being 10% of the lower explosive limit of 2.5%) (NIOSH 1996).

c: **EEL** (Emergence Exposure Limit, National Research Council, Committee on Toxicology)

The EEL is defined as a ceiling limit for an unpredictable single exposure, usually lasting 60 min or less, and never more than 24 hours – an occurrence expected to be rare in the lifetime of any person. It reflects an acceptance of the statistical likelihood of the occurrence of a nonincapacitating, reversible effect in an exposed population. It is designed to avoid substantial decrements in performance during emergencies and might contain no uncertainty factor. The use of uncertainty factors will depend on the specific compound in question and on the type of effect produced by the compound. The values for acetone are based on neurotoxic symptoms in humans (NRC 1984).

d: **SMAC** (Spacecraft Maximum Allowable Concentrations for Selectd Airborne Contaminants, National Research Council, Committee on Toxicology)

SMACs are intended to provide guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. Short-term (1 - 24 hr) SMACs refer to concentrations of airborne substances (such as a gas, vapor, or aerosol) that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposures might cause reversible effects, such as mild skin or eye irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies. The values for acetone are based on effects (fatigue, headache) in humans (NRC 2000).

e: **OSHA PEL-TWA** (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average) for 8 hours (OSHA) (NSC 2003).

f: **Acceptable Peak OSHA** (Occupational Health and Safety Administration, Permissible Exposure Limits; OSHA) (NSC 2003).

g: **REL-TWA NIOSH** (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH), is defined analogous to the ACGIH-TLV-TWA.

h: **ACGIH TLV-TWA** (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH, 1999; NSC 2003):

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

k: **MAK** (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungs-gemeinschaft [German Research Association], Germany) (DFG 1993)

is defined analogous to the ACGIH-TLV-TWA.

l: **MAK Spitzenbegrenzung** (Kategorie I, 2) (Peak Limit Category I, 2) (DFG 2000)

constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes (mean value) no more than 2 times per workshift.

n: **Einsatztoleranzwert** (Buff and Greim 2000)

Einsatztoleranzwert (Action Tolerance Levels), Vereinigung zur Förderung des deutschen Brandschutzes e. V. (Federation for the Advancement of German Fire Prevention) constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 hours without any health risk.

8.3 Data Adequacy and Research Needs

The data base on humans includes controlled clinical studies and studies at the workplace. These studies showed that acetone may be irritating to eyes and mucous membranes of the upper respiratory tract. Several studies investigated neurobehavioral effects. Effects on the central nervous system were observed in accidents following exposure to higher but less precisely known concentrations and following ingestion of large amounts of hundreds of mL of acetone. Metabolism studies are also available. Few data are available with respect to long-term exposure of humans.

Studies with acute to subacute exposure of animals – mostly rats, but also baboons, mice, and guinea pigs – addressed irritation, effects on the central nervous system including behavior, and lethality. Developmental toxicity and genotoxicity data are also available. Frequent use of acetone in dermal carcinogenicity studies has not provided any evidence for a carcinogenic effect, but there no oral or inhalation carcinogenicity study has been conducted with acetone. However, isopropanol – which is metabolized primarily to acetone – was not considered carcinogenic in an inhalation study with rats and mice.

9 REFERENCES

AIHA. 1997. Odor thresholds for chemicals with established occupational health standards. American Industrial Hygiene Association (AIHA), Fairfax, VA.

Amoore, J.E. and E. Hautala. 1983. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3: 272-290.

Ashley, D.L., M.A. Bonin, F.L. Cardinali, J.M. McCraw, and J.V. Wooten. 1994. Blood concentrations of volatile organic compounds in a nonoccupationally exposed US population and in groups with suspected exposure. Clin. Chem. 40: 1401-1404.

ATSDR. 1994. Toxicological profile for acetone. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry, Atlanta, Georgia.

Axelsson, G., C. Lutz, and R. Rylander. 1984. Exposure to solvents and outcome of pregnancy in university laboratory employees. Br. J. Ind. Med. 41: 305-312. Cited from abstract in MEDLINE (http://gateway.nlm.nih.gov/gw/Cmd).

Brown, W.D., J.V. Setzer, R.B. Dick, F.C. Phipps, and L.K. Lowry. 1987. Body burden profiles of single and mixed solvent exposures. J. Occup. Med. 29: 877-883.

Bruckner, J.V. and R.G. Peterson. 1981a. Evaluation of toluene and acetone inhalant abuse. I. Pharmacology and pharmacodynamics. Toxicol. Appl. Pharmacol. 61: 27-38.

Bruckner, J.V. and R.G. Peterson. 1981b. Evaluation of toluene and acetone inhalant abuse. II. Model development and toxicology. Toxicol. Appl. Pharmacol. 61: 302-312.

Buff, K. and H. Greim. 2000. Der Einsatztoleranzwert als Instrument der raschen Gefahrenbewertung am Brandort und beim Gefahrstoffeinsatz. In: Bundesamt für Zivilschutz (ed.): Zivilschutz-Forschung. 45., 46. und 48. Jahrestagung der Schutzkommission beim Bundesminister des Innern - Vorträge. Schriftenreihe der Schutzkommission beim Bundesminister des Innern. Neue Folge Band 42, p. 221-228. Medienhaus Froitzheim AG, Bonn, Berlin.

Burleigh-Flayer, H., R. Garman, D. Neptun, C. Bevan, T. Gardiner, R. Kapp, T. Tyler, and G. Wright. 1997. Isopropanol vapor inhalation oncogenicity study in Fischer 344 rats and CD-1 mice. Fundam. Appl. Toxicol 36: 95-111. Cited from abstract in TOXLINE (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE).

Charbonneau, M., J. Brodeur, S.P. du, and G.L. Plaa. 1986. Correlation between acetone-potentiated CCl4-induced liver injury and blood concentrations after inhalation or oral administration. Toxicol Appl. Pharmacol 84: 286-294.

Chatterton, C.C. and R.B. Elliott. 1946. Acute acetone poisoning from leg casts of a synthetic plaster substitute. J. A. Med. Assoc. 130: 1222-1223.

Clewell, H.J., P.R. Gentry, J.M. Gearhart, T.R. Covington, M.I. Banton, and M.E. Andersen. 2001. Development of a physiologically based pharmacokinetic model of isopropanol and its metabolite acetone. Toxicol Sci. 63: 160-172.

Cossmann, T. 1903. Azetonvergiftung nach Anlegen eines Zelluloid-Mullverbandes. Münch. Med. Wochenschr. 50: 1556-1557.

Dalton, P. 1999. Cognitive influences on health symptoms from acute chemical exposure. Health Psychol. 18: 579-590. Cited from abstract in MEDLINE (http://gateway.nlm.nih.gov/gw/Cmd).

Dalton, P., D.D. Dilks, and M.I. Banton. 2000. Evaluation of odor and sensory irritation thresholds for methyl isobutyl ketone in humans. AIHAJ. 61: 340-350.

Dalton, P. and C.J. Wysocki. 1996. The nature and duration of adaptation following long-term odor exposure. Percept. Psychophys. 58: 781-792.

Dalton, P., C.J. Wysocki, M.J. Brody, and H.J. Lawley. 1997a. Perceived odor, irritation, and health symptoms following short-term exposure to acetone. Am. J. Ind. Med. 31: 558-569.

Dalton, P., C.J. Wysocki, M.J. Brody, and H.J. Lawley. 1997b. The influence of cognitive bias on the perceived odor, irritation and health symptoms from chemical exposure. Int. Arch. Occup. Environ. Health 69: 407-417.

de Ceaurriz, J., J.C. Micillino, B. Marignac, P. Bonnet, J. Muller, and J.P. Guenier. 1984. Quantitative evaluation of sensory irritating and neurobehavioural properties of aliphatic ketones in mice. Food Chem. Toxicol 22: 545-549.

de Ceaurriz, J.C., J.C. Micillino, P. Bonnet, and J.P. Guenier. 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicol Lett. 9: 137-143.

DFG. 1993. Acetone. In: Greim, H. (ed.): Occupational Toxicants. Critical Data Evaluation for MAK Values and Classification of Carcinogens. Vol. 7. Wiley-VCH, Weinheim, Germany.

DFG. 2000. Acetone. In: Greim, H. (ed.): Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, 30. Lieferung. Wiley-VCH, Weinheim, Germany.

Dick, R.B., W.D. Brown, J.V. Setzer, B.J. Taylor, and R. Shukla. 1988. Effects of short duration exposures to acetone and methyl ethyl ketone. Toxicol Lett. 43: 31-49.

Dick, R.B., J.V. Setzer, B.J. Taylor, and R. Shukla. 1989. Neurobehavioural effects of short duration exposures to acetone and methyl ethyl ketone. Br. J. Ind. Med. 46: 111-121.

Dietz, D. 1991. NTP Toxicity studies of Acetone (CAS No. 67-64-1) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). Toxic. Rep. Ser. 3: 1-38.

Dietz, D.D., J.R. Leininger, E.J. Rauckman, M.B. Thompson, R.E. Chapin, R.L. Morrissey, and B.S. Levine. 1991. Toxicity studies of acetone administered in the drinking water of rodents. Fundam. Appl. Toxicol 17: 347-360. Cited from abstract in MEDLINE (http://gateway.nlm.nih.gov/gw/Cmd).

DiVincenzo, G.D., F.J. Yanno, and B.D. Astill. 1973. Exposure of man and dog to low concentrations of acetone vapor. Am. Ind. Hyg. Assoc. J. 34: 329-336.

EHRT. 1987. Screening of priority chemicals for reproductive hazards: benzethonium chloride (CAS No. 121-54-0); 3-ethoxy-1-propanol (CAS No. 111-35-3); acetone (CAS No. 67-64-1). NTIS PB89-139083. NIOSH (National Institute for Occupational Safety and Health), Cincinnati, Ohio. Cited in WHO (1998).

Ernstgard, L., E. Gullstrand, G. Johanson, and A. Lof. 1999. Toxicokinetic interactions between orally ingested chlorzoxazone and inhaled acetone or toluene in male volunteers. Toxicol Sci. 48: 189-196.

Fiserova-Bergerova, V. and M.L. Diaz. 1986. Determination and prediction of tissue-gas partition coefficients. Int. Arch Occup. Environ Health 58: 75-87.

Fitzpatrick, L.J., C.C. D´Arcy, and N.J. Teaneck. 1947. Acute acetone poisoning (resulting from synthetic plaster substitute in Spica Cast). Curr. Res. Anesth. 26: 86-87.

Flury, F. and W. Wirth. 1934. Zur Toxikologie der Lösungsmittel. (Verschiedene Ester, Aceton, Methylalkohol) [On the Toxicology of Solvents. (Several Esters, Acetone, Methyl Alcohol)]. Arch. Hyg. 5: 1-90.

Flury, F. and F. Zernik. 1931. Schädliche Gase [Noxious Gases]. Unveränderter Nachdruck 1969 [Unchanged Reprint 1969]. Julius Springer, Berlin, Heidelberg, New York.

Foley, R.J. 1985. Inhaled industrial acetylene. A diabetic ketoacidosis mimic. JAMA 254: 1066-1067.

Frantik, E., M. Hornychova, and M. Horvath. 1994. Relative acute neurotoxicity of solvents: isoeffective air concentrations of 48 compounds evaluated in rats and mice. Environ. Res. 66: 173-185.

Frantik, E., L. Vodickova, M. Hornychova, and M. Nosek. 1996. Pattern of inhalation exposure: blood levels and acute subnarcotic effects of toluene and acetone in rats. Cent. Eur. J. Public Health 4: 226-232. Cited from abstract in MEDLINE (http://gateway.nlm.nih.gov/gw/Cmd).

Freeman, J.J. and E.P. Hayes. 1985. Acetone potentiation of acute acetonitrile toxicity in rats. J. Toxicol Environ. Health 15: 609-621. Cited in ATSDR (1994).

Gamis, A.S. and G.S. Wasserman. 1988. Acute acetone intoxication in a pediatric patient. Pediatr. Emerg. Care 4: 24-26.

Garcia, C.R., I. Geller, and H.L. Kaplan. 1978. Effects of ketones on lever-pressing behavior of rats. Proc. West Pharmacol Soc. 21: 433-438.

Geller, I., E. Gause, H. Kaplan, and R.J. Hartmann. 1979a. Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. Pharmacol Biochem Behav. 11: 401-406.

Geller, I., R.J. Hartmann, S.R. Randle, and E.M. Gause. 1979b. Effects of acetone and toluene vapors on multiple schedule performance of rats. Pharmacol Biochem Behav. 11: 395-399.

Germanova, A.L. 1986. Acetone. In: Izmerov, N. F. (ed.): Scientific Reviews of Soviet Literature on Toxicity and Hazard of Chemicals 97. UNEP (United Nations Environment Programme) - IRPTC (International Register of Potentially Toxic Chemicals); Centre for International Projects, USSR State Committee for Science and Technology; Moscow.

Gitelson, S., A. Werczberger, and J.B. Herman. 1966. Coma and hyperglycemia following drinking of acetone. Diabetes 15: 810-811. Cited in Morgott (1993).

Glowa, J.R. and P.B. Dews. 1987. Behavioral toxicology of volatile organic solvents. IV. Comparisons of the rate-decreasing effects of acetone, ethyl acetate, methyl ethyl ketone, toluene, and carbon disulfide on schedule-controlled behavior of mice. J. Am. Coll. Toxicol. 6: 461-469.

Goldberg, M.E., H.E. Johnson, D.C. Pozzani, and H.F.Jr. Smyth. 1964. Effect of repeated inhalation of vapors of industrial solvents on animal behavior. I. Evaluation of nine solvents vapors on pole-climb performance in rats. Am. Ind. Hyg. Assoc. J. 25: 369-375.

Göschke, H. and T. Lauffenburger. 1975. Aceton in der Atemluft und Keton im Venenblut bei vollständigem Fasten normal- und übergewichtiger Personen [Breath acetone and ketonemia in normal- and overweight subjects during total fasting]. Res. Exp. Med. 165: 233-244.

Haggard, H.W., L.A. Greenberg, and J.M. Turner. 1944. The phsiological principles governing the action of acetone together with the determination of toxicity. J. Ind. Hyg. Toxicol. 26: 133-151.

Hallier, E., J.G. Filser, and H.M. Bolt. 1981. Inhalation pharmacokinetics based on gas uptake studies. II. Pharmacokinetics of acetone in rats. Arch. Toxicol. 47: 293-304.

Hift, W. and P.L. Patel. 1961. Acute acetone poisoning due to a synthetic plaster cast with a discussion of acetone metabolism. South African Medical Journal 35: 246-250.

Holden, H.E., R.E. Stoll, J.W. Spalding, and R.W. Tennant. 1998. Hemizygous Tg.AC transgenic mouse as a potential alternative to the two-year mouse carcinogenicity bioassay: evaluation of husbandry and housing factors. J. Appl. Toxicol 18: 19-24. Cited from abstract in MEDLINE (http://gateway.nlm.nih.gov/gw/Cmd).

IOMC. 2000. SIDS Initial Assessment Profile. Acetone. IOMC (Inter-organization Programme for the Sound Management of Chemicals). Screening Information Data Set (SIDS) for High Production Volume Chemicals. Volume 6, Part 1. United Nations, New York and Geneva. http://irptc.unep.ch/irptc/sids/sidspub.html.

Israeli, R., Y. Zoref, Z. Tessler, and J. Braver. 1977. Reaktionszeit als Mittel zur Aceton-TLV-(MAK)-Wertbestimmung [Reaction time as a means for aceton-TLV-(MAK) value determination]. Zentralbl. Arbeitsmed. Arbeitsschutz. Prophyl. 27: 197-199.

Izmerov, N.F., I.V. Sanotsky, and K.K. Sidorov. 1982. Toxicometric parameters of industrial toxic chemicals under single exposure. UNEP-IRPTC, Centre for International Projects, GKNT, Moscow.

Jakubowski, M. and H. Wieczorek. 1988. The effects of physical effort on pulmonary uptake of selected organic compound vapours. Pol. J. Occup. Med. 1: 62-71.

Kagan, E. 1924. Experimentelle Studien über den Einfluß technisch und hygienisch wichtiger Gase und Dämpfe auf den nOrganismus [Experimental studies on the effects of gases of technical and hygienic relevance on the organism.]. Arch. Hyg. 94: 41-53.

Kalapos, M.P. 1999. Possible physiological roles of acetone metabolism in humans. Med. Hypotheses 53: 236-242.

Kane, L.E., R. Dombroske, and Y. Alarie. 1980. Evaluation of sensory irritation from some common industrial solvents. Am. Ind. Hyg. Assoc. J. 41: 451-455.

Kimura, E.T., D.M. Ebert, and P.W. Dodge. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol Appl. Pharmacol. 19: 699-704.

Koehler, A.E., E. Windsor, and E. Hill. 1941. Acetone and Acetoacetic Acid in Man. J. Biol. Chem. 140: 811-825.

Kosugi, K., V. Chandramouli, K. Kumaran, W.C. Schumann, and B.R. Landau. 1986. Determinants in the pathways followed by the carbons of acetone in their conversion to glucose. J. Biol. Chem. 261: 13179-13181.

Krasavage, W.J., J.L. O´Donoghue, and G.D. DiVincenzo. 1982. Ketones. In: Patty´s Industrial Hygiene and Toxicology. 3rd ed., Vol. II, pp. 4709 - 4800. Clayton, G.E. and F.E. Clayton (ed.). John Wiley & Sons, New York.

Larsen, J.J., M. Lykkegaard, and O. Ladefoged. 1991. Infertility in rats induced by 2,5-hexanedione in combination with acetone. Pharmacol Toxicol 69: 43-46. Cited in WHO (1998).

Lehmann, K.B. and F. Flury. 1938. Toxikologie und Hygiene der technischen Lösungsmittel. Verlag von Julius Springer, Berlin.

Leonardos, G., D. Kendall, and N. Barnard. 1969. Odor threshold determinations of 53 odorant chemicals. J. Air Pollut. Control Assoc. 19: 91-95.

Litovitz, T.L., W. Klein-Schwartz, E.M. Caravati, J. Youniss, B. Crouch, and S. Lee. 1999. 1998 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 17: 435-487.

Litovitz, T.L., W. Klein-Schwartz, K.S. Dyer, M. Shannon, S. Lee, and M. Powers. 1998. 1997 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 16: 443-497.

Litovitz, T.L., W. Klein-Schwartz, G.C. Rodgers, Jr., D.J. Cobaugh, J. Youniss, J.C. Omslaer, M.E. May, A.D. Woolf et al. 2002. 2001 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 20: 391-452.

Litovitz, T.L., W. Klein-Schwartz, S. White, D.J. Cobaugh, J. Youniss, A. Drab, and B.E. Benson. 2000. 1999 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 18: 517-574.

Litovitz, T.L., W. Klein-Schwartz, S. White, D.J. Cobaugh, J. Youniss, J.C. Omslaer, A. Drab, and B.E. Benson. 2001. 2000 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 19: 337-395.

Litovitz, T.L., M. Smilkstein, L. Felberg, W. Klein-Schwartz, R. Berlin, and J.L. Morgan. 1997. 1996 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 15: 447-500.

Mast, T.J., J.J. Evanoff, R.L. Rommerheim, K.H. Stoney, R.J. Weigel, and R.B. Westerberg. 1988. Inhalation Developmental Toxicology Studies: Teratology Study of Acetone in Mice and Rats. NIH-Y01-ES-70153. Pacific Northwest Laboratory. Prepared for the National Institute of Environmental Health Sciences, National Toxicology Program (NTP), Richland, Washington.

Matsushita, T., A. Yoshimune, T. Inoue, S. Yamaka, and H. Suzuki. 1969a. [Experimental studies for determining the MAC value of acetone. I. Biological reactions in the "one-day exposure" to acetone.]. Sangyo Igaku 11: 477-485. (Japanes, English summary).

Matsushita, T., A. Yoshimune, T. Inoue, S. Yamaka, and H. Suzuki. 1969b. [Experimental studies for determining the MAC value of acetone. II. Biological reactions in the "six-day exposure" to acetone.]. Sangyo Igaku 11: 507-511. (Japanes, English summary).

Morgott, D.A. 1993. Acetone. In: Patty´s Industrial Hygiene and Toxicology. 4th ed., Vol. II, Part A, Chapter 5, pp. 149 - 281. Clayton, G.E. and F.E. Clayton (ed.). John Wiley & Sons, New York.

Nakaaki, K. 1974. An experimental study on the effect of exposure to organic solvent vapor in human subjects. J. Sci. Labour 50: 89-96.

Nelson, K.W., J.F. Ege, M. Ross, L.E. Woodman, and L. Silverman. 1943. Sensory response to certan industrial solvent vapors. J. Ind. Hyg. Toxicol. 25: 282-285.

NIOSH. 1996. Acetone. IDLH documentation. U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Divison of Standards Development and Technology Transfer, Technical Information Branch, Cincinnati, OH, http://www.cdc.gov/niosh/idlh/67461.htm.

Nomiyama, K. and H. Nomiyama. 1974a. Respiratory elimination of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. Int. Arch Arbeitsmed. 32: 85-91.

Nomiyama, K. and H. Nomiyama. 1974b. Respiratory retention, uptake and excretion of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. Int. Arch Arbeitsmed. 32: 75-83.

NRC. 1984. Acetone. In: Emergency and continuous exposure limits for selected airborne contaminants. Vol. 1, pp. 5 - 24. National Research Council, C.o.T. (ed.). National Academy of Science, National Academy Press, Washington, D.C.

NRC. 2000. Spacecraft Maximum Allowable Concentrations for Seleted Airborne Chemicals. National Research Council (NRC), Committee on Toxicology. National Academy of Science, National Academy Press, Washington, D.C.

NRC. 2001. Standing Operating Procedure for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. National Research Council (NRC), Committee on Toxicology. National Academy of Science, National Academy Press, Washington, D.C.

NSC. 2003. Acetone chemical backgrounder. NSC (National Safety Council), http://www.nsc.org/library/chemical/Acetone.htm. Printed 14. January 2003.

NTP. 1988. Inhalation Developmental Toxicity Studies: Acetone (CAS No. 67-64-1) in Mice and Rats. National Toxicology Program (NTP), http://ntp-server.niehs.nih.gov/htdocs/TT-studies/TER87036.html (Abstract).

NTP. 1991. Toxicity Studies of Acetone in F344/N Rats and B6C3F1 Mice (Drinking Water Studies) (CAS No. 67-64-1). National Toxicology Program (NTP), http://ntp-server.niehs.nih.gov/htdocs/ST-studies/TOX003.html (Abstract).

Ott, M.G., L.K. Skory, B.B. Holder, J.M. Bronson, and P.R. Williams. 1983a. Health evaluation of employees occupationally exposed to methylene chloride. General study design and environmental considerations. Scand. J. Work Environ. Health 9 Suppl 1: 1-7.

Ott, M.G., L.K. Skory, B.B. Holder, J.M. Bronson, and P.R. Williams. 1983b. Health evaluation of employees occupationally exposed to methylene chloride. Mortality. Scand. J. Work Environ. Health 9 Suppl 1: 8-16.

Pezzagno, G., M. Imbriani, S. Ghittori, E. Capodaglio, and J. Huang. 1986. Urinary elimination of acetone in experimental and occupational exposure. Scand. J. Work Environ Health 12: 603-608.

Pitarque, M., A. Vaglenov, M. Nosko, A. Hirvonen, H. Norppa, A. Creus, and R. Marcos. 1999. Evaluation of DNA damage by the Comet assay in shoe workers exposed to toluene and other organic solvents. Mutat. Res. 441: 115-127. Cited from abstract in MEDLINE (http://gateway.nlm.nih.gov/gw/Cmd).

Pomerantz, R.B. 1950. Acute poisoning from castex. Am. J. Surg. 80: 117-118.

Pozzani, D.C., C.S. Weil, and C.P. Carpenter. 1959. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Am. Ind. Hyg. Assoc. J. 20: 364-369.

Raleigh, R.L. and W.A. McGee. 1972. Effects of short, high-concentration exposures to acetone as determined by observation in the work area. J. Occup. Med. 14: 607-610.

Ramu, A., J. Rosenbaum, and T.F. Blaschke. 1978. Disposition of acetone following acute acetone intoxication. West J. Med. 129: 429-432.

Reichard, G.A., A.C. Haff, C.L. Skutches, P. Paul, C.P. Holroyde, and O.E. Owen. 1979. Plasma acetone metabolism in the fasting human. J. Clin. Invest 63: 619-626.

Renshaw, P.K. and R.M. Mitchell. 1956. Acetone poisoning following the application of a leightweight cast. Brit. Med. J. 1: 615.

Ross, D.S. 1973. Acute acetone intoxication involving eight male workers. Ann. Occup. Hyg. 16: 73-75.

Ruth, J.H. 1986. Odor thresholds and irritation levels of several chemical substances: a review. Am. Ind. Hyg. Assoc. J. 47: A142-A151.

Ryazanow, V.A. 1962. Sensory physiology as basis for air quality standards. Arch Environ Health 5: 86-100.

Sack, G. 1941. Ein Fall von gewerblicher Azetonvergiftung [A case of industrial acetone intoxication]. Arch. Gewerbepathol. Gewerbehyg. 10: 80-86.

Sakami, W. 1950. Formation of formate and labile methylgroups from acetone in the intact rat. J. Biol. Chem. 187: 369-378.

Satoh, T., K. Omae, H. Nakashima, T. Takebayashi, H. Matsumura, T. Kawai, M. Nakaza, and H. Sakurai. 1996. Relationship between acetone exposure concentration and health effects in acetate fiber plant workers. Int. Arch. Occup. Environ. Health 68: 147-153.

Schaller, K.H. and G. Triebig. 1996. Addendum zu Aceton (Propanon). In: Deutsche Forschungsgemeinchaft (DFG) (ed.): Biologische Arbeitsstoff-Toleranzwerte (BAT-Werte) und Expositionsäquivalente für krebserzeugende Arbeitsstoffe (EKA) - Arbeitsmedizinisch-toxikologische Begründungen, 8. Lieferung. Wiley-VCH, Weinheim, Germany.

Schrikker, A.C., W.R. de Vries, A. Zwart, and S.C. Luijendijk. 1985. Uptake of highly soluble gases in the epithelium of the conducting airways. Pflugers Arch 405: 389-394.

Schrikker, A.C., W.R. de Vries, A. Zwart, and S.C. Luijendijk. 1989. The excretion of highly soluble gases by the lung in man. Pflugers Arch 415: 214-219.

Seeber, A., M. Blaszkewicz, E. Kiesswetter, and M. Vangala. 28-2-1993. Untersuchungsbericht zum Einfluss von Aceton auf das Befinden von Schichtmitarbeitern. Institut für Arbeitsphysiologie an der Universität Dortmund.

Seeber, A. and E. Kiesswetter. 1991. Exposure to mixtures of organic solvents: Subjective symptoms as valid effects? In: Proceeding of the 4th International Conference on the Combined Effects of Environmental Factors. pp. 71 - 74. Fletcher, L.D. (ed.).

Seeber, A., E. Kiesswetter, and M. Blaszkewicz. 1992a. Correlations between subjective disturbances due to acute exposure to organic solvents and internal dose. Neurotoxicology 13: 265-269.

Seeber, A., E. Kiesswetter, D. Giller, M. Blaszkewicz, K. Golka, M. Vangala, and H.M. Bolt. 1991. Akute Wirkungen von Aceton und Ethylacetat: Vergleich der Expositionsdauer von 4 gegenüber 8 Stunden [Acute effects of acetone and ethyl acetate: Comparison of 4 and 8 hour exposure.]. In: Arbeitsmedizin für eine gesunde Umwelt [Occupational Health for a healthy environment]. pp. 145 - 148. Fletcher, L.D. (ed.). Gentner Verlag, Stuttgart.

Seeber, A., E. Kiesswetter, M. Vangala, M. Blaszkewicz, and K. Golka. 1992b. Combined exposure to organic solvents: An experimental approach using acetone and ethyl acetate. Appl. Psychol. Int. Rev. 41: 281-292.

Smith, A.R. and M.R. Mayers. 1944. Study of poisoning and fire hazards of butanone and acetone. Ind. Bull. NYS Dept. Labor 23: 174-176. Cited in Morgott (1993).

Smyth, H.F.Jr., C.P. Carpenter, C.S. Weil, D.C. Pozzani, and J.A. Striegel. 1962. Range-Finding Toxicity Data: List VI. Am. Ind. Hyg. Assoc. 23: 95-107.

Specht, H., J.W. Miller, and P.J. Valaer. 1939. Acute response of Guinea pigs to the inhalation of dimethylketone (acetone) vapor in air. Public Health Rep. 54: 944-954.

Stewart, R.D., C.L. Hake, A. Wu, S. Graff, D.G. Graham, H.V. Forster, W.H. Keeler, A.J. Lebrun, P.E. Newton, and R.J. Soto. 1975. Acetone: Development of a Biologic Standard for the Industrial Worker by Breath Analysis. NTIS PB82172917. The Medical College of Wisconsin Department of Environmental Medicine, Milwaukee, Wisconsin.

Strong, G.F. 1944. Acute acetone poisoning. Can. Med. Assoc. J. 51: 359-362.

Suzuki, H. 1973. An experimental study on physiological functions of the autonomic nervous system of man exposed to acetone gas. Jap. J. Ind. Health 15: 147-164.

Ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Haz. Mat. 13: 301-309.

US DoE. 2002. Revision 18 of ERPGs and TEELs for Chemicals of Concern. DoE (U.S.Department of Energy´s Chemical Safety Program). Table 2. U.S. Department of Energy´s Chemical Safety Program, http://tis.eh.doe.gov/web/chem_safety/teel.html and http://www.bnl.gov/scapa/teels.htm.

US EPA. 2001. Toxicological Review of Acetone (CAS No. 67-64-1) (Draft). National Center for Environmental Assessment. U.S. Environmental Protection Agency, Washington, DC. http://www.epa.gov/nceawww1/acetone.htm.

van Doorn, R., M.W. Ruijten, and C.J. van Leeuwen. 2001b. Guidance for the Development of a Level of Odor Annoyance as a Endpoint for AEGL-1 and ERPG-1. Presented at the NAC/AEGL-meeting.

van Doorn, R., M.W. Ruijten, and C.J. van Leeuwen. 2001a. Guidance for the Development of a Level of Odor Annoyance as a Endpoint for AEGL-1 and ERPG-1. Presented at the NAC/AEGL-meeting.

van Doorn, R., M.W. Ruijten, and C.J. van Leeuwen. 2001. Guidance for the Development of a Level of Odor Annoyance as a Endpoint for AEGL-1 and ERPG-1. Presented at the NAC/AEGL-meeting.

Vicas, I.M. and R. Beck. 1993. Fatal inhalational isopropyl alcohol poisoning in a neonate. J. Toxicol. Clin. Toxicol. 31: 473-481.

Vigliani, E.C. and N. Zurlo. 1955. Erfahrungen der Clinica del Lavoro mit einigen maximalen Arbeitsplatzkonzentrationen von Industriegiften. [Experience of the Clinica del Lavoro with some maximal workplace concentrations (MAC) of industrial poisons.]. Arch. Gewerbepathol. Gewerbehyg. 13: 528-534. (In German).

Wang, G., G. Maranelli, L. Perbellini, E. Raineri, and F. Brugnone. 1994. Blood acetone concentration in "normal people" and in exposed workers 16 h after the end of the workshift. Int. Arch Occup. Environ Health 65: 285-289.

Weast, R.C. 1973. Handbook of chemistry and physics. 54th ed. CRC Press, Cleveland, Ohio.

WHO. 1998. Acetone. Environmental Health Criteria (EHC) 207. International Programme on Chemical Safety (IPCS); World Health Organization, Geneva, Switzerland.

Wigaeus, E., S. Holm, and I. Astrand. 1981. Exposure to acetone. Uptake and elimination in man. Scand. J. Work Environ Health 7: 84-94.

Wigaeus, E., A. Lof, and M. Nordqvist. 1982. Distribution and elimination of 2-[14C]-acetone in mice after inhalation exposure. Scand. J. Work Environ Health 8: 121-128.

Wysocki, C.J., P. Dalton, M.J. Brody, and H.J. Lawley. 1997. Acetone odor and irritation thresholds obtained from acetone-exposed factory workers and from control (occupationally unexposed) subjects. Am. Ind. Hyg. Assoc. J. 58: 704-712.

Zarani, F., P. Papazafiri, and A. Kappas. 1999. Induction of micronuclei in human lymphocytes by organic solvents in vitro. J. Environ Pathol. Toxicol Oncol. 18: 21-28. Cited from abstract in MEDLINE (http://gateway.nlm.nih.gov/gw/Cmd).

Zeller, H., Th. Hofmann, K.H. Meineke, and H. Oettel. 1964. Naunyn Schmiedebergs Arch. Pharmacol. 247: 359.

Zettinig, G., N. Watzinger, B. Eber, G. Henning, and W. Klein. 1997. [Survival after poisoning due to intake of ten-times lethal dose of acetone]. Dtsch. Med. Wochenschr. 122: 1489-1492.

APPENDIX A: DERIVATION OF AEGL VALUES

Derivation of AEGL-1

Key study:	Ernstgard et al. 1999; Matsushita et al., 1969a; Nelson et al. 1943; Stewart et al. 1975
Toxicity endpoint:	NOAEL for slight irritation
Scaling:	None
Uncertainty/ modifying factors	None
Calculations	The 200 ppm concentration is used for all exposure durations.
10-minute AEGL-1	200 ppm (475 mg/m³)
30-minute AEGL-1	200 ppm (475 mg/m³)
1-hour AEGL-1	200 ppm (475 mg/m³)
4-hour AEGL-1	200 ppm (475 mg/m³)
8-hour AEGL-1	200 ppm (475 mg/m³)

Derivation of AEGL-2

Key study:	Goldberg et al. 1964; Bruckner and Peterson 1981a
Toxicity endpoint:	NOAEL for ataxia in rats exposed to 6,000 ppm for 4 hours/day
Scaling:	$C^{1.7} \times t = k$ for extrapolation to all points; $k = 6000^{1.7}$ ppm$^{1.7} \times 4$ h $= 1.059 \times 10^7$ ppm$^{1.7}$ h.
Uncertainty/ modifying factors	1 for interspecies variablity 4.2 for intraspecies variability Combined uncertainty factor of 4.2

Calculations

10-minute AEGL-2	$C^{1.7} \times 0.167$ h $= 1.059 \times 10^7$ ppm$^{1.7}$ h C = 38,860 ppm 10-min AEGL-2 = 38,860 ppm/4.2= 9300 ppm (22,000 mg/m³)
30-minute AEGL-2	$C^{1.7} \times 0.5$ h $= 1.059 \times 10^7$ ppm$^{1.7}$ h C = 20,400 ppm 30-min AEGL-2 = 20,400 ppm/4.2= 4900 ppm (11,000 mg/m³)
1-hour AEGL-2	$C^{1.7} \times 1$ h $= 1.059 \times 10^7$ ppm$^{1.7}$ h C = 13,600 ppm 1-hour AEGL-2 = 13,600 ppm/4.2= 3200 ppm (7,700 mg/m³)
4-hour AEGL-2	$C^{1.7} \times 4$ h $= 1.059 \times 10^7$ ppm$^{1.7}$ h C = 6000 ppm 4-hours AEGL-2 = 6000 ppm/4.2= 1400 ppm (3,400 mg/m³)
8-hour AEGL-2	$C^{1.7} \times 8$ h $= 1.059 \times 10^7$ ppm$^{1.7}$ h C = 4000 ppm 8-hours AEGL-2 = 4000 ppm/4.2= 950 ppm (2,300 mg/m³)

Derivation of AEGL-3

Key study:	Bruckner and Peterson 1981a; Smyth et al. 1962
Toxicity endpoint:	No death in rats at exposure to 12,600 ppm for 3 hours
Scaling:	$C^{1.7} \times t = k$ for extrapolation to all points; $k = 12{,}600^{1.7}$ ppm$^{1.7} \times 3$ h $= 2.804 \times 10^7$ ppm$^{1.7}$ h.
Uncertainty/ modifying factors	1 for interspecies variablity 4.2 for intraspecies variability Combined uncertainty factor of 4.2

Calculations

10-minute AEGL-3	$C^{1.7} \times 0.167$ h $= 2.804 \times 10^7$ ppm$^{1.7}$ h C = 69,000 ppm 10-min AEGL-2 = 69,000 ppm/4.2= 16,000 ppm (39,000 mg/m³)
30-minute AEGL-3	$C^{1.7} \times 0.5$ h $= 2.804 \times 10^7$ ppm$^{1.7}$ h C = 36,200 ppm 30-min AEGL-2 = 36,200 ppm/4.2= 8600 ppm (20,000 mg/m³)
1-hour AEGL-3	$C^{1.7} \times 1$ h $= 2.804 \times 10^7$ ppm$^{1.7}$ h C = 24,000 ppm 1-hour AEGL-2 = 24,000 ppm/4.2= 5700 ppm (14,000 mg/m³)
4-hour AEGL-3	$C^{1.7} \times 4$ h $= 2.804 \times 10^7$ ppm$^{1.7}$ h C = 11,000 ppm 4-hours AEGL-2 = 11,000 ppm/4.2= 2500 ppm (6000 mg/m³)
8-hour AEGL-3	$C^{1.7} \times 8$ h $= 2.804 \times 10^7$ ppm$^{1.7}$ h C = 7100 ppm 8-hours AEGL-2 = 7100 ppm/4.2= 1700 ppm (4000 mg/m³)

APPENDIX B:
DERIVATION OF EXPONENTIAL FUNCTION FOR TEMPORAL SCALING

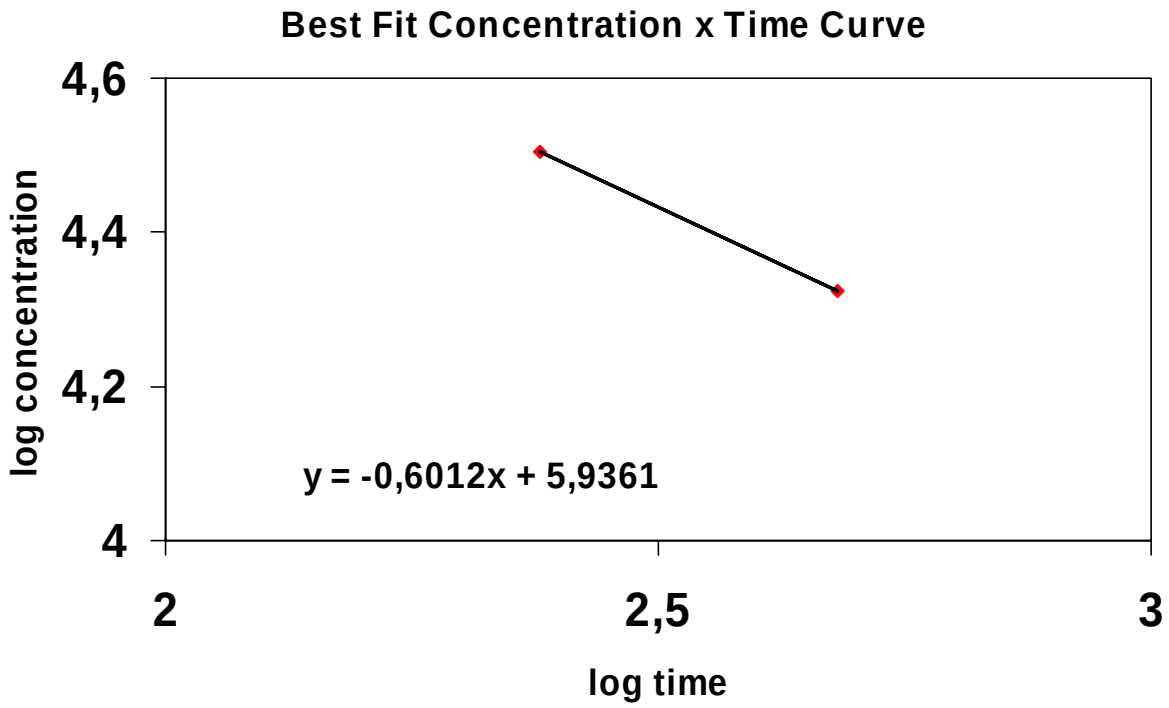
Concentration-Time Mortality Response Relationship for Rats

Data source: Pozzani et al. 1959

Time (min)	Conc. (ppm)	lg Time	lg Conc.
240	31,996	2.3802	4.5051
480	21,092	2.6812	4.3241

n = 1.7

k = 7.477×10^9



APPENDIX C:
DERIVATION OF THE LEVEL OF DISTINCT ODOR AWARENESS

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2001).

Several studies were available in which both the odor detection threshold of acetone and of the reference chemical n-buatnol were determined (see 2.2.2). Among these, the lowest median odor detection threshold for acetone was 41 ppm (mean 247 ppm, geometric mean 50 ppm; 32 "naïve" subjects (Wysocki et al. 1997).

Odor detection threshold for acetone (Wysocki et al. 1997): 41 ppm

Odor detection threshold for n-butanol (Wysocki et al. 1997): 0.16 ppm

Corrected odor detection threshold (OT_{50}) for acetone:

41 ppm * 0.04 ppm : 0.16 ppm = 10.25 ppm

The concentration (C) leading to an odor intensity (I) of distinct odor awareness (I=3) is derived using the Fechner function:

$$I = k_w * \log (C / OT_{50}) + 0.5$$

For the Fechner coefficient, the default of $k_w = 2.33$ will be used due to the lack of chemical-specific data:

$$3 = 2.33 * \log (C / 10.25) + 0.5 \quad \text{and}$$

$$C = 120 \text{ ppm}$$

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life factors, such as sex, age, sleep, smoking, upper airway infections and allergy as well as distraction, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4 / 3 = 1.33

$$LOA = C * 1.33 = 120 \text{ ppm} * 1.33 = 160 \text{ ppm}$$

The LOA for acetone is set to 160 ppm.

APPENDIX D:
DERIVATION SUMMARY FOR ACETONE AEGLS

ACUTE EXPOSURE GUIDELINE LEVELS FOR ACETONE

DERIVATION SUMMARY

AEGL-1 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
200 ppm	**200 ppm**	**200 ppm**	**200 ppm**	**200 ppm**

Key References: Ernstgard, L., E. Gullstrand, G. Johanson, and A. Lof. 1999. Toxicokinetic interactions between orally ingested chlorzoxazone and inhaled acetone or toluene in male volunteers. Toxicol Sci. 48: 189-196.

Matsushita, T., A. Yoshimune, T. Inoue, S. Yamaka, and H. Suzuki. 1969a. [Experimental studies for determining the MAC value of acetone. I. Biological reactions in the "one-day exposure" to acetone.]. Sangyo Igaku 11: 477-485. (Japanes, English summary).

Nelson, K.W., J.F. Ege, M. Ross, L.E. Woodman, and L. Silverman. 1943. Sensory response to certan industrial solvent vapors. J. Ind. Hyg. Toxicol. 25: 282-285.

Stewart, R.D., C.L. Hake, A. Wu, S. Graff, D.G. Graham, H.V. Forster, W.H. Keeler, A.J. Lebrun, P.E. Newton, and R.J. Soto. 1975. Acetone: Development of a Biologic Standard for the Industrial Worker by Breath Analysis. NTIS PB82172917. The Medical College of Wisconsin Department of Environmental Medicine, Milwaukee, Wisconsin.

Test Species/Strain/Number:
10 human subjects (Nelson et al. 1943)
10 human subjects (Ernstgard et al. 1999)
5 or 6 human subjects (Matsushita et al. 1969a)
4 human subjects (Stewart et al. 1975)

Exposure Route/Concentrations/Durations: Inhalation
200, 300, 500 ppm, 3-5 minutes (Nelson et al. 1943)
0, 250 ppm (Ernstgard et al. 1999)
100, 250, 500, 1000 ppm (Matsushita et al. 1969a)
0, 200, 1000, 1250 ppm (Stewart et al. 1975)

Effects: 200 ppm unobjectionable, irritation not more often reported than in controls (Nelson et al. 1943; Stewart et al. 1975); at 250 ppm slight irritation and few complaints about subjective discomfort in one study (Matsushita et al. 1969a) but not in the other (Ernstgard et al. 1999), slight irritation at 300 ppm and subjective irritation in the majority of volunteers exposed at 500 ppm (Nelson et al. 1943).

Endpoint/Concentration/Rationale: NOAEL for slight irritation/subjective discomfort at 200 ppm

Uncertainty Factors/Rationale:
Interspecies: 1, test subjects were humans
Intraspecies: 1, intensity of discomfort is not expected to vary greatly among the general population.

Modifying factor: NA

Animal to Human Dosimetric Adjustment: NA

Time Scaling: Not applied, complaints about discomfort were reported not to increase during several hours of exposure.

Confidence and Support for AEGL values: Values are based on data from several controlled human studies which provide consistent evidence for the relevance of selected endpoint and concentration.

1

AEGL-2 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
9300 ppm	**4900 ppm**	**3200 ppm**	**1400 ppm**	**950 ppm**

Key References: Bruckner, J.V. and R.G. Peterson. 1981a. Evaluation of toluene and acetone inhalant abuse. I. Pharmacology and pharmacodynamics. Toxicol. Appl. Pharmacol. 61: 27-38.

Goldberg, M.E., H.E. Johnson, D.C. Pozzani, and H.F.Jr. Smyth. 1964. Effect of repeated inhalation of vapors of industrial solvents on animal behavior. I. Evaluation of nine solvents vapors on pole-climb performance in rats. Am. Ind. Hyg. Assoc. J. 25: 369-375.

Test Species/Strain/Number: Rats/ Carworth Farms Elias/ Groups of 8-10 females (Goldberg et al. 1964)
Rats/ Sprague-Dawley/ Groups of 5 male (Bruckner and Peterson 1981a)

Exposure Route/Concentrations/Durations:
Inhalation 12600, 19000, 25300 ppm, 3 hours (Bruckner and Peterson 191a)
0, 3000, 6000, 12000, 16000 ppm, 4 hours (Goldberg et al. 1964)

Effects: Reversible ataxia was observed in rats exposed to 12,600 ppm for 3 hours (Bruckner and Peterson 1981a) and to 12,000 ppm for 4 hours (Goldberg et al. 1964). At 12,000 ppm, inhibition of escape reponse in 12 % of the animals also was observed (Goldberg et al. 1964). No inhibition of escape response and no ataxia were observed at 6,000 ppm (Goldberg et al. 1964).

Endpoint/Concentration/Rationale: Exposure to 6,000 ppm for 4 hours was a NOAEL for ataxia.

Uncertainty Factors/Rationale:
Interspecies: 1. An interspecies factor of 3 which is often used in the derivation of volatile solvents like acetone which act as CNS-depressants would have resulted in AEGL-2 of 480 ppm for 4 hours and of 320 ppm for 8 hours that are contradicted by data from numerous controlled human studies in which exposures up to 1000 - 1200 ppm resulted in irritation and slight headaches but no more severe effects. Furthermore, available data for humans show that an exposure to 480 ppm for 4 hours or 320 ppm for 8 hours would lead to acetone concentration in blood below 50 mg/L. Such concentrations are still in the physiological range which can be observed in healthy fasting humans.
Intraspecies: 4.2 This substance specific factor was derived from a study with rats of different ages in which it was observed that the lethal dose of acetone ($LD_{50\ oral}$) was 4.2-fold lower in newborn than in adult rats (Kimura et al. 1971). Additionally, in humans it is consistently observed for volatile anesthetics that newborns are the most sensitive age group (NRC 2001).

Modifying factor: NA

Animal to Human Dosimetric Adjustment: NA

Time Scaling: Extrapolation was made to the relevant AEGL time points using the relationship $C^n \times t = k$ with a value of n = 1.7 which was derived from extrapolation of the LC_{50} in rats for 4- and 8 hours (Pozzani et al. 1959).

Confidence and Support for AEGL values: Extensive data base of controlled human studies addressing irritation, CNS-effects, and toxikokinetics, and animal studies addressing irritation, CNS-effects,toxikokinetics, and developmental toxicity; mostly performed with rats, but also with mice, babons, guinea pigs, cats.

2

1

AEGL-3 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
16,000 ppm	**8600 ppm**	**5700 ppm**	**2500 ppm**	**1700 ppm**

Key References: Bruckner, J.V. and R.G. Peterson. 1981a. Evaluation of toluene and acetone inhalant abuse. I. Pharmacology and pharmacodynamics. Toxicol. Appl. Pharmacol. 61: 27-38.

Smyth, H.F.Jr., C.P. Carpenter, C.S. Weil, D.C. Pozzani, and J.A. Striegel. 1962. Range-Finding Toxicity Data: List VI. Am. Ind. Hyg. Assoc. 23: 95-107.

Test Species/Strain/Number: Rats/ Sprague-Dawley/ Groups of 5 male (Bruckner and Peterson 1981a)
Rats/ Carworth-Wistar/ Groups of 6 females (Smyth et al. 1962)

Exposure Route/Concentrations/Durations:
Inhalation 12600, 19000, 25300, 50600 ppm, 3 hours (Bruckner and Peterson 1981a)
0, 16000, 32000 ppm, 4 hours (Smyth et al. 1962)

Effects: No death following exposure to 12,000 for 3 hours (Bruckner and Peterson 1981a); 1 of 6 rats died following exposure to 16,000 ppm for 4 hours (Smyth et al. 1962)

Endpoint/Concentration/Rationale: no lethality after 3-hour exposure to 12,600 ppm (Bruckner and Peterson 1981a)

Uncertainty Factors/Rationale:
Interspecies: 1, because the same toxic effects (CNS-depression) which are relevant for AEGL-2 are also relevant in case of AEGL-3. Also, an interspecies factor of 3 (together with an intraspecies factor of 4.2) would result in AEGL-3 of 840 ppm for 4 hours and 560 ppm for 8 hours that are contradicted by data from a controlled human study in which no life-threatening effects were observed at exposures up to 2110 ppm for 8 hours and a number of other studies in which no severe effects on the CNS were observed at exposures up to 1000 - 1200 ppm for 6 - 7.5 hours.
Intraspecies: 4.2 This substance specific factor was derived from a study with rats of different ages in which it was observed that the lethal dose of acetone ($LD_{50\ oral}$) was 4.2-fold lower in newborn than in adult rats (Kimura et al. 1971). Additionally, in humans it is consistently observed for volatile anesthetics that newborns are the most sensitive age group (NRC 2001).

Modifying factor: NA

Animal to Human Dosimetric Adjustment: NA

Time Scaling: Extrapolation was made to the relevant AEGL time points using the relationship $C^n \times t = k$ with a value of n = 1.7 which was derived from extrapolation of the LC_{50} in rats for 4- and 8 hours (Pozzani et al. 1959).

Confidence and Support for AEGL values: Values are based on a no-effect level for lethality in rats and are considered conservative.

2