



CHEMICAL MANUFACTURERS ASSOCIATION

August 24, 1994

Dear Vinyl Chloride Health Committee Members:

The National Research Council's monograph on Spacecraft Maximum Allowable Concentration for vinyl chloride is enclosed. The monograph briefly reviews toxicology literature and could be a useful reference document. Jonathon Ramlow should review the developmental and reproductive effects sections to see if there are references that could be useful in preparation of the industry position on the need for additional teratogenic or reproductive effects testing.

I also have enclosed a proposal from Richard Reitz for his services. I will seek your approval of his proposal on our September 9 conference call.

I am looking forward to talking to you on September 9.

Sincerely,

*Has Shah*

Hasmukh C. Shah, Ph.D.  
Manager, Vinyl Chloride

Enclosures

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VINYL CHLORIDE

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# Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants

*Volum 1*

SL 107467

## NATIONAL ACADEMY PRESS

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COMMITTEE ON TOXICOLOGY  
NATIONAL RESEARCH COUNCIL

***Spacecraft Maximum Allowable  
Concentrations for Selected  
Airborne Contaminants***

**Volume 1**

VINYL CHLORIDE

**Subcommittee on Spacecraft Maximum  
Allowable Concentrations**

**Committee on Toxicology**

**Board on Environmental Studies  
and Toxicology**

**Commission on Life Sciences**

**National Research Council**

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# ***B11*** ***Vinyl Chloride***

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## **PHYSICAL AND CHEMICAL PROPERTIES**

Vinyl chloride is a colorless gas with a high flammability and an odor like that of ether (ACGIH, 1986).

|                                    |                                                                  |
|------------------------------------|------------------------------------------------------------------|
| Synonyms:                          | Chloroethene, chloroethylene                                     |
| Formula:                           | CH <sub>2</sub> CHCl                                             |
| CAS number:                        | 75-01-4                                                          |
| Molecular weight:                  | 62.5                                                             |
| Boiling point:                     | -13.9°C                                                          |
| Melting point:                     | Not applicable                                                   |
| Vapor pressure:                    | 2530 mm Hg at 20°C                                               |
| Conversion factors at 25°C, 1 atm: | 1 ppm = 2.55 mg/m <sup>3</sup><br>1 mg/m <sup>3</sup> = 0.39 ppm |

## **OCCURRENCE AND USE**

Vinyl chloride is used primarily in the manufacture of polyvinyl chloride resins (ACGIH, 1986). It is also used in organic syntheses. There is no known use of vinyl chloride in spacecraft, and it has never been found in air samples taken during space-shuttle missions. However, vinyl chloride has been predicted to be off-gassed in the space station (Leban and Wagner, 1989).

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## PHARMACOKINETICS AND METABOLISM

When inhaled, vinyl chloride is absorbed quite well by human subjects. In male human volunteers exposed to 7.5-60 mg/m<sup>3</sup> (3-24 ppm) for 6 h, about 42% of the inhaled vinyl chloride was retained by the respiratory system; i.e., the exhaled concentration was 42% less than the inhaled concentration (Krajewski et al., 1980). The degree of respiratory retention achieved a relatively stable level 30 min into the 6-h exposure and appeared not to vary significantly with the exposure concentration, which ranged from 3 to 24 ppm.

Rats tend to readily absorb vinyl chloride in inhalation exposure. In rats exposed to <sup>14</sup>C-labeled vinyl chloride at 20,000 ppm for 5 min, radioactivity was detected in the liver, bile duct, kidney, and gastrointestinal tract within 10 min (Duprat et al., 1977). Similarly, in rats exposed to <sup>14</sup>C-labeled vinyl chloride at 50 or 100 ppm for 5 or 6 h, liver and kidney had the highest concentration of radioactivity among all the tissues after the exposure (Bolt et al., 1976; Watanabe et al., 1976).

In rats exposed to vinyl chloride at 1000 ppm for 1-6 h, it has been postulated that vinyl chloride was oxidized to 2-chloroacetaldehyde via three pathways, listed as follows (Hefner et al., 1975). (1) At low concentrations, vinyl chloride is oxidized first to 2-chloroethanol, which is further oxidized by alcohol dehydrogenase to 2-chloroacetaldehyde. (2) When the first pathway is saturated, vinyl chloride is oxidized by mixed function oxidase to an epoxide, 2-chloroethylene oxide, which arranges to 2-chloroacetaldehyde. (3) Alternatively, when the first pathway is saturated, vinyl chloride is oxidized by catalase to 2-chloroethyl hydroperoxide, which in turn is converted to 2-chloroacetaldehyde.

Because pretreatment of rats with 6-nitro-1,2,3-benzothiadiazole, which inhibits some microsomal cytochrome P-450 pathways, completely blocked vinyl chloride metabolism in rats exposed to vinyl chloride, Bolt et al. (1977) postulated that microsomal mixed function oxidase is the major enzyme for vinyl chloride metabolism.

Most of the 2-chloroacetaldehyde formed from vinyl chloride reacts with sulfhydryl groups in the cells, but some of it is oxidized by aldehyde dehydrogenase to 2-chloroacetic acid (Hefner et al., 1975). The reaction of 2-chloroacetaldehyde with sulfhydryl groups explains the formation of *n*-acetyl-S-(2-hydroxyethyl) cysteine, S-(2-hydroxyethyl) cysteine, and mercaptoacetic acid in the urine of rats exposed to vinyl chloride (Wata-

nabe et al., 1976, 1978a). Urinary mercaptoacetic acid has also been found in workers exposed to vinyl chloride (Shu, 1986).

Bolt et al. (1977) exposed rats to vinyl chloride at 50-1200 ppm in a closed inhalation system and they found that vinyl chloride metabolism was saturated at about 250 ppm. Similarly, Buchter et al. (1980) discovered that vinyl-chloride metabolism in rhesus monkeys was saturated at 200 ppm. In rats exposed to vinyl chloride at 10, 1000, or 5000 ppm for 6 h, Watanabe's group presented evidence that vinyl chloride metabolism appeared to be saturated at 1000 ppm (Watanabe et al., 1976, 1978a; Watanabe and Gehring, 1976). At 10 ppm, 68% of the body burden was excreted in the urine, 12% was expired as CO<sub>2</sub>, 4% was excreted in the feces, and about 2% was expired unchanged (Watanabe et al., 1976; Watanabe and Gehring, 1976). When the exposure level was increased to 1000 ppm, however, the fraction of the body burden eliminated in the urine was reduced to 56% and that expired as vinyl chloride increased to 12%.

There is evidence that vinyl chloride's epoxide metabolite, 2-chloroethylene oxide, and its rearrangement product, 2-chloroacetaldehyde, could bind to macromolecules in rats. Watanabe and his colleagues showed that, in rats exposed to vinyl chloride, the amount of macromolecular binding directly increased with the exposure concentration or phenobarbital pretreatment (Watanabe et al., 1978a,b; Guengerich and Watanabe, 1979). It has been postulated that the epoxide metabolite is the active metabolite of vinyl chloride and the macromolecular binding is responsible for vinyl chloride's carcinogenicity.

There are few data on vinyl chloride metabolism in humans. However, it has been shown that incubation of *Salmonella typhimurium* with S-9 fraction isolated from human liver increased the mutational frequency in a similar magnitude as incubation with rat S-9 fraction (Sabadie et al., 1980). This indicates that electrophilic metabolites could be formed by the action of human mixed function oxidase on vinyl chloride.

## TOXICITY SUMMARY

## Acute and Short-Term Toxicity

## Mucosal Irritation

Vinyl chloride is known to cause mucosal irritation at 500 ppm i

humans (Lefaux, 1968). Baretta et al. (1969) reported that two of seven human subjects complained of dryness of nose and eyes in an exposure to 500-ppm vinyl chloride lasting for 3.5 h. The dryness of nose and eyes was probably an indication of very slight mucosal irritation. It appears that 500 ppm is probably the threshold for vinyl chloride's mucosal irritation. Since none of the four subjects exposed to 250 ppm for 7.5 h complained of dryness of nose or eyes (Baretta et al., 1969), the no-observed-adverse-effect level (NOAEL) for mucosal irritation is 250 ppm.

### Miscellaneous Symptoms

In a study by Lester et al. (1963) nausea was reported in five of six human subjects exposed to vinyl chloride at 16,000 ppm for 5 min. In that study, one of six human subjects exposed to vinyl chloride at 20,000 ppm for 5 min experienced headache, which lasted for 30 min. Baretta et al. (1969) reported that two of seven men exposed to 500 ppm for 3.5 h complained of mild headache, but they did not complain of nausea. Therefore, the concentration of vinyl chloride causing headache is lower than that causing nausea. Because nausea was detected only at such a high exposure concentration (it was absent in a 5-min exposure at 12,000 ppm or less), nausea will not be relied on in setting the SMACs. None of the four men in the study of Baretta et al. (1969) complained of headache in a 7.5-h exposure to 250-ppm vinyl chloride. The NOAEL for headache is 250 ppm in acute vinyl chloride exposures.

### Liver Toxicity

As will be discussed later, liver is the major target organ of vinyl chloride in subchronic and long-term exposures. Whether vinyl chloride could cause non-neoplastic liver toxicity in humans in acute exposures is debatable. A group of Hungarian scientists exposed mice, rats, and rabbits to vinyl chloride at 1500 ppm for 24 h (Tatrai and Ungvary, 1981). No liver pathology was found in rats and rabbits. However, in mice, vasomotor paralysis and shock developed during the exposure, followed by hepatic histopathology, which included coagulation necrosis and confluent hemorrhages in the centrilobular zone, and ultrastructural changes, such as dilation of the cisterns of rough endoplasmic reticulum and Golgi apparatus

and atrophy of some mitochondria. All the mice died as a result of the 24-h exposure at 1500 ppm, whereas a 12-h exposure killed 16 of 20 mice. In contrast, no rats or rabbits were killed by the 24-h exposure (Tatrai and Ungvary, 1981). In a human study, Baretta et al. (1969) failed to detect any changes in the serum levels of glutamyl pyruvate transaminase, alkaline phosphatase, lactic dehydrogenase, bilirubin, blood urea nitrogen, and creatinine in four men 24 h after a 7.5-h exposure to vinyl chloride at 500 or 250 ppm. Therefore, if vinyl chloride is indeed acutely toxic to the liver in humans, 500 ppm appears to be the NOAEL.

### Central Nervous System Toxicity

Vinyl chloride could impair the central nervous system (CNS). Lester et al. (1963) reported that light-headedness, dizziness, and dulling of vision and hearing were detected in five of six human subjects exposed at 16,000 ppm for 5 min. When these six subjects were exposed at 12,000 ppm for 5 min, two subjects felt slight dizziness. At 8000 ppm, only one of six subjects felt light-headed. No CNS symptoms were detected in a 5-min exposure at 4000 ppm (Lester et al., 1963). According to Lefaux (1968), vinyl chloride at 1000 ppm produces drowsiness, slight visual disturbances, tingling sensation on the limbs, numbness, and faltering gait. Vinyl chloride has no perceptible action on the CNS below 1000 ppm (Lefaux, 1968). Baretta et al. (1969) reported no CNS impairment in seven subjects exposed to vinyl chloride at 500 ppm for 3.5 h or in four subjects exposed for 7.5 h. The NOAEL for acute CNS impairment is, therefore, 500 ppm.

### Mortality

A person was reported killed by a massive exposure to vinyl chloride at an unknown concentration (Damziger, 1966). Although the lethal concentration of vinyl chloride in humans is not known for certain, it is probably over 10,000 ppm based on the animal data of Mastromatteo et al. (1960). This group of scientists exposed five mice, five rats, and five guinea pigs to various concentrations of vinyl chloride for 30 min. No deaths occurred at 10,000 ppm. One of five mice died but no rats or guinea pigs died at 20,000 ppm. At 30,000 ppm, all five mice and all five rats died, and one of the five guinea pigs died. Because the lethal concentration of vinyl

chloride is estimated to be much higher than the concentrations required to cause other toxic effects, mortality is not used as a toxic end point in deriving the SMACs.

### Subchronic and Chronic Toxicity

#### Liver Toxicity

Liver is the major target organ of vinyl chloride. Liver function impairment and hepatic histological changes have been reported in workers employed in places where vinyl chloride was manufactured or used (Lillis et al., 1975; Popper and Thomas, 1975; Tamburro et al., 1984). Clinically, occupational exposure to vinyl chloride might cause abdominal pain in the upper right-hand quadrant, hepatomegaly, portal hypertension, esophageal varices, and liver cirrhosis (Lillis et al., 1975; Popper and Thomas, 1975; Lee et al., 1977). No exposure-concentration data were given in these reports. In a study conducted with 168 workers in two Romanian factories where they were exposed to vinyl chloride from 1962 to 1972, the investigators compared, among other things, the rates of nervous symptoms and gastroenterological symptoms in the workers in 1962 with those in 1966 (Suciu et al., 1975).

Without specifying the analytical method, the investigators reported that the average vinyl chloride concentrations in 1962 and 1966 were 2298 and 98 mg/m<sup>3</sup> (896 and 38 ppm), respectively (Suciu et al., 1975). They detected a higher rate of euphoria, dizziness, somnolence, nervousness, headache, complete narcosis, weight loss, anorexia, epigastric pains, and hepatomegaly in the year the workers were exposed to 896 ppm than in the year they were exposed to 38 ppm (Suciu et al., 1975). The rate of pains in the right hypochondrium was lower, however, at 896 ppm than at 38 ppm. Because no control group was used and because of a lack of information on how the exposure concentrations were determined, the Romanian data are not used in setting SMACs. Nevertheless, the data illustrate the potential toxicity of vinyl chloride in the CNS and liver in human workers.

Kramer and Mutchler (1972) did a medical study with 98 workers employed over two decades in two vinyl chloride polymerization facilities. These workers were exposed mainly to vinyl chloride, but there were exposures to vinylidene chloride, which was at lower concentrations.

The exposures to vinylidene chloride in the second decade of the occupational exposure were probably negligible because vinylidene chloride was frequently detected only at trace levels. During the two decades of employment, there were environmental monitoring and medical surveillance. The investigators did not report all the results of the environmental monitoring during the two decades, but they stated that "in more recent measurements, infrared and gas chromatographic techniques have established that the vinyl chloride concentrations average 10 ppm." When compared with a control group, the vinyl-chloride workers had no significant disease. There were no differences in chest x-rays and electrocardiograms between the two groups. No acroosteolysis was detected. Based on the medical history taken periodically in the medical surveillance program, the exposed workers reported a higher history of asthma and kidney stone and blood urine but a lower history of gastrointestinal and hepatic trouble and nervous symptoms. By physical examinations, the investigators found a higher rate of anal and rectal abnormalities in the exposed workers than in the controls. From a regression analysis of the data collected, the investigators estimated that, in 60-y-old workers who had been on the job for 20 y, vinyl chloride at 300 ppm time-weighted average (TWA) would increase the bromsulphalein clearance time by five-fold, 150 ppm would raise it by two fold, and 50 ppm would increase it by 80%. They concluded that repeated exposure to vinyl chloride at 300 ppm or higher for a working lifetime could cause some impairment in liver function.

In a study by Ho et al. (1991) 12 of over 100 workers in a polyvinyl chloride plant in Singapore were found to have elevated serum glutamic pyruvic transaminase and gamma glutamyl transpeptidase levels, when they worked in an environment with the vinyl chloride concentrations ranging between 1 and 21 ppm, with a geometric mean of 6 ppm for 1-13 y. Nine of the 12 workers had mild-to-moderate nonspecific fatty changes on liver biopsies. None of them had a history of jaundice, Raynaud's disease, or blood transfusion. No liver function impairment attributable to vinyl chloride was detected in the workers after the vinyl chloride was lowered to 0.6-2.9 ppm, with a geometric mean of 1.5 ppm, in 1983. In workers afflicted by vinyl-chloride-induced liver disease, their liver function improved within 0.5-2 y after they were removed from further exposure (Ho et al., 1991). Based on the human data of Ho et al., the NOAEL for non-neoplastic liver toxicity is about 1.5 ppm.

Lee et al. (1977) showed that increased cell turnover and DNA synthesis were detected in the livers of rats exposed to vinyl chloride at 50 or 25

ppm, 6 h/d, 5 d/w for 12 mo. Because increased cell turnover and DNA synthesis, by themselves, are not considered adverse clinically, the SMACs are not set to prevent them. Similarly, increased liver weight by itself is not considered a significant toxic end point. So the SMACs are not derived from the discovery made by Bi et al. (1985) that the liver weight increased in rats exposed to vinyl chloride at 10, 100, or 3000 ppm, 6 h/d, 6 d/w for 6 mo.

Torkelson et al. (1961) found that there were species differences in the sensitivity to vinyl chloride's liver toxicity. In a 6-mo exposure, at 7 h/d, 5 d/w, of guinea pigs, rats, and rabbits to 200-ppm vinyl chloride, no changes were seen in guinea pigs, but increased liver weight was detected in rats and the liver in rabbits developed centrilobular degeneration and necrosis (Torkelson et al., 1961). Therefore, the rat is more sensitive than the guinea pig. However, it is not clear whether the rabbit is more sensitive than the rat because only three male and three female rabbits were used in the experiment, making it difficult to draw a conclusion.

In the study of Torkelson et al. (1961) a 4.5-mo exposure of rats at 500 ppm resulted in centrilobular degeneration in liver. A similar exposure of rats at 100 or 200 ppm led to increased liver weight, but an exposure at 50 ppm failed to cause any significant changes.

There are reports of liver toxicity in animals subchronically exposed to very high concentrations of vinyl chloride. The group of Feron showed that an exposure of rats to 5000 ppm, 7 h/d, 5 d/w for 52 w produced degeneration, hyperplasia, hepatocellular carcinoma, and angiosarcoma in the liver (Feron and Kroes, 1979). Viola (1970) discovered hepatomegaly, hepatitis, and liver necrosis in male rats exposed to vinyl chloride at 30,000 ppm for 4 h/d, 5 d/w for 1 y.

### Kidney Toxicity

Kidney is the second major organ affected by vinyl chloride. At a very high concentration of 30,000 ppm, Viola (1970) found that vinyl chloride produced tubular nephrosis and chronic interstitial nephritis in rats exposed 4 h/d, 5 d/w for 1 y. Tubular nephrosis was also produced in rats exposed to vinyl chloride at 5000 ppm for 7 h/d, 5 d/w for 1 y (Feron and Kroes, 1979). Torkelson et al. (1961) discovered that 500-ppm vinyl chloride could cause histopathology in the interstitial and tubular areas of the kidney

in rats exposed 7 h/d, 5 d/w for 4.5 mo. Because a similar exposure of rats at 200 ppm failed to produce any histological changes (Torkelson et al., 1961), the NOAEL for kidney toxicity is 200 ppm.

### Neurological Toxicity

Psychiatric disease and mild distal axonal neuropathy have been reported in workers exposed to vinyl chloride repetitively at unknown concentrations (Halama et al., 1985; Perticoni et al., 1986). Since the exposure concentrations were not measured, these human data cannot be used to set the SMACs. In the experiment conducted by Viola (1970) an exposure to vinyl chloride at 30,000 ppm for 4 h/d, 5 d/w for 1 y led to diffuse degeneration of the white and gray matter in the brain and atrophy of granular cells in the cerebellum in rats. Because Feron and Kroes (1979) showed that 5000 ppm failed to cause any nonneoplastic injuries in the brain of rats exposed 7 h/d, 5 d/w for 1 y, the NOAEL for brain toxicity is 5000 ppm.

### Effects on the Extremities

Occupational exposures to vinyl chloride are known to cause circulatory disturbance in the extremities, Raynaud's disease (Lillis et al., 1975; Preston et al., 1976), acroosteolysis, and scleroderma (Dinman et al., 1971; Wilson et al., 1967; Sakabe, 1975). Unfortunately, the exposure concentrations at which these effects were seen in workers are not known. Because Raynaud's disease was usually detected before acroosteolysis in vinyl-chloride workers, vascular lesion is believed to precede the bone changes (Dodson and Dinman, 1971). Viola (1970) reported that an exposure of rats at 30,000 ppm for 4 h/d, 5 d/w for 1 y resulted in pathology in the paws, such as metaplasia of metatarsal bones, chondroid metaplasia, epidermal edema, epidermal hyperkeratosis, and degeneration of basal cells. These pathological changes in rats somewhat resemble the acroosteolysis and scleroderma seen in vinyl-chloride workers. Because there are no concentration-response data and 30,000 ppm is a very high concentration, Viola's data on the paws of rats are not suitable for setting the SMACs.

### Effects on the Respiratory System

In an epidemiology study performed by Wong et al. (1991), a significant mortality excess from emphysema and chronic obstructive pulmonary disease was found in vinyl-chloride workers. Since emphysema and chronic obstructive pulmonary disease have not been found to be associated with occupational vinyl chloride exposures in other epidemiology studies, it is uncertain whether vinyl chloride causes emphysema or chronic obstructive pulmonary disease in humans. However, there is some evidence of the pulmonary toxicity of vinyl chloride in animals. Suzuki (1978, 1980) exposed male mice to vinyl chloride at 2500 or 6000 ppm for 5 h/d, 5 d/w for 5 or 6 mo. In the exposed mice, he found hyperplasia of the alveolar epithelium, degeneration of the alveolar septal cells, hypertrophy and hyperplasia of Clara cells and ciliated epithelial cells in the terminal bronchioles, and bronchiolitis. It appears that the lowest-observed-effect level (LOEL) for lung toxicity is 2500 ppm. Taken together, the epidemiology data of Wong et al. and Suzuki's data in mice show that vinyl chloride might produce lung injuries in humans, so the SMACs are prudently set to prevent this toxic end point.

### Effects on the Reproductive System

There were two Soviet reports on the reproductive effects of vinyl chloride in workers (Makarov, 1984; Makarov et al., 1984). A decline in sexual function, which was evaluated by questionnaire, was found in men and women exposed to vinyl chloride occupationally. In the exposed women workers, gynecological examinations revealed increased incidences of ovarian dysfunction, benign uterine growths, and prolapsed genital organs. The Agency for Toxic Substances and Disease Registry characterized the two reports as "not adequately reported for proper evaluation; therefore, such data cannot be used to identify thresholds" (ATSDR, 1989). So the SMACs are not set relying on the Soviet data. Instead the animal data of Bi et al. (1985) are used.

In the study of Bi et al., 74 or 75 male rats were exposed to vinyl chloride at 0, 10, 100, or 3000 ppm, 6 h/d, 6 d/w for 1 y. Sacrifices were made of 8, 30, 6, and 10 rats at the 3rd, 6th, 9th, and 12th mo, respectively, and the surviving rats were killed 6 mo after the 12-mo exposure. Testicular histology was evaluated in the rats sacrificed and also in rats that

died before the interim and final sacrifices. A reduction in the testicular to-body-weight ratio was found in the 100- and 3000-ppm groups after 6 mo of exposure. With the rats killed at different time points taken together, Bi et al. (1985) reported a statistically higher rate of testicular injuries in the 100- and 3000-ppm groups, but not in the 10-ppm group. There was fusion of spermatids or spermatocytes into giant cells. Spermatids disappeared first, followed by sloughing of secondary and primary spermatocytes into the lumen of seminiferous tubules, leaving behind spermatogonia and Sertoli cells. The degeneration and necrosis distributed randomly in the testis without any relationship to the vascular system.

### Carcinogenicity

Vinyl chloride was found to cause liver cancers, especially angiosarcoma, in vinyl-chloride workers in the 1970s (Health et al., 1975; Tabershaw and Gaffey, 1974; Nicholson et al., 1975; Fox and Collier, 1977). An epidemiology study showed that the mortality excess from liver cancer increased with duration of employment (Health et al., 1975). Other than liver cancers, there have been epidemiological reports that vinyl-chloride exposures may produce cancer in other tissues. For instance, Heldaas et al. (1987) observed 6 cases of malignant melanoma in 454 vinyl-chloride and polyvinyl-chloride workers in Norway, where only 1.1 cases were expected. Nevertheless, Heldaas et al. admitted that it was difficult to make a solid conclusion on the causality between vinyl chloride and malignant melanoma.

More recently, there have been reports of a multiplant cohort study in the United States by Wong et al. (1991) and one in Europe by Simonato et al. (1991). Both the U.S. and European studies confirmed the findings of earlier epidemiology studies on the excesses of liver cancers in general and angiosarcoma in particular caused by occupational exposures to vinyl chloride (Wong et al., 1991; Simonato et al., 1991). Both studies also found an increase in brain tumors in vinyl-chloride workers. In addition, an increase in biliary-tract cancers was discovered in the U.S. study and an increase in lymphoma was found in the European study. In the European study, the mortality excess from liver cancers was found to be related to time since initial exposure to vinyl chloride, duration of employment, and estimated exposure levels (Simonato et al., 1991).

The mortality excesses from lymphoma and brain tumor, however, were not correlated with these exposure variables in the European study (Simonato et al., 1991). That makes it doubtful whether vinyl chloride could cause lymphoma and brain tumor. Similarly, a case-control study by Wu et al. (1989) found mortality excesses due to liver, lung, and brain cancers in 3635 workers exposed to vinyl chloride. Wu et al. also demonstrated that, among tumors in those three sites, only the excess mortality for liver cancer was significantly associated with the cumulative dose of vinyl chloride. It can be concluded from these recent epidemiology studies that vinyl chloride could cause liver cancers in humans, but the evidence that vinyl chloride also causes tumors in other sites in humans is rather weak.

Viola et al. (1971) were the first group to demonstrate vinyl chloride's carcinogenicity in laboratory animals. They exposed rats to vinyl chloride at 30,000 ppm for 4 h/d, 5 d/w for 1 y and found that vinyl chloride caused lung carcinoma, osteochondroma, and epidermoid carcinoma in the skin. In a study conducted by Lee et al. (1978), an exposure of rats or mice to vinyl chloride at 50, 250, or 1000 ppm for 6 h/d, 5 d/w for 1 y resulted in liver hemangiosarcoma in rats at 250 ppm or greater and liver hemangiosarcoma and bronchoalveolar adenoma in the lung in mice at 50 ppm or greater. The most extensive animal bioassay was done by Maltoni and co-workers (Maltoni, 1977; Maltoni et al., 1981). They also exposed rats to vinyl chloride for 1 y (4 h/d, 5 d/w) but held the rats for 83-103 w after exposure before sacrificing them. Maltoni et al. found that, in Sprague-Dawley rats, vinyl chloride produced liver angiosarcoma at as low as 100 ppm and nephroblastoma in the kidney at 25 ppm or greater. The incidences of these tumors in male and female rats combined are shown in Table 11-1.

Maltoni and co-workers also tested with mice and hamsters in the bioassays. In mice exposed to vinyl chloride 4 h/d, 5 d/w for 30 w and held for observation for 51 w, increased incidences of liver angiosarcoma and lung tumor were detected at 250 ppm or greater. They found that 79 w after hamsters were exposed to vinyl chloride at 2500 ppm or greater for 30 w, papillomas and acanthomas of the forestomach were increased.

The data gathered in the literature indicate that vinyl chloride is a potent carcinogen in rodents because many studies showed that vinyl chloride was carcinogenic after an exposure for less than half of the normal lifespan of the test species (Viola et al., 1971; Lee et al., 1978; Maltoni, 1977;

TABLE 11-1 Incidence of Liver Angiosarcoma and Nephroblastoma in Rats

| Concentration,<br>ppm | Liver<br>Angiosarcoma | Kidney<br>Nephroblastoma |
|-----------------------|-----------------------|--------------------------|
| 10,000                | 18/60                 | 5/60                     |
| 6000                  | 13/59                 | 5/59                     |
| 2500                  | 13/60                 | 6/60                     |
| 500                   | 6/60                  | 6/60                     |
| 250                   | 3/59                  | 5/59                     |
| 200                   | 12/120                | 7/120                    |
| 150                   | 6/119                 | 11/119                   |
| 100                   | 1/120                 | 10/120                   |
| 50                    | 1/60                  | 1/60                     |
| 25                    | 5/120                 | 1/120                    |
| 10                    | 1/119                 | 0/119                    |
| 5                     | 0/119                 | 0/110                    |
| 1                     | 0/118                 | 0/118                    |
| 0                     | 0/363                 | 0/363                    |

Maltoni et al., 1981). Hong et al. (1981) showed that vinyl chloride was carcinogenic in mice for an exposure lasting as little as 1 mo. It took a vinyl chloride exposure of only 1 mo at 6 h/d, 5 d/w to cause bronchoalveolar tumors in mice at 250 ppm or greater (Hong et al., 1981).

Age also plays a role in the carcinogenicity of vinyl chloride in rats. Drew et al. (1983) found that the earlier in life a rat is exposed to vinyl chloride, the higher the tumor risk. In a 2-y study, Drew et al. exposed three groups of rats to vinyl chloride at 50 ppm and three groups to 200 ppm for 6 h/d, 5 d/w for 12 mo and then held the rats without exposure for the remaining 12 mo. For two groups of rats, they started the exposures (50 or 200 ppm) at the beginning of the 2-y study. For four other groups, the exposures (two groups at 50 ppm and two at 200 ppm) were started 6 or 12 mo into the 2-y study. For each of the exposure concentrations, Drew et al. then compared the tumor incidences in the three groups exposed to the same concentration at three different ages. The rats that were exposed for 12 mo at the beginning of the 2-y study had the highest inci-

dences of hepatocellular carcinomas, hemangiosarcomas, and mammary gland carcinomas. The rats that were held for 6 mo before being exposed also developed tumors, albeit at lower incidences. However, there were no statistically significant increases in tumor incidences in the rats exposed in the last 12 mo of the 2-y study.

Based on the data available, the International Agency for Research on Cancer concluded that there is sufficient evidence to support vinyl chloride's carcinogenicity to both humans and animals (IARC, 1987). The U.S. Environmental Protection Agency also classified vinyl chloride as a known human carcinogen (EPA, 1984).

### Genotoxicity

There are *in vivo* data showing that vinyl chloride is genotoxic in humans. Hansteen et al. (1978) found an increase in the percent of peripheral lymphocytes with chromosomal aberrations in workers exposed to 25-ppm vinyl chloride but not in workers exposed to 1-ppm. In another study, an increase in peripheral lymphocytes with chromosomal aberrations was noted in workers exposed to about 50-ppm vinyl chloride (Anderson et al., 1980). No significant increase in chromosomal aberrations was seen in the workers after the vinyl chloride concentration had been lowered to a level estimated to be less than 5 ppm (Anderson et al., 1980). There is also *in vivo* evidence of the genotoxicity of vinyl chloride in animals. Vinyl chloride was tested negative in the dominant lethal test and positive in the micronucleus test in mice (Jenssen and Ramel, 1980; Purchase et al., 1975).

Vinyl chloride has been shown to be genotoxic in various *in vitro* assays in numerous reports. Only some of them will be summarized here. Vinyl chloride was shown to be mutagenic in the Ames test, with or without activation by S-9 fraction, by Bartsch et al. (1975) and Andrews et al. (1976). Even without S-9 activation, vinyl chloride produced forward mutation in Chinese hamster cell V79 and cell transformation of neonatal hamster kidney cells (Drevon and Kuroki, 1979; Styles, 1977).

### Developmental Toxicity

There is conflicting evidence on whether vinyl chloride causes devel-

opmental toxicity in humans. In an Ohio city, Edmonds et al. (1975) found no differences between how far parents of malformed infants lived from a local polyvinyl chloride plant and how far parents of normal infants lived from it. They concluded that malformations were not associated with parental exposures to vinyl chloride. Theriault et al. (1983) conducted a similar study in a Canadian town with a polyvinyl chloride plant and arrived at the same conclusion as Edmonds et al. In contrast, Infante et al. (1976) reported a higher rate of fetal loss, based on questionnaires, in pregnant wives of vinyl-chloride workers than in rubber workers not exposed to vinyl chloride. Infante (1976) also found a higher incidence of malformations in three Ohio cities that have a polyvinyl chloride production plant than in other parts of the counties where the three cities are situated. These two studies of Infante have been criticized as being deficient in the way the studies were conducted and in the data analyses, so the "positive" findings are highly questionable (Hatch et al., 1981; Stallones, 1987).

Animal data showed that vinyl chloride caused some malformations in rats at concentrations that also caused maternal toxicity (John et al., 1977). Vinyl chloride did not produce any malformations in mice and rabbits (John et al., 1977). Therefore, it can be concluded that vinyl chloride does not appear to be a serious teratogenic threat. John et al. (1977) showed that vinyl chloride, at 500 or 2500 ppm, failed to produce developmental toxicity and maternal toxicity in rabbits exposed 7 h/d on gestation days 6-18. In the same study, a similar exposure of rats to vinyl chloride at 2500 ppm on gestation days 6-15 increased the incidence of dilated ureters in the fetuses and reduced the body-weight gain and food consumption in the mothers. An exposure of rats to 500 ppm increased the incidence of lumbar spurs in the fetuses and reduced the body-weight gain in the mothers. In mice, an exposure of 500 ppm for 7 h/d on gestation days 6-15 failed to produce any malformations, but vinyl chloride caused increased fetal resorption, decreased fetal weight, reduced litter size, retarded ossification of the cranium and sternum in the fetuses. Vinyl chloride exposure at 500 ppm was also toxic to the mothers, causing mortality, reduced body weight gain, and decreased liver weight (John et al., 1977). It should be noted that the measurement of maternal body weight for days 6-18 of gestation might not be adequate. Nevertheless, these data indicate that vinyl chloride does not have selective developmental toxicity because it produced developmental effects only in the exposure range that also affected the mothers.

## Synergistic Effects

Pretreatments of rats with chemicals, such as phenobarbital and polychlorinated biphenyls, which induce microsomal enzymes, are known to potentiate vinyl chloride's acute hepatotoxicity (Jaeger et al., 1974; Reynolds et al., 1975). These findings support the theory that vinyl chloride acts through its epoxide metabolite formed via microsomal oxidation. Therefore, in the event that an astronaut is exposed to vinyl chloride and a known microsomal inducer, one should be aware of the potential toxicity of vinyl chloride.

TABLE 11-2 Toxicity Summary<sup>a</sup>

| Concentration           | Exposure Duration              | Species         | Effects                                                                                                                                                                                                                                                                                                              | Reference                 |
|-------------------------|--------------------------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| 1-21 ppm (mean = 6 ppm) | 40 h/w for 1-13 y (mean = 5 y) | Human (workers) | Elevated serum glutamic pyruvate transaminase and serum gamma glutamyl transpeptidase. Mild-to-moderate fatty liver.                                                                                                                                                                                                 | Ho et al., 1991           |
| Mean = 1.5 ppm          | 40 h/w (y unknown)             | Human (workers) | No liver function impairment.                                                                                                                                                                                                                                                                                        | Ho et al., 1991           |
| 50 or 250 ppm           | 7.5 h                          | Human           | 0 of 6 men at 50 ppm and 0 of 4 men at 250 ppm complained of irritation, eye and nose dryness, and headache. No neurological symptoms or dexterity impairment. No changes in serum levels of SGPT, LDH, alkaline phosphatase, bilirubin, BUN, and creatinine levels. 4/4 men at 250 ppm detected a very slight odor. | Baretta et al., 1969      |
| 300 ppm                 | 40 h/w for 20 y                | Human (workers) | Slight increases in bromsulphalein clearance, but no clinically apparent liver disease.                                                                                                                                                                                                                              | Kramer and Mutchler, 1972 |
| 500 ppm                 | N.S. <sup>b</sup>              | Human           | Eye irritation.                                                                                                                                                                                                                                                                                                      | Lefaux, 1968              |
| 500 ppm                 | 3.5 h                          | Human           | 5/7 men detected an odor, which disappeared after 5 min. 2/7 men complained of mild headache, eye and nose dryness.                                                                                                                                                                                                  | Baretta et al., 1969      |
| 500 ppm                 | 7.5 h                          | Human           | No neurological symptoms. No changes in manual dexterity, coordination or mental ability. No changes in serum levels of SGPT, LDH, alkaline phosphatase, bilirubin, BUN, and creatinine.                                                                                                                             | Baretta et al., 1969      |
| 1000 ppm                | N.S.                           | Human           | Drowsiness, slight anesthesia, slight visual disturbances, tingling of the limbs, numbness, and faltering gait.                                                                                                                                                                                                      | Lefaux, 1968              |
| 4000 ppm                | 5 min                          | Human           | No CNS symptoms.                                                                                                                                                                                                                                                                                                     | Lester et al., 1963       |
| 8000 ppm                | 5 min                          | Human           | Slight light-headedness in 1/6 subjects.                                                                                                                                                                                                                                                                             | Lester et al., 1963       |
| 8000 ppm                | 5 min                          | Human           | Dizziness in 2/6 subjects                                                                                                                                                                                                                                                                                            | Lester et al., 1963       |

TABLE 11-2 (Continued)

| Concentration       | Exposure Duration          | Species            | Effects                                                                                                                                                                                          | Reference                |
|---------------------|----------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| 16,000 ppm          | 5 min                      | Human              | Light-headedness, dizziness, nausea, dulling of hearing and vision in 5/6 subjects.                                                                                                              | Lester et al., 1963      |
| 20,000 ppm          | 5 min                      | Human              | Same symptoms as in 16,000-ppm exposure in 6/6 subjects, but symptoms were more intense and appeared sooner.                                                                                     | Lester et al., 1963      |
| 10 ppm              | 6 h/d, 6 d/w for 3-12 mo   | Rat                | Increased liver weight. No change in testicular weight. No testicular injury.                                                                                                                    | Bi et al., 1985          |
| 50 ppm              | 7 h/d, 5 d/w for 6 mo      | Rat                | No change in histology, organ weight, and serum levels of enzymes.                                                                                                                               | Torkelson et al., 1961   |
| 50 ppm              | 7 h/d on gestation d 6-15  | Mouse              | No malformations, no fetotoxicity, and no maternal toxicity.                                                                                                                                     | John et al., 1977        |
| 50 or 100 ppm       | 7 h/d, 5 d/w for 6 mo      | Rabbit             | No significant changes.                                                                                                                                                                          | Torkelson et al., 1961   |
| 50, 100, or 200 ppm | 7 h/d, 5 d/w for 6 mo      | Guinea pig         | No significant changes.                                                                                                                                                                          | Torkelson et al., 1961   |
| 50 or 250 ppm       | 6 h/d, 5 d/w for 12 mo     | Rat                | Increased cell turnover and DNA synthesis in liver.                                                                                                                                              | Lee et al., 1977         |
| 100 or 200 ppm      | 7 h/d, 5 d/w for 6 mo      | Rat                | Increased liver weight. No histopathology.                                                                                                                                                       | Torkelson et al., 1961   |
| 100 or 3000 ppm     | 6 h/d, 6 d/w for 3-12 mo   | Rat                | Increased testicular weight. Fusion of spermatids and spermatocytes. Degeneration and necrosis of some seminiferous tubules.                                                                     | Bi et al., 1985)         |
| 200 ppm             | 7 h/d, 5 d/w for 6 mo      | Rabbit             | Centrilobular degeneration and necrosis in liver.                                                                                                                                                | Torkelson et al., 1961   |
| 500 ppm             | 7 h/d, 5 d/w for 4.5 mo    | Rat                | Male and female: Centrilobular degeneration in liver, tubular and interstitial changes in kidneys. Male: Increased liver weight.                                                                 | Torkelson et al., 1961   |
| 500 ppm             | 7 h/d on gestation d 6-15  | Mouse              | No malformation. Fetotoxicity: Increased fetal resorption, reduced fetal weight and litter size, retarded ossification of cranium and sternum. Maternal toxicity: Death and reduced body weight. | John et al., 1977        |
| 500 ppm             | 7 h/d on gestation d 6-15  | Rat                | Increased incidence of lumbar spurs; reduced fetal weight. Maternal toxicity: Reduced body-weight gain.                                                                                          | John et al., 1977        |
| 500 or 2500 ppm     | 7 h/d on gestation d 6-18  | Rabbit             | No malformation, fetotoxicity, or maternal toxicity.                                                                                                                                             | John et al., 1977        |
| 1500 ppm            | 24 h                       | Rat, mouse, rabbit | Rats and rabbits: no pathology in liver. Mice: vasomotor paralysis, shock, pathological changes in liver and lung.                                                                               | Tatrai and Ungvary, 1981 |
| 2500 ppm            | 7 h/d on gestation d 6-15  | Rat                | Increased incidence of dilated ureters. Maternal toxicity: Death, reduced food consumption, and increased liver weight.                                                                          | John et al., 1977        |
| 2500 or 6000 ppm    | 5 h/d, 5 d/w for 5 mo      | Mouse              | Proliferation of cells lining the terminal bronchioles, epithelial hyperplasia in alveoli, and degeneration of alveolar septal cells.                                                            | Suzuki, 1978             |
| 5000 ppm            | 7 h/d, 5 d/w for 4 or 13 w | Rat                | 4 w: ultrastructural changes in liver morphology. 13 w: histopathology at light microscopic level.                                                                                               | Feron et al., 1979a      |
| 5000 ppm            | 7 h/d, 5 d/w for 52 w      | Rat                | Liver: angiosarcoma, hepatocellular carcinoma, hyperplasia, and degeneration. Increased mortality.                                                                                               | Feron et al., 1979b      |
| 5000 ppm            | 7 h/d, 5 d/w for 52 w      | Rat                | Tumors of the nasal cavity, ceruminous glands, brain, and lungs. Increased hematopoiesis in spleen, mild focal degeneration of myocardium, and tubular nephrosis.                                | Feron and Kroes, 1979    |

TABLE 11-2 (Continued)

| Concentration | Exposure Duration      | Species                | Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                | Reference                 |
|---------------|------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| 5000 ppm      | 7 h/d, 5 d/w for 52 w  | Rat                    | Mortality; mild retardation of body growth; increases in the weight of heart, kidney, and spleen, blood urea nitrogen, and serum K <sup>+</sup> ; and slight reduction of blood clotting time.                                                                                                                                                                                                                                                         | Feron et al., 1979a       |
| 20,000 ppm    | 8 h/d, 5 d/w for 3 mo  | Rat                    | Increase in liver weight and decrease in spleen weight. No changes in body-weight gain, hematocrit, hemoglobin levels, prothrombin time, and differential white blood cell counts.                                                                                                                                                                                                                                                                     | Lester et al., 1963       |
| 30,000 ppm    | 4 h/d, 5 d/w for 12 mo | Rat                    | Hepatomegaly, liver necrosis, Kupffer's cell proliferation, and diffuse interstitial hepatitis. Tubulonephrosis and chronic interstitial nephritis. Goiter and parafollicular hyperplasia in thyroid. Diffuse degeneration of the brain and atrophy of the granular cells in the cerebellum. Metatarsal bone metaplasia and chondroid metaplasia. In the paws: epidermal hyperkeratosis, epidermal edema, and degeneration of the basal cells in skin. | Viola, 1970               |
| 100,000 ppm   | 30 min                 | Mouse, rat, guinea pig | No death.                                                                                                                                                                                                                                                                                                                                                                                                                                              | Mastromatteo et al., 1960 |
| 100,000 ppm   | 2 h/d, 5 d/w for 90 d  | Guinea pig             | Increase in kidney weight. No change in liver weight. Parenchymal necrosis, proliferation of Kupffer cells and fibroblasts in liver. Marked degeneration of tubules and moderate degeneration of glomeruli in kidneys. Disappearance of the red pulp in the spleen.                                                                                                                                                                                    | Prodan et al., 1975       |
| 200,000 ppm   | 30 min                 | Mouse, rat, guinea pig | 1/5 mice, 0/5 rats, and 0/5 guinea pigs died.                                                                                                                                                                                                                                                                                                                                                                                                          | Mastromatteo et al., 1960 |
| 300,000 ppm   | 30 min                 | Mouse, rat, guinea pig | 5/5 mice, 5/5 rats, and 1/5 guinea pigs died.                                                                                                                                                                                                                                                                                                                                                                                                          | Mastromatteo et al., 1960 |

<sup>a</sup>Only inhalation data are included.  
<sup>b</sup>N.S. = not specified.

TABLE 11-3 Exposure Limits Set by Other Organizations

| Organization | Concentration, ppm                       |
|--------------|------------------------------------------|
| ACGIH's TLV  | 5 (TWA)                                  |
| OSHA's PEL   | 1 (TWA)<br>5 (ceiling)                   |
| NIOSH's REL  | Lowest reliably detectable concentration |

TLV = threshold limit value. TWA = time-weighted average. PEL = permissible exposure limit. REL = recommended exposure limit.

TABLE 11-4 Spacecraft Maximum Allowable Concentrations

| Duration         | ppm | mg/m <sup>3</sup> | Target Toxicity                             |
|------------------|-----|-------------------|---------------------------------------------|
| 1 h              | 130 | 330               | Liver dysfunction, CNS impairment, headache |
| 24 h             | 30  | 80                | Liver dysfunction, CNS impairment           |
| 7 d <sup>a</sup> | 1   | 2.6               | Testicular toxicity                         |
| 30 d             | 1   | 2.6               | Testicular toxicity                         |
| 180 d            | 1   | 2.6               | Testicular toxicity                         |

<sup>a</sup>Former 7-d SMAC = 0.1 ppm.

## RATIONALE

For each toxic end point worth considering, an acceptable concentration (AC) is derived for each of the exposure durations, namely 1 h, 24 h, 7 d, 30 d, and 180 d. The lowest AC among all the toxic end points is then chosen to be the SMAC for that exposure duration.

## Mucosal Irritation

Lefaux (1968) reported that vinyl chloride irritates human eyes at a concentration over 500 ppm. According to the data of Baretta et al

(1969), 500 ppm appears to be the threshold for mucosal irritation in acute exposures of human subjects, and 250 ppm is the NOAEL in a 7.5-h exposure. Two of seven human subjects experienced dryness of the nose and eyes at 500 ppm (Baretta et al., 1969). Since slight mucosal irritation is acceptable in contingency situations, the 1-h and 24-h ACs are derived from the LOAEL of 500 ppm.

1-h and 24-h ACs based on mucosal irritation  
 = 3.5-h LOAEL  
 = 500 ppm  
 = 500 ppm.

The 7-d, 30-d, and 180-d ACs, however, should be established at a no-effect level. The 7.5-h NOAEL of 250 ppm is based on the data of only four men (Baretta et al., 1969), so a safety margin is needed by applying a factor for "small  $n$ ."

7-d, 30-d, and 180-d ACs based on mucosal irritation  
 = 7.5-h NOAEL  $\times$  1/safety factor for small  $n$   
 = 250 ppm  $\times$  (square root of  $n$ )/10  
 = 250 ppm  $\times$  (square root of 4)/10  
 = 50 ppm.

The same value is chosen for the 7-d, 30-d, and 180-d ACs because mucosal irritation is not expected to get worse when the exposure is extended beyond 7.5 h.

### Headache

Vinyl chloride produced mild headache in two of seven men at 500 ppm in 3.5 h, but all of the four men exposed to 250 ppm for 7.5 h were free of any headache (Baretta et al., 1969). Since mild headache is acceptable in contingency situations, the 1-h AC based on headache is set at the LOAEL of 500 ppm. Unlike mucosal irritation, headache tends not to diminish in severity as the exposure continues, so the 24-h AC for headache should be set lower than the 1-h AC. The 7.5-h NOAEL of 250 ppm is chosen to be the starting point for the 24-h AC based on headache.

24-h AC based on headache  
 = 7.5-h NOAEL  $\times$  (square root of  $n$ )/10  $\times$  time adjustment  
 = 250 ppm  $\times$  (square root of 4)/10  $\times$  7.5 h/24 h  
 = 50 ppm.

Because the use of Haber's rule to extrapolate from the 7.5-h NOAEL to an AC for an exposure lasting 7-d, 30-d, or 180-d is probably not valid, the setting of 7-d, 30-d, and 180-d ACs for headache is not attempted.

### CNS Impairment

The NOAEL for CNS impairment was 500 ppm for 3.5 h based on the data of seven men; it was 500 ppm for 7.5 h based on the data from four men (Baretta et al., 1969).

1-h AC based on CNS effects  
 = 3.5-h NOAEL  $\times$  1/safety factor for small  $n$   
 = 500 ppm  $\times$  (square root of  $n$ )/10  
 = 500 ppm  $\times$  (square root of 7)/10  
 = 130 ppm.

24-h AC based on CNS effects  
 = 7.5-h NOAEL  $\times$  1/safety factor for small  $n$   $\times$  time adjustment  
 = 500 ppm  $\times$  (square root of  $n$ )/10  $\times$  7.5 h/24 h  
 = 500 ppm  $\times$  (square root of 4)/10  $\times$  7.5 h/24 h  
 = 30 ppm.

Due to a lack of data on the time response of vinyl chloride's CNS impairment, no acceptable concentrations are estimated beyond 24 h.

### Non-neoplastic CNS Injury

In long-term exposures, vinyl chloride has been shown to cause degeneration of the white and gray matter of the brain and atrophy of the granular cells in the cerebellum of rats (Viola, 1970). The NOAEL for CNS injury, based on a 1-y exposure of rats, is 5000 ppm.

7-d and 30-d ACs based on CNS injury

$$\begin{aligned} &= 1\text{-y NOAEL} \times 1/\text{species factor} \\ &= 5000 \text{ ppm} \times 1/10 \\ &= 500 \text{ ppm.} \end{aligned}$$

The time adjustment for 180 d

$$\begin{aligned} &= 1820 \text{ h}/(24 \text{ h/d} \times 180 \text{ d}) \\ &= 1820 \text{ h}/4320 \text{ h.} \end{aligned}$$

180-d AC based on CNS injury

$$\begin{aligned} &= 1\text{-y NOAEL} \times \text{time adjustment} \times 1/\text{species factor} \\ &= 5000 \text{ ppm} \times (7 \text{ h/d} \times 5 \text{ d/w} \times 52 \text{ w})/(24 \text{ h/d} \times 180 \text{ d}) \times 1/10 \\ &= 5000 \text{ ppm} \times 0.42 \times 1/10 \\ &= 210 \text{ ppm.} \end{aligned}$$

Because vinyl chloride is not known to cause CNS injuries acutely, no 1-h and 24-h ACs are needed for this end point.

#### Liver Toxicity

Tatrai and Ungvary (1981) discovered liver histopathology in mice exposed to vinyl chloride at 1500 ppm for 24 h. In contrast, Baretta et al. (1969) did not detect any changes in the serum levels of SGPT, alkaline phosphatase, lactic dehydrogenase, and bilirubin in seven workers exposed to vinyl chloride at 500 ppm for 3.5 h or in four workers exposed for 7.5 h (Baretta et al., 1969). Therefore, the NOAEL for acute vinyl chloride exposures appears to be 500 ppm.

1-h AC based on non-neoplastic liver toxicity

$$\begin{aligned} &= 3.5\text{-h NOAEL} \times 1/\text{safety factor for small } n \\ &= 500 \text{ ppm} \times (\text{square root of } n)/10 \\ &= 500 \text{ ppm} \times (\text{square root of } 7)/10 \\ &= 130 \text{ ppm.} \end{aligned}$$

24-h AC based on non-neoplastic liver toxicity

$$\begin{aligned} &= 7.5\text{-h NOAEL} \times 1/\text{safety factor for small } n \times \text{time adjustment} \\ &= 500 \text{ ppm} \times (\text{square root of } n)/10 \times 7.5 \text{ h}/24 \text{ h} \end{aligned}$$

$$\begin{aligned} &= 500 \text{ ppm} \times (\text{square root of } 4)/10 \times 7.5 \text{ h}/24 \text{ h} \\ &= 30 \text{ ppm.} \end{aligned}$$

Based on the occupational data of Ho et al. (1991), liver dysfunction is possible when the vinyl chloride concentration in the workplace averages 6 ppm and no liver dysfunction would be found at about 1.5 ppm. It appears that the NOAEL for non-neoplastic liver toxicity is about 1.5 ppm in occupational exposure. The NOAEL of 1.5 ppm is based on data from over 100 workers exposed to vinyl chloride for at least 1 y since 1983 (Ho et al., 1991). For simplicity sake, the NOAEL is assumed to be based on a 1-y occupational exposure. Because this type of liver dysfunction is believed to be reparable, a NOAEL for a 1-y occupational exposure ought to be devoid of liver toxicity for 7, 30, or 180 d.

7-d, 30-d, and 180-d ACs based on non-neoplastic liver toxicity

$$\begin{aligned} &= 1\text{-y NOAEL} \\ &= 1.5 \text{ ppm.} \end{aligned}$$

#### Kidney Toxicity

As discussed in "Toxicity Summary," the NOAEL for non-neoplastic kidney toxicity is 200 ppm, based on data from a 6-mo exposure of rats (Torkelson et al., 1961).

7-d and 30-d ACs based on kidney toxicity

$$\begin{aligned} &= 6\text{-mo NOAEL} \times 1/\text{species factor} \\ &= 200 \text{ ppm} \times 1/10 \\ &= 20 \text{ ppm.} \end{aligned}$$

Because vinyl chloride's kidney injuries are believed to be reparable, the 180-d AC is set to equal the 30-d AC of 20 ppm. Since kidney injuries have never been reported in acute vinyl chloride studies, no 1-h and 24-h ACs are needed for this end point.

#### Lung Toxicity

Vinyl chloride has been shown to produce non-neoplastic lung injuries in

mice (Suzuki, 1978, 1980). The LOAEL based on a 6-mo exposure of mice is 2500 ppm (Suzuki, 1978, 1980), so the NOAEL is estimated to be 250 ppm.

$$\begin{aligned} & \text{7-d and 30-d ACs based on lung toxicity} \\ &= 6\text{-mo NOAEL} \times 1/\text{species factor} \\ &= 250 \text{ ppm} \times 1/10 \\ &= 25 \text{ ppm.} \end{aligned}$$

$$\begin{aligned} & \text{180-d AC based on lung toxicity} \\ &= 6\text{-mo NOAEL} \times \text{time adjustment} \times 1/\text{species factor} \\ &= 250 \text{ ppm} \times (5 \text{ h/d} \times 5 \text{ d/w} \times 26 \text{ w}) / (24 \text{ h/d} \times 180 \text{ d}) \times 1/10 \\ &= 250 \text{ ppm} \times 650 \text{ h/4320 h} \times 1/10 \\ &= 250 \text{ ppm} \times 0.15 \times 1/10 \\ &= 4 \text{ ppm.} \end{aligned}$$

No 1-h and 24-h ACs are needed because vinyl chloride is not known to cause lung toxicity acutely.

### Testicular Toxicity

According to the data of Bi et al. (1985), vinyl chloride is known to cause testicular injuries in rats in long-term exposures. A reduction in testicular weight was noted in rats exposed to vinyl chloride at 100 or 3000 ppm for 6 h/d, 6 d/w for 6 mo. Bi et al. expressed the pathology data by combining the histopathological data of rats sacrificed after a 3-, 6-, 9-, or 12-mo exposure to vinyl chloride at 0, 10, 100, or 3000 ppm. They found that exposures to 100 or 3000 ppm produced a higher percent of rats with fusion of cells and degeneration of seminiferous tubules in the testis than the control. The NOAEL was 10 ppm. Since the number of rats sacrificed after 6 mo of exposure approximately equaled the combined number of rats sacrificed immediately after a 3-, 9-, or 12-mo exposure, the NOAEL of 10 ppm is assumed to represent a NOAEL based on a 6-mo exposure.

$$\begin{aligned} & \text{7-d and 30-d ACs based on testicular toxicity} \\ &= 6\text{-mo NOAEL} \times 1/\text{species factor} \\ &= 10 \text{ ppm} \times 1/10 \\ &= 1 \text{ ppm.} \end{aligned}$$

Because the cell types that could be injured by vinyl chloride are spermatids and spermatocytes, vinyl chloride's testicular injuries are believed to be reversible. As a result, the 180-d AC is set to equal the 30-d AC.

$$\begin{aligned} & \text{180-d AC based on testicular toxicity} \\ &= 30\text{-d AC} \\ &= 1 \text{ ppm.} \end{aligned}$$

Because there is no evidence that acute vinyl chloride exposures are toxic to the testis, the 1-h and 24-h ACs are not derived.

### Carcinogenicity

Vinyl chloride exposures could lead to the production of tumors in several organs, especially in the liver. Based on the rat data from Maltoni and his colleagues (Maltoni, 1977), the U.S. Environmental Protection Agency, using the linearized multistage model, estimated that a life-time exposure of humans at 1 ppm has a tumor risk of  $6.80 \times 10^{-3}$  (EPA 1984). The life-time exposure concentration that would yield a  $10^{-4}$  tumor risk, which is the tumor risk accepted by NASA, is calculated as follows:

$$\begin{aligned} & \text{Life-time exposure concentration that would generate a } 10^{-4} \text{ tumor risk} \\ &= (1 \text{ ppm} / 6.80 \times 10^{-3}) \times 10^{-4} \\ &= 0.0147 \text{ ppm.} \end{aligned}$$

This life-time exposure concentration is converted to the ACs using the Crump and Howe approach as suggested by the NRC's Committee on Toxicology (NRC, 1992; Crump and Howe, 1984). Setting  $k = 3$ ,  $t = 25,550$  d, and  $s_1 = 10,950$  d, the adjustment factor is calculated to be 26,082 for estimating a near-instantaneous exposure level that would yield the same excess tumor risk as a continuous life-time exposure.

$$\begin{aligned} & \text{24-h AC based on carcinogenicity} \\ &= 0.0147 \text{ ppm} \times 26,082 \\ &= 380 \text{ ppm.} \end{aligned}$$

For the 7-d, 30-d, and 180-d ACs based on carcinogenicity the adjustment factor is 1.

factors are 3728, 871, and 146.7, respectively, assuming  $k = 3$ ,  $t = 25,550$  d, and the earliest age of exposure to be 30 y.

7-d AC based on carcinogenicity  
 $= 0.0147 \text{ ppm} \times 3728$   
 $= 55 \text{ ppm.}$

30-d AC based on carcinogenicity  
 $= 0.0147 \text{ ppm} \times 871$   
 $= 13 \text{ ppm.}$

180-d AC based on carcinogenicity  
 $= 0.0147 \text{ ppm} \times 146.7$   
 $= 2 \text{ ppm.}$

#### Establishment of SMACs

By selecting the lowest ACs among the various toxic end points for an exposure duration, the 1-h, 24-h, 7-d, 30-d, and 180-d SMACs are set at 130, 30, 1, 1, and 1 ppm, respectively. Because these toxic end points are not expected to be affected by any microgravity-induced physiological changes, the SMACs are not adjusted any further.

TABLE 11-5 Acceptable Concentrations

| Toxic End Point     | Acceptable Concentration, ppm |      |     |      |       |
|---------------------|-------------------------------|------|-----|------|-------|
|                     | 1 h                           | 24 h | 7 d | 30 d | 180 d |
| Mucosal irritation  | 500                           | 500  | 50  | 50   | 50    |
| Headache            | 130                           | 50   | —   | —    | —     |
| CNS impairment      | 130                           | 30   | —   | —    | —     |
| Liver toxicity      | 130                           | 30   | 1.5 | 1.5  | 1.5   |
| Kidney toxicity     | —                             | —    | 20  | 20   | 20    |
| Lung toxicity       | —                             | —    | 25  | 25   | 4     |
| Testicular toxicity | —                             | —    | 1   | 1    | 1     |
| Carcinogenicity     | —                             | 380  | 55  | 130  | 2     |
| SMAC                | 130                           | 30   | 1   | 1    | 1     |

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