on respiration has not been investigated. Studies in the rat showed that metabolism of VC in closed chamber is saturated at a concentration of 250 ppm (Sec. C3a).

Average ventilation values were used to obtain estimates of the sustained doses listed in Tables I and III. In addition, average values for the body weight of the animals and estimates of body surface area and conversion factors (Freireich et al., 1966) were employed in the calculations (see Footnote a for Table .). Thus, only crude estimates could be obtained. Based on these, mice may be slightly more sensitive to a concentration of 250 ppm than rats or hamsters (Table III). However, as noted above, actual in vivo levels of VC are not available, and hence any difference in quantitative carcinogenesis may depend on such values, rather than intrinsic distinct species-linked responses.

Better relative estimates could be obtained with good dosimetry data on the three species.

5. Human Studies

i. Conclusion

VC is implicated in the etiology of hepatic angiosarcoma and possibly brain and lung tumors, and other kinds of cancer.

ii. Literature and Evaluation

Angiosarcoma of the liver was first recognized as a VC-associated occupational cancer in 1974 (Creech and

Johnson, 1974). Soon after the first cases were reported, several studies revealed that individuals working and living near to PVC-polymerization facilities had excess mortality from cancer of the brain and the lung (Monson, et al., 1974; Tabershaw and Gaffey, 1974). A Dow Chemical Corporation study found that observed deaths due to malignancy exceeded those expected among workers in the high-exposure category; exposure was measured in two production units, and was reported to range from 10 to 385 ppm in one and from 5 to 325 ppm in the other; occasional maximum excursions reached up to 4,000 to 1,300 ppm, respectively (Ott et al., 1975). Waxweiler ett al (1976) in a study of a cohort with minimum five-year direct exposure and 10-year latency confirmed excessive mortality from neoplasms of the brain and CNS, the respiratory system, liver and lymphatic and hematopoietic systems. There was some indication that the large-cell undifferentiated type of lung cancer was more prevalent than expected. Excess mortality from "other respiratory disease" was also found (Waxweiler et al., 1976). A slight but significant excess was found for deaths from lymphomas. There was evidence that biliary and liver cancer deaths required a 10-year latent period to show a mortality excess, while a 15-year latent period was required for brain, respiratory system, lymphatic and hematopoietic systems (Infante et al., 1976)

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Hepatic angiosarcoma is the best-defined VC-induced cancer in man. Some 63 cases had been reported by 1977.

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Most of the tumors were observed in reactor cleaners. However, an accountant employed for 10 years in a vinyl fabric factory also developed this tumor, which otherwise occurs at a rate of 25-30 cases/yr in the entire U.S. population (Bartsch and Montesano, 1975). Another five persons with liver angiosarcoma could be shown to have lived within 500 to 4,500 ft of a VC or PVC factory for 8 to 62 years prior to diagnosis. Their ages at diagnosis ranged from 31 to 62. It was stated that in one of the cases, ambient emissions of VC from the factory were as high as 92,800 ppm, and the person lived only 1,700 feet away for 62 years. The air levels of VC around the residences were not known. It was also found that in 1955 through 1975, 14 cases of hepatic angiosarcoma were diagnosed among New York State residents who never had exposure (direct or indirect) to VC. The possibility of exposure to arsenic or thorium dioxide known to be associated with angiosarcoma was also excluded. It was concluded that New York State might have a disporportionately high annual incidence of liver angiosarcoma in 1970 through 1975 (0.25 per million vs 0.14 million in U.S.), and other toxic substances besides VC, arsenic and thorium dioxide were suspected to have contributed to the tumor incidence (Brady et al., 1977). Typically, occupational liver angiosarcoma has been diagnosed in men ranging in age from 36 to 58 ($\bar{X}$ = 46.7 years) and having had 7-28 ($\bar{X}$ = 17) years of employment. In almost all cases, the latent period exceeded 10 years.

Industrial Exposure

Barnes (1976) has pointed out that all significant medical effects such as liver angiosarcoma and acroosteolysis have been observed exclusively in workers in polymerization plants or, in two cases, plants handling liquid VC under pressure. No significant abnormalities were said to be found among those workers who handle PVC dust during drying and packing.

The polymer slurry contains around 500 ppm of VC; during centrifuging and drying the content is reduced to about 50 ppm (Barnes, 1976).

According to Barnes, the average atmospheric exposure for polymerization workers in the past might have been of the following orders:

1945-1955	1,000 ppm
1955-1960	400-500 ppm
1960-1970	300-400 ppm
1975	5 ppm

However, levels as high as 3,000 ppm are alleged to have been encountered by reactor cleaners in the early days.

The study by Kramer and Mutchler (1972) of Dow Chemical Corporation produced time-weighted average exposure of 155 ppm in 1950, and 30 ppm in 1965; again, these figures do not reflect peak levels and either indicate that analytical methods were probably quite inadequate, or reflect a "clean" process. On-the-spot measurements by Baretta et al. (1969)

yielded a time-weighted average concentration for a polymerization operator (not a "pot-cleaner") of 50-200 ppm.

Prior to degassing, the concentration inside the reactor is some 3,000 ppm (Lange et al., 1974). Men enter the reactors a. a concentration of 50-100 ppm, but realistically, the range is 600 to 1,000 ppm (Cook et al., 1971; Nicholson et al., 1975). Filatova and Gronsberg (1957) describing the conditions in a USSR factory write that maximum tolerated levels were set at 4(to .12 ppm, but occasional bursts amounting to 34,000 ppm occurred.

<u>Latent Period and Effective Dose</u>

In one documented case, exposure at "high concentration" for 4 years lead to the development of hepatic angiosarcoma and death eight years after the first exposure (Fox and Collier, 1977). On average, the latent period is closer to 20 years (Anonym., 1976), and employment period in the reactor-cleaning job (usually followed by years in a less exposed job) ranges from several months to several years.

It is difficult to estimate the total dose for a reactor cleaner, because of considerable variation in job definitions and in the technologic process. The general consensus (Barnes 1976; Nicholson et al., 1975) is that a polymerization plant operator, would be exposed to an average VC concentration of 1,000 ppm. Assuming that this is a reasonable estimate for a reactor cleaner, a year spent in this job corresponds to a total dose of (2.56 mg/L)(4800 L/day) (5days/wk) (50

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wk/yr = 22 g/kg. The average occupational exposure of workers is given as 18 yrs (IARC, 1974) and the average exposure of workers that developed hepatic angiosarcoma was 18 years (Nicholson et al., 1975). For exposures of this duration, the cummulative dose would be 396 g/kg.

The above daily dose estimate is perhaps on the high side; however, hepatic angiosarcoma appears to cluster in certain plants, whereas others have no cases at all (Bartsch and Montesano, 1975). It seems reasonable to assume that cases arise more frequently where hygiene is less stringent (Dinman et al., 1971). In support of the importance of high exposure, Heath et al (1975) have noted that there is a possible dose-response relationship between the duration of employment as a reactor cleaner and the latent period to development of heptic angiosarcoma.

However, it is unknown whether humans display a saturation limit similar to the rat (Sec C 3a) in the ability to absorb and metabolize VC. Thus far, the data are not consistent with such a limit, since most cases of angiosarcoma as noted, are associated with high exposures. These exposures, however, may be necessary to achieve the saturation limit, which in rats is 250 ppm. If 250 ppm is a maximally effective dose, then the cummulative dose would be reduced by one-fourth.

Incidence

In estimation of the human carcinogenic dose is difficult, the incidence of hepatic angiosarcoma can likewise be related

to dose but in an imprecise way. Fox and Collier (1977) point out that 4 cases of liver cancer had been reported in Great Britain where over 7,000 men were at some time between 1940 and 1974 exposed to the monomer in PVC manufacture. Two of them had angiosarcoma, both in men with high VC exposure. However, only 8% of the working force had been employed for over 20 years, and of those, only 34 were exposed to constant high levels. This leads to an incidence estimate of 2:34 (6%). However, exposure to constant high levels is probably not necessary. In the U.S., where about 20,000 workers have been exposed to VC (Heath et al., 1975) 17 cases were reported up to 1975 (Falk and Waxweiler, 1976; Lloyd, 1975). Nine of these cases were found in a single plant employing less than 300 workers i.e. 3% (Bartsch and Montesano, 1975). In the absence of better data and latent period-adjusted analysis, a reasonable and reliable estimate of incidence as a function of dose in human subjects is difficult, but may be as high as 20-25% if only the reactor cleaner population at obvious high risk is considered.

However, a number of cases can be associated knowingly with only indirect exposure. This may indicate a nonlinear dose-response curve for man, and probably a degree of individual susceptibility, but these cannot be assigned any numerical values at this point. Also, there have been suggestions that some individuals not directly concerned with high level

reactor cleaning were "addicted sniffers". It is most difficult to evaluate such speculative information in relation to possible disease development.

6. Human Extrapolation

i. Conclusion

VC is a potent carcinogen in animals (Sec. B1) causing mostly angiosarcomas in the liver and other sites, and also brain and skin tumors over a range of dosage by several routes of entry. VC is mutagenic to bacteria, yeast, and drosophila, and therefore is a genotoxic carcinogen. As such it would be predicted to present a cancer hazard to humans. In humans, VC causes angiosarcoma of the liver and possibly also tumors of the brain and lungs.

Quantitative extrapolation of risk from animals to man on the basis of existing experimental data and environmental levels is difficult, because a number of crucial questions remain unanswered. In the absence of evidence to indicate otherwise, a conservative approach commands that man be considered sensitive to doses of the same order of magnitude as those active in the most sensitive animal species.

ii. Literature and Evaluation

VC has been shown to be directly mutagenic for Salmonella typhimurium (Bartsch et al., 1975; Malaveille et al., 1975; McCann et al., 1975; Rosenkranz et. al., 1974). This mutagenic effect was attributed to a direct action of

exposures, due for example, to VC or by metabolites formed by enzyme systems (Bartsch et al., 1975). The latter explanation is more likely because mutagenicity in these systems is increased by the presence of liver extracts or hepatic microsomes (Bartsch et al., 1975; Malaveille et al., 1975).

Drosophila melanogaster (fruitfly) males, exposed to graded concentrations of VC in air, produced progeny with recessive-lethal mutations which correlated with dose. The lowest effective concentration in a two-day test was 850 ppm (Verburgt and Vogel, 1977).

In higher animals, inhalation of VC appears to have a dose-related carcinogenic effect (Sec. B1). However, the actual in vivo doses in the specific species were not known (Sec. B4).

In humans, the problem of dose effect needs further study. It appears that most cases of angiosarcoma of the liver were seen in individuals who at some time worked as reactor cleaners, and were, thus, most likely exposed to 1,000 ppm or more (Sec. B5). However, more recent surveys have indicated that several cases of this otherwise rare tumor developed in persons who never worked with VC, but lived closer to a VC plant than their matched controls. It appears therefore, that higher exposure carries a higher risk, but low exposure may be sufficient to induce a small number of tumors, perhaps in sensitive individuals.

Metabolic studies in rats suggest that at extremely high concentrations, VC cannot be metabolized in proportion

to the dose (Sec. C 3a). Absorption from the air phase no doubt, also plays a role. It obviously cannot be determined directly whether humans display similar limits in the capacity to absorb and activa e VC. If they did, then exposure duration, rather thai VC concentration, might determine the risk of developing cancer. It should be noted that animal experiments with varying duration of daily exposure are lacking, and should be designed. It is to be hoped that more than one species will be utilized, and that the problem of dosimetry as formulated in Sec. B4 receives adequate attention. Strain studies are also needed to resolve the question of individual susceptibility to the carcinogenic effects of VC.

Dosages of vinyl chloride were usually expressed as concentrations of VC in air. The effective dosage in tissues in animals depends on the rate of absorption of VC from air in the repiratory tract. This in turn is a function of respiratory rate and transfer of VC from the air phase to blood. An animal with a rapid respiratory rate, like the mouse, might equilibrate more rapidly than an animal with a slower rate. A man at rest, for example in a factory sitting at a control panel, would have a slower respiratory rate than a reactor cleaner inside a tank actively engaged in hard work. Eventually, the limiting element with respect to patholgoical effects will be the equilibrium value between inhaled VC, exhaled material, and saturation effects. The

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latter depends in turn on the rate of removal of VC itself through metabolism. We concluded that the values tabulated in this document are approximations which depend a great deal on the parameters we have listed here. The literature does not now provide direct measurements of blood levels of question of individual susceptibility to the carcinogenic effects of VC.

Bearing in mind, all these limitations the data reveal a 7% incidence of hepatic angiosarcoma in rats at 7.5 g/kg, 37% in mice at 45 g/kg (Sec B1) and 3-6% in man at 396 g/kg (Sec B5). Thus no more than a 50 fold difference in apparent sensitivity to hepatic angiosarcoma induction exists between these species Evaluation of the human data suggests that the estimated dose may be too high and the incidence figures estimated in the literature are probably too low because 1) the denominator describing individuals certainly exposed was too inclusive and 2) the potential expression of disease of exposed individuals has not been completed. Therefore, the final human incidence may prove to be greater, further narrowing any distinction in sensitivity. If a saturation limit for the carcinogenic effect of VC to the liver in humans is assumed, similar to that in rodents (Sec B5), the cummulative effective dose would be reduced to abut 100 g/kg. In this case, species differences would be no more than an order of magnitude. We believe that this is a more realistic estimate than others in view of the uncertainties, all of which lead to underestimation of the human risk.