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VINYL CHLORIDE
(CAS Reg. No. 75-01-4)

INTERIM ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)

for NAS/COT-Subcommittee on AEGLs
- December 2006

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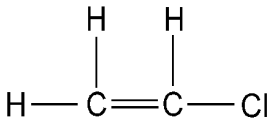

INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

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. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

AEGL-1 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 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 odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

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EXECUTIVE SUMMARY

Vinyl chloride (VC) is a colorless, flammable gas with a slightly sweet odor. It is heavier than air and accumulates at the bottom of rooms, tanks etc. Its worldwide production is approximately 27,000,000 tons. Most is polymerized to PVC. Combustion of VC in air produces carbon dioxide and hydrogen chloride. Odor thresholds of VC were reported in the range of 10 to 25,000 ppm. Validated studies providing a quantitative odor recognition and detection limit are not available. Therefore, a Level of Odor Awareness (LOA) can not be derived.

Vinyl chloride is an anaesthetic compound. After 5 minute exposure to 16,000 ppm VC, volunteers showed dizziness, lightheadedness, nausea, visual and auditory dulling (Lester et al., 1963). Mild headache and some dryness of the eyes and nose were the only complaints of volunteers exposed to 491 ppm VC for several hours (Baretta et al., 1969). No data on developmental or reproductive toxicity of VC in humans after acute exposure are available. Occurrence of chromosomal aberrations in lymphocytes of humans were associated with accidental exposure to VC. After chronic occupational exposure, VC is a known human carcinogen inducing liver angiosarcoma, possibly hepatocellular carcinoma and brain tumors. Evidence for tumors at other locations is contradictory. Two recent epidemiological studies (Mundt et al., 2000; Ward et al., 2001) did not find an increased Standard Mortality Ratio after 5 years of occupational exposure to VC, whereas one other study suggested such an increase after 1 year of exposure (Boffetta et al., 2003).

Acute exposure of experimental animals to VC results in narcotic effects (Mastromatteo et al., 1960), cardiac sensitization (Clark and Tinston, 1973; 1982), and hepatotoxicity (Jaeger et al., 1974). Prodan et al. (1975) reported LC_{50} values for mice, rats, rabbits, and guinea pigs of 117,500 ppm, 150,000 ppm, 240,000 ppm and 240,000 ppm, respectively, after 2 hours. No investigations of reproductive or developmental toxicity after single exposure are available. After repeated exposure developmental toxicity in mice, rats and rabbits (e.g. delayed ossification) was only observed at maternally toxic concentrations. Embryo-fetal development of rats was not affected by 2-week- exposure (6h/d) up to 1,100 ppm (Thornton et al., 2002). Positive results on genotoxicity after in vitro and single and repeated in vivo treatment have been reported for VC. Elevated etheno-adducts were observed after single and short term exposure and associated with mutational events (Swenberg et al., 2000; Barbin, 2000). Higher adduct levels were seen in young animals than in adult animals after identical treatment (Fedtke et al., 1990; Laib et al., 1989; Ciroussel et al.,1990, Morinello et al., 2002). From a study with single exposure of adult rats to 45 ppm for 6 hours, it may be concluded that no increase of relevant etheno-adducts above background occurred (Watson et al., 1991).

Induction of liver tumors has been reported in rats after short term (5 week and 33 days, respectively) exposure (Maltoni et al., 1981; 1984; Froment et al., 1994). Vinyl chloride induces lung tumors in mice after single exposure to high concentrations of VC (Hehir et al., 1981). Short term exposure experiments from Drew et al. (1983), Maltoni et al. (1981) and Froment et al. (1994) indicated increased susceptibility of tumor formation in newborn and young animals.

The AEGL-1 was based on the study of Baretta et al. (1969) with 4-7 volunteers, two individuals experienced mild headache during 3.5 and during 7.5 hours (3.5 hours, 0.5 hours break, 3.5 hours) of exposure to 491 ppm. The time of onset of headaches is not clearly stated and was assumed to be after 3.5 hours. A total uncertainty factor of 3 was used. Since the AEGL-1 is based on human data no interspecies extrapolation was used. The intraspecies uncertainty factor of 3 is used to account for both toxicokinetic

and toxicodynamic differences among individuals. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods, due to the lack of suitable experimental data for deriving the value of n. The extrapolation to 10 minutes from a 3.5 hour exposure is justified because exposure of human at 4,000 ppm for 5 minutes did not result in headache (Lester et al., 1963).

The AEGL-2 was based on prenarcotic effects observed in human volunteers. After 5 minute exposure to 16,000 ppm VC, 5 of 6 persons showed dizziness, lightheadedness, nausea, and visual and auditory dulling. At concentrations of 12,000 ppm one of six persons showed dizziness and "swimming head, reeling". No effects were observed at 4,000 ppm in this study. A single person reported slight effects ("slightly heady") of questionable meaning at 8,000 ppm (this volunteer felt also slightly heady at sham exposure and reported no response at 12,000 ppm) (Lester et al., 1963). 12,000 ppm was regarded as the no effect for impaired ability to escape. A total uncertainty factor of 3 is used to account for toxicodynamic differences among individuals. As the unmetabolized VC is responsible for the effect, no relevant differences in toxicokinetics are assumed. In analogy to other anesthetics the effects are assumed to be solely concentration dependent. Thus, after reaching steady state at about 2 hours of exposure, no increase in effect is expected. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using an n of 2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects in mice and guinea pigs after less than steady state exposure conditions. Time extrapolation was performed from 5 to 10, 30, 60 minutes and 2 hours, where the steady state concentration was calculated.

The AEGL-3 was based on cardiac sensitization and the no effect level for lethality. Short term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 or 71,000 ppm in two independent experiments) (Clark and Tinston, 1973; Clark and Tinston, 1982). Severe cardiac sensitization is a life threatening effect, but at 50,000 ppm no animals died. A total uncertainty factor of 3 is used to account for toxicodynamic differences among individuals. As the challenge with epinephrine and the doses of epinephrine used represent a conservative scenario, no interspecies uncertainty factor was used. As the unmetabolized VC is responsible for the effect, no relevant differences in toxicokinetics are assumed. In analogy to other halocarbons (e.g., Halon 1211, HFC 134a) which lead to cardiac sensitization the effects are assumed to be solely concentration dependent. Thus, after reaching steady state at about 2 hours of exposure, no increase in effect is expected. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using an n of 2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects (muscular incoordination, side position and unconsciousness, effects which occur immediately before lethality) in mice and guinea pigs after less than steady state exposure conditions. Time extrapolation was performed from 5 to 10, 30, 60 minutes and 2 hours, where the steady state concentration was calculated.

The calculated values are listed in the table below.

SUMMARY TABLE OF INTERIM AEGL VALUES FOR VINYL CHLORIDE						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Non-disabling)	450 ppm 1200 mg/m^3	310 ppm 800 mg/m^3	250 ppm 650 mg/m^3	140 ppm 360 mg/m^3	70 ppm 180 mg/m^3	mild headaches in 2/7 humans (Baretta et al.,1969)
AEGL-2# (Disabling)	2800 ppm 7300 mg/m^3	1600 ppm 4100 mg/m^3	1200 ppm 3100 mg/m^3	820 ppm 2100 mg/m^3	820 ppm 2100 mg/m^3	mild dizziness in 1/6 humans (Lester et al.,1963); no effect level for impaired ability to escape
AEGL-3 (Lethal)	12000 ppm* 31000 mg/m^3	6800 ppm* 18000 mg/m^3	4800 ppm* 12000 mg/m^3	3400 ppm 8800 mg/m^3	3400 ppm 8800 mg/m^3	cardiac sensitization (Clark and Tinston, 1982; 1973); no effect level for lethality

***** The explosion limits for VC in air range from 38,000 to 293,000 ppm. The AEGL-3 values at 10 minutes, 30 minutes, and 1 hour exceed 10% of the lower explosion limit (LEL). Therefore, safety considerations against the hazard of explosion must be taken into account.

Derived AEGL-2 values do not protect for potential mutations or malignancies due to short term exposure to VC.

The estimation of cancer risk was based on the study of Maltoni et al. (1981). Newborn rats were exposed from day 1 to 5 weeks of age at 6,000 or 10,000 ppm VC by inhalation (4 hr/day, 5 d/week). Liver angiosarcomas were found in 17 of 42 newborn rats exposed to 6,000 ppm and 15 of 44 newborn rats exposure to 10,000 ppm. No angiosarcomas were found in the dams exposed identically. A 6,000 ppm exposure in rats for 4 h/day, 5 d/week, for 5 weeks was found to be equivalent to a continuous human exposure of 51 ppm using a PBPK model. From this, a 1 in 10,000 risk was calculated to be at 33 μg/m^3 and 24 hour exposure was 34.7 mg/m^3 (13.2 ppm). Further exposure duration calculations were done using the PBPK model for VC and are shown in the following table and Appendix C. It must be emphasized that there are substantial uncertainties in calculating cancer risk from a single exposure.

Estimation of carcinogenic potency (10^{-4} risk) after single exposure				
	30-minute	**1-hour**	**4-hour**	**8-hour**
Maltoni et al., 1981; from 5-weeks-study; Human equivalent dose to 6000 ppm	1200 ppm (3100 mg/m^3)	350 ppm (910 mg/m^3)	81 ppm (210 mg/m^3)	40 ppm (100 mg/m^3)

The values corresponding to 10^{-5} and 10^{-6} risk are in Appendix C. The risk for 10 minutes has not been calculated due to extreme uncertainty.

The occurrence of DNA-adducts and tumorigenicity after single exposure at or below AEGL-concentrations may not be excluded. No increase of relevant etheno-adducts above background is expected at single exposure to 3.4 ppm for 8 hours. This includes extrapolation for sensitive subgroups like newborns by the use of an uncertainty factor of 10 (for details, see calculation D; Appendix C).

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1. INTRODUCTION

Vinyl chloride (VC) is a colorless, flammable gas with a slightly sweet odor. It is heavier than air and accumulates at the bottom of rooms, tanks etc. Its worldwide production is approximately 27,000,000 tons. Most VC is polymerized to PVC, which subsequently is used to produce packaging materials, building materials, electric appliances, medical care equipment, toys, agricultural piping and tubing and automobile parts. Currently the largest single use is in the building sector (WHO, 1999a). About 10,000 tons annually go into the production of 1,1,1-trichloroethane and other chlorinated solvents (Kielhorn et al., 2000).

Most VC is produced either by hydrochlorination of acetylene, mainly in Eastern European countries, or by thermal cracking of 1,2-dichloroethane. It is stored either under pressure at ambient temperature, or refrigerated at atmospheric pressure (WHO, 1999a). Since VC does not polymerize readily it is stored without additives. Combustion of VC in air produces carbon dioxide and hydrogen chloride (WHO, 1999a).

Relevant chemical and physical properties are listed in Table 1.

TABLE 1: CHEMICAL AND PHYSICAL DATA

Parameter	Value	Reference
Molecular formula	C_2H_3Cl	WHO, 1999a
Molecular weight	62.5 g/mol	WHO, 1999a
CAS Registry Number	75-01-4	WHO, 1999a
Physical state	gaseous (at room temperature)	WHO, 1999a
Color	colorless	WHO, 1999a
Synonyms	vinyl chloride monomer, monochlorethene, monochlorethylene, 1-chloroethylene, chlorethylene, chloroethene	WHO, 1999a
Vapor pressure	78 kPa at -20 °C 165 kPa at 0 °C 333 kPa at 20 °C	WHO, 1999a
Density	0.910 g/cm^3 at 20 °C	WHO, 1999a
Melting point	- 153.8 °C	WHO, 1999a
Boiling point	- 13.4 °C	WHO, 1999a
Solubility in water	soluble in almost all organic solvents, slightly soluble in water	WHO, 1999a
Odor	slightly sweet	WHO, 1999a
Explosion limits in air	3.8 - 29.3 vol% in air at 20 °C 4 - 22 vol%	WHO, 1999a
Conversion factors	1 ppm = 2.59 mg/m^3 at 20 °C, 101.3 kPa 1 mg/m^3 =0.386 ppm	WHO, 1999a

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Danziger (1960) describes two deaths due to accidental exposure of workers to VC. No concentration or exposure time is given, but circumstances suggest inhalation of very high concentrations. Autopsy results show cyanosis, congestion of lung and kidneys and failure of blood coagulation (Danziger, 1960). Citing older results from Schaumann et al., 12% VC (120,000 ppm) is given as "dangerous concentrations" (Danziger, 1960; Oster et al., 1947).

At very high concentrations, VC causes asphyxia likely due to narcosis-induced respiratory failure (NLM, 2000).

2.2. Nonlethal Toxicity

Only few data on acute human toxicity of VC after acute exposure are available. Whereas a large experience on the long term effects of VC exposure at the workplace exists. Relevant data are described below.

2.2.1. Neurotoxicity

Vinyl chloride has been considered as a potential anaesthetic. Narcotic limit concentration for man is 7% - 10% (70,000 - 100,000 ppm) (Oster et al., 1947, Danziger, 1960, Lehmann and Flury, 1938). Schauman (1934) reported somewhat higher concentrations to lead to narcosis. Exposure to unknown high concentrations (e.g., during the cleaning of autoclaves) also resulted in narcotic effects (Suciu, 1975).

Acute exposure

Lester et al. (1963) exposed 6 volunteers - 3 men, 3 women - to 0, 0.4, 0.8, 1.2, 1.6 or 2% VC (0, 4,000, 8,000, 12,000, 16,000, or 20,000 ppm, nominal concentration) for 5 minutes using a plastic breathing mask covering the mouth and nose. The total gas flow was 50 liters per minute. The desired concentrations were obtained by metering air and VC (gas chromatography of the liquid phase indicated more than 99% VC) through flow meters and passing the appropriate flows through a 2 l mixing chamber. The concentration was continuously monitored by a thermal conductivity meter (less than 5% deviation from the desired concentration). All volunteers were exposed to every concentration in a randomized fashion, separated by a 6-hour interval. Dizziness (“slightly heady”) was experienced by 1 of 6 volunteers at 8,000 ppm (the same subject reported slight dizziness at sham exposure and reported no response at 12,000 ppm). At 12,000 ppm 4/6 persons reported no response, one subject reported reeling, swimming head and another subject was unsure of some effects. He had a somewhat dizzy feeling in the middle of exposure. At 16,000 ppm 5 of 6 and at 20,000 ppm 6 of 6 persons complained of dizziness, nausea, headache, and dulling of visual and auditory cues. All symptoms disappeared shortly after termination of exposure; headache persisted for 30 minutes in one subject after exposure to 20,000 ppm

Two experimenters were exposed to 25,000 ppm (nominal concentration) for 3 minutes by entering an exposure chamber which resulted in dizziness and slight disorientation as to space and size of surrounding objects and a burning sensation in the feet. They immediately recovered on leaving the

chamber and complained only of a slight headache which persisted for 30 minutes. No further details were presented (Patty et al., 1930).

Baretta et al. (1969) exposed 4 - 6 volunteers to 59, 261, 491 ppm VC (analytical concentrations) for 7.5 h (including a 0.5 h lunch period; corresponding to time weighted average concentrations of 48, 248 or 459 ppm over a period of 7.5 h), seven persons were exposed to 491 ppm for only 3.5 hours. Persons were exposed in an exposure chamber (41 feet by 6 feet wide by 7.5 feet high) with a continuous positive air supply and exhaust system. Air was recirculated with a squirrel cage fan through a series of inlet and outlet ducts spanning the length of the chamber. VC concentration was monitored by an infrared spectrophotometer. The vapors were introduced from a pressurized storage cylinder through 6 feet of 1/8 inch I.D. stainless-steel tubing into a rotometer prior to entering the circulating air duct. A heating tape wrapped around the stainless-steel tubing prevented condensation of the VC. Subjective and neurological responses of the volunteers as well as clinical parameters were measured. The only complaints were those of two subjects who reported mild headache and some dryness of their eyes and nose after exposure to the highest concentration. The time of onset of headaches is not clearly stated. It is assumed that headaches occurred in both experiments, after 3.5 hours and during or after 7.5 hours.

According to a literature review from Schottek (1969), acute human exposure to 1000 ppm for 1 hour leads to fatigue and vision disturbances (Lefaux, 1966). 5000 ppm for 60 minutes should lead to nausea and disorientation (Oettel, 1954), with similar effects after 6000 ppm for 30 minutes (Patty et al., 1930). 6000 to 8000 ppm are said to lead to prenarcotic symptoms (von Oettingen, 1964). Examination of the primary literature sources did not show how those figures were derived. No experimental background or observation data are provided.Thus, the referred results may not be used for risk assessment.

Occupational exposure

Suciu et al. (1975) report acute effects after VC exposure from 1684 workers from two factories. During periods with high air concentrations of VC between the years 1963 and 1964, acute and subacute poisonings occurred: After the first breaths of exposure to “a high concentration of VC” several symptoms (pleasant taste in the mouth, euphoric conditions, slow movements, giddiness, inebriety-like condition) were observed. Continued exposure caused more pronounced symptoms (somnolence, complete narcosis). After repeated exposures to unknown high concentrations, workers complained about headaches, irritability, diminution of memory, insomnia, general asthenia, paresthesia, tingling, and loss of weight. In addition to an “onset of an asthenovegetative syndrome” various other systemic and local effects were observed (e.g., cardiovascular effects, hepatomegaly, digestive responses, respiratory changes). Workplace concentrations in this factory were 2300 mg/m^3 (about 890 ppm) in 1963 and decreased in the following years. This reported VC concentration in air may have been an average exposure (not specified by the authors). However, no information on peak concentrations and duration of episodes with short term high concentrations of VC exposure is provided. Some of the reported activities, such as cleaning autoclaves, are to be associated with very high exposures.

Occurrence of headache in workers chronically exposed to VC has been described by several authors. However, exposure concentration and duration were not specified and always was characterized as “high” (Lilis et al., 1975; Suciu et al., 1975; EPA, 1987).

2.2.2. Odor

Odor thresholds reported vary over a wide range: 10 - 25,000 ppm (26 - 65,000 mg/m^3). Hori et al. (1972) reported an odor threshold of 20 ppm in production workers and 10 ppm in workers from other departments of polyvinyl-chloride (PVC) facilities (number of workers involved not presented). The VC-odor was perceived by 50% of the "non production" workers at 200 ppm and by 50% of the "production" workers at 350ppm. Odor threshold was tested by two methods. PVC was diluted with air at fixed concentrations and was supplied from a glass injector to the subject's nostrils at a rate of 100 milliliters over 5 to 10 seconds. This was repeated at gradually higher concentrations until the subject perceived VC. The second method involved measurement of atmospheric concentrations of VC. Production workers were less sensitive to VC than workers from other departments. When workders from different facilities were compared even greater ranges were observed. However, inter-individual differences and measurement techniques which were not strictly controlled. This odor threshold was reviewed by the AIHA. The value has been rejected based on specified criteria (e.g. no calibration of panel odor sensitivity, not stated whether the given limit was due to recognition or detection, number of trials not stated; AIHA 1997).

Baretta et al. (1969) reported, that none of six subjects perceived odor entering an exposure chamber at 59 ppm, while at 261 ppm all four subjects detected a very slight odor. Five of seven subjects entering the exposure chamber at 491 ppm were able to detect the odor of VC, but after 5 minutes of exposure the odor was no longer perceived (for study details see above).

Two persons who were exposed to 25,000 ppm (nominal concentration) for 3 minutes while entering an experimental exposure chamber reported a "fairly pleasant odor" (Patty et al., 1930).

Amoore and Hautala (1983) reported an odor threshold of 3,000 ppm for VC. This value represents the geometric average of three literature studies (individual studies not mentioned), studies reporting extreme points and duplicate quotations were omitted. It was not stated whether this was the detection or recognition threshold.

2.2.3. Irritation

Acute exposure

Irritating effects of VC are only observed after exposure to very high concentrations: lesions of the eyes (wedge shaped brown discoloration of the bulbar conjunctiva, palpebral slits, conjunctiva and cornea appeared dried out) were observed at autopsy in a worker who died due to inhalation of very high concentrations of VC. The lesions were explained by the local effects of VC. At autopsy intensely hyperemic lungs, with desquamation of the alveolar epithelium were observed (Danziger, 1960).

Chronic exposure

Tribukh et al. (1949) reported mucous irritation of the upper respiratory tract and chronic bronchitis in PVC workers; however, these effects were not mentioned by Lilis et al. (1975) and Marsteller et al. (1975).

Suciu et al. (1975) describe coughing and sneezing after exposure of workers to VC during one shift; no other acute pulmonary effects or irritation are mentioned. These workers had been regularly exposed to VC for an extended time period.

In chronically exposed VC workers, evidence for adverse respiratory disease is conflicting. Lung function (respiratory volume and vital capacity, oxygen and carbon dioxide transfer) deteriorate over time. Emphysema/chronic obstructive pulmonary disease (COPD), respiratory insufficiency, dyspnea, and pulmonary fibrosis have been described (Suciu et al., 1975; Walker et al., 1976; Lloyd et al., 1984). Some of these observations have been attributed to smoking as a possible confounder.

2.2.4. Cardiovascular effects

A slight decrease in blood pressure in VC workers has been attributed to the narcotic effects of VC (Suciu et al., 1975). In older exposure experiments in human volunteers no cardiovascular parameters have been measured (Lester et al., 1963).

Chronic exposure

In VC workers, Raynauds disease has been correlated to extended exposure to high VC concentrations (ATSDR, 1997), with histologic alterations of small vessels (Veltman et al., 1975). Other symptoms observed in VC workers are splenomegaly, hypertension, portal hypertension, generally increased cardiovascular mortality, and vasospastic symptoms (ATSDR 1997; Suciu et al., 1975; Byron et al., 1976). According to Kotseva, elevated occupational exposure to VC increases the incidence of arterial hypertension, but there is no conclusive evidence that it is associated on its own with an increased risk of coronary heart disease (Beck et al., 1973).

2.2.5. Other Endpoints

Hematology and immunology

Blood tests in VC victims indicated failure of blood coagulation (Danziger et al., 1960).

Hepatotoxicity

More or less pronounced hepatitis and enlargement of the liver have been reported in chronic exposed workers (ECB, 2000; Marsteller et al., 1975). Others reported impaired liver function and periportal liver fibrosis in workers from a PVC producing plant (no further details presented; Lange et al., 1974). Liver function disturbances have been reported for workers from PVC factories (Fleig and Thiess, 1978). Focal hepatocellular hyperplasia and focal mixed hyperplasia has been observed in VC-exposed workers; some of the individuals with focal mixed hyperplasia developed liver angiosarcoma (Tamburro et al., 1984). No data on liver effects after acute exposure are available.

TABLE 2: SUMMARY OF ACUTE EFFECTS IN HUMANS AFTER INHALATION OF VINYL CHLORIDE

Concentration (ppm)	Exposure Time	Study type and effects	Reference
very high	not stated	irritation to the eyes	Danziger, 1960
25,000 ppm	3 min	dizziness, disorientation to space and size, burning sensation in feet, persisting headache	Patty et al., 1930
20,000 ppm	5 min	6/6 dizziness, lightheadedness, nausea, visual and auditory dulling, persisting headache in 1/6	Lester et al., 1963
16,000 ppm	5 min	5/6 dizziness, lightheadedness, nausea, visual and auditory dulling; no effects in one volunteer	Lester et al., 1963
12,000 ppm	5 min	1/6 volunteers dizzy, 1/6 "swimming head, reeling", second person was “unsure“ of effects, somewhat dizzy in the middle of exposure	Lester et al., 1963
8,000 ppm	5 min	1/6 volunteers "slightly heady" (this volunteer felt also slightly heady at sham exposure and reported no effects at 12,000 ppm)	Lester et al., 1963
4,000 ppm	5 min	no effects	Lester et al., 1963
3,000 ppm	not stated	odor threshold (geometric averages of three studies, omitting extreme points and duplicate quotations)	Amoore and Hautala, 1983
not specified, high	not stated	prenarcotic and narcotic effects; repeated exposure: headaches, asthenovegetative syndrome, cardiovascular effects , hepatomegaly	Suciu et al., 1975
491 or 459 ppm	3.5 h	2/7 volunteers reported mild headache and dryness of the eyes and nose	Baretta et al., 1969
261 ppm	not stated	detection of the odor by 4/4 subjects	Baretta et al., 1969
20 ppm	not stated	odor threshold in PVC production workers	Hori et al.,1972
10 ppm	not stated	odor threshold in workers from a PVC facility, not working in PVC production	Hori et al., 1972

2.3. Developmental / Reproductive Toxicity

No data on developmental or reproductive toxicity in humans after single exposure to VC were identified.

2.4. Genotoxicity

Huettner and Nikolova (1998) investigated lymphocyte chromosomal aberrations in 29 non-exposed and 29 persons exposed to VC and its combustion byproducts after a train accident in Schoenebeck, Germany. The authors found increased incidences of chromosomal aberrations (gaps, chromatid breaks, acentric chromosomes). Blood samples were drawn 2 - 4 month after the accident.

Sixty per cent of the exposed individuals complaint of health problems ascribed to the pollutants. More than 15 hours after the accident, atmospheric VC concentrations were 1 - 8 ppm (Huettner and Nikolova, 1998). Hahn et al. (1998) reported maximum VC-concentrations of 30 ppm near the center of the accident. Exposure level to VC and/or other combustion products of those persons included into the investigation is highly uncertain. In a follow-up study two years later in the same cohort of accidentally exposed people, Becker et al. (2001) found enhanced chromosome aberrations in peripheral lymphocytes as an indicator of clastogenic activity of VC, while no increased mutagenic activity (mutations in the hypoxanthine-guanine-phosphoribosyl-transferase (HPRT) gene) was observed in exposed persons.

Chronic exposure

Clastogenic DNA damage has been detected by various tests in chronically VC exposed workers. Chromosomal defects (inversions, translocations, rings) and/or micronuclei have been detected at exposure concentrations estimated at 1 ppm (Fucic et al., 1995; short exposure spikes up to 300 ppm VC were reported), and 5 ppm VC (Graj-Vrhovac et al., 1990). Also increased frequencies of sister chromatid exchanges were reported (Fucic et al., 1992; Sinués et al., 1991). Awara et al. (1998) observed an increased incidence of DNA damage (detection by single-cell gel electrophoresis) in workers exposed to VC. The amount of DNA-damage was increasing with exposure time. Average VC concentrations were highest in the production area (about 3 ppm).

Covalent binding to macromolecules due to VC exposure in humans has not been directly assessed. However, gene mutations were found in human tumors associated with exposure to etheno-adduct-forming chemicals such as VC. Specifically, in angiosarcoma of the human liver in 5 of 6 cases G->A transitions of the Ki-*ras* gene and A->T transitions of *p53* were observed in 3 of 6 cases, which may be attributed to the formation of ethenobases in DNA (Barbin, 2000).

2.5. Carcinogenicity

No data about cancer induction in humans after single exposure have been reported. From two large epidemiological studies of occupational exposure of adult workers (Ward et al., 2000; Mundt et al., 1999), there is some evidence that risk for liver cancer or biliary tract cancer was only increased after extended exposure time. However, conflicting results are also published (Weber et al., 1981) demonstrating a steep increase of the Standard Mortality Rate after very limited exposure duration (for details, see Appendix D). There exist no epidemiological studies which include newborn children as specific risk group.

Chronic exposure

There are sufficient epidemiological data demonstrating a statistically significant elevated risk of liver cancer, specifically angiosarcomas (ASL), from chronic exposure to VC (summarized in EPA, 2000a, b; WHO, 1999a; Boffetta et al.,2003). The possible association of brain, soft tissue, and nervous system cancer with VC exposure was also reported. However, the evidence supporting a causal link between brain cancer and VC exposure is limited (EPA, 2000a, b). Some other studies found an association between VC exposure and cancer of the hematopoetic lymphatic systems (Simonato et al., 1991; Greiser et al., 1982). Lung cancer has also been associated with VC exposure, but the increased risk of lung cancer observed in some cohorts may be due to exposure to PVC dust rather than VC monomer (Mastrangelo et al., 2003). In angiosarcoma of the human liver, mutations were observed which may be attributed to the formation of ethenobases in DNA (Barbin, 2000).

Quantitative risk estimates for VC based on epidemiologic studies have been derived by the Netherlands (Anonymous, 1987; unit risk $1 \cdot 10^{-6}$ per $\mu g/m^3$), the WHO (1987; 1999b; unit risk $1 \cdot 10^{-6}$ per $\mu g/m^3$) and Clewell et al. (Clewell et al., 2001; unit risk 0.2 - 1.7 x 10^{-6}).

2.6. Summary

Odor thresholds of VC were reported in the range of 10 to 25,000 ppm (Hori et al., 1972; Baretta et al., 1969; AIHA, 1997; Patty et al., 1930). Amoore and Hautala (1983) reported an odor threshold of 3,000 ppm for VC. This value represents the geometric average of three literature studies, extreme points and duplicate quotations were omitted. Validated studies detecting the recognition and the detection limit are not available from literature. Vinyl chloride is an anaesthetic compound. Effects observed in acutely exposed VC workers and human volunteers indicate a characteristic sequence of events from euphoria and dizziness, followed by drowsiness and loss of consciousness. After five minutes exposure of volunteers, health effects have been described at concentrations ≥8,000 ppm, no effects were observed at 4,000 ppm (Lester et al., 1963). 25,000 ppm VC for 3 minutes caused dizziness, slightly disorientation and a burning sensation in feet in two volunteers (Patty et al., 1930). Mild headache and some dryness of the eyes and nose were the only complaints of volunteers exposed to 491 ppm VC (the onset of headaches is not specified and is assumed to have occurred after 3.5 hours of exposure) (Baretta et al., 1969). Irritation of the eyes was reported in the context of an accidental exposure to lethal VC concentrations (exposure concentration unknown) (Danziger et al., 1960).

No data on developmental or reproductive toxicity of VC in humans after acute exposure are stated in the literature.

Occurrence of chromosomal aberrations in lymphocytes of humans accidentally exposed to VC were reported by Huettner and Nikolova (1998). More than 15 hours after the accident, atmospheric VC concentrations were 1 - 8 ppm. In a two year follow up clastogenic activity was still detectable (Becker et al., 2001).

Vinyl chloride is a known human carcinogen inducing liver angiosarcoma and possibly brain tumors. Evidence for other tumor locations including hepatocellular carcinoma is contradictory (EPA, 2000a, b). In angiosarcoma of the human liver mutations were observed, which may be attributed to the formation of ethenobases in DNA (Barbin, 2000). Unit risk estimates based on epidemiologic studies have been published (Anonymous, 1987; WHO, 1987, 1999b; Clewell et al., 2001).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute inhalation toxicity tests were performed in rats, mice, rabbits, and guinea pigs. However, no LC_{50} study complying with today‘s standards is available. The lethality data are summarized in Table 3.

3.1.1. Rats

Mastromatteo et al. (1960) exposed 5 rats per group to 10, 20, 30 or 40% VC (100,000 to 400,000 ppm) for up to 30 minutes (purity 99.5% maximum). The animals were exposed in an inhalation chamber of 56.6 liters. The VC concentration was adjusted by mixing VC and air in a flow meter outside of the exposure chamber. The stream of air and VC was led to the animal chamber inlet to deliver a continuing stream (flow not given, VC concentrations were not determined in the test chamber). Observations were made continuously and are summarized in Table 3. No animals died after exposure to 100,000 and 200,000 ppm. All animals died after 15 minutes exposure to 300,000 ppm. At 300,000 ppm the lungs of the animals which died revealed congestion with hemorrhagic areas, in addition congestion of the liver and the kidney were observed.

Prodan et al. (1975) exposed rats for 2 hours in exposure chambers of the Pravdin type with 580 liters capacity (total of 70 rats, at least 10 animals per group, strain not given). The animals were exposed, according to Krakov‘s method, to variable concentrations of VC. After the animals were placed in the exposure chamber, the gas was introduced at the beginning at the lower part of the chamber, without any ventilation. The gas was permanently stirred up by an inside pellet and was measured volumetrically with a Zimmermann type spirometer. At VC-concentrations of 15, 16, 17, 20, and 21% (150,000 to 210,000 ppm, nominal concentration) the lethality was 23, 80, 90, 90, and 100%, respectively. The authors calculated a LC_{50} of 15% VC (about 150,000 ppm) and a LC_{100} of 21% (about 210,000 ppm). All LC_{50} and LC_{100} values from these experiments are given by the authors for 2h exposure irrespective of the time of death. Findings shortly before death were general convulsions, respiratory failure, exopthalmia and deflection of the head on the abdomen. Surviving animals rapidly recovered after termination of the exposure. At autopsy, dead animals showed general congestion of the internal organs (lungs, liver, kidney, brain and spleen); some animals (no number given) had pulmonary edema, marmorated liver and kidney swelling.

In the context of a teratology study John et al. (1981) exposed Sprague-Dawley rats intermittently with 500 or 2,500 ppm VC for 7 days. At 2,500 ppm VC 1 of 17 rats died, the exact day of death was not specified by the authors (for study details see 3.3.).

Exposure of 18 Sherman rats (9 male; 9 female) to 100,000 VC for 8 hours resulted in deep anaesthesia, with consciousness regained 5 to 10 minutes after removal to air. After two exposures one female rat died and the remaining showed signs of chronic toxicity (not specified) prompting the authors to lower the VC concentration to 80,000 ppm in order to minimize mortality. Despite this decrease mortality was considerable especially in male rats exposed for longer than 8 days. The animals were exposed in a 1100 liter steel chamber. The concentration was initially raised rapidly to the desired level by admitting VC without admixture with air until the effluent from the (mixing) chamber attained the desired level as noted on the thermal conductivity meter. A fan mixed the VC with the air within the (mixing)

chamber. Thereafter, the effluent from the 2-liter mixing vessel was admitted to the chamber, the throughput was 20 l/min (Lester et al., 1963).

Exposure of 2 Sherman rats in a 10 liter all glass exposure chamber to 150,000 ppm resulted in deep anaesthesia within five minutes, one of two animals died due to respiratory failure after 42 minutes (Lester et al., 1963) (study details see above).

3.1.2. Mice

Five mice were exposed to 10, 20, 30 or 40% VC (100,000 to 400,000 ppm, nominal concentration) for up to 30 minutes (for study details see 3.1.1.) (Mastromatteo et al., 1960). One mouse died after 25 min exposure to 200,000 ppm and all mice died after 10 min exposure to 300,000 ppm. No death occurred at 100,000 ppm. At 300,000 ppm the lungs of the animals which died revealed congestion of the lungs with hemorrhagic areas, in addition congestion of the liver and the kidney were observed.

In ventilated exposure chambers of the Pravdin type, 100,000 ppm VC was not lethal to mice during 2 hours, whereas 150,000 ppm killed 46/61 mice within one hour, and all animals within 2 hours. The authors calculated a LC_{50} of 117,500 ppm and a LC_{100} of 150,000 ppm for mice (for study details and symptoms before death see 3.1.1.), for 2 hours. Under unstirred conditions 42,900 ppm was lethal to 70% (13 of 20) of the animals within less than an hour (Prodan et al., 1975).

Tátrai and Ungváry (1981) exposed CFLP mice to 1,500 ppm VC for 2, 4, 8, 12 or 24 hours (n=20). Animals were observed for 24 hours after exposure. In addition, 40 animals were exposed for 12 h and survivors were investigated two month after the exposure. Animals were exposed in dynamic exposure chambers with vertical air flow. The volume of the exposure chambers was 0.3 m^3; the vertical flow rate of the air was 3 m^3/hour at a temperature of 20 - 23 °C and 50 - 55% relative humidity. After 24 hours exposure time all animals died within 24 h after exposure, 90% of the mice exposed over 12 hours died. No death is reported in animals exposed for shorter periods. Exposure caused hemorrhages and vasodilatation characteristic of shock in the lungs. Additionally, shock-liver developed. The authors do not comment on the concentration difference between their experiments and earlier reports indicating much higher total VC concentrations as lethal; however, in these studies asphyxia is given as the cause of death. This effect is not conformed in other studies.

In a study designed to investigate long term hepatic effects of VC, Lee et al. (1977) exposed CD-1 mice to 1,000 ppm for 6 hr/day. Three out of seventy-two mice died between day 3 and 9; all other mice, as well as replacement mice appeared healthy throughout 12 month VC exposure. Upon autopsy animals had acute toxic hepatitis with diffuse coagulation type necrosis of hepatocytes, as well as tubular necrosis in the renal cortex.

In the context of a teratology study, John et al. (1981) exposed mice to 50 or 500 ppm VC for 7 h/d on day 6 - 15 of gestation. At 500 ppm VC 5 of 29 mice died, the exact day of death was not specified by the authors.

3.1.3. Guinea Pigs

Patty et al. (1930) found 15 - 25% VC (150,000 - 250,000 ppm) to be lethal to guinea pigs within one hour, 40% VC (400,000 ppm) resulted in death of the animals within 10 - 20 min. Gross pathology

examinations of these animals revealed intense congestion and edema of the lungs and a hyperaemia of the kidneys and livers. The lungs were light pink in color, the cut section was uniformly light red, and bled freely. The authors concluded that VC is irritating to the lungs. No eye or nasal irritation was described. However, from the paper it is unclear whether sufficient mixing of the atmosphere had occurred, furthermore, the number of animals per group was not mentioned.

Prodan et al. (1975) reported a LC_{50} of 238,000 ppm and a LC_{100} of 280,000 ppm for guinea pigs exposed in a exposure chamber of the Pravdin type (the gas was permanently stirred up by an inside pellet; study details are described in 3.1.1.) for 2 hours. No animals died within 2 hours at 200,000 ppm.

Yant (cited from Prodan et al., 1975) determined a lethal concentration of 400,000 ppm for 10 min for guinea pigs.

Exposure of guinea pigs to 10, 20, or 30% VC (100,000 - 300,000 ppm) (5 animals per group) did not result in death within 30 min of exposure time, but one animal of the 300,000 ppm group died within 24 h following exposure. Thirty minutes exposure to 40% VC (400,000 ppm) resulted in death of one animal, another animal died within 24 h following exposure whereas the other 3 animals recovered (Mastromatteo et al., 1960; for study details see 3.1.1.). The liver of the animal which died at 300,000 ppm showed severe fatty degeneration, the liver was distended and very friable, the liver effects were less pronounced at 400,000 ppm. There was marked congestion of the lungs with hemorrhages in the dead animals.

3.1.4. Rabbits

Rabbits were exposed for 2 h in exposure chambers of the Pravdin type. 200,000 ppm did not result in death of 4 animals. 50% of the animals (2/4) exposed to 240,000 ppm died within the first hour of exposure and all animals (4/4) exposed to 280,000 ppm (Prodan et al., 1975) (for details see 3.1.1.).

In the context of a teratology study, John et al. (1981) exposed rabbits intermittently to 500 or 2,500 ppm VC for 7 days. At 2,500 ppm VC, 1 of 7 rabbits died, the exact day of death was not specified by the authors.

3.1.5. Other Species

No data on acute lethality in other species are available.

TABLE 3: SUMMARY OF ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS

Species	Concentration (ppm)	Exposure Time	Number of animals	Effect	Reference
mouse	500	several days for 7 h/d	29	LC_{17}	John et al., 1977; 1981
mouse	1000	at least 3 x 6 h	72	LC_{low}	Lee et al., 1977
mouse	1500	8 h	20	LC_{0}	Tátrai and Ungváry, 1981
mouse	1500	12 h	60	LC_{90}	Tátrai und Ungváry, 1981
mouse	1500	24 h	20	LC_{100}	Tátrai und Ungváry, 1981
mouse	100000	2 h	40	LC_{0}	Prodan et al., 1975
mouse	117500	2 h	39	LC_{50}	Prodan et al., 1975
mouse	150000	2 h	61	LC_{100}	Prodan et al., 1975
mouse	300000	10 min	5	LC_{100}	Mastromatteo et al., 1960
rat	100000	8 h	18	LC_{0}	Lester et al., 1963
rat	150000	2 h	10	LC_{50}	Prodan et al., 1975
rat	150000	2 h	2	LC_{50}	Lester et al., 1963
rat	200000	30 min	5	LC_{0}	Mastromatteo et al., 1960
rat	210000	2 h	10	LC_{100}	Prodan et al., 1975
rat	300000	15 min	5	LC_{100}	Mastromatteo et al., 1960
rabbit	200000	2 h	4	LC_{0}	Prodan et al., 1975
rabbit	240000	2 h	4	LC_{50}	Prodan et al., 1975
rabbit	280000	2 h	4	LC_{100}	Prodan et al., 1975
guinea pig	100000	6 h	not stated	LC_{0}	Patty et al., 1930
guinea pig	200000	2 h	4	LC_{0}	Prodan et al., 1975
guinea pig	240000	2 h	12	LC_{50}	Prodan et al., 1975
guinea pig	150,000 to 250,000	18 - 55 min	not stated	LC_{100} [a]	Patty et al., 1930
guinea pig	280000	2 h	4	LC_{100}	Prodan et al., 1975
guinea pig	300000	30 min	5	LC_{20}	Mastromatteo et al., 1960
guinea pig	400000	10 - 20 min	not stated	LC_{100} [a]	Patty et al., 1930
guinea pig	400000	30 min	5	LC_{40}	Mastromatteo et al., 1960

a: number of animals per group and animals that died not stated

3.2. Nonlethal Toxicity

3.2.1. Dogs

Oster et al. (1947) exposed 2 beagle dogs to 50% VC/50% oxygen for induction of anesthesia (no time given) and subsequently with 7% VC (70,000 ppm) in oxygen for narcosis maintenance (no further study details described). Narcosis induction was rapid, all animals showed salivation. Muscle relaxation was incomplete with good relaxation of the abdomen, and rigidity and uncoordinated movements in legs. The recovery period was prompt but accompanied by violent excitation. In four dogs anesthetized with 10% VC (100,000 ppm) mixed with oxygen, no effects on blood pressure were observed, but cardiac irregularities (intermittent tachycardia, extraventricular systoles and vagal beats) were observed. All symptoms disappeared rapidly upon change to ethyl ether, as well as after termination of narcosis.

Cardiac sensitizing potential of VC was tested in beagle dogs. Conscious dogs (4-7 per dose group) were exposed to VC by means of a face mask for 5 minutes. Oxygen was added when high concentrations were used. During the last 10 seconds of the exposure period, a bolus injection of epinephrine (5µg/kg) was given via a cephalic vein and the ECG changes were recorded. A further injection of adrenaline was also given 10 minutes after the end of exposure. Cardiac sensitization was deemed to have occurred when ventricular tachycardia or ventricular fibrillation resulted from the challenge injection of epinephrine. An increased number of ventricular ectopic beats was not regarded as evidence of sensitization since they could often be produced by a challenge injection of epinephrine during control air exposures. The EC_{50} for cardiac sensitization was 50,000 ppm (95 % CI: 37,000 – 68,000 ppm). The post exposure injection of epinephrine did not result in arrhythmias (Clark and Tinston, 1973).

A second study on cardiac sensitization to epinephrine in beagle dogs (6 male or female, not further specified) after 5 minutes exposure to VC was published by Clark and Tinston (1982). Methods were apparently identical to the study published in 1973 (Beck et al., 1973). The EC_{50} for cardiac sensitization was 71,000 ppm (95% CI: 61,000 – 83,000 ppm). These concentrations were below the concentrations which caused effects on the central nervous system in rats (EC_{50}: 38,000 ppm after 10 minutes exposure). The authors did not comment on their earlier findings which indicated a lower EC_{50} for cardiac sensitization. The authors discussed, that cardiac sensitization is unlikely to occur in man in the absence of any effects on the CNS and that dizziness should act as an early warning that a dangerous concentration was reached.

3.2.2. Rats

In rats exposed to 100,000 ppm, increased motor activity occurred after 5 min, pronounced tremor, unsteady gait and muscular incoordination occurred after 15 min, side position occurred at 20 min, and deep narcosis occurred after 30 min. When the VC concentration was increased, deep narcosis occurred at 200,000 ppm after 15 min and at 300,000 ppm after 5 min and muscular incoordination after 2 or 1 min, respectively. At autopsy, lungs of the animals of the 100,000 ppm group showed a very slight hyperemia even 2 weeks after exposure; at 200,000 ppm congestion of the lung in all animal and some fatty infiltration in the liver of one rat were observed. Irritation (not further explained) was described to occur immediately after onset of exposure to 10, 20, or 30% VC (Mastromatteo et al., 1960).

Lester et al. (1963) exposed Sherman rats for up to 2 hours with 50,000 - 150,000 ppm VC. The total gas flow was 50 liters per minute. The desired concentrations were obtained by metering air and VC (gas chromatography of the liquid phase indicated more than 99% VC) through flow meters and passing the appropriate flows through a 2 l mixing chamber. The desired concentration was passed through a 10-liter all-glass exposure chamber containing 2 rats. The concentration was continuously monitored by a thermal conductivity meter (less than 5% deviation from the desired concentration). At 50,000 ppm VC for 2 hours moderate intoxication was observed, but the righting reflex was lost; at 60,000 ppm for 2 hours intoxication was more intense but the righting reflex was still present (lost at 70,000 ppm). The corneal reflex was lost at 100,000 ppm VC. On removal from the chamber the animals returned to the pre-exposure state rapidly. Exposure to 150,000 VC resulted in deep anesthesia within 5 minutes, one of two animals died after 42 minutes by respiratory failure. Autopsy revealed edema and congestion of the lungs. The second rat recovered quickly after removal from the exposure chamber.

Exposure of 18 Sherman rats to 100,000 VC for 8 hours resulted in deep anesthesia, with consciousness regained 5 to 10 minutes after removal to air. After two exposures one female rat died and the remaining showed signs of toxicity (not specified) (Lester et al., 1963; study details presented in 3.1.1.).

Male Holtzman rats were exposed once to 0.5, 5 or 10% VC (5,000, 50,000, or 100,000 ppm) for 6 h in a dynamic inhalation chamber. Animals were killed 24 hours after the exposure (no further details described). Exposure to 0.5% or 5% for a single 6 h period did not cause a substantial rise in serum alanine-α-ketoglutarate transaminase (AKT) or sorbitol dehydrogenase (SDH), two cytoplasmic liver enzymes whose appearance in serum correlates with liver injury. Only after exposure to 10% VC was a slight increase in either parameter of hepatoxic response and centrilobular hepatocellular vacuolization noted. At the lower dose levels livers were histologically normal. During exposure to 10% VC animals appeared to be anesthetized (Jaeger et al., 1974).

Rats exposed to 30,000 ppm VC for 4 hours were slightly soporific (Viola et al., 1970). No other acute toxicity data were reported, animals were exposed for total of 12 month.

Tátrai and Ungváry (1981) exposed CFY rats to 1,500 ppm VC for 24 hours (n=20; study details are presented in 3.1.2.). Livers were investigated by histochemical methods. No morphological changes were observed.

Fischer 344 or Sprague-Dawley rats were treated for 1 h with 50, 500, 5,000 or 50,000 ppm VC (about 90 animals per group). The chambers were Rochester type, stainless steel, 1,000 liter, constructed to provide laminar air flow and ensure uniform exposures to VC to test animals. The concentration of gas in the inhalation chamber was monitored by a gas chromatograph. No remarkable signs of toxicity were observed. Upon removal from the test atmosphere, all animals recovered to normal appearance within 24 hours (Hehir et al., 1981). Viola et al. (1971) also reported that exposure of rats to 50,000 ppm for one hour did not result in toxicity.

Effects after repeated exposure

Pregnant rats exposed to 1,500 ppm for 7 or 9 days (day 1-9 or 8 - 14 of gestation) showed increased absolute and relative maternal liver weight, without light microscopic visible changes (liver weight to body weight ratio (%), exposure day 1-9 of gestation: control: 3.71; exposed: 4.25). This effect was not observed in animals treated from day 14-21 of gestation. Additionally, an increased number of

resorbed fetuses and fetal losses were observed in animals exposed during the first 9 days of pregnancy (Ungváry et al., 1978, for study details see 3.3.).

Intermittent exposure of rats to 500 ppm or 2,500 ppm VC during day 6 - 15 of pregnancy resulted in increased relative and absolute maternal liver weights and an increased number of absorbed fetuses and fetal losses at 2,500 ppm (NOAEL 500 ppm) (absolute liver weight: control: 14.27 g; 2500 ppm: 15.55 g; relative liver weight: control: 34.4 mg/g bw; 2500 ppm: 37.8 mg/g bw). One dam died at 2,500 ppm (John et al., 1977, 1981; for details see 3.3).

After repeated inhalation exposure (4 weeks) of rats to 5,000 ppm VC (7h/day, 5 days/week) vacuolized hepatocytes with swollen mitochondria were found in male and female animals (Feron et al., 1979). After 13 weeks inhalation exposure even at the lowest dose level (10 ppm VC) an increase of the relative liver weight was seen in male rats and centrilobular hypertrophy in females (Thornton et al., 2002).

3.2.3. Mice

Mice exposed to 100,000 ppm VC for 30 min showed increased motor activity after 5 min, twitching of extremities after 10 min and pronounced tremor, unsteady gait and muscular incoordination occurred after 15 min, side position at 20 min, and deep narcosis occurred after 30 min. When the VC concentration was increased deep narcosis occurred at 200,000 ppm after 15 min (side position after 5 min) and at 300,000 ppm after 5 min (lethal after 10 min). Mice of the 100,000 ppm group showed slight hyperemia of the lungs, one of five animals showed degenerative changes in the tubular epithelium of the kidney with hydropic swelling. 200,000 ppm for 30 min resulted in congestion of the lungs persisting for 2 weeks. Irritation (no further details) was described to occur immediately after onset of exposure to 10, 20, or 30% VC (Mastromatteo et al., 1960).

Prodan et al. (1975) exposed white mice (no strain specified) for 2 hours to 90,000 to 200,000 ppm VC with ventilation in a exposure chamber (for study details see 3.1.1.); no shorter exposure time was reported. Salivation and lacrimation appeared shortly after onset of exposure, with narcosis reached within less than one hour in the majority of the animals. Typical narcosis stages of excitement with tonic-clonic convulsions and muscular contractions, tranquility and relaxation were described. Other symptoms were accelerated respiration, proceeding to bradypnea, Cheyne-Stokes type of respiration and respiratory failure. No differentiation of the symptoms according to the single exposure levels were made. Concentrations of 110,000 and higher were lethal. In surviving mice all symptoms were rapidly reversible.

Male mice exposed to 50,000 ppm VC for 1 h exhibited hyperventilation after 45 min, with twitching and ataxia. Female mice became hyperactive after 40 min exposure and respiratory difficulty and ataxia was observed in approximately 25% of the female mice after 55 min. At 5,000 ppm no mice were visibly affected. Study details are presented in 3.2.2 (Hehir et al., 1981).

Tátrai and Ungváry (1981) exposed CFLP-mice to 1,500 ppm VC for 2 to 24 hours. After 2 hours, histology demonstrated circulation stasis in the liver, with concomitant decreases in enzyme activities (succinic dehydrogenase and acid phosphatase), subcellular damage, and centriobular necrosis. After 24 h shock liver developed. Severity of changes increased with exposure time; after 12 hours the lungs showed hemorrhages and vasodilatation as signs of circulatory disturbances. No changes were

observed in brain and kidney. 90% of the animals died after exposure for 12 hours, and 100% after 24 hours.

Kudo et al. (1990) exposed male ICR mice (4 or 5 per group) to 5,000 and 10,000 ppm VC for 4 hours on 5 or 6 successive days, respectively. Basophilic stippled erythrocytes indicating disturbances in erythropoiesis appeared in peripheral blood smears on the second day indicating possible bone marrow damage after a single exposure; no difference between the doses was observed, reticulocyte numbers were also increased, albeit not statistically significant. The authors discuss that the increase was partly due to repeated blood sampling and was not entirely due to VC-exposure. Exposure at lower concentrations, i.e. 30 - 40 ppm induced basophilic stippled erythrocytes after 3 days.

Lee et al. (1977) exposed CD-1 mice with 1,000 ppm for 6 hr/day in the context of a long term hepatotoxicity and carcinogenicity study. Besides 5% short term mortality within the first days due to acute toxic hepatitis no sign of VC toxicity was observed in the other animals.

Aviado and Belej (1974) reported that exposure of mice (male, Swiss strain) to 100,000 ppm VC for 6 minutes did not cause arrhythmia, whereas 200,000 ppm induced a 2nd degree block and ventricular ectopics (animals were anesthetized with sodium pentobarbital). Cardiac sensitization was observed after 6 min exposure to 100,000 ppm VC (animals were anesthetized with sodium pentobarbital). Mice were exposed through a face mask which was in contact with a 6 l flaccid bag. The inhalation gas was balanced with oxygen in order to prevent asphyxia. The number of animals per dose group was not presented. For testing cardiac sensitization the animals received 6 µg/kg adrenaline hydrochloride intravenously.

3.2.4. Guinea Pigs

Guinea pigs exposed to 100,000 ppm VC for 30 min showed increased motor activity after 5 min, unsteady gait and muscular incoordination occurred after 15 min, tremors and twitching of extremities after 20 min, and side position with tremors after 30 min- one unconscious. When the VC concentration was increased deep narcosis occurred at 200,000 ppm and 300,000 ppm after 30 min and at 400,000 ppm after 5 min. Guinea pigs of the 100,000 ppm group showed only slightly hyperemic lungs 2 weeks after exposure. At 200,000 ppm congestion of the lungs was observed. At 300,000 and 400,000 ppm survivors showed marked pulmonary congestion with hemorrhagic areas and edema. In one animal of the 400,000 ppm group the tracheal epithelium was completely absent. In the same animals blood was unable to clot. Irritation (no further details) was described to occur immediately after onset of exposure to 400,000 ppm of VC, but irritation was not described at lower dose levels (Mastromatteo et al., 1960).

Prodan et al. (1975) exposed Guinea pigs (no strain given) to 20 - 28% VC (200,000 - 280,000 ppm) for 2 hours. Symptoms of progressing anesthesia as described for mice were observed in a time depending manner; muscular contractions were more pronounced in guinea pigs than in mice. Lethality increaed with increasing concentration, in surviving animals all symptoms were rapidly reversible. Concentrations of 200,000 ppm were not lethal within 2 h (n=4). Observation of the animals did not exceed 2 h.

Exposure of guinea pigs to 5,000 or 10,000 ppm for up to 8 h did not produce any visible symptoms. 25,000 ppm resulted in apparent unconsciousness and deep narcosis after 90 min and a slow, shallow respiration within 6 to 8 h. No deaths were observed within 8 h lasting exposure. Similar symptoms were observed at 50,000 ppm (unconsciousness within 50 min, slow, shallow respiration within

360 min, no death within 6 h). 100,000 ppm lead to an incomplete narcosis already 2 minutes after onset of exposure, none of the animals died within the 6 h lasting exposure period (Patty et al., 1930).

3.2.5. Rabbits

Prodan et al. (1972) exposed rabbits (no strain given) to 20 - 28% VC (200,000 - 280,000 ppm) for 2 hours. Symptoms of progressing anesthesia as described for mice were observed in a time dependent manner, rabbits showed heavy respiration, salivation and muscular contractions. Lethality increased with increasing VC concentrations, all symptoms were rapidly reversible in survivors. No death was observed within 2 hours (n=4).

Tátrai and Ungváry (1981) exposed 20 New-Zealand-rabbits to 1,500 ppm VC for 24 hours. No acute clinical effects or pathological changes of the liver were noted 24 h after exposure.

3.2.6 Monkeys

In monkeys, only myocardial depression after inhalation of 2.5-10% VC was observed. Rhesus monkeys were anesthetized by i.v. injection of 30 mg/kg sodium pentobarbital. An electrocardiograph was implanted for continuous monitoring. 3 monkeys received 2.5, 5, or 10% of VC. The inhalation period lasted 5 minutes, alternating with room air for 10 minutes. The myocardial force was reduced by 2.3, 9.1 and 28.5% respectively, with a significant effect only at 10% VC. There was no effect on the heart rate in compasison to controls. It is not clearly stated whether an addition challenge with epinephrine was applied or not (Belej et al., 1974).

TABLE 4: SUMMARY OF NON-LETHAL EFFECTS IN LABORATORY ANIMALS

Species	Concentration (ppm)	Exposure Time	Effect	Reference
dog	50000	5 min	EC50 cardiac sensitization towards epinephrine	Clark and Tinston, 1973
dog	71000	5 min	EC50 cardiac sensitization towards epinephrine	Clark and Tinston, 1982
dog	100000	not stated	anesthesia accompanied by cardiac arrhythmia	Oster et al., 1947
mouse	1500	2 h	stasis of blood flow, decreasing enzyme activities in liver, subscellular liver damage, centrilobular necrosis	Tátrai and Ungváry, 1981
mouse	5000	1 h	no clinical signs of toxicity	Hehir et al., 1981
mouse	50000	40 min	twitching, ataxia, hyperventilation, hyperactivity	Hehir et al., 1981
mouse	100000	6 min	no induction of cardiac arrhythmia	Aviado and Belej, 1974
mouse	100000	6 min	cardiac sensitization towards adrenaline	Aviado and Belej, 1974
mouse	100000	15 min	pronounced tremor, unsteady gait and muscular incoordination	Mastromatteo et al., 1960
mouse	100000	30 min	unconsciousness, side position already after 20 min; lung hyperemia persisting for > 2 weeks	Mastromatteo et al., 1960
mouse	100000	2 h	intense salivation and lacrimation immediately after onset of exposure, narcosis within 1 h	Prodan et al., 1975
mouse	200,000	6 min	Induction of cardiac arrhythmia (2^{nd} degree block, ventricular ectopics)	Aviado and Belej, 1974
mouse	200000	30 min	deep narcosis, side position after 5 min, congestion of the lung for > 2 weeks	Mastromatteo et al., 1960
rat	500	10 x 7 h	no effects on liver weight (LOAEL: 2,500 ppm) (exposure: day 6-15 of pregnancy)	John et al., 1977
rat	1500	24 h	no acute toxicity reported	Tátrai and Ungváry, 1981
rat	1500	9 x 24 h	increased relative and absolute liver weight; increased number of absorbed fetuses and fetal losses (exposure: day 1-9 of pregnancy)	Ungváry et al., 1978
rat	30000	4 h	slightly soporific	Viola et al., 1970

TABLE 4: SUMMARY OF NON-LETHAL EFFECTS IN LABORATORY ANIMALS

	Species	Concentration (ppm)	Exposure Time	Effect	Reference
1	rat	50000	1 h	no clinical signs of toxicity	Viola et al., 1971; Hehir et al. 1981
2	rat	50000	2 h	moderate intoxication (not further specified), loss of righting reflex	Lester et al., 1963
3	rat	50000	6 h	no clinical and histological signs of hepatic toxicity	Jaeger et al., 1974
4	rat	60000	2 h	intense intoxication, righting reflex still present	Lester et al., 1963
5	rat	100000	15 min	tremor, ataxia	Mastromatteo et al., 1960
6	rat	100000	30 min	deep narcosis; persisting lung hyperemia for > 2 weeks	Mastromatteo et al., 1960; Jaeger et al., 1974
7	rat	100000	2 h	deep anesthesia, loss of corneal reflex, no visible gross pathology	Lester et al., 1963
8	rat	100000	6 h	anesthesia, liver centrilobular vacuolization, slight increase of AKT and SDH activity in serum	Jaeger et al., 1974
9	rat	100000	8 h	deep anesthesia	Lester et al., 1963
10	rat	200000	2 min	muscular incoordination	Mastromatteo et al., 1060
11	rat	200000	30 min	deep narcosis, fatty liver infiltration, lung congestion for > 2 weeks	Mastromatteo et al., 1960
12	guinea pig	10000	8 h	no visible effects	Patty et al., 1930
13	guinea pig	25000	5 min	ataxia, unsteadiness on feet	Patty et al., 1930
14	guinea pig	25000	90 min	quiet, apparent unconsciousness	Patty et al., 1930
15	guinea pig	25000	6 - 8 h	narcosis, slow and shallow respiration, unsteadiness	Patty et al., 1930
16	guinea pig	100000	15 min	unsteady gait and muscular incoordination	Mastromatteo et al., 1960
17	guinea pig	100000	30 min	unconsciousness, slightly hyperemic lungs persisting for 2 weeks after exposure	Mastromatteo et al., 1960
18	guinea pig	200000	30 min	congestion of the lung even 2 weeks after exposure	Mastromatteo et al., 1960
19	guinea pig	200000	2 h	deep narcosis	Prodan et al., 1975
20	rabbit	200000	2 h	deep narcosis	Prodan et al., 1975

TABLE 4: SUMMARY OF NON-LETHAL EFFECTS IN LABORATORY ANIMALS

Species	Concentration (ppm)	Exposure Time	Effect	Reference
monkey	25,000-100,000	5 min	myocardial depression	Belej et al., 1974

3.3. Developmental/Reproductive Toxicity

No studies concerning the effect of single VC exposure on developmental or reproductive toxicity have been identified. John et al. (1977, 1981) exposed pregnant CF-1-mice to 50 or 500 ppm VC, Sprague-Dawley-rats and New-Zealand-rabbits to 500 or 2,500 ppm VC during organogenesis (7 h/day, days 6 - 15 for mice and rats and days 6 - 18 in rabbits). Exposure of bred animals was conducted in stainless steel chambers of 3.7 m^3 volume under dynamic conditions. The atmosphere of VC was generated by diluting gaseous VC with filtered room air at a rate calculated to give the desired concentration. The actual atmosphere was measured with an infrared spectrophotometer (no further details presented). Animals were sacrificed on day 18 (mice), 21 (rats) or 29 (rabbits) and a variety of parameters determined.

Exposure to 500 ppm VC was maternally toxic to mice (5 of 29 bred females died), weight gain, food consumption, and the absolute liver weight were decreased. Maternal toxicity was not evident in mice exposed to 50 ppm. In mice exposed to 500 ppm VC, the number of live fetuses per litter and fetal weight were decreased, this was probably due to the increased maternal toxicity, and fetal resorption was increased. Moreover, fetal resorption was within the range of historical controls. Fetal crown rump-length was significantly increased in mice exposed to 50 ppm VC, but not in mice of the 500 ppm group. Delayed ossifications in skull and sternum bones and unfused sternebrae were observed at 500 ppm in mice fetus.

Rats exposed to 500 ppm gained less weight than controls, but the body weight was not significantly different from the control. At 2,500 ppm, one maternal death among 17 bred females, decreased food consumption and an increase in absolute and relative liver weight were observed. No significant changes were observed in rat fetuses, except for reduced fetal body weight and increased crown-crump length at 500 ppm (both effects not observed at 2,500 ppm). At 2,500 ppm the incidence of dilated ureter was significantly increased in comparison to the control group and the number of lumbar spurs was increased at 500 ppm but not at 2,500 ppm.

One of seven bred female rabbits died at 2,500 ppm, rabbits exposed to 500 ppm showed a decreased food consumption, but body weight was not significantly affected. The number of live fetuses per litter was slightly decreased as compared to concurrent air controls among litters of rabbits exposed to the lower level of 500 ppm (live fetuses/litter: 8 and 7 at 0 and 500 ppm, respectively), but no effect on litter size resulted from exposure to 2,500 ppm of VC. Ossification of the sternebrae was delayed at 500 ppm, but not at 2,500 ppm.

Most of the observed effects were exaggerated when feeding 15% ethanol in the drinking water indicating an additive fetotoxic effect of ethanol and VC. This difference between species should be correlated to the doses which in rats and rabbits exceed the threshold of metabolic saturation, whereas in mice this threshold likely has not been reached. The authors attribute the observed developmental changes

to maternal toxicity "exposure to VC did not cause significant embryonal or fetal toxicity and was not teratogenic...".

CFY rats were exposed to 1,500 ppm VC for 24 h/d during the first (day 1-9)), second (day 8-14) or third trimester (day 14 to 21) of gestation. The volumes of the inhalation chambers were 0.13 m^3, the vertical flow rate of the air 2 m^3/h at a regulated temperature of 24 - 25 °C and 50 - 55% relative humidity. VC concentration in the inhalation chamber was determined by a gas chromatograph. Section was performed on the 21st day of gestation. Treatment resulted in significantly increased frequency of resorptions in the group exposed during the first trimester (2 fetuses resorbed in the control group vs. 12 fetuses in the exposed group; fetal loss in %: 1.7 in the control group and 5.5 in the exposed group). Two cases of central nervous system malformations were recorded in treated animals (not significant), no increase in other malformations were detected. The absolute and relative maternal liver weight was increased in animals treated in the first and second week of pregnancy without light microscopic visible changes, but not in animals exposed during the third week of pregnancy (Ungváry et al., 1978).

A study investigating embryo-fetal/developmental toxicity and reproduction (2-generation) was conducted by Thornton et al. (2002). In the developmental toxicity study, Sprague-Dawley rats were exposed during day 6-19 of gestation to VC-concentrations of 0, 10, 100 or 1100 ppm for 6 h/day. During exposure animals were housed in stainless steel, wire mesh cages within a 6000 liter stainless steel and glass exposure chamber. Placement of the animals was rotated at each exposure. No feed was provided during exposure, but water was available ad libitum. The temperature was 16-28 degree Celsius; the relative humidity was 29-79 %; the air flow rate was 1200 liters per minute. VC was delivered from a compressed gas cylinder to a Scott Specialty Gases regulator equipped with inlet and outlet back pressure gauges, gas test atmosphere was analyzed hourly with an Ambient Air analyzer equipped with a strip chart recorder. Maternal body weight gains were slightly, but statistically significantly suppressed at all exposure levels during GD 15-20 and 6-20. At 100 ppm the relative kidney weight and at 1100 ppm the relative kidney and liver weights were statistically significantly increased in maternal animals. No further adverse effects were observed in this study.

In the 2 generation study, (Thornton et al., 2002) exposure started 10 weeks pre-mating. Other experimental details are provided above. One male rat in the 10 ppm group and one female rat in the control group died. Mating indices and pregnancy rates for the F0 generation were comparable between control and VC exposed groups. The live birth index was significantly decreased while the number of stillborn pups was significantly increased in the F0 generation group exposed to 1100 ppm (the authors did not regard these effects as exposure related as they were not dose dependent and in the range of the historical controls). In the F0 generation male rats, absolute and relative liver weights were significantly increased in all exposure groups. Absolute epididymis and kidney weights were increased in 100 ppm male rats of the F0. Whereas there were no changes in the liver weight of female F0 rats, there were histological alterations in the liver at all dose groups (hepatocytes were enlarged with increased acidophilic cytoplasm within the centrilobular areas of the liver). Centrilobular hypertrophy was observed in male and female rats exposed to 100 and 1100 ppm and in 2 females of the 10 ppm group.

One male rat in the control group of the F1 died due to unknown reasons. In the F2 litters, there was a statistically significant decrease in the mean number of pups delivered in the 1100 ppm group. The authors regarded this effect not as exposure related as the values were lower than respective F1 control group values, but comparable to the F0 control group values. In the F1 there was a statistically significant increase in the absolute and relative liver weight for male rats exposed to 100 and 1100 ppm (absolute liver weight also increased in female rats, but not statistically significant). Also the absolute and relative spleen weight was increased in male rats of the highest dose group. Male (100 and 1100 ppm) and female

(all dose groups) rats showed centrilobular hypertrophy. Additionally, altered foci (acidophilic, basophilic and clear cell foci) were observed in male and female rats of the F1 of the 1100 ppm group, sometimes even at the 100 ppm group (foci were also observed in 2 male rats of the F0 at 1100 ppm).

3.4. Genotoxicity

The mutagenic properties of VC have been tested in a variety of bacteria with the Ames test. S. typhimurium TA 100 and TA 1535 yield positive results at high concentrations and long exposure times, especially with metabolic activation systems added. In other test systems VC is genotoxic only after metabolic activation, e.g. in forward mutation assays and gene conversion assays in yeast, cell transformation assays, UDS or SCE assays in mammalian cells (summarized in WHO, 1999a). The tests were performed either with 5 - 100% VC in the atmosphere or 0.025 - 50 mM VC in the culture medium.

In vivo assays for genotoxicity were performed with mice, rats, and hamsters. VC has also been tested in Drosophila melanogaster. Increased host-mediated forward mutations were observed after oral VC exposure, whereas dominant lethal assays in mice exposed by inhalation and rats as well as a mouse spot test gave negative results. Micronucleus formation in mice (50,000 ppm, 4 - 6h, 1,000 ppm 2 x 4h), cytogenetic aberrations in rats (1,500 ppm for 1 - 12 weeks) and hamsters (25,000 ppm for 6 - 24 hours) and loss of sex chromosomes in Drosophila melanogaster (50,000 ppm for 48 hours) indicated dose related chromosomal abnormalities. Also, increased DNA damage was demonstrated by alkaline elution assays in mice and SCE formation in hamsters (summarized in WHO, 1999a). Further experiments with known VC metabolites indicate that genotoxic effects are likely mediated by reactive intermediates with chloroethylene oxide being most effective.

DNA adducts of VC metabolites with miscoding properties have been directly detected after incubation of bacterial or phage DNA in vitro or in E. coli cells with DNA adduct indicator systems in vivo with activated VC (summarized in WHO, 1999a). Covalent binding has been frequently observed after single and short term exposure.

Bolt et al. (1980) detected irreversible attachment of radioactivity [1,2-^{14}C] VC to hepatic macromolecules in the rat. After single exposure of adult rats to 250 ppm [^{14}C] VC for 5 hours the total amount metabolized per individual rat was 37 µmol. 23 pmol VC-metabolites/ 100 mg liver wet weight were irreversibly bound to DNA. d-guanosine alkylation products amounted to 0.35 pmol.

Laib et al. (1989) exposed adult Wistar rats to 700 ppm [1,2-^{14}C]VC. The animals received either a single 6-h exposure, or 2 single 6-h exposures separated by a treatment free interval of 15h. The following amounts of [^{14}C]VC-derived radioactivity in liver DNA was observed: after a single exposure of male rats the activity was 3.6±0.2 pmol 7-(2'-oxoethyl)guanine (OEG) /mg DNA, after 2 exposures (female rats): 5.2±0.5 pmol OEG/mg DNA±SD.

Watson et al. (1991) exposed adult male Fisher 344 rats (nose only) for 6 hours to atmospheres containing nominally 1, 10, or 45 ppm [1,2-^{14}C] VC. The alkylation frequencies of OEG in liver DNA were 0.026, 0.28 and 1.28 residues OEG per 10^6 nucleotides respectively. These data indicate a linear relationship between exposure dose and DNA dose in rats. There was no evidence to indicate the formation of the cyclic adducts 1,N^6-ethenoadenine (εA) or 3,N^4-ethenocytosine (εC). The threshold for detection of these adducts were about 1 adduct per 1 x 10^8 nucleotides.

Swenberg et al. (2000) reported dose-dependent data on etheno-adducts using a new combination of immunoaffinity /GC-high resolution MS. Adult F344 rats were exposed to 0, 10, 100, 1100 ppm VC

for 6 hours/day, 5 days/week for 1 or 4 weeks. The mean for N^2,3-ethenoguanine (εG) in a mixed liver cell suspension from unexposed control rats was 90 ± 40 fmol/µmol guanine. Exposure to 10 ppm VC for 1 or 4 weeks resulted in 200 ± 50 and 530 ± 11 fmol/µmol guanine, while exposure to 100 ppm VC caused 680 ± 90 and 2280 ± 180 fmol / µmol guanine at 1 or 4 weeks, respectively. A much lesser effect was evident for the 11-fold greater exposure of 1100 ppm due to saturation of metabolic activation, with 1250 ± 200 and 3750 ± 550 fmol/µmol guanine being present in liver.

In addition to these studies, there exist several investigations on the differences in sensitivity of young (preweanling) vs. adult animals. Laib et al. (1989) tested 11-day-old and adult Wistar rats by exposure to 700 ppm [1,2-^{14}C]VC. Adult rats received either a single 6-h exposure, or 2 single 6-h exposures separated by a treatment free interval of 15h. Pups received 2 single 6h-exposures, according to the same treatment schedule. The following amounts of [^{14}C]VC-derived radioactivity in liver DNA was observed after 2 exposures (female adults, male and female pups): 5.2±0.5 pmol OEG/mg DNA±SD (adults), 25.5±3.0 pmol OEG/mg DNA(pups). After a single exposure of adult male rats the activity (3.6±0.2 pmol OEG/mg DNA) was close to the observation after two exposures.

After a five day exposure of F344 rats to 600 ppm (4h/d) the adduct levels in the liver were 162 ± 36 pmol OEG/ µmol guanine and 1.81 ± 0.25 pmol εG / µmol guanine for the pups and 43 ± 7 pmol OEG/ µmol guanine and 0.47 ± 0.14 pmol εG / µmol guanine for the adult animals (Swenberg et al., 1999).

Ciroussel et al. (1990) compared the levels of 1,N^6-ethenodeoxyadenosine (εdAdo) and 3,N^4-ethenodeoxycytidine (εdCyd) in BD VI rats with pups (7 days old) vs. adults (13-week-old animals). These rats had been exposed to 500 ppm VC for 2 weeks (7h/d, 7d/w). The molar ratios (x 10^{-7}) in the liver were 1.30, 1.31 (two analyses; εdAdo/dAdo) and 4.92, 4.67 (εdCyd/dCyd) for the newborn compared to 0.19 (εdAdo/dAdo) and 0.8 (εdCyd/dCyd) for the adult animals.

Fedtke et al. (1990) measured the εG content in the liver of lactating Sprague-Dawley rats and their 10 days old pups exposed to VC (600ppm, 5 days, 4h/d). εG concentrations found in DNA livers of the dams were 470 ±140 (adults) compared with 1810 ±250 fmol/µmol (pups). The mean background found in the control DNA was 60 ±40 fmol/µmol (background subtracted from εG concentration). Similarly, Morinello et al. (2002) demonstrated higher εG-adduct levels in hepatocytes after exposure of weanling rats to 10 ppm for 1 week (6h/d) compared to adult animals (control adult: 0.55 ±0.14 mol εG / 10^7 mol guanine; pups: 0.16 ±0.01; exposed adult: 1.4 ±0.4; pups: 4.1 ±0.8). Adducts largly persisted after recovery over 5 weeks.

Etheno adducts may be repaired by DNA glycolases, but a) did not fully return to background levels after a exposure free period of 14 days (εG: directly after exposure 1,8 pmol/µmol, after 14 days: 0,47 pmol/µmol; control level: 90 fmol/µmol), b) have a miscoding potential in vitro and in vivo (Swenberg et al., 1999).

Gene mutations were found in animal tumors associated with exposure to etheno-adduct-forming chemicals such as VC. Specifically, in rat hepatocellular carcinoma in 7 of 8 cases A->T mutations of the Ha-*ras* gene have been found and in angiosarcoma of the rat liver in 10 of 25 cases various base pair substitutions as mutations of *p53* were observed, which may be attributed to the formation of ethenobases in DNA (Barbin, 2000).

3.5. Carcinogenicity

Inhalation exposure of rats to VC causes liver tumors, especially angiosarcomas and hepatocellular carcinoma and neoplastic liver nodules. Furthermore, angiosarcomas of other sites are reported. Additionally, tumors at other locations are found, e.g. Zymbal gland, neuroblastoma and nephroblastoma in rats; lung tumors in mice; mammary gland tumors in rats, mice, and hamsters, and skin tumors in rabbits and hamsters (summarized in WHO, 1999a, ATSDR 1997). Similar tumor localizations are observed after oral exposure. There is evidence that liver tumors are induced in female rats at lower doses than in males. There is also evidence, that animals are more susceptible to tumor induction early in life (WHO, 1999a).

Short term exposure experiments from Drew et al. (1983) and Maltoni et al. (1981) indicate increased susceptibility of newborn and young animals. Drew et al. (1983) found increased incidences of tumors in rats, mice and hamsters when exposed for the first 6 month in life, but not at later exposure times, e.g. exposure of rats to 100 ppm VC during month 0-6 or 6-12 resulted in a tumor incidence (hemangiosarcoma of the liver) of 5.3% or 3.8%, respectively, but no tumors occurred when rats were exposed during month 12 - 18 or 18 to 24.

Maltoni et al. (1981, 1984) exposed newborn rats postnatally from day 1 to 5 weeks of age to 6,000 ppm or 10,000 ppm VC by inhalation (4 h/d; 5 d/w). At 6,000 ppm the number of exposed animals were 42 (18 male; 24 female); at 10,000 ppm the respective number was 44 (24 male; 20 female). The number of respective breeders were 6 for each exposure concentration. No direct control group was used; however, in parallel experiments breeders and newborn animals without exposure were included (see Experiment BT 4001, 4006). The newborn animals were simultaneously exposed to milk from exposed dams (D. Soffritti, Laboratory of Prof. Maltoni, personal communication, August, 2003). The authors found liver angiosarcomas in newborn SD rats in 17/42 and 15/44 animals respectively, exposed to 6,000 ppm or 10,000 ppm, but none in their mothers which were treated identically. No angiosarcoma were found in a control group of 304 rats (parallel experiment). Additionally, hepatoma incidence was increased in newborn rats (20/42 and 20/42, respectively), but no hepatoma were observed in their mothers. Only 1 hepatoma were found in a control group of 304 rats (parallel experiment). Results were provided after 124 weeks of observation. The internal concentration of VC may have been influenced by oral uptake from milk from exposed dams. However, due to the very high inhalation exposure and due to saturation of metabolism, the oral uptake by contaminated milk may have contributed only a limited amount to the overall organ concentration of VC metabolites.

Froment et al. (1994) exposed 4 female Sprague-Dawley rats together with their pups (22 males and 22 females) for 8h/d, 6d/w to 500 ppm VC from day 3 through 28 postpartum. At day 28 postpartum, the young animals were weaned, and the males and females were separated and exposed for further 2 weeks (total exposure: 33 days). The surviving animals were all sacrificed at 19 month of age. In the 44 VC-exposed rats 66 hepatic lesions were identified including nodular hyperplasia, endothel cell hyperplasia, peliosis, adenomas, benign cholangiomas, angiosarcoma of the liver (ASL) and hepatocellular carcinoma (HCC). Liver tumors included 8 HCC, 15 ASL and 2 benign cholangioma. No further details were provided. It is assumed that oral exposure via mothers´milk and inhalation exposure occurred simultaneously.

Maltoni et al., (1981, 1984) also exposed rats 30 breeders/ exposure group to 6,000 and 10,000 ppm for 1 week (4h/d; 12^{th} until 18^{th} day of pregnancy). 32 (13 males; 19 females) and 51 (22 males; 29 females) offsprings were investigated after exposure to the lower or the higher concentration, respectively. Angiosarcoma of the liver and hepatoma were not increased in the transplacentally exposed offsprings.

However, Zymbal gland carcinoma and nephroblastoma were found elevated after transplacental exposure. Differences between pre- and postnatal exposure and carcinogenic outcome may possibly be explained by hepatic CYP2E1 activity, which is expressed to a lower extent prenatally than postnatally, both in rats (Carpenter et al., 1997) and in humans (Cresteil, 1998).

Hehir et al. (1981) found increased lung tumor incidences in ICR mice exposed once for 1 h to VC (age of the animals not stated). Animals were exposed in an inhalation chamber to single one-hour doses of VC ranging from 50 to 50,000 ppm (Rochester type inhalation chambers, 1,000 liter with laminar air flow) and were then observed for the remainder of their lives. Tumor response was dose related: Adenoma of the lung increased from 12/120 to 14/139, 18/139, 24/143, 45/137 respectively for exposure to 0, 50, 500, 5000, 50000 ppm. For carcinoma of the lung, there was only a slight occurrence of 0/120, 0/139, 1/143, 3/137 (data from both sexes, combined). A slight increase in hepatic cell carcinoma occurred in male mice, but without dose response (2/50; 2/64; 9/67; 6/68; 4/63). No increase in tumor incidence was observed in liver and lung of rats treated in an identical fashion. Additional studies in A/J mice which were exposed to 500 ppm VC for 1 h/d over 10 days or 50 ppm VC for 1 h/d over 100 days revealed that for short term exposure the concentration may be the most critical factor. In both experiments primarily pulmonary adenomas were observed. However, the incidence in the induction of adenomas and progression to carcinoma are considered only marginal and not statistically significant in mice exposed to 50 ppm for 100 times (44.1% exposed; 34.5% control) whereas a significant increase of pulmonary adenomas was observed in animals exposed to 500 ppm for 10 days (about 74% exposed; 34.4% control).

Suzuki (1983) also reported that short term exposure (6 h/d; 5 d/w; 4 weeks) of young CD1 mice (5 - 6 weeks old at first exposure) to VC resulted in tumor formation. At sacrifice 12 weeks after exposure pulmonary tumors were observed in the two highest dose groups (300 and 600 ppm). Forty or 41 weeks after exposure pulmonary tumors were observed in all animals exposed (1 ppm to 600 ppm) but not in control mice. In addition, subcutaneous and hepatic hemangiosarcoma were found. The angiosarcoma of the liver occurred in one animal exposed to 600 ppm for 4 weeks as observed at necroscopy 56 weeks after exposure (Suzuki, 1981).

After a single 12 hour exposure to 1,500 ppm of mice a hepatocellular adenoma developed. The respective concentration was lethal to most of the animals (Tátrai and Ungváry, 1981). However, the observed effects (asphyxiation) were not seen in other studies with similar concentrations.

In addition to angiosarcoma of the liver several studies with limited exposure duration to VC confirm the occurrence of hepatocellular carcinomas and/or other preneoplastic parenchymal changes in adult animals (Feron et al., 1979; Thornton et al., 2002). However, these changes were seen to a much lesser extent than angiosarcoma in the adult animals or hepatocellular changes in young animals (see below).

In accordance with these investigations in newborn rats, Laib et al. (1985a,b) reported that hepatocellular ATPase-deficient foci (pre-malignant stages) were observed in rats which were exposed to VC. The exposure regimen was a) Wistar -rats for 10 weeks starting on day 1 after birth (10 to 2,000 ppm; 5 d/w; 8 h/d) (Laib et al., 1985a), b) Wistar and Sprague-Dawley rats to 2.5 to 80 ppm VC for 3 weeks (8h/d) starting on day 3 of life (Laib et al., 1985a), c) Wistar rats exposed to 2,000 ppm VC for 5,11,17,47 or 83 days (8h/d; 7d/w) with different ages (after birth or from an age of 7 or 21 onwards) at the start of exposure (Laib et al.,1985b). Exposure to 2,000 ppm did not result in ATPase deficient foci in very young (exposure period: day 1 to 5) or in adult animals (exposure period: from day 90 to 160). However, relevant foci areas were demonstrated for short periods during animal growth, eg., exposure for 11 days

(exposure period: from day 1 to 11)or for 21 days (from day 7-28). The foci persisted until evaluation at the age of 4 month (Laib et al., 1985b). After exposure over 10 weeks, induction of ATPase deficient foci was dose dependent (nearly linear) for concentrations between 10 ppm and 500 ppm and it was shown for both strains of rat, Wistar and Sprague-Dawley. This finding is in accordance with the findings that VC-metabolism follows first order kinetics until saturation occurs at high exposure concentrations (Laib et al., 1985a).

Quantitative risk assessments based on animal experiments have been published by several authors and are summarized in Table 5.

TABLE 5: QUANTITATIVE ASSESSMENT OF CARCINOGENIC POTENCY OF VC BASED ON ANIMAL EXPERIMENTS

Author	**Unit Risk (per µg/m³)**
Chen und Blancato, 1989	6.5×10^{-7} - 1.4×10^{-6}
EPA, 2000 a, b	8.8×10^{-6}
Clewell et al., 1995	6×10^{-7} - 2×10^{-6}
Clewell et al., 2001	1.1×10^{-6}
Reitz et al., 1996	5.7×10^{-7}

These risk estimates are based on the experimental data in adult animals exposed for lifetime published by Maltoni et al. (1981; 1984). There are only slight differences in the human cancer risk estimated by Clewell and Reitz who both used pharmacokinetic (PBPK)-models for the transfer of the animal data on the human situations. These data are in good agreement with the unit risk estimates derived from epidemiologic data, confirming the order of magnitude. However, these risk estimates were only validated with data from adult animals and epidemiologic data from the workplace. A higher sensitivity of children was not incorporated into quantification (see data from Drew et al., 1983; Maltoni et al., 1981).

Chen and Blancato (1989) use a modified multistage model for risk estimation on base of liver tumors, considering pharmacokinetic models. Additionally, increased sensitivity in early life stages has been considered. They evaluated female and male animals separately, expressed by the range of tumor incidences.

The most recently published risk estimate by EPA (2000a, b) is based on the animal experiments published by Maltoni et al. (1981, 1984). Differences in the metabolism between animals and humans have been taken into consideration by use of a pharmacokinetic model. The increased sensitivity of children was taken into consideration. Additionally, tumors in sites other than the liver were considered. Unit risk estimates based on epidemiologic studies were regarded as uncertain due to the shortcomings of the epidemiologic studies. Besides the unit risk estimate for full lifetime exposure (birth through death) of 8.8×10^{-6} per µg/m³, EPA provided an estimate of risk for early life exposure of 4.4×10^{-6} per µg/m³ and an estimate of risk for adult only exposure of 4.4×10^{-6} per µg/m³. This unit risk for adults is based on the PBPK-modeling from Clewell et al. (2001), with only slight modifications in some parameters.

3.6. Summary

Acute exposure of experimental animals towards VC results in narcotic effects, cardiac sensitization, and hepatotoxicity. Narcotic effects are characterized by a typical sequence of events from euphoria and dizziness, followed by drowsiness and loss of consciousness. Finally, animals die due to respiratory failure. Prodan et al. (1975) reported LC_{50} values for mice, rats, rabbits, and guinea pigs of 117,500 ppm, 150,000 ppm, 240,000 ppm and 240,000 ppm, respectively, for 2 hours. Dead animals showed congestion of the internal organs (especially lung, liver and kidney), lung edema and hemorrhagia (Prodan et al., 1975; Mastromatteo et al., 1960). No lethality was seen in mice after exposure to 100,000 ppm for 2 hours (Prodan et al., 1975). However, Tátrai and Ungváry (1981) reported that exposure of mice to 1,500 ppm for 24 h resulted in death of all animals, reduction of exposure time to 12 h resulted in death of 90% of the animals. These results are not in accordance with other lethality data.

Short term exposure (up to 30 minutes) of experimental animals to VC-concentrations of 100,000 to 300,000 ppm resulted mainly in ataxia, motor activity, side position and unconsciousness, slow and shallow respiration, the typical reactions observed before the onset of narcosis (Mastromatteo et al., 1960). Narcosis was observed in rats and mice after 30 min exposure to 200,000 ppm VC (Mastromatteo et al., 1960). Short term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 or 71,000 ppm in two independent experiments) (Clark and Tinston, 1973; 1982). These effects were also seen in mice at higher concentrations (Aviado and Belej, 1974). In monkeys, only myocardial depression after inhalation of 2.5-10% VC was observed. It is not clearly stated whether an addition challenge with epinephrine was applied or not (Belej et al., 1974). Single inhalation exposure of rats for 6 hours to 100,000 ppm VC resulted in histopathological changes of the liver (vacuolization), but was not observed in lower concentrations (50,000 ppm) (Jaeger et al., 1974). However, in mice Tátrai and Ungváry (1981) reported that stasis of the liver developed 2 and 4 h after the beginning of inhalation. The authors observed decreasing enzyme activities in liver and subcellular liver damage at exposure concentrations of 1,500 ppm VC for 2 h; after 24 h shock liver developed. Repeated exposure of rats to 1,500 ppm VC for up to 9 days during pregnancy caused increased relative and absolute liver weights without light microscopic visible changes (Ungváry et al., 1978). In another developmental study increased absolute and relative liver weights have been observed in rats exposed intermittently to 2,500 ppm from day 6 - 15 of pregnancy, the NOAEL was 500 ppm (John et al., 1977; 1981). In rats exposed to 5,000 ppm for 7 hours/day and 5 days/week after 4 weeks vacuolized liver cells were observed (Feron et al., 1979).

No investigations of reproductive or developmental toxicity after single exposure are published. John et al. (1977, 1981) investigated developmental effects after repeated exposure in mice, rats and rabbits. Developmental toxicity (e.g. delayed ossification) was only observed at maternal toxic concentrations. Ungváry et al. (1978) reported that in maternal rats which were exposed to 1,500 ppm VC for 24 h/d during the first (day 1-9) or second (day 8-14) trimester of gestation maternal liver toxicity occurred. Frequency of resorptions was significantly increased in the group exposed during the first trimester. A recently published developmental toxicity study in rats (exposure on day 6-19 of gestation towards 10, 100 or 1100 ppm VC, 6 h/d) indicated that up to 1100 ppm embryo-fetal development was not affected by VC exposure. The only toxic effects observed were an increased relative organ to body weight ratio for the kidney and liver at 1100 ppm and for the kidney at 100 ppm in dams (Thornton et al., 2002). In a 2-generation study in rats no adverse effects on embryo-fetal development or reproductive capability were observed over 2 generations in concentrations up to 1100 ppm (F_0: exposure: 10 weeks premating, 3-weeks mating, gestation, lactation; F_1: identical exposure pattern; F_2: until postnatal day 21). The primary target organ of VC, the liver, was affected as evidenced by an increase in liver weight and/or histopathologically identified cellular alterations, such as centrilobular hypertrophy and induction of

altered hepatocellular foci at 100 and 1,000 ppm, with increased incidence in the F_1 generation (Thornton et al., 2002).

Positive results on genotoxicity after in vitro and single and repeated in vivo treatment (e.g. induction of micronuclei, 4 - 6 h, 50,000 ppm; chromosomal aberrations, 6 - 24 h, 25,000 ppm) have been reported for VC (WHO, 1999a). Elevated DNA-adducts were seen after single 5 hour exposure of adult rats to 250 ppm (Bolt ,1976). Watson et al. (1991) exposed adult male Fisher 344 rats for 6 hours to atmospheres containing 1, 10, 45 ppm VC. The alkylation frequencies of 7-(2'-oxoethyl)guanine (OEG) in liver DNA were 0.026, 0.28 and 1.28 residues OEG per 10^6 nucleotides respectively. With these air concentrations, there was no evidence to indicate the formation of the cyclic adducts $1,N^6$-ethenoadenine (εA) or $3,N^4$-ethenocytosine (εC). The threshold for detection of these adducts were about 1 adduct per 1 x 10^8 nucleotides. Adult rats repeatedly (5 days) exposed to 10 ppm VC for 6 hours/day showed slightly elevated etheno-adducts for N^2,3-ethenoguanine (εG) compared to control (200 ± 50 vs. 90 ± 40 fmol/ µmol guanine) (Swenberg et al., 2000). Higher adduct levels were seen in young animals than in adult animals after identical treatment (Fedtke et al., 1990; Laib et al., 1989; Ciroussel et al. (1990). OEG are not likely to cause mutations, however, the cyclic adducts εA, εC, εG have miscoding potential; respective mutations (e.g., G->A transitions, A->T transitions) were observed in VC-induced tumors (Barbin, 2000). Despite relevant repair, no full reduction to background was observed for these adducts two weeks after a 5 day exposure (4 hours/day) to 600 ppm (Swenberg et al., 2000).

Induction of liver tumors has been reported in rats after subacute (5 week and 33 days, respectively) exposure (Maltoni et al., 1981; 1984; Froment et al. , 1994). The liver is the primary localization of tumors after chronic exposure (for review see EPA, 2000a, b).Vinyl chloride induces lung tumors in mice after single one hour exposure to 5,000 ppm or 50,000 ppm (Hehir et al., 1981). After a single 12 hour exposure to 1,500 ppm of mice a hepatocellular adenoma developed. The respective concentration was lethal to most of the animals (Tátrai and Ungváry, 1981). Suzuki (1983) reported that short term exposure (6 h/d; 5 d/w; 4 weeks) of young CD1-mice (5 - 6 weeks old at first exposure) to VC resulted in lung tumor formation. Additionally, subcutaneous and hepatic hemangiosarcoma were found in this study. Short term exposure experiments from Drew et al. (1983), Maltoni et al. (1981) and Froment et al. (1994) also indicated increased susceptibility of newborn and young animals towards tumor formation. Hepatoma (Maltoni et al., 1981) or hepatocellular carcinoma (Froment et al.,1994) developed to a greater extent in young than in adult animals. Laib et al. reported that hepatocellular ATPase-deficient foci (pre-malignant stages) were observed in rats which were exposed to VC. Relevant foci areas were demonstrated after short periods of exposure during animal growth, eg., exposure to 2,000 ppm for 11 days (exposure period: from day 1 to 11) or for 21 days (from day 7-28). The foci persisted until histological examination at the age of 4 month (Laib et al., 1985b).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Krajewski et al. (1980) estimated the retention of VC after inhalation through a gasmask in 5 male human volunteers by measuring the difference between inhaled and exhaled concentrations. Exposure to concentrations between 3 and 24 ppm VC for 6 hours revealed an average retention of 42%, independent from VC concentration. Thirty minutes after the beginning initially higher retention values (maximum 46% on average) dropped down and stayed on a relative constant level. Interindividual retention rates varied from 20.2% to 79% at 12 ppm. Immediately after cessation of inhalation the VC concentration in the expired air dropped rapidly. After 30 minutes less than 5% of the initial chamber concentration could be measured. Buchter et al. (1978) determined a retention rate of 26 - 28% at 2.5 ppm VC in two individuals 3 - 5 min after the start of inhalation. Given the variability of VC retention found by Krajewski these values may be attributed to interindividual differences. WHO (1999a) reports an average of 30 - 40% absorption after inhalation, without citing the relevant studies.

An absorption of inspired VC of about 40% was calculated for rats (calculation based on the decline of ^{14}C-VC in a closed system) (Bolt et al., 1976). In Rhesus monkeys VC is also efficiently absorbed after inhalation as can be deduced from data on the metabolic elimination (no further quantification) (Buchter et al., 1980).

Whole body (excluding the head) exposure of rhesus monkeys to radioactive VC indicated that only very little VC was absorbed through the skin (about 0.031% and 0.023% at 800 and 7,000 ppm, respectively after 2 - 2.5 h) (ATSDR, 1997). No further data on dermal absorption are available.

The percentage of the dose remaining in the carcass after oral application after 72 h was 10, 11, and 2% for the 0.05, 1 and 100 mg/kg doses. The data suggest that almost complete elimination of VC occurred (Watanabe et al., 1976b). Seventy two hours after exposure to 10 and 1,000 ppm radioactive VC 14 and 15%, respectively, of the recovered ^{14}C-activity remained in the carcass of rats, VC per se was not found in tissues. Radioactivity was detected in the liver, skin, plasma, muscle, lung fat and kidney, representing non volatile metabolites of VC (Watanabe et al., 1976a) or incorporation into C_1-pool (Laib et al., 1989).

Data on serum concentrations of VC are scarce. Ungváry et al. (1978) exposed pregnant rats to 2,000 - 12,000 ppm VC; they determined blood concentrations ranging from 19 µg/ml at 2,000 ppm to 48.4 µg/ml at 12,000 ppm VC indicating no direct proportionality between air VC concentration and blood concentration. Feron et al. (1975) reported a peak blood concentration of 1.9 µg/ml 10 min after gavage of 300 mg/kg VC; this value is much smaller than expected compared to blood concentrations after inhalation which might be due to the effective presystemic hepatic clearance of VC after oral uptake.

Similar to other inhalation anaesthetics, maximal blood concentration of VC after inhalation exposure depends on the partial pressure of VC in the air. Blood respectively brain concentration, which directly correlates with the depth of narcosis (see below) and - presumably - with cardiac sensitization level, can be controlled by changing the concentration of VC in the air, i.e. by changing the partial pressure of VC in the air. If equilibrium is reached between the partial pressure of VC in the air and in the blood (steady state), no further increase of VC concentration in the blood is possible, even if the exposure time is prolonged (Forth et al., 1987). The time necessary to set up steady state mainly depends on the blood/air partition coefficient of a substance. The blood/air partition coefficient of VC in humans is 1.2 (Csanady and Filser, 2001), similar to that of the inhalation anaesthetic isoflurane (1.4; Forth et al., 1987).

For this substance the equilibrium is reached after about 2 hours, derived by graphical extrapolation of the data on isoflurane (Goodman and Gilman, 1975). For VC, in much lower concentrations an elimination half-time of VC of 20.5 minutes has been derived (Buchter, 1979; Bolt et al., 1981). From that, for low concentrations a steady state concentration for VC in blood of about 5 x 20.5 = 102.5 minutes can be calculated by standard estimation rules. Thus, in high or low concentrations a relevant increase of internal concentrations of VC is not to be expected after more than 2 hours of exposure. However, for shorter periods of exposure a relevant influence of time on the built-up of VC on internal concentrations has to be taken into account.

VC is oxidized by cytochrome P450 2E1 to the highly reactive epoxide 2-chloroethylene oxide which can directly interact with DNA and proteins or spontaneously rearrange to 2-chloroacetaldehyde which might bind to proteins and DNA. 2-Chloroethylene oxide can also be transformed to glycol aldehyde by epoxide hydrolase or react with glutathione leading to the formation N-acetyl-S-(2-hydroxyethyl)-cysteine. Chloroacetaldehyde is oxidized by aldehyde dehydrogenase to 2-chloroacetic acid which reacts with glutathione leading to the formation of thiodiglycolic acid (which leads to the liberation of carbon dioxide). Comparison of in-vitro metabolism with rat liver microsomes and in-vivo experiments in rats show that virtually all the metabolic activation of VC in vivo occurs in the liver (WHO, 1999a). After low doses VC is metabolically eliminated and non volatile metabolites excreted mainly in the urine. At doses that saturate the metabolism, the major route of excretion is exhalation of unchanged VC. Excretion of metabolites via feces is only a minor route, independent of applied dose (WHO, 1999a).

Buchter et al. (1980) exposed rhesus monkeys with 100 - 800 ppm VC and measured the time-dependent disappearance of VC from the atmosphere. The maximum metabolic rate was determined at 45 µmol/kg-hr; this turnover is obtained at 400 ppm VC; no attempt was made to identify the metabolites formed. From the decrease in atmospheric VC concentration metabolic clearance rates were calculated in liter air/hour/kg body weight. Clearance rates for monkeys, rabbit and humans are 2.0 - 3.55 l/hr-kg, for gerbils and rats 11.0 to 12.5, and 25.6 l/hr-kg for mice, indicating major species differences, which are in accordance with allometric scaling.

After oral ingestion of 0.05, 1.0 or 100 mg/kg body weight, male rats metabolize VC to the epoxide which is further metabolized (e.g. to thiodiglycolic acid: about 25% of the ^{14}C containing urinary metabolites). Of the total dose, 9, 13.3 and 2.5% are excreted as CO_2 or 1.4, 2.1 or 66.6% VC, respectively at the low, mid and high dose (Watanabe et al., 1976b). At 100 mg/kg bw pulmonary elimination showed a biphasic clearance with an initial half life of 15 min and a terminal half life of 41 min. After 0.05 and 1 mg/kg VC only monophasic pulmonary clearance could be observed with half life values of 53 - 58 min (Watanabe et al., 1976b). Initial urinary excretion of metabolites followed first order-kinetics with half life values of 4.5 - 4.6 hours, followed by a slow terminal phase (Watanabe et al., 1976b). Thus, the equilibrium concentration for metabolites will not be reached within 8 hours or less. The ratio of the metabolites excreted in the urine does not vary in dependence on dose.

Vinyl chloride metabolism is saturated at concentrations exceeding 380 ppm in Rhesus monkeys (Buchter et al., 1980) (see table 6). In humans, 24 ppm appears to be below the threshold of saturation (Krajewski et al., 1980) since no difference in pulmonary retention could be observed between 3, 6, 12 and 24 ppm VC. When exposing rats in a closed system with 50 - 1,000 ppm VC metabolic clearance was slowed at concentrations above 220 ppm as evidenced by longer half lives (Hefner et al., 1975). Bolt et al. (1977) exposed rats in a similar system and found metabolic saturation to occur at 250 ppm (see table 6). These data are in accordance with the data from Watanabe et al. (1976a): after inhalation of 1,000 ppm in

rats metabolism was saturated, whereas at 100 ppm VC saturation was not evident (no intermediate concentration was tested).

Saturation of the metabolism has also been observed after oral application: at high doses (100 mg/kg) metabolism was saturated as is evident from the increase in VC expiration from 2.1% at 1 mg/kg to 66,6% at 100 mg/kg (Watanabe et al., 1976b).

TABLE 6: METABOLIC SATURATION CONCENTRATIONS OF VC IN RATS AND MONKEYS	
Rhesus Monkey	about 380 ppm (Buchter et al., 1980)
Rat	250 ppm (Bolt et al., 1977)

VC metabolites are assumed to destroy cytochrome P450 enzymes responsible for its epoxidation (Du et al., 1982; Pessayre et al., 1979). On the other hand activity of glutathione-S-transferase and glutathione reductase is elevated after VC exposure of rats (glutathione content is reduced) representing an early hepatocellular adaption to VC exposure (Du et al., 1982).

4.2. Mechanism of Toxicity

Acute neurotoxicity by inhalation of high VC concentrations is likely dependent upon VC concentrations and independent of VC metabolism. This assumption is supported by comparison of narcotic concentrations which are similar for the four species guinea pig, mouse, rabbit and rat (Prodan et al., 1975; Mastromatteo et al., 1960). Vinyl chloride has been investigated as a possible human anesthetic (Oster et al., 1947; Peoples and Leake, 1933) but was abandoned because of its induction of cardiac arrhythmia.

Acute toxicity/lethality is mainly accompanied by congestion of all internal organs, pulmonary edema, liver and kidney changes (up to necrosis) (Prodan et al., 1975). The mechanism of action is not evident, toxic effects are possible mediated by reactive metabolites.

VC genotoxicity and carcinogenicity has been attributed to formation of reactive metabolites, especially 2-chloroethylene oxide and 2-chloroacetaldehyde (see WHO, 1999a). 2-Chloroethylene oxide interacts directly with DNA and produces alkylation products (Fedtke et al., 1990). This alkylation results in a highly efficient base-pair substitution that leads to neoplastic transformation (ATSDR, 1997). VC-DNA ethenobases are shown to lead to miscoding and are found in VC-induced tumors in animals and humans (Barbin, 2000). Despite relevant repair, no full reduction to background was observed for these adducts two weeks after a 5 day exposure (4 hours/day) to 600 ppm (Swenberg et al., 1999). For vinyl fluoride, when all of the data for rats and mice on εG and hemangiosarcomas were compared by regression analysis, a high correlation was seen (r^2=0.88) (Swenberg et al.,1999). However, in case of VC there is a close correlation in the occurrence of εA, εC, εG and there are indications that also εA might be related to tumor formation (Barbin, 1999; Barbin, 2000). In adults, nonparenchymal cells have a higher rate of proliferation than hepatocytes. Thus, this cell population is more likely to convert promutagenic DNA adducts into mutations (Swenberg et al.,1999). During rapid growth of the liver this relationship may be changed: Young animals demonstrate a high rate of etheno-adducts in the liver and a high rate of preneoplastic foci of the liver. These foci persisted over several month even after short durations of exposure (Laib et al., 1989). In young animals a high rate of hepatoma and hepatocellular carcinoma have been found after short term exposure to VC (Maltoni et al., 1981; 1984; Froment et al., 1994).

In humans occupationally exposed to VC „vinyl chloride disease“ (characterized by Raynaud‘s phenomena and scleroderma) is a common finding after prolonged exposure. No similar observations have been made in experimental animals after single exposition experiments. These effects are probably due to immunological abnormalities (caused by interaction of reactive VC metabolites with proteins) as has been proposed by Grainger et al. (1980) and Ward et al. (1976), however, no definitive mechanism has been elucidated to date.

4.3. Other Relevant Information

4.3.1 PBPK-Modeling

Physiology-based pharmacokinetic (PBPK) models have been proposed to predict VC metabolism and cancer risk (Reitz et al., 1996; Clewell et al., 1995 and Clewell et al., 2001). PBPK models have been developed to account for physiological differences among species relevant to VC uptake, distribution, metabolism and excretion and should allow a better comparison across species.

Current models use four compartments (liver, fat, slowly perfused tissues, richly perfused tissues) and partition coefficients determined in vitro. Metabolism is modeled by one (Reitz et al., 1996) or two (Clewell et al., 1995) saturable pathways. The model of Clewell et al. (1995, 2001) uses one high affinity, low capacity pathway likely pertaining to cytochrome P450 2E1, and one low affinity, high capacity pathway tentatively assigned to cytochromes P450 2C11/6 and 1A1/2). Since VC readily reacts with glutathione (GSH) and is known to deplete hepatic GSH stores, description of the GSH kinetics was also included.

4.3.2. Interspecies Variability

A comparison of the metabolic activity across species indicates mice to be the metabolically most active species with a first order metabolic clearance rate for VC of 25.6 l/h per kg bw at VC concentrations below metabolic saturation (Buchter et al., 1980). Clearance of rats, rhesus monkey, rabbits and men is lower (11.0, 3.55, 2.74 and 2.02 l/h per kg bw, respectively). Because the metabolism of VC is perfusion-limited (Filser and Bolt, 1979), comparison of clearance rates on body weight basis is not satisfying. If clearance is compared on a body surface area basis these mammalian species exhibit similar clearance rates (WHO, 1999a).

Comparison of lethal concentrations (lethality occurring in the context of narcosis) in mice, rats, rabbits and guinea pigs point to certain interspecies variations with the guinea pig and rabbit being less sensitive than mice and rats. Comparing the most sensitive species (mouse) with the at least sensitive species (rabbit and guinea pig) point to a factor of 2.

LC_{50} mouse; exposure time 2 h:	117,500 ppm (Prodan et al., 1975)
LC_{50} rat; exposure time 2 h:	150,000 ppm (Prodan et al., 1975; Lester et al., 1963)
LC_{50} rabbit; exposure time 2 h:	240,000 ppm (Prodan et al., 1975)
LC_{50} guinea pig; exposure time 2 h:	240,000 ppm (Prodan et al., 1975)

Concerning non lethal, pre-narcotic effects marginal interspecies differences are observed indicating that rats and mice are a little bit more sensitive than guinea pigs: e.g. thirty minutes exposure of guinea pigs, rats and mice to 100,000 ppm VC resulted in the same symptoms: unconsciousness (in all rats and mice but only in one of five guinea pigs) and a lung hyperaemia persisting for more than 2 weeks, rats and mice fell aside after 20 min exposure and guinea pigs showed side position after 30 min exposure

(Mastromatteo et al., 1960). No comparable data on humans are available. Concerning hepatic effects mice seem to be more sensitive than rats and rabbits: Exposure of mice to 1,500 ppm VC for 2 h caused severe liver effects, resulting in shock liver and death of the mice. But no hepatic and lethal effects were observed in rats and rabbits treated identically for 24 h (Tátrai and Ungvary, 1981). The reasons for these interspecies differences are not known. Data on acute hepatic effects of VC in humans are not available.

Concerning the similar clearance rates of VC on a body surface area there does not seem to be a large toxicokinetic difference between various species. Due to these findings we suggest to use a reduced interspecies factor of 3, accounting for toxicodynamic differences, in cases where the toxicity of VC is mediated by VC metabolites.

With respect to lethality and VC induced (pre-) narcotic symptoms there seem to be only minimal interspecies differences. Use of a reduced extrapolation factor of 3 is recommended in this context.

4.3.3. Intraspecies Variability

Cytochrome P450 isoenzyme 2E1 is the key enzyme converting VC to 2-chloroethylene oxide. CYP2E1 activity in human liver microsomes may vary up to 12-fold between individuals (substrate: p-nitrophenol; Seaton et al., 1994). These data indicate a potential interindividual variability in VC metabolism.

Investigation of VC retention in the lung of human volunteers revealed large interindividual differences in VC retention (minimum 20.2% of the exposure concentration; maximum 79% of the exposure concentration; Krajewski et al., 1980).

Interindividual differences in the response of human subjects to varying concentrations of VC were observed by Lester et al. (1963): 8,000 ppm VC did not cause any response in 5 individuals, but one person felt „slightly heady“. Other subjects complained about adverse health effects at concentrations of ≥ 12,000 ppm, indicating that there are only small interindividual differences in the response to neurotoxic effects of VC.

Relevant interindividual differences were not described in animal experiments.

Due to these observations a factor of 3 is used for the characterization of intraspecies variabilities in the context with neurotoxic effects or cardiac sensitization. A factor of 10 is used to describe intraspecies differences which are mediated by metabolites of VC.

4.3.4. Concurrent Exposure Issues

Concurrent administration of ethanol and VC leads to an increase of liver angiosarcoma in rats in comparison to animals exposed only to VC. This effect may be due to the interaction of ethanol (a known CYP2E1 inducer) with VC metabolism (WHO, 1999a).

Induction of certain enzymes of the mixed-function oxidase system by pretreatment with phenobarbital or the mixture of polychlorinated biphenyls enhanced acute hepatotoxicity in rats as measured by increased activity of hepatic enzymes and /or focal hepatic necrosis. On the other hand, inhibitors of the mixed-function oxidase system like SKF-525A have an opposite effect (WHO, 1999a).

5. RATIONALE AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

Detection of 261 ppm VC by entering the exposure chamber was reported by Baretta et al. (1969). The authors also described that 5 of 7 persons detected the odor of VC entering a chamber with 491 ppm VC, but after 5 minutes of exposure detection was not any longer possible.

Amoore and Hautala (1983) reported an odor threshold of 3,000 ppm for VC. This value represents the geometric average of three studies, extreme points and duplicate quotations were omitted. It was not stated whether it is the detection or recognition threshold.

A “fairly pleasant odor” was reported by two persons exposed to 25,000 ppm for 3 minutes. At these concentrations dizziness and slight disorientation occurred (Patty et al., 1930).

Hori et al. (1972) reported an odor threshold for VC of 10 - 20 ppm (20 ppm in production workers and 10 ppm in workers from other sites). This value was reviewed by the AIHA and the value has been rejected because of several shortcomings of the experimental procedure (e.g. no calibration of panel odor sensitivity, not stated whether the given limit was due to recognition or detection, number of trials not stated).

Irritating effects of VC are only observed at very high concentrations: accidental exposure to lethal concentrations was accompanied by lesions of the eyes (Danziger, 1960).

Baretta et al. (1969) exposed 4 - 6 volunteers to 59, 261, 491 ppm VC (analytical concentrations) for 7.5 h (including a 0.5 h lunch period; corresponding to time weighted average concentrations of 48, 248 or 459 ppm over a period of 7.5 h), seven persons were exposed to 491 ppm for only 3.5 hours. The only complaints were those of two subjects who reported mild headache and some dryness of their eyes and nose during exposure to the highest concentration (the time of onset of headaches is not specified and is assumed to have occurred after 3.5 hours of exposure).

5.2. Animal Data Relevant to AEGL-1

Lacrimation occurred shortly after onset of exposure in animals exposed to VC (exposure of mice, rats, guinea pigs, and rabbits to concentrations between 42,900 ppm to 280,000 ppm, no differentiated evaluation according to lacrimation). Lethal effects have been observed in mice and rats even in the lowest exposure concentrations (42,900 ppm without ventilation in mice and 150,000 ppm with ventilation in rats) (Prodan et al., 1975). Mastromatteo et al. (1960) described that irritation (no further details) was occurring immediately after onset of exposure to 100,000, 200,000 or 300,000 ppm VC in rats and mice; in guinea pigs irritation was not described in concentrations below 400,000 ppm VC. However, 100,000 ppm VC already resulted in unconsciousness of the animals. No other data on irritation of VC in animals are available from literature.

5.3. Derivation of AEGL-1

Vinyl chloride is a compound with poor odor warning properties. Reports on odor threshold vary over a wide range (10 to 25,000 ppm). There is no qualified study determining the detection or recognition threshold. According to the report of Baretta et al. (1969) people seem to get used to the odor of VC. In humans and animals irritation is only reported in the context of exposure to very high

concentrations which are lethal or cause unconsciousness. So, derivation of AEGL-1 values on base of the odor detection or irritation is not possible.

Occurrence of headache has been reported by Baretta et al. (1969) in two subjects after acute exposure (the time of onset of headaches is not specified and is assumed to have occurred after 3.5 hours of exposure) . These findings are supported by data from occupationally exposed persons who developed headache after VC exposure (Lilis et al., 1975; Suciu et al., 1975). The endpoint "mild headache" in the study from Baretta et al. (1969) can be regarded as a no effect level for notable discomfort (491 ppm for 3.5 h). An intraspecies factor of 3 is employed: it is assumed that the effects are due to VC itself and not due to a metabolite, so only small interindividual differences are expected. The relationship between concentration and duration of exposure as related to lethality was examined by Ten Berge et al. (1986) for approximately 20 irritant or systemically-acting vapors and gases. The authors subjected the individual animal data sets to Probit analysis with exposure duration and exposure concentration as independent variables. An exponential function (C^n x t = k), where the value of n ranged from 0.8 to 3.5 for different chemicals was found to be an accurate quantitative descriptor for the chemicals evaluated. Approximately 90 percent of the values of n range between n=1 and n=3. Consequently, these values were selected as the reasonable lower and upper bounds of n to use when data are not available to derive a value of n. A value of n=1 is used when extrapolating from shorter to longer time periods because the extrapolated values are conservative and therefore, reasonable in the absence of any data to the contrary. Conversely, a value of n=3 is used when extrapolating from longer to shorter time periods because the extrapolated values are conservative and therefore reasonable in the absence of any data to the contrary. The default values for “n“ are used, as the mechanism for the induction of headache is not well understood. The extrapolation to 10 minutes from a 3.5 hour exposure is justified because exposure of human at 4,000 ppm for 5 minutes did not result in headache (Lester et al., 1963).

TABLE 7: AEGL-1 VALUES FOR VINYL CHLORIDE

AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	450 ppm 1200 mg/m^3	310 ppm 800 mg/m^3	250 ppm 650 mg/m^3	140 ppm 360 mg/m^3	70 ppm 180 mg/m^3

6. RATIONALE AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

Lester et al. (1963) reported that 5 min exposure to 8,000 ppm caused dizziness in 1/6 subjects (the same subject reported slight dizziness at sham exposure and no effect at 12,000 ppm). No complaints were made by any volunteer at 4,000 ppm. At 12,000 ppm one subject reported clear signs of discomfort (reeling, swimming head) and another subject another was unsure of some effect; he had a "somewhat dizzy" feeling in the middle of exposure. At 16,000 ppm (5/6) and 20,000 ppm (6/6) persons complained about dizziness, nausea, headache, dulling of visual and auditory cues. All symptoms disappeared shortly after termination; headache persisted for 30 minutes in one subject after exposure to 20,000 ppm.

Three minutes exposure to 25,000 ppm resulted in dizziness and slight disorientation as to space and size of surrounding objects and a burning sensation in the feet in two persons. They immediately recovered on leaving the chamber and complained only of a slight headache which persisted for 30 minutes (Patty et al., 1930).

Baretta et al. (1969) exposed 4 - 6 volunteers to 59, 261, 491 ppm VC (analytical concentrations) for 7.5 h (including a 0.5 h lunch period; corresponding to time weighted average concentrations of 48, 248 or 459 ppm over a period of 7.5 h), seven persons were exposed to 491 ppm for only 3.5 hours. The only complaints were those of two subjects who reported mild headache and some dryness of their eyes and nose during exposure to the highest concentration (the time of onset of headaches is not specified and is assumed to have occurred after 3.5 hours of exposure) .

6.2. Animal Data Relevant to AEGL-2

Animal toxicity after short term exposure is characterized by cardiac sensitization, (pre-) narcotic and hepatic effects. Short term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 or 71,000 ppm in two independent experiments) (Clark and Tinston, 1973; 1982). This observation is confirmed in higher concentrations by additional experimental data).

Hehir et al. (1981) reported that single exposure of mice to 50,000 ppm VC caused twitching, ataxia, hyperventilation and hyperactivity, beginning 40 min after start of exposure. Consistent with these data Mastromatteo et al. (1960) reported that 100,000 ppm VC induced pronounced tremor, unsteady gait and muscular incoordination in mice 15 min after onset of exposure. Exposure of mice to 1,500 ppm VC for 2 h resulted in stasis of blood flow, decreasing enzyme activities in the liver, subcellular liver damage, and shock liver after 24 h of exposure (Tátrai and Ungváry, 1981).

Viola et al. (1970) reported that rats exposed to 30,000 ppm for 4 h/d were slightly soporific (no further details). At higher concentrations (50,000 ppm for 2 h) moderate intoxication and loss of righting reflex and intense intoxication at 60,000 ppm for 2 h (but righting reflex still present) have been reported by Lester et al. (1963). Intoxication was not further characterized. Higher VC concentrations (100,000 ppm) resulted in a loss of the corneal reflex (exposure for 2 h) (Lester et al., 1963). Already 15 min after onset of exposure to 100,000 ppm tremor and ataxia were observed by Mastromatteo et al. (1960).Guinea pigs exposed to 25,000 ppm for 5 min showed motor ataxia, unsteadiness on feet, after 90 min the animals were unconscious (NOAEL 10,000 ppm) (Patty et al., 1930). Mastromatteo et al. (1960) reported the unsteady gait and muscular incoordination in guinea pigs exposed for 15 min to 100,000 ppm.

Single inhalation exposure of rats for 6 hours to 100,000 ppm VC resulted in histopathological changes of the liver (vacuolization), but was not observed in lower concentrations (50,000 ppm) (Jaeger et al., 1974). However, in mice Tátrai and Ungváry (1981) reported that stasis of the liver developed 2 and 4 h after the beginning of inhalation. The authors observed decreasing enzyme activities in liver and subcellular liver damage at exposure concentrations of 1,500 ppm VC for 2 h; after 24 h shock liver developed. Repeated exposure of rats to 1,500 ppm VC for up to 9 days during pregnancy caused increased relative and absolute liver weights without light microscopic visible changes. Also, no histopathological effects were observed in rabbits treated identically (Ungváry et al., 1978). In another developmental study increased absolute and relative liver weights have been observed in rats exposed intermittently to 2,500 ppm from day 6 - 15 of pregnancy, the NOAEL was 500 ppm (John et al., 1977; 1981).

6.3. Derivation of AEGL-2

Short term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 or 71,000 ppm in two independent experiments) (Clark and Tinston, 1973; 1982). A NOAEL for this effect can be reasonably estimated by using a factor of 3 on EC_{50} (50,000 ppm) resulting in a concentration of about 17,000 ppm. This concentration already leads to CNS-effects in humans after 5 minutes exposure (Lester et al.,1963). Thus, the endpoint of cardiac sensitization would not be the critical effect for AEGL-2 derivation. However, the AEGL-2 derived below is supported by the data on cardiac sensitization.

Liver toxicity is a major endpoint after long term exposure to VC and may possibly be linked to tumor development in young animals (see section 4.2. for further discussion). The NOAEL for irreversible effects to the liver after single exposure is 50,000 ppm (6h, rat data). The effects seen in lower concentrations (liver weight changes) may not be regarded as key studies for AEGL-2 derivation.

Narcotic effects seem to predominate in rats, mice and guinea pigs acutely exposed to high concentrations of VC. These effects are relevant AEGL-2 endpoints as they impair the possibility to escape. Although guinea pigs seem to be less sensitive than rats and mice concerning lethality (see 7.2) they are more sensitive than rats and mice with regard to early signs of narcotic effects: exposure of guinea pigs for 5 min to 25,000 ppm resulted in early signs of narcotic effects (motor ataxia, unsteadiness on feet), after 90 minutes animals were unconscious (NOAEL 10,000 ppm) (Patty et al., 1930). Rats exposed to 30,000 ppm VC for 4 h were only slightly soporific (Viola et al., 1970), and single exposure of mice to 50,000 ppm VC caused twitching, ataxia, hyperventilation and hyperactivity, beginning 40 min after start of exposure (Hehir et al., 1981) .

The observations in animals are in good accordance with the effects observed in humans: dizziness, reeling, swimming head, nausea etc., which can be regarded as early signs of narcosis, have been reported in humans exposed to VC in concentrations $\geq$12,000 ppm for 5 min. No effects were reported at 4,000 ppm (Lester et al., 1963). The effects observed at 12,000 ppm (dizziness, reeling, swimming head) were only seen in 1 or 2 of 6 persons (one person was unsure of an effect) and do not yet impair the capability to escape, whereas, the effects observed at concentrations $\geq$ 16,000 ppm (dizziness, nausea, headache, dulling of visual and auditory cues) might possibly impair escape. Therefore, 12,000 ppm is interpreted as the no effect level for impaired ability to escape and is used to derived the AEGL-2 values.

By analogy to other anaesthetics the effects are assumed to be solely concentration dependent. Thus, after reaching steady state at about 2 hours of exposure, no increase in effect is expected. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using a factor of n=2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects in mice and guinea pigs after less than steady state exposure conditions (For details see Appendix B). With this, time extrapolation was performed from 5 to 10, 30, 60 minutes and 2 hours, where the steady state concentration was calculated. However, the resulting AEGL-2 values may not provide a sufficient margin safety to avoid mutational events or malignancies after short-term exposure to VC.

The calculations of exposure concentrations scaled to AEGL-2 time points are shown in Appendix A. The data are listed in the table below.

TABLE 8: AEGL-2 VALUES FOR VINYL CHLORIDE

AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-2	2,800 ppm (7300 mg/m³)	1,600 ppm (4100 mg/m³)	1,200 ppm (3100 mg/m³)	820 ppm (2100 mg/m³)	820 ppm (2100 mg/m³)

7. RATIONALE AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

Only two cases of accidental death due to VC exposure are described in literature. Exposure concentrations and exposure time are unknown, but circumstances suggest inhalation of very high concentrations. At autopsy cyanosis, congestion of lung and kidneys and blood coagulation failure were observed (Danziger, 1960).

7.2. Animal Data Relevant to AEGL-3

LC_{50} values reported for mice, rats, rabbits and guinea pigs indicate similar sensitivity of mice and rats and of rabbits and guinea pigs. According to the data presented by Prodan et al. (1975) the following LC_{50} values were obtained:

mice	117,500 ppm
rats	150,000 ppm
rabbits	240,000 ppm
guinea pigs	240,000 ppm

The findings in rats are supported by the data of Lester et al. (1963) who described that exposure of 2 rats to 150,000 ppm for 2 hours resulted in the death of one rat whereas the other rat recovered on removal to air.

The following LC_{00} values have been reported for these species.

mice	100,000 ppm (2 h, Prodan et al., 1975)
rats	100,000 ppm (8 h, Lester et al., 1963)
	200,000 ppm (0,5 h, Mastromatteo et al., 1960)
rabbits	200,000 ppm (2 h, Prodan et al., 1975)
guinea pigs	100,000 ppm (6 h, Patty et al., 1930)
	200,000 ppm (2 h, Prodan et al., 1975)

In addition, relevant data on cardiac sensitization exist: Short term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 or 71,000 ppm in two independent experiments) (Clark and Tinston, 1973; 1982). These effects were also seen in mice at higher concentrations (Aviado and Belej, 1974). In monkeys, only myocardial depression after inhalation of 2.5-10% VC was observed. It is not clearly stated whether an addition challenge with epinephrine was applied or not (Belej et al., 1974).

7.3. Derivation of AEGL-3

Lethality data provide AEGL-3 values that are marginally higher than those derived based on cardiac sensitization. Thus, animal data (Clark and Tinston, 1973; 1982) on cardiac sensitization after exposure for 5 minutes were used to derive AEGL-3. Severe cardiac sensitization is a life threatening effect, but at 50,000 ppm no animal died in the reported study and is used to derive AEGL-3 values. A total uncertainty factor of 3 is used to account for toxicodynamic differences among individuals. As the challenge with epinephrine and the doses of epinephrine used represent a conservative scenario, no

interspecies uncertainty factor was used. As the unmetabolized VC is responsible for the effect, no relevant differences in toxicokinetics are assumed. In analogy to other halocarbons (e.g., Halon 1211, HFC 134a) which lead to cardiac sensitization the effects are assumed to be solely concentration dependent. Thus, after reaching steady state at about 2 hours of exposure, no increase in effect is expected. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using an n of 2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects (muscular incoordination, side position and unconsciousness, effects which occur immediately before lethality) in mice and guinea pigs after less than steady state exposure conditions. With this, time extrapolation was performed from 5 to 10, 30, 60 minutes and 2 hours, where the steady state concentration was calculated.

The values are listed in the table below.

TABLE 9: AEGL-3 VALUES FOR VINYL CHLORIDE

AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-3	12,000 ppm (31,000 mg/m³)	6,800 ppm (18,000 mg/m³)	4,800 ppm (12,000 mg/m³)	3,400 ppm (8,800 mg/m³)	3,400 ppm (8,800 mg/m³)

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 10. AEGL-1 values have been derived based on mild headaches observed in volunteers (Baretta et al.,1969); odor threshold was not determined in a validated manner and seems to vary over a wide range. AEGL-2 values are based on CNS-effects, which may impair escape capacity (Lester et al.,1963). Data on cardiac sensitization (Clark and Tinston, 1982; 1973) are supported by lethality concentrations (LC_{00}) in slightly higher concentrations (Prodan et al.,1975) and are used for AEGL-3 derivation.

TABLE 10: SUMMARY/RELATIONSHIP OF PROPOSED AEGL VALUES

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Non-disabling)	450 ppm 1200 mg/m^3	310 ppm 800 mg/m^3	250 ppm 650 mg/m^3	140 ppm 360 mg/m^3	70 ppm 180 mg/m^3
AEGL-2 (Disabling)	2,800 ppm 7,300 mg/m^3	1,600 ppm 4,100 mg/m^3	1,200 ppm 3,100 mg/m^3	820 ppm 2,100 mg/m^3	820 ppm 2,100 mg/m^3
AEGL-3 (Lethal)	12,000 ppm (31,000 mg/m$^{3)}$	6,800 ppm (18,000 mg/m^3)	4,800 ppm (12,000 mg/m^3)	3,400 ppm (8,800 mg/m^3)	3,400 ppm (8,800 mg/m^3)

Inhalation data are summarized in Figure 1 below. The data were classified into severity categories chosen to fit into definitions of the AEGL level health effects. The category severity definitions are "No effect"; "Disabling"; "Lethal" and "AEGL".

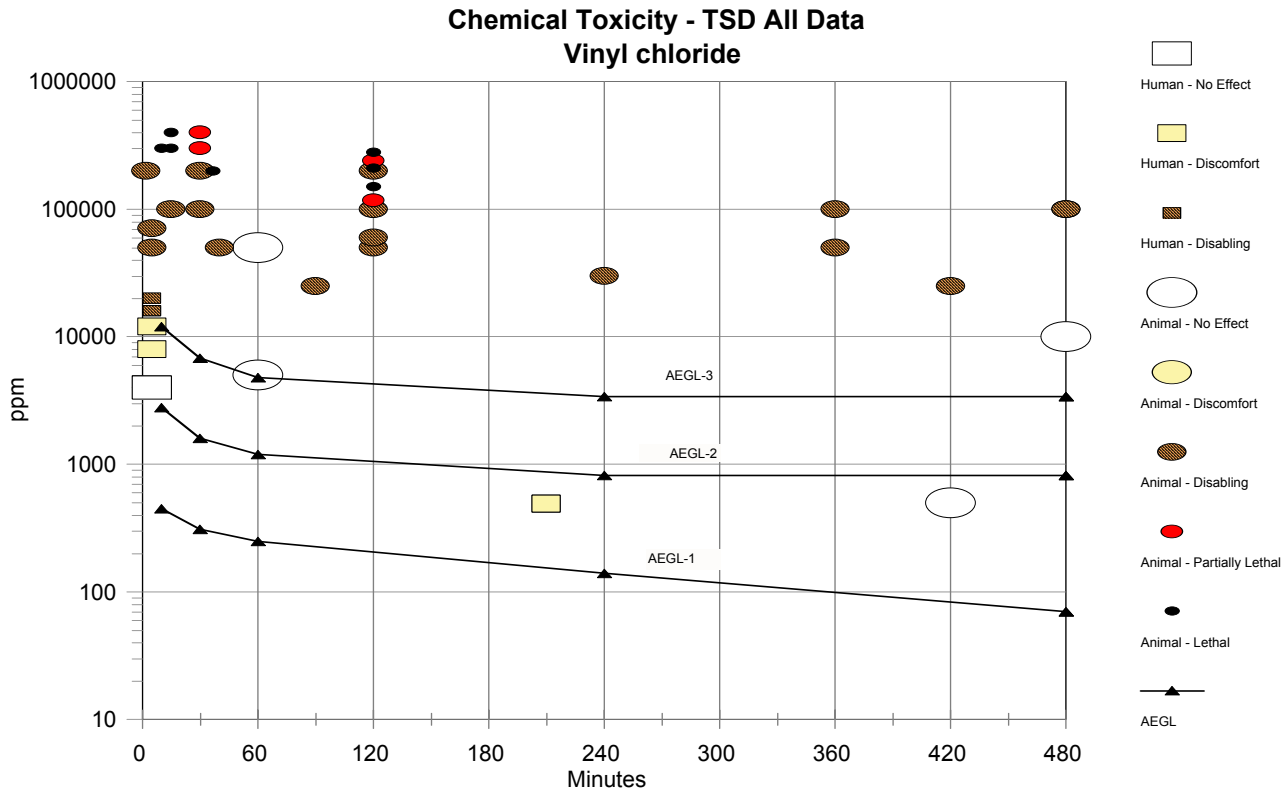

FIGURE 1: CATEGORICAL REPRESENTATION OF VINYL CHLORIDE INHALATION DATA (data where the exposure time exceeded 500 min are not included)

8.2. Comparison with Other Standards and Criteria

Other standards and guidance levels for workplace and community exposures are listed in Table 11.

TABLE 11: EXISTENT STANDARDS AND GUIDELINES FOR VINYL CHLORIDE

Guideline	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	310 ppm	310 ppm	250 ppm	140 ppm	70 ppm
AEGL-2	2,800 ppm	1,600 ppm	1,200 ppm	820 ppm	820 ppm
AEGL-3	12,000 ppm	6,800 ppm	4,800 ppm	3,400 ppm	3,400 ppm
PEL-TWA (OSHA) [a]					1 ppm
STEL (OSHA) [b]	5 ppm [for 15 min]				
TLV-TWA (ACGIH) [c]					5 ppm
TEEL-0 (CSP) [d]			1 ppm		
TEEL-1 (CSP) [e]			5 ppm		
TEEL-2 (CSP) [f]			5 ppm		
TEEL-3 (CSP) [g]			75 ppm		
TRK (Germany) [h]					2 (3) ppm
Einsatztoleranzwerte (Greim, Germany) [i]				100 ppm	
Störfallbeurtei-lungswert (VCI) [j]			1,000 ppm		

[a] **OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA, 2002) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[b] **OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)** (OSHA, 2002) is defined as a 15 minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the PEL-TWA. Exposures above the PEL-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[C] **ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH, 1998). The time-weighted average concentration for a normal 8-hour workday and a 40-hour work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. The value was based on a calculation of the carcinogenic potency of vinyl chloride by Gehring and coworkers. The TLV-Committee concluded that a TLV-TWA of 5 ppm should not result in a detectable increase in the incidence of occupational cancers, specifically angiosarcoma of the liver.

[d] **TEEL-0 (U.S. department of Energy‘s Chemical safety Program, Temporary Emergency Exposure Limit)** (CSP, 2002). The threshold concentration below which most people will experience no appreciable risk of health effects.

[e] **TEEL-1 (U.S. department of Energy's Chemical safety Program, Temporary Emergency Exposure Limit)** (CSP, 2002). 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.

[f] **TEEL-2 (U.S. department of Energy's Chemical safety Program, Temporary Emergency Exposure Limit)** (CSP, 2002). 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.

[g] **TEEL-3 (U.S. department of Energy's Chemical safety Program, Temporary Emergency Exposure Limit)** (CSP, 2002). The maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing or developing life-threatening health effects.

[h] **TRK (Technische Richtkonzentrationen [Technical Guidance Concentration], Deutsche Forschungsgemeinschaft [German Research Association], Germany)** (DFG, 2001). TRK is defined as the air concentration of a substance which can be achieved with the current technical standards. TRK-values are given for those substances for which no maximum workplace concentration can be established. Compliance of the TRK should minimize the risk of health effects, but health effects cannot be excluded even at this concentration. (A value of 3 ppm is given for existing plants and the production of VC and PVC, in all other cases 2 ppm should not be exceeded.)

[i] **Einsatztoleranzwert [Action Tolerance Levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention])** (Greim, 1995/1996) constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 hours without any health risks. The value is based on the observation that no acute toxic effects or irritating effects have been observed during exposure to 500 ppm for 4 hours.

[j] **Störfallbeurteilungswert [Emergency Assessment Value] (VCI, Verband der Chemischen Industrie, Deutschland [Association of the Chemical Industry in Germany])** (VCI, 1990).These values have been set for an exposure time of up to 1 h. Considering that VC leads to anaesthesia in concentrations of 7%, to pre-narcotic syndroms at 0.5%, and to respiratory arrest the Emergency Assessment Value has been set at 1,000 ppm.

8.3. Data Adequacy and Research Needs

As VC has only poor warning properties there is only a very limited data base to derive AEGL-1. Additional studies with volunteers may not be performed due to ethical reasons. AEGL-2 values are based on animal experiments regarding CNS-effects. The respective concentration range is well established but excludes potential mutagenic or carcinogenic effects after short term exposure, which might occur in lower concentrations. However, quantitative estimates of the respective risk are highly uncertain. For derivation of AEGL-3 values, the dogs studies on cardiac sensitization are in good accordance with lethality data in slightly higher concentrations.

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APPENDIX A - Derivation of AEGL values

AEGL-1

Key study:	Baretta et al. (1969)
Toxicity endpoint:	Mild headache in 2 subjects during exposure to highest concentration (i.e. 491 ppm for 3.5 h)
Uncertainty/ modifying factors:	Total uncertainty factor of 3 for intraspecies variability
Time Scaling:	$C^3 \times t = k$ for extrapolation to 1-hour and 30-minute (10-minute = 30-minute value); $C^1 \times t = k$ for extrapolation to 4- and 8-hour $k = (491\ ppm)^3 \times 210\ min = 2.49 \times 10E+10\ ppm^3\ min$ $k = (491\ ppm)^1 \times 210\ min = 103110\ ppm\ min$
Calculations:	
10-minute AEGL-1	$C^3 \times 10\ min = 2.49 \times 10E+10\ ppm^3\ min$ $C = 1355\ ppm$ 10-min AEGL-1 = 1355 ppm/3 = 450 ppm (= 1170 mg/m^3)
30-minute AEGL-1	$C^3 \times 30\ min = 2.49 \times 10E+10\ ppm^3\ min$ $C = 939.25\ ppm$ 30-min AEGL-1 = 939 ppm/3 = 310 ppm (= 810 mg/m^3)
1-hour AEGL-1	$C^3 \times 60\ min = 2.49 \times 10E+10\ ppm^3\ min$ $C = 745.48\ ppm$ 1-h AEGL-1 = 745 ppm/3 = 250 ppm (= 640 mg/m^3)
4-hour AEGL-1	$C \times 240\ min = 103110\ ppm\ min$ $C = 429.63\ ppm$ 4-h AEGL-1 = 430 ppm/3 = 140 ppm (= 370 mg/m^3)
8-hour AEGL-1	$C \times 480\ min = 103110\ ppm\ min$ $C = 214.81\ ppm$ 8-h AEGL-1 = 214 ppm/3 = 70 ppm (= 190 mg/m^3)

AEGL-2

Key study:	Lester et al. (1963)
Toxicity endpoint:	Prenarcotic effects were observed in human volunteers. After 5 minute exposure to 16,000 ppm VC 5 of 6 persons showed dizziness, lightheadedness, nausea, visual and auditory dulling. At concentrations of 12,000 ppm one of six persons showed "swimming head, reeling". Another individual was unsure of some effect and was somewhat dizzy. A single person reported slight effects ("slightly heady") of questionable meaning at 8,000 ppm (this volunteer felt also slightly heady at sham exposure and reported no response at 12,000 ppm). No effects were observed at 4,000 ppm. (Lester et al., 1963). 12,000 ppm was regarded as a concentration below AEGL-2 level and taken as NOAEL.
Uncertainty/ modifying factors:	Total uncertainty factor of 3 for intraspecies variability
Time Scaling:	$C^2 \times t = k$ for extrapolation 2-hour,1-hour, 30-minute, and 10-minute, flatlining from 4h to 8 h (based on 2 hours steady state concentration) $k = (12{,}000\ ppm)^2 \times 5\ min = 7.2 \times 10E{+}8\ ppm^2\ min$
Calculations:	
10-minute AEGL-2	$C^2 \times 10\ min = 7.2 \times 10E{+}8\ ppm^2\ min$ $C = 8485.28\ ppm$ 10-min AEGL-2 = 8485 ppm/3 = 2800 ppm (= 7300 mg/m^3)
30-minute AEGL-2	$C^2 \times 30\ min = 7.2 \times 10E{+}8\ ppm^2\ min$ $C = 4898.98\ ppm$ 30-min AEGL-2 = 4899 ppm/3 = 1600 ppm (= 4100 mg/m^3)
1-hour AEGL-2	$C^2 \times 60\ min = 7.2 \times 10E{+}8\ ppm^2\ min$ $C = 3464.11\ ppm$ 1-h AEGL-2 = 3464 ppm/3 = 1200 ppm (= 3100 mg/m^3)
2-hour steady state	$C^2 \times 120\ min = 7.2 \times 10E{+}8\ ppm^2\ min$ $C = 2449.49\ ppm$ 2-h steady state= 2450/3 ppm/3 = 820 ppm (= 2100 mg/m^3)
4-hour AEGL-2	= 2-hour steady state/3 = 820 ppm (= 2100 mg/m^3)
8-hour AEGL-2	= 4-hour AEGL-2 = 820 ppm (= 2100 mg/m^3)

AEGL-3

Key study:	Clark and Tinston, 1973; 1982
Toxicity endpoint:	Short term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 or 71,000 ppm in two independent experiments) (Clark and Tinston, 1973; 1982). These effects were also seen in mice at higher concentrations (Aviado and Belej, 1974). 50,000 ppm was used as NOAEL for life threatening effects
Uncertainty/ modifying factors:	Combined uncertainty factor of 3 1 for interspecies variability 3 for intraspecies variability
Time Scaling:	$C^2 \times t = k$ for extrapolation to 2-hour, 1-hour, and 30-minute and 10-minutes; flatlining from 4h to 8 h (based on 2 hours steady state concentration) $k = (50{,}000 \text{ ppm})^2 \times 5 \text{ min} = 1{,}25\ 10E{+}10 \text{ ppm}^2 \text{ min}$
Calculations:	
10-minute AEGL-3	$C^2 \times 10 \text{ min} = 1{,}25\ 10E{+}10 \text{ ppm}^2 \text{ min}$ C = 35,355.34 ppm 30-min AEGL-2 = 35,355 ppm/3 = 12,000 ppm (= 31,000 mg/m^3)
30-minute AEGL-3	$C^2 \times 30 \text{ min} = 1{,}25\ 10E{+}10 \text{ ppm}^2 \text{ min}$ C = 20,412.41 ppm 30-min AEGL-2 = 20,412 ppm/3 = 6,800 ppm (= 18,000 mg/m^3)
1-hour AEGL-3	$C^2 \times 60 \text{ min} = 1{,}25\ 10E{+}10 \text{ ppm}^2 \text{ min}$ C = 14433.76 ppm 1-h AEGL-2 = 14434 ppm/10 = 4,800 ppm (= 12,000 mg/m^3)
2-hour steady state	$C^2 \times 120 \text{ min} = 1{,}25\ 10E{+}10 \text{ ppm}^2 \text{ min}$ C = 10,206.21 ppm 2-h steady state = 10,206 ppm/3 = 3,400 ppm (= 8,800 mg/m^3)
4-hour AEGL-3	= 2-h steady state/3 =3,400 ppm (= 8,800 mg/m^3)
8-hour AEGL-3	= 4-h AEGL-3 =3,400 ppm (= 8,800 mg/m^3)

1

2 APPENDIX B - Time Scaling Calculations for Vinyl Chloride AEGLs

Time Scaling for Vinyl Chloride AEGLs

The relationship between dose and exposure time to produce a toxic effect for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicologic and pharmacologic properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's rule (i.e., C x t = k, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to a toxic effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation C^n x t = k, where n represents a chemical-specific and even a toxic endpoint-specific exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs. t (NRC, 2001).

Acute CNS-toxicity and lethality of VC are dominated by its narcotic effects characterized by a typical sequence of effects (increased motor activity, tremor, muscular incoordination, side position, unconsciousness, resulting in deep narcosis). The occurrence and time sequence of these effects in rats, mice and guinea pigs has been described by Mastromatteo et al. (1960). These experimental data are used for the derivation of values of n by linear regression analysis of the log-log transformed plot of C vs. t.

Three data sets of toxic effects in mice and rats or guinea pigs described by Mastromatteo et al. (1960) were analyzed. As the time-concentration relationships for mice and rats were identical the following evaluation concentrates on the data obtained in mice and guinea pigs. Regression analysis has been performed for the endpoints unconsciousness, muscular incoordination, and side position. The time-concentration relation ships are described below.

Time dependency is only true as long as no steady state is reached. Similar to other inhalation anesthetics, maximal blood concentration of VC after inhalation exposure depends on the partial pressure of VC in the air. Blood respectively brain concentration, which directly correlates with the depth of narcosis (see below) and - presumably - with cardiac sensitization level, can be controlled by changing the concentration of VC in the air, i.e. by changing the partial pressure of VC in the air. If equilibrium is reached between the partial pressure of VC in the air and in the blood (steady state), no further increase of VC concentration in the blood is possible, even if the exposure time is prolonged (Forth et al., 1987). The time necessary to set up steady state mainly depends on the blood/air partition coefficient of a substance. The blood/air partition coefficient of VC in humans is 1.2 (Csanady and Filser, 2001), similar to that of the inhalation anesthetic isoflurane (1.4; Forth et al., 1987). For this substance the equilibrium is reached after about 2 hours, derived by graphical extrapolation of the data on isoflurane (Goodman and Gilman, 1975). For VC, in much lower concentrations an elimination half-time of VC of 20.5 minutes has been derived (Buchter, 1979; Bolt et al., 1981). From that, for low concentrations a steady state concentration for VC in blood of about 5 x 20.5 = 102.5 minutes can be calculated by standard estimation rules. Thus, in high or low concentrations a relevant increase of internal concentrations of VC is not to be expected after more than 2 hours of exposure. However, for shorter periods of exposure a relevant influence of time on the built-up of VC on internal concentrations has to be taken into account:

Unconsciousness:

The time after which unconsciousness was observed in mice after exposure to 100,000, 200,000 or 300,000 ppm VC was 25 min, 10 min, and 5 min, respectively:

Time min	Concentration ppm	Log time	Log Concentration
5	300000	0.699	5.477
10	200000	1	5.301
25	100000	1.398	5

The time after which unconsciousness was observed in guinea pigs after exposure to 100,000, 200, 000, 300,000, and 400,000 ppm VC was 30 min, 10 min, 5 min and 5 min, respectively:

Time min	Concentration ppm	Log time	Log Concentration
5	400000	0.699	5.602
5	300000	0.699	5.477
10	200000	1	5.301
30	100000	1.477	5

Regression analysis of the data is shown in figure 2:

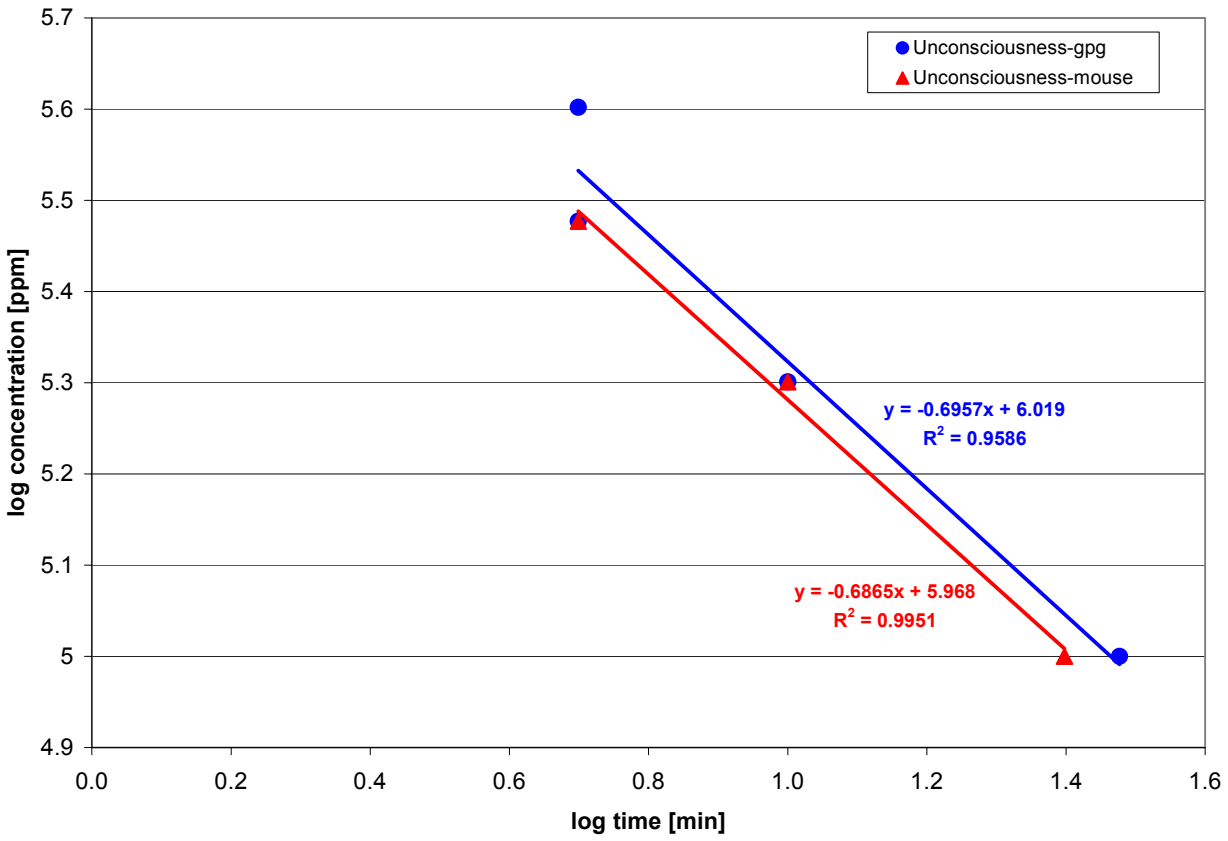

FIGURE 2: REGRESSION ANALYSIS OF THE LOG-LOG TRANSFORMED CONCENTRATION-TIME CURVE REGARDING UNCONSCIOUSNESS IN MICE AND GUINEA-PIGS (DATA FROM MASTROMATTEO ET AL., 1960)

The slope of the regression line was -0.6865 and -0.6957 in mice and guinea pigs, respectively, corresponding to a value of 1.46 and 1.44 for n.

Muscular incoordination:

The time after which muscular incoordination was observed in mice after exposure to 100,000, 200,000 or 300,000 ppm VC was 15 min, 2 min, and 1 min, respectively:

Time min	Concentration ppm	Log time	Log Concentration
1	300000	0	5.477
2	200000	0.301	5.301
15	100000	1.176	5

The time after which muscular incoordination was observed in guinea pigs after exposure to 100,000, 200,000, 300,000, or 400,000 ppm VC was 15 min, 5 min, 2 min, and few seconds, respectively:

Time min	Concentration ppm	Log time	Log Concentration
few seconds*	400000	--	5.602
2	300000	0.301	5.477
5	200000	0.699	5.301
15	100000	1.176	5

*: this value was not regarded in regression analysis

Regression analysis of the data is shown in figure 3:

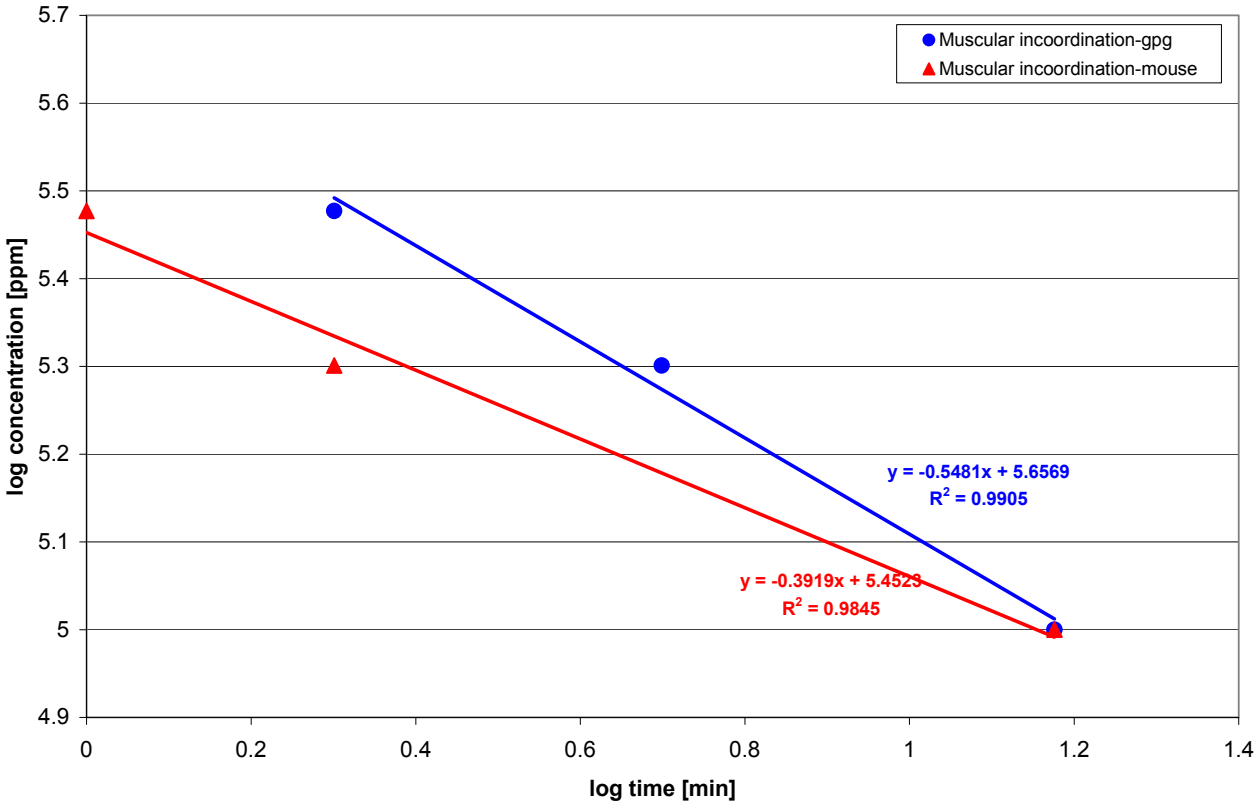

FIGURE 3: REGRESSION ANALYSIS OF THE LOG-LOG TRANSFORMED CONCENTRATION-TIME CURVE REGARDING MUSCULAR INCOORDINATION IN MICE AND GUINEA-PIGS (DATA FROM MASTROMATTEO ET AL., 1960)

The slope of the regression line was -0.3919 and -0.5481 in mice and guinea pigs, respectively, corresponding to a value of 2.6 and 1.8 for n.

Side position:

The time after which side position was observed in mice after exposure to 100,000, 200,000 or 300,000 ppm VC was 20 min, 5 min, and 2 min, respectively:

Time min	Concentration ppm	Log time	Log Concentration
2	300000	0.301	5.477
5	200000	0.699	5.301
20	100000	1.301	5

The time after which side position was observed in guinea pigs after exposure to 100,000, 200,000, or 300,000 ppm VC was 30 min, 10 min, 2-5 min (set to 3.5), respectively:

Time min	Concentration ppm	Log time	Log Concentration
35	300000	0.544	5.477
10	200000	1	5.301
30	100000	1.477	5

Regression analysis of the data is shown in figure 4:

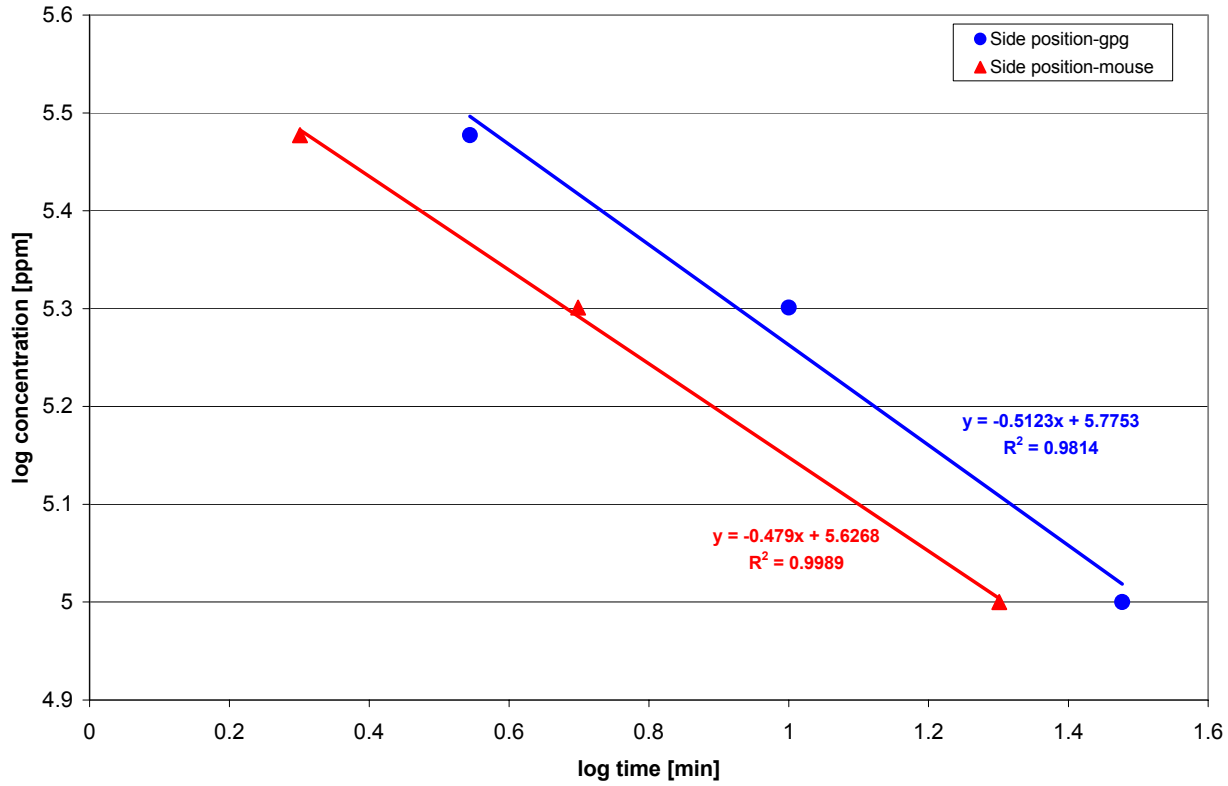

FIGURE 4: REGRESSION ANALYSIS OF THE LOG-LOG TRANSFORMED CONCENTRATION-TIME CURVE REGARDING SIDE POSITION IN MICE AND GUINEA-PIGS (DATA FROM MASTROMATTEO ET AL., 1960)

The slope of the regression line was -0.479 and -0.5123 in mice and guinea pigs, respectively, corresponding to a value of 2.1 and 2.0 for n.

Regarding the three different endpoints and the data obtained for mice and guinea pigs values for n were in the range of 1.44 to 2.6 (1.44; 1.46; 1.8; 2.0; 2.1; 2.6; arithmetic mean: 1.9 +/- 0.4). Based on these data it is justified to use a value of n=2 for the time extrapolation for AEGL-2 (CNS-effects) and AEGL-3 (cardiac sensitization) values up to two hours. Concentrations for these “less-than-steady-state“ durations (i.e. 10, 30, 60 and 120 minutes) should be calculated according to

$$C^2 * t = \text{const.}$$

APPENDIX C - Cancer Assessment of Vinyl Chloride

Cancer Assessment of Vinyl Chloride

The most recently published risk estimate from the US EPA seems to be the best unit risk estimate currently available (US EPA 2000 a, b). The values are 8.8×10^{-6} $(\mu g/m^3)^{-1}$ for continuous lifetime exposure, including childhood, and 4.4×10^{-6} $(\mu g/m^3)^{-1}$ for continuous exposure as an adult. These risk values indicate that exposure during childhood results in a similar tumor incidence as exposure as an adult. The EPA unit risk calculation was derived by using the PBPK model of Clewell et al. (1995, 2002). These risk values are based on model-derived estimates of internal dose of the active metabolite in animals and the continuous external exposure in humans that would result in these same internal dose of the active metabolite.

Several calculations for cancer risk are presented below. These are:

Calculation A: based on the unit risk for continuous lifetime exposure from EPA (2002 a, b), transformed to a single 24 hour exposure estimate by the default procedure recommended in the SOP on AEGL development (that is, linear transformation, correction by a factor of 6 to account for the relevance of sensitive stages in development). Exposures of less than 24 hours are derived using the PBPK model of Clewell et al. (1995, 2002).

Calculation B: based on the unit risk for childhood exposure only (possibly the first 10 years of age) as estimated by US EPA (2002 a, b), transformed to a single 24 hour exposure estimate by the default procedure recommended in the SOP on AEGL development (that is, linear transformation, correction by a factor of 6 to account for the relevance of sensitive stages in development). Exposures of less than 24 hours are derived using the PBPK model of Clewell et al. (1995, 2002).

Calculation C: based on the cancer incidence as evident from a five-weeks animal study from Maltoni et al. (1981), assuming that 5 weeks of exposure of animal is equivalent to about 150 weeks exposure of humans, with linear transformation to a single 24 hour exposure without further correction for potential sensitive stages of tumor development. Exposures of less than 24 hours are derived using the PBPK model of Clewell et al. (1995, 2002).

Calculation D: based on the NOAEL for DNA adducts after single in vivo exposure of adult animals and the application of an uncertainty factor for intraspecies variability.

Calculation C is judged to be the best basis for estimation of the risk for carcinogenic effects after single exposure and is included into the main part of the TSD. However, substantial uncertainties on risk quantification exist.

Calculation A: based on the unit risk for continuous lifetime exposure from EPA (2002 a, b), transformed to a single 24 hour exposure estimate by the default procedure recommended in the SOP on AEGL development (that is, linear transformation, correction by a factor of 6 to account for the relevance of sensitive stages in development). Exposures of less than 24 hours are derived using the PBPK model of Clewell et al. (1995, 2002).

AEGL SOP Calculation

The US EPA's unit risk estimate for continuous lifetime exposure (inclusive of childhood) is 8.8 x 10^{-6} ($\mu g/m^3$)$^{-1}$. This unit risk was derived using the PBPK model of Clewell et al (1995, 2002) which relates liver tumor incidence in animals with the lifetime average daily dose of the vinyl chloride metabolite in the liver believed responsible for the tumor response (that is, the internal dose of the metabolite). The model then uses human parameters to transform that internal dose to an external exposure concentration for humans.

Unit risk for continuous lifetime exposure: 8.8 x 10^{-6} per $\mu g/m^3$

Exposure at a risk of 1 in 10,000: 11.36 $\mu g/m^3$

To convert a 70 year exposure to a 24 hour exposure, the exposure is multiplied by the number of days in 70 years. Under this strict c x t assumption, these exposures are considered equipotent.

11.36 $\mu g/m^3$ x 25,600 = 291 mg/m^3

To account for uncertainty regarding the variability in the stage of the cancer process at which VC or its metabolites may act, a multistage factor of 6 is applied (NRC, 2001).

291 mg/m^3 x 1/6 = 48.5 mg/m^3 (18.4 ppm)

Based on this transformation, a 24 hour VC exposure at this concentration would result in a 10^{-4} risk. For 10^{-5} and 10^{-6} risk, the 10^{-4} value is reduced by 10- and 100-fold, respectively. This estimate is based on the assumption of a strict c x t relationship.

PBPK model calculations for an exposure less than 24 hours

As mentioned above, the basis of US EPA's risk estimate is the internal dose, the lifetime average daily dose(LADD) of VC metabolite in the liver. For numerous reasons this metric may be quite different after a single exposure of less than 24 hours. Rather than make any assumption about the extent to which c x t may or may not be operative, the PBPK model was used to estimate directly the internal dose to the liver under different external exposure regimes. These data are shown in the table and figure below.

From above, the external exposure corresponding to a 10^{-4} risk with a 24 hour exposure is 48.5 mg/m^3. Values for less than 24 hour exposure are determined by interpolation using Table 1. The internal dose metric (mg/L Liver) corresponding to a 10^{-4} risk with a 24 hour exposure is 51.4 mg/L (48.5 mg/m^3 divided by 100 mg/m^3 times 106 mg/L. The external exposure necessary to give 51.4 mg/L Liver after an 8 hour exposure is 147 mg/m^3 (51.4 mg/L divided by 35.0 mg/L times 100 mg/m^3). A corresponding calculation was made for each exposure duration (0.5 hours, 1 hr, 4 hrs, and 8 hrs) and each risk level (10^{-4}, 10^{-5}, and 10^{-6}).

Dose to the liver (mg/L) of active metabolite at 24 hours after exposure to VC

mg/m^3	0.5 hr	1 hr	4 hr	8 hr	24 hr/70 yrs
1	0.022	0.044	0.176	0.352	1.07
10	0.220	0.441	1.76	3.52	10.7
100	2.19	4.38	17.5	**35.0**	**106**
200	4.36	8.72	34.8	69.4	211
300	6.50	13.0	51.8	103	313
400	8.61	17.2	68.4	136	413
500	10.7	21.3	84.5	169	510
600	12.7	25.2	100	199	604
700	14.6	29.1	115	229	692
800	16.5	32.7	129	256	775
900	18.2	36.1	142	282	850
1000	19.9	39.3	153	304	917
2000	30.4	57.7	211	412	1220
3000	35.7	65.8	231	442	1300
4000	39.7	71.9	243	461	1350
5000	43.3	77.2	254	476	1390
6000	46.6	82.1	264	490	1420
7000	49.7	86.7	273	502	1460
8000	52.3	91.1	279	513	1490
9000	54.7	95.3	284	523	1520
10000	57.0	99.3	289	533	1540

Figure 5 shows the PBPK modeling results graphically (with a cut-off for the external concentration at 2000 mg/m^3).

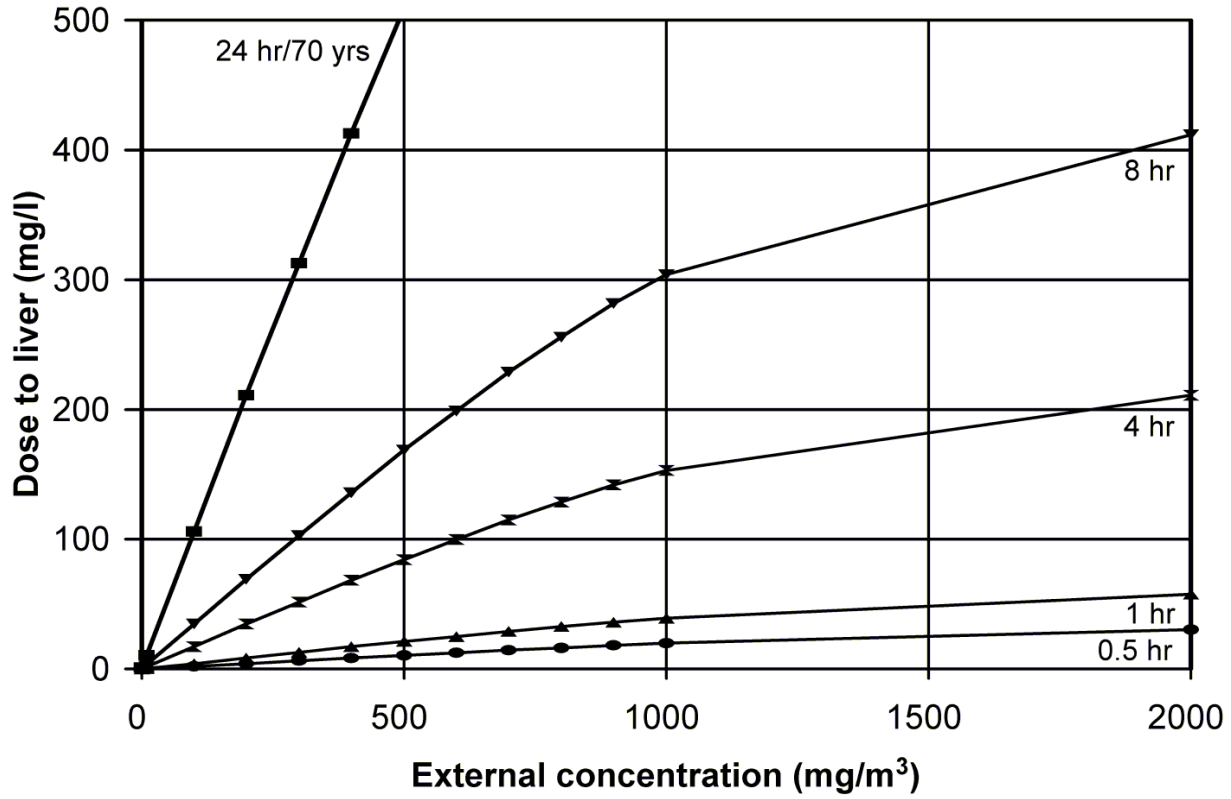

FIGURE 5: EXTERNAL CONCENTRATION (mg/m^3) AND DOSE TO LIVER (mg/L) AS CALCULATED BY PBPK-MODELING BY EPA (Personal Communication, Gary Foureman, US EPA, NCEA-RTP, June 2003)

If the exposure is limited to a fraction of a 24-hour period, the exposure corresponding to the various risk levels are presented in the table below.

Exposure Duration	10^{-4} risk	10^{-5} risk	10^{-6} risk
8 hours	147 mg/m^3 (55.9 ppm)	14.6 mg/m^3 (5.55 ppm)	1.46 mg/m^3 (0.555 ppm)
4 hours	298 mg/m^3 (113 ppm)	29.2 mg/m^3 (11.1 ppm)	2.92 mg/m^3 (1.11 ppm)
1 hour	1780 mg/m^3 (676 ppm)	117 mg/m^3 (44.5 ppm)	11.6 mg/m^3 (4.45 ppm)
30 minutes	7870 mg/m^3 (2990 ppm)	236 mg/m^3 (89.7 ppm)	23.3 mg/m^3 (8.97 ppm)

Calculation B: based on the unit risk for childhood (possibly first 10 years of age) as estimated by EPA (2000 a,b), transformed to a single exposure estimate by the default procedure, recommended in the SOP on AEGL development (i.e. linear transformation, correction by a factor of 6 to account for the relevance of sensitive stages in development). Exposures of less than 24 hours derived using the PBPK model of Clewell et al. (1995, 2002).

The unit risk calculation of EPA is based on the occurrence of angiosarcoma in newborn rats (5 weeks exposure) which were observed with similar incidences as in adult female rats (52 weeks exposure beginning at 13 weeks of age; see Table C1). Thus, the unit risk for adults (long term study) was directly calculated and was assumed to be roughly identical for childhood (first 10 years of exposure).

unit risk for continuous childhood exposure: 4.4×10^{-6} per $\mu g/m^3$ (first 10 years)
dose at risk 1 : 10,000: 22.73 $\mu g/m^3$

To convert a 10 year exposure (= 10 x 365.7 = 3657) to a 24 hours exposure, the dose is multiplied by the number of days in 10 years:

$22.73\ \mu g/m^3 \times 3657 = 83.1\ mg/m^3$

To account for uncertainty regarding the variability in the stage of the cancer process at which VC or its metabolites may act, a multistage factor of 6 is applied (NRC, 2001):

$83.1\ mg/m^3 \times 1/6 = 13.85\ mg/m^3$

Therefore, based upon the potential carcinogenicity of VC during early life, a 24 h exposure corresponding to a 10^{-4} risk would be 13.85 mg/m^3 (5.26 ppm). For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold and 100-fold, respectively.

If the exposure is limited to a fraction of a 24-hour period, the exposure corresponding to the various risk levels are presented in the table below. These values were calculated using the PBPK model for vinyl chloride as described above for calculation A.

Exposure Duration	**10^{-4} risk**	**10^{-5} risk**	**10^{-6} risk**
8 hours	42.1 mg/m^3 (16.0 ppm)	4.21 mg/m^3 (1.60 ppm)	0.421 mg/m^3 (0.160 ppm)
4 hours	84.5 mg/m^3 (32.1 ppm)	8.41 mg/m^3 (3.20 ppm)	0.840 mg/m^3 (0.329 ppm)
1 hour	342 mg/m^3 (130 ppm)	33.6 mg/m^3 (12.8 ppm)	3.36 mg/m^3 (1.28 ppm)
30 minutes	709 mg/m^3 (269 ppm)	67.5 mg/m^3 (25.7 ppm)	6.72 mg/m^3 (2.55 ppm)

Calculation C: based on the cancer incidence as evident from a five-weeks animal study from Maltoni et al. (1981), assuming that 5 weeks of exposure of animal is equivalent to about 150 weeks exposure of humans, with linear transformation to a single 24 hour exposure without further correction for potential sensitive stages of tumor development. Exposures of less than 24 hours are derived using the PBPK model of Clewell et al. (1995, 2002).

The study seems to be relevant, as

- investigations were performed with newborn rats which represent a sensitive subgroup for the endpoint carcinogenesis
- exposure was over a short period of time
- endpoints (incidence of liver angiosarcoma) are relevant for humans.

Data are shown in table C1:

TABLE C1: INCIDENCE OF TUMORS IN THE STUDIES FROM MALTONI ET AL., 1981, (EXPERIMENTS BT 14 AND BT 1), CITED FROM EPA, 2000a

Administered concentration (ppm)	Angiosarcoma	Hepatoma
4 hours/day, 5 days/week for **5 weeks** starting **at day 1** (BT 14)		
6000	20/42 (48%), all* 17/42 (40.5%) ,LAS*	20/42 (47,6 %)
10000	18/44 (41%), all* 15/44 (34.1%), LAS*	20/44 (45,4 %)
4 hours/day, 5 days/week for **52 weeks** starting **at age 13 weeks** (BT 1)		
6000	22/42 (52%), all* 13/42 (31%), LAS*	1/27 (3,7%)
10000	13/46 (28 %), all* 7/46 (15%), LAS*	1/24 (4,2%)

* Angiosarcoma, all sites include extra-liver angiosarcoma, including angioma; LAS: liver angiosarcoma (only those were taken for further risk quantifications)

Derivation on the Inhalation Unit Risk

Exposure concentration: 6,000 ppm
liver angiosarcoma 40.5 %

6,000 ppm corresponds to a human equivalent concentration of 51 ppm (132 mg/m^3), based on the PBPK model published by Clewell et al. (1995). Corresponding data are shown in table C2 (note that rats exposure is intermittent (4hours/day; 5 days/week) compared to HEC (human equivalent exposure) which is given for continuous exposure (24 hours/day)). Note further that saturation in rats leads to only minor increases of metabolite concentrations, when exposure exceeds 250 ppm (intermittent exposure). The derivation of the Inhalation Unit Risk is based on the assumption that the tumor response is a linear function of the concentration of the active metabolite in the liver (HEC). See Table C2.

132 mg/m^3 = 40.5%;
=> 3.3 mg/m^3 = 1%;
=> 33 µg/m^3 = 0.01% = 1:10,000

dose at risk (1:10,000): 33.0 μg/m^3

conversion from 5 weeks to 24 h exposure:

Newborn rats grow about 30 times faster than newborn humans (NRC, 1993), which is similar to the ratio of lifetime 75 years (human): 2.5 years (rat) = 30. 5 x 7 x 30 =1050

33,0 μg/m^3 x 1050 days = 34.7 mg/m^3 (14 ppm)

An additional factor to adjust for uncertainties in assessing potential cancer risks under short term exposures is not applied, as exposure was short-term in the underlying study.

Therefore, based upon the potential carcinogenicity of VC during early life, a 24 h exposure corresponding to a 10^{-4} risk would be 34.7 mg/m^3 (13.2 ppm). For 10^{-5} and 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold and 100-fold, respectively.

If the exposure is limited to a fraction of a 24-hour period, the exposure corresponding to the various risk levels are presented in the table below. These values were calculated using the PBPK model for vinyl chloride as described above for calculation A.

Exposure Duration	**10^{-4} risk**	**10^{-5} risk**	**10^{-6} risk**
8 hours	106 mg/m^3 (40.3 ppm)	10.5 mg/m^3 (3.99 ppm)	1.05 mg/m^3 (0.399 ppm)
4 hours	213 mg/m^3 (80.9 ppm)	21.0 mg/m^3 (7.98 ppm)	2.10 mg/m^3 (0.798 ppm)
1 hour	922 mg/m^3 (350 ppm)	84.4 mg/m^3 (32.1 ppm)	8.40 mg/m^3 (3.19 ppm)
30 minutes	3110 mg/m^3 (1180 ppm)	170 mg/m^3 (64.6 ppm)	16.8 mg/m^3 (6.38 ppm)

A similar result is obtained if the tumor data from Froment et al. (1994) are used. Froment et al. exposed the newborn animals to only 500 ppm. Hence, fewer extrapolations were needed compared to the Maltoni et al. data. (Data and calculation not shown). For both calculations, relevant uncertainty on the influence of the oral uptake of mothers´milk has to be stated. Because of metabolic saturation at high level inhalation exposure, this influence may have been limited. However, no estimate of the quantitative consequences of this multi pathway exposure may be given.

TABLE C2: CONVERSION OF ADMINISTERED VC DOSE TO A HUMAN EQUIVALENT CONCENTRATION (data from EPA, 2000a, b)

Admin. conc. (ppm)[a]	Metabolite (mg/L liver)[b]	HEC (ppm)[c]
0	0	0
1	0.59	0.2
5	2.96	1
10	5.9	2
25	14.61	4.6
50	31.27	10.1
100	55.95	19
150	76.67	26
200	90	31
250	103.45	35
500	116.94	40
2500	134.37	48
6000	143.72	51

a Animals exposed 4 hours/day, 5 days/week for 52 weeks.
b Dose metric (lifetime average delivered dose in female rats) calculated from PBPK modeling of the administered animal concentration.
c Continuous human exposure concentration over a lifetime required to produce an equivalent mg metabolite/L of liver.

Calculation D: based on the NOAEL for DNA adducts after single in vivo exposure of adult animals and the application of an uncertainty factor for intraspecies variability.

DNA-adducts seem to be relevant and quantitatively linked to carcinogenic potency of VC:

- ethenobases were shown to possess miscoding properties (Barbin, 2000) and are slowly repaired (Morinello et al., 2002a)
- ethenobases generate mainly base pair substitution mutations (Barbin, 2000)
- ethenobases assumed to be initiating lesions in carcinogenesis (Barbin, 2000)
- high correlation between DNA-adducts formation (εG) and incidence of haemangiosarcoma in mice after exposure to vinyl fluoride (Swenberg et al., 1999)

Elevated DNA-adducts were seen after single 5 hour exposure of adult rats to 250 ppm VC (Bolt et al.,1980). Watson et al. (1991) exposed adult male Fisher 344 rats for 6 hours to atmospheres containing 1, 10, or 45 ppm VC. The alkylation frequencies of 7-(2'-oxoethyl)guanine (OEG) in liver DNA were 0.026, 0.28 and 1.28 residues OEG per 10^6 nucleotides respectively. With these air concentrations, there was no evidence to indicate the formation of the cyclic adducts 1,N^6-ethenoadenine (εA) or 3,N^4-etheno-cytosine (εC). The threshold for detection of these adducts were about 1 adduct per 1 x 10^8 nucleotides.

Swenberg et al. (1999) reported a factor 1/10 - 1/100 to calculate the amount of N^2,3-ethenoguanine (εG) in relation to OEG. Thus, εG would be lower than 0.1 - 0.01 per 10^6 nucleotides at 45 ppm. This would equal the reported background of εG (Swenberg et al., 1999). It may be concluded that single exposure to 45 ppm VC (6 hours) would not lead to an increase of relevant cyclic adducts (εA, εC, εG) in adult rats.

With higher DNA-adduct levels (at higher single exposure, or in young rats, or after repeated short term exposure) there apparently is a relevant correlation to mutations, foci or carcinogenicity: Adult rats repeatedly (5 days) exposed to 10 ppm VC for 6 hours/day showed slightly elevated etheno-adducts (εG) compared to control (Swenberg et al., 2000). Higher adduct levels were seen in young animals than in adult animals after identical treatment (Fedtke et al., 1990; Laib et al., 1989; Ciroussel et al.,1990, Morinello et al., 2002a). Respective mutations (e.g., G->A transitions, A->T transitions) were observed in VC-induced tumors (Barbin, 2000). Despite relevant repair, no full reduction to background was observed for these adducts two weeks after a 5 day exposure (4 hours/day) to 600 ppm (Swenberg et al., 1999).DNA-adducts formation (εG) in whole liver DNA or hepatocytes increased linearly from 5 days to 8 weeks after exposure of rats to 500 ppm or 10 ppm VC (Morinello et al.,2002a). Table C3 presents the data for relevant DNA-adducts after short term exposure to VC for different concentrations and exposure durations and gives an indication about the reversibility.

TABLE C3: DNA-ADDUCTS AFTER SINGLE AND SHORT TERM VC EXPOSURE

VC-inhalation (ppm)	0	1	10	45	100	600
7-(2'-oxoethyl)guanine (OEG) [adducts/ nucleotides][1]		$0.026/10^6$	$0.28/10^6$	$1.28/10^6$		
$1,N^6$-ethenoadenine (εA)[1]				$<1/10^8$		
$3,N^4$-ethenocytosine (εC)[1]				$<1/10^8$		
N^2,3-ethenoguanine (εG)*				$\approx 1/10^8$		
for comparison[2]:						
εG- Background (rat)	$0.9/10^7$					
εG, 5 days			$2/10^7$		$6.8/10^7$	
εG, 20 days			$5.3/10^7$		$2.3/10^6$	
εG, 4h/d, 5d, immed. after exposure						$3.8/10^6$
εG, 4h/d, 5d, 14 days after exposure						$4.7/10^7$
εG- Background (human)	$6/10^8$ -$7/10^7$					

* estimated (εG) by the authors of the TSD from ratio ≈ 1/100 OEG/εG in other VC experiments

[1] data from Watson et al.,1991; [2] data from Swenberg et al.,1999

TABLE C4: ADDUCTS RATIO NEONATE: ADULT FOR VINYL CHLORIDE			
Swenberg et al., 1999 (OEG) 600 ppm 5d, 4h/d, rat	Swenberg et al., 1999 (εG) 600 ppm 5d, 4h/d, rat	Ciroussel et al., 1990 (εdAdo/dAdo) 500 ppm 2 weeks, 7h/d, rat	Ciroussel et al., 1990 (εdCyd/dCyd) 500 ppm 2 weeks, 7h/d, rat
162/43≈3.8	1.81/0.47≈3.9	1.3/0.19≈6.8	4.92/0.8≈6.15

calculation of an practical threshold ("NAEL") for short term exposure:

Intraspecies: Because of the high sensitivity of young animals an intraspecies factor of 10 is regarded as necessary. This is supported by comparisons between effects at different ages based on tumors, foci or DNA-adducts. For DNA-adducts a comparison is shown in table C4.

Interspecies: There is no apparent higher sensitivity of men compared to rats, which is supported by the comparison of unit risks derived from animal data respectively human data (Clewell et al., 2001). This leads to an uncertainty factor for interspecies differences of 1 (EPA, 2000a).

Exponent for time extrapolation: Steady state is not reached within 8 hours as evidenced by the longer halftime of metabolites. Thus, default time extrapolation should be performed based on the observed NOAEL at 6 hours exposure. This leads to an estimated close to background level as quantified by the calculations below:

Key study:	Watson et al.,1991; Swenberg et al., 1999; Barbin, 2000
Toxicity endpoint:	DNA-adducts; background adduct levels at single 45 ppm exposure of rats is taken as practical "NAEL" (6 hours)
Uncertainty/ modifying factors:	Combined uncertainty factor of 10 1 for interspecies variability 10 for intraspecies variability
Time Scaling:	$C^3 \times t = k$ for extrapolation to 4-hour, 1-hour, and 30-minute; $k = (45\ ppm)^3 \times 360\ min = 3{,}2 \times 10E{+}7\ ppm^3\ min$ $C^1 \times t = k$ for extrapolation to 8-hours; $k = 45\ ppm \times 360\ min = 16{,}200\ ppm^1\ min$
30-minute:	$C^3 \times 30\ min = 3{,}2 \times 10E{+}7\ ppm^3\ min$ $C = 103\ ppm$ 30-min NAEL = 103 ppm/10 = **10 ppm** (= 26 mg/m^3)
1-hour:	$C^3 \times 60\ min = 3{,}2 \times 10E{+}7\ ppm^3\ min$ $C = 81.8\ ppm$ 1-h NAEL = 81.8 ppm/10 = **8.2 ppm** (= 21 mg/m^3)

4-hour: C^3 x 240 min = 3,2 x 10E+7 ppm^3 min
C = 51.5 ppm
4-h NAEL = 51.5 ppm/10 = **5.1 ppm** (= 13 mg/m^3)

8-hour: C x 480 min = 16200 ppm min
C = 33.75 ppm
8-h NAEL = 34 ppm/10 = **3.4 ppm** (= 8.8 mg/m^3)

Concluding remark:

Table C5 provides an overview of the calculations on carcinogenic potency after single exposure as derived above compared to the AEGL- values derived based on nonmalignant effects.

TABLE C5: COMPARISON OF AEGL VALUES (VC) BASED ON NONMALIGNANT EFFECTS AND DIFFERENT ESTIMATIONS OF CARCINOGENIC RISK AFTER SINGLE EXPOSURE

[ppm]	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1(Baretta et al., UF:3; n=3,1)	450	310	250	140	70
AEGL-2 (Lester et al.,UF:3; n=2 to 2h; 2h=4h=8h)	2800	1600	1200	820	820
AEGL-3 (Clark & Tinston; UF:3; n=2 to 2h; 2h=4h=8h)	12000	6800	4800	3400	3400
Estimation of carcinogenic potency (10^{-4} risk):					
CALCULATION A (unit risk) default SOP; linear transformation lifetime unit risk x 6		2990	676	113	55.9
CALCULATION B (unit risk) linear transformation, early life=10 years, x 6		269	130	32.1	16
CALCULATION C (Maltoni et al., 1981, risk-direct from 5w-study); Human equivalent dose to 6000 ppm; growth rate rat/hum: 30		1180	350	80.9	40.3
CALCULATION D (Watson et al., (DNA)), UF:3; n=3: 30,60, 120,480 min; n=1: 8h; 10 min=30min.		10	8.2	5.1	3.4

Calculation C is judged to be the best basis for estimation of the risk for carcinogenic effects after single exposure and is included into the main part of the TSD. However, substantial uncertainties on risk quantification persists.

APPENDIX D - Occupational epidemiological studies on carcinogenicity (focus: limited exposure time)

Two large studies of workers employed in the VCM/PVC industry prior to 1974 were completed. Both studies were retrospective cohort mortality studies. The first study was done in Europe and included study populations in Italy, Norway, Sweden and United Kingdom. The second study included plants in the United States and Canada. Each study has been updated multiple times and has been the subject of numerous papers. Only the results from the most recent updates are discussed here. The focus is to review the liver cancer incidence in workers exposed to VCM for relatively short time periods or where the cumulative dose (ppm-years) was known to have been low. Both studies have more deaths than expected from ASLs among workers with high and/or long exposure to VCM (Ward et al., (2000) and Mundt et al., (1999)). A third study from Weber et al. (1981) with epidemiologic data from Germany shows conflicting results to the above cited large studies.

European Study

The European study includes approximately 12,700 men with at least one year of employment in the VCM/PVC industry from 1955 to 1974 (Ward et al., 2000). Three of the 19 plants had incomplete records and thus the starting date for these three plants ranged from 1961 to 1974. The vital status follow-up was complete through 1997. Age- and calendar period-specific mortality rates for males from Italy, Norway, Sweden and United Kingdom were used to calculate the Standardized Mortality Ratios (SMR) and Confidence Intervals (CI). Typical exposure scenarios were estimated by industrial hygienists based on job exposure matrices. These job exposure matrices were based primarily on job title and were reviewed by two other industrial hygienists with several years of experience in the VC industry. Information provided in the job exposure matrix was used to develop a ranked level of exposure index. Quantitative estimates of exposure were obtained for 82% of the cohort.

The total number of person-years at risk by the cohort is 324,701. The work force was classified by duration of employment, <3, 3-6, 7-11, 12-18 and 19+ ppm-years. The SMR (CI) for liver cancer for workers with less than 3 years experience was 62 (2-345), below the expected value (Table D1). For workers exposed to VCM/PVC for a longer time period, the incidence of liver cancer was higher than expected. In general, the incidence of liver cancer increased with years of employment in the VCM/PVC industry.

In addition, Ward et al., (2000), examined cumulative exposure for the cohort (Table D2). Again, the work force was subdivided into 0-734, 735-2379, 2380-5188, 5189-7531 and 7532+ ppm-years. The SMR (CI) was 107 (54-192) based on 11 observed liver cancers and 10.26 expected. Assuming workers are employed in the industry for up to 30 years, to be included in this first category, the highest average concentration the worker would have been exposed to was ~25 ppm. Workers with shorter work histories may have been exposed to much higher concentrations. Under this scenario there was no increase in the incidence of liver cancer. As previously noted, the incidence of liver cancer increased with cumulative exposure with an SMR (CI) of 1140 (571-2050) for those workers with a cumulative exposure of 7532+ ppm-years. However, of the 11 liver cancers observed in the 0-734 ppm-year cumulative exposure group, fours were angiosarcomas. These four angiosarcomas occurred in individuals with 287-734 ppm-years cumulative exposure (Ward et al., 2001). There were no angiosarcomas reported in workers with less than 287 ppm-years cumulative exposure.

North American Study

The North American study consists of approximately 10,100 men employed for at least one year in the VCM/PVC industry from 1942-1974 (Mundt et al., 1999). This group was followed through December 31, 1995. Thus, most workers have been followed for at least twenty one years. Since the VCM/PVC industry was located in 16 states and one Province of Canada, mortality rates for 16 states were used to calculate SMR's. For the Province of Canada, mortality rate data from the state of Michigan was used since it was geographically the closest to the plant. As of December 31, 1995, 30% of the study group were deceased Although the authors of previous studies had attempted to categorize individuals by exposures, no consistent criteria had been used and thus no attempt was made to estimate exposure levels in this study.

The age at first exposure, duration of exposure and year of first exposure appeared to be related to cancer of the liver and biliary tract (data not shown). Of these, duration of exposure had the greatest significance and appeared to be independent of age at first exposure and year of first exposure (Table D3). Mundt categorized the cohort into groups working 1-4, 5-9, 10-19 or 20+ years in the VCM/PVC industry. Nearly half of the cohort worked for less than 5 years in the VCM/PVC industry with fewer workers in each of the subsequent groups. This data shows that working in the VCM/PVC industry for 1-4 years resulted in a slightly lower liver cancer rate than expected. Working in this industry for longer periods of time resulted in higher death rates than expected for liver and biliary tract cancer. Mundt et al. (2000) also examined the incidence of angiosarcomas based on duration of exposure. Three individuals working in the VCM/PVC industry for 1-4 years have ASLs. No further information on exposure or job classification was provided.

Both of these studies have shown that working in the VCM/PVC industry for <3 years or to a low, but still relevant, estimated concentration of VCM resulted in liver cancer rates very close to expected values. A low incidence of ASLs was reported by both Ward et al. (2000) and Mundt et al. (2000) but based on the Ward study appeared to be related to higher ppm-years exposure.

TABLE D1: LIVER CANCER INCIDENCE FOR ALL EUROPEAN COUNTRIES BY DURATION OF EMPLOYMENT[A]

Duration of Employment (years)	Incidence Number of Individuals[b]	Number of person years	(Observed/ Expected)	SMR (95%CI)[c]
<3	10961	91970	1/1.61	62 (2-345)
3-6	8999	79747	3/1.44	208 (43-609)
7-11	6919	65789	7/1.35	517 (208-1060)
12-18	4610	55149	5/1.42	352 (114-821)
19+	2006	32050	13/1.46	893 (475-1530)
Total	12700	324706	29/7.29	398 (267-572)

[a] From Tables T1.7 and D7 of Ward et al., (2000).
[b] Number of individuals cited for various employment intervals add up to greater than 12,700 since individuals can meet more than one criteria as defined by the author.
[c] SMR = Observed/Expected *100. CI = Confidence Intervals.

TABLE D2: LIVER CANCER INCIDENCE FOR ALL EUROPEAN COUNTRIES BY CUMULATIVE EXPOSURE[A]				
Cumulative Exposure (ppm-years)	**Number of Individuals[b]**	**Number of person years**	**Incidence (Observed/ Expected)**	**SMR (95%CI)[c]**
Unknown	2243	52300	2/3.19	63 (8-227)
0-734	9552	188204	11/10.26	107 (54-192)
735-2379	2772	43174	9/3.32	271 (124-515)
2380-5188	1463	26480	10/2.62	382 (183-703)
5189-7531	515	9274	10/1.77	566 (271-1040)
7532+	215	5274	11/0.96	1140 (571-2050
Total	12700	324706	53/22.11	240 (1800-3140)

[a] From Tables 12 and D7 of Ward et al., (2000).
[b] Number of individuals cited for various employment intervals add up to greater than 12,700 since individuals can meet more than one criteria
[c] SMR = Observed/Expected *100. CI = Confidence Intervals.

TABLE D3: LIVER AND BILIARY TRACT CANCER INCIDENCE FOR THE UNITED STATES BY DURATION OF EMPLOYMENT[A]				
Duration of Employment (years)	**Number of Individuals**	**Number of person years**	**Incidence (Observed/ Expected)**	**SMR (95%CI)[b]**
1-4	4774	136200	7/8.43	83 (33-171)
5-9	2383	71806	10/4.65	215 (103-396)
10-19	1992	69015	39/5.74	679 (483-929)
20+	960	39524	24/3.49	688 (440-1023)
Total	10109			

[a] From Tables 21 and 23 of Mundt et al., (1999).
[b] SMR = Observed/Expected *100. CI = Confidence Intervals.

Study from Weber et al., 1981

Three German cohorts were investigated: Group 1 (VCM/PVC production; 7021 persons; 73734 person years, Group 2, (reference group, 4910 persons; 76029 person years), Group 3 (PVC processing, 4007 persons; 52 896 person years). West German reference mortality rates were used for comparison. Malignant tumors of the liver occurred in 12 cases (VCM/PVC production; SMR=1523) or 4 cases in the reference group (SMR=401) or 3 cases in PVC processing (SMR=434). No confidence intervals were provided. No exposure concentration is known. The subclassification according to duration of employment demonstrates increased mortality already after little more than 1 year of exposure (Table D4). Results from this study together with the results from the studies cited above are included in a meta-analysis from Boffetta et al. (2003) and illustrated by graphical presentation (see figure 1; Boffetta et al.,

2003) showing the conflicting information about minimum exposure duration for adult workers to have a increased tumor risk.

TABLE D4: LIVER CANCER IN VCM/PVC-PRODUCTION AND DURATION OF EXPOSURE[a]

Duration of Employment (months)	Cases	SMR	
<12	0	-	-
13-60	2	874	beyond 95th confidence interval
61-120	3	1525	beyond 99th confidence interval
>121	7	2528	beyond 99th confidence interval
Total	12		

[a] From Table 3, Weber et al., 1981.

APPENDIX E - Derivation Summary for Vinyl Chloride AEGLs

ACUTE EXPOSURE GUIDELINES FOR VINYL CHLORIDE (CAS Reg. NO. 75-01-4)

AEGL-1 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
450 ppm	310 ppm	250 ppm	140 ppm	70 ppm

Reference: Baretta, E.D., R.D. Stewart, J.E. Mutchler, 1969. Monitoring exposures to vinyl chloride vapor: breath analysis and continuous air sampling. *American Industrial Hygiene Association Journal*, 30, 537-544.

Test Species/Strain/Sex/Number: human volunteers, male, 4-7 individuals

Exposure Route/Concentrations/Durations: inhalation; 3.5 hours; 459 - 491 ppm, 3.5 - 7.5 hours

Effects: mild headache, some dryness of eyes and nose in 2/7 subjects

Endpoint/Concentration/Rationale: Endpoints relevant for the derivation of AEGL-1 values for VC have are: a) headache, b) odor recognition or detection, c) irritation. Occurrence of mild headache has been reported by Baretta et al. (1969) in two subjects after acute exposure, an endpoint which can be regarded as NOAEL for AEGL-1. No qualified studies on odor recognition or detection are reported for VC. Irritation in humans or animals is only reported in the context of exposure to very high concentrations which are lethal or cause unconsciousness. The mechanism by which headaches developed are not clearly understood. The derived AEGL-1 does not necessarily exclude mutagenic or tumorigenic effects by VC at similar or lower concentrations.

Uncertainty Factors/Rationale: The intraspecies uncertainty factor of 3 is used to compensate for both, toxicokinetic and toxicodynamic differences between individuals. For headaches, no or only very slight effects would be expected for the general public after inclusion of an intraspecies factor of 3 on the "mild" effects observed in volunteers.

Modifying Factor: not applicable

Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: The duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent. The extrapolation to 10 minutes from a 3.5 hour exposure is justified because exposure of human at 4,000 ppm for 5 minutes did not result in headache (Lester et al., 1963).

Data Adequacy: The study of Baretta et al. (1969) has been regarded as qualified for the derivation of AEGL-1 values and the endpoint is supported by several findings from occupational studies (Lilis et al., 1975; Suciu et al., 1975; EPA, 1987). Confirmation of the observed effects in other studies with controlled exposure would be helpful, but may not be performed due to ethical reasons.

ACUTE EXPOSURE GUIDELINES FOR VINYL CHLORIDE (CAS Reg. NO. 75-01-4)

AEGL-2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
2,800 ppm	1,600 ppm	1,200 ppm	820 ppm	820 ppm

Reference: Lester, D., L.A. Greenberg, W.R. Adams, 1963. Effects of single and repeated exposures of humans and rats to vinyl chloride. *American Industrial Hygiene Association Journal*, 24, 265-275; Clark, D.G., D.J. Tinston, 1973. Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties. Br. J. Pharm., 49, 355-357. Mastromatteo, E., A.M. Fisher, H. Christie, H. Danziger, 1960. Acute inhalation toxicity of vinyl chloride to laboratory animals. Am. Ind. Hyg. Assoc. J., 21, 394-398.

Test Species/Strain/Sex/Number: human male (n=3) and female (n=3) volunteers, 6 persons

Exposure Route/Concentrations/Durations: Inhalation, single exposure, 0, 4,000, 8,000, 12,000, 16,000, 20,000 ppm for 5 minutes

Effects: After 5 minute exposure to 16,000 ppm VC 5 of 6 persons showed dizziness, lightheadedness, nausea, visual and auditory dulling. At concentrations of 12,000 ppm one of six persons reported "swimming head, reeling", another was unsure of an effect and felt somewhat dizzy. A single person reported slight effects ("slightly heady") of questionable meaning at 8,000 ppm (this volunteer felt also slightly heady at sham exposure and reported no response at 12,000 ppm). No effects were observed at 4,000 ppm.12,000 ppm was regarded as a concentration below AEGL-2 level and taken as NOAEL. Derived AEGL-2 levels are supported by the an assumed NOAEL for cardiac sensitization of 17,000 ppm in dogs after epinephrine challenge (5 minutes exposure; Clark and Tinston, 1993), leading to similar values. However, the resulting AEGL-2 values may not provide a sufficient margin of safety to avoid mutational events or malignancies after short-term exposure to VC.

Endpoint/Concentration/Rationale: Severe dizziness may influence capability to escape and thus is relevant as endpoint for AEGL-2. At 12,000 ppm no such effects were seen.Derived AEGL-2 levels are supported by the an assumed NOAEL for cardiac sensitization of 17,000 ppm in dogs after epinephrine challenge (5 minutes exposure; Clark and Tinston, 1993), leading to similar values.

Uncertainty Factors/Rationale: A total uncertainty factor of 3 is used to compensate for both, toxicokinetic and toxicodynamic variability, with small interindividual differences in case of CNS-effects. As the unmetabolized VC is responsible for the effects no relevant differences in kinetics are assumed.
Total uncertainty factor: 3
Interspecies: 1
Intraspecies: 3

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: In analogy to other anaesthetics the effects are assumed to be solely concentration dependent. Thus, after reaching steady state (about 2 hours), at 4 and 8 hours no increase of effect-size by duration is expected. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using a factor of n=2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects in mice and guinea pigs after less than steady state exposure conditions. With this, time extrapolation was performed from 5 to 10, 30, 60 minutes and 2 hours, where the steady state concentration was calculated.
Data Adequacy: The overall quality of the key study (Lester et al., 1963) is medium. There is an observed dose-/response relationship supporting the quantitative figures. Subjective reporting of effects leads to limited preciseness.

ACUTE EXPOSURE GUIDELINES FOR VINYL CHLORIDE (CAS Reg. NO. 75-01-4)

AEGL-3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
12,000 ppm	6,800 ppm	4,800 ppm	3,400 ppm	3,400 ppm

References: Clark, D.G., D.J. Tinston, 1973. Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties. *British Journal of Pharmacology*, 49, 355-357. Clark, D.G., D.J. Tinston, 1982. Acute inhalation toxicity of some halogenated and non-halogenated hydrocarbons. *Human Toxicology*, 1, 239-247., Aviado, D.M., M.A. Belej, 1974. Toxicity of aerosol propellants in the respiratory and circulatory systems. I. Cardiac arrhythmia in the mouse. Toxicology, 2, 31-42.; Belej, M.A., D.G. Smith, D.M. Aviado, 1974. Toxicity of aerosol propellants in the respiratory and circulatory systems. IV. Cardiotoxicity in the monkey. Toxicology, 2, 381-395; Prodan, L., I. Suciu, V. Pislaru, E. Ilea, L. Pascu, 1975. Experimental acute toxicity of vinyl chloride (monochloroethene). Ann. NY Acad. Sci., 246, 154-158. Mastromatteo, E., A.M. Fisher, H. Christie, H. Danziger, 1960. Acute inhalation toxicity of vinyl chloride to laboratory animals. Am. Ind. Hyg. Assoc. J., 21, 394-398.

Test Species/Strain/Sex/Number: dog, beagle, sex not reported, 4-7 dogs/dose level (Clark and Tinston, 1973)

Exposure Route/Concentrations/Durations: inhalation /"several doses" / 5 minutes (Clark and Tinston, 1973)

Effects: Short term exposure (5 min) of dogs to VC induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 or 71,000 ppm in two independent experiments; Clark and Tinston, 1973; 1982). The lower reported EC_{50} (50,000 ppm) was taken as NOAEL for life threatening effects. These effects were also seen in mice at higher concentrations (Aviado and Belej, 1974). In monkeys, only myocardial depression after inhalation of 2.5-10% VC was observed. It is not clearly stated whether an addition challenge with epinephrine was applied or not (Belej et al., 1974). Severe cardiac sensitization is a life threatening effect, but at 50,000 ppm no animal died in the reported study, providing a NOAEL for AEGL-3 derivation.

Endpoint/Concentration/Rationale: Considering possible sensitive subpopulations and increased excitement in case of emergency reaction epinephrine induced cardiac reactions may occur and may be enhanced by high exposure concentrations to VC. The respective effects are well known for certain unsubstituted and halogenated hydrocarbons. The test method using beagle dogs is well established. Supported by lethality data in slightly higher concentrations (Prodan et al., 1975).

Uncertainty Factors/Rationale: A total uncertainty factor of 3 is used to compensate for both, toxicokinetic and toxicodynamic differences between individuals and interspecies differences. As the challenge with epinephrine and the doses of epinephrine used represent a conservative scenario an interspecies factor of 1 was employed. As the unmetabolized VC is responsible for the effects no relevant differences in kinetics are assumed.
Total uncertainty factor: 3
Interspecies: 1
Intraspecies: 3

Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Insufficient data
Time Scaling: In analogy to other halocarbons (e.g., Halon 1211, HFC 134a) which lead to cardiac sensitization the effects are assumed to be solely concentration dependent. Thus, after reaching steady state (about 2 hours), at 4 and 8 hours no increase of effect-size by duration is expected. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using a factor of n=2, based on data from Mastromatteo et al. (1960). Mastromatteo et al. observed various time-dependent prenarcotic effects (muscular incoordination, side position and unconsciousness, effects which occur immediately before lethality) in mice and guinea pigs after less than steady state exposure conditions. With this, time extrapolation was performed from 5 to 10, 30, 60 minutes and 2 hours, where the steady state concentration was calculated.
Data Adequacy: Due to some discrepancies between the two studies from Clark and Tinston (1973, 1982) the data quality is judged to be medium with adequate data from human experience lacking.