COMMENTS ON EPA TOXICOLOGICAL PROFILE ON VCM

VOID

GENERAL COMMENTS

As described in Section 2.3.1., SARA directs EPA to prepare toxicology profiles that will include an examination of the data, a determination of adequacy, and, where appropriate, an identification of needed toxicology testing. Although the draft Toxicological Profile for VCM (1988) is intended to meet this requirement, it falls far short of both the letter and spirit of the Act in many ways.

1) This document fails to incorporate key data.

2) It fails to provide the critical review necessary to draw a conclusion.

3) Because there is no identification of toxicological testing needs, we assume that all the data is considered adequate. The graphs appear to indicate the data is adequate. However, there is no clear statement in the test to this point and the detail of discussion of this subject is not adequate to draw any conclusions.

4) Referencing of data in tables and texts is inadequate.

5) There are some instances where reference books and computerized databases are utilized instead of the original references. The problem with this procedure is that it does not allow critical review and it presents the opportunity for perpetuating errors and misstatements. We know for a fact that this has been a frequent problem or real concern for at least one of the reference books used.

6) The detail of information provided generally is insufficient to provide any confidence in the NOAEL, LOAEL, Minimal Risk levels or conclusions or a clear understanding of how they arrived at these. To this end we would recommend the use of NAS guidelines for use of safety factors (NAS, 1982).

7) The authors' use of a number of terms is questionable. The term FEL is misused on page 42, paragraph 1. Increase in DNA synthesis is not a frank effect. Also the descriptor "minimal" (page 44 General Discussion) is a poor choice. Standardized terms such as "Adequate" (or "Clear"), "Some" (or "Limited"), "Equivocal), "No Evidence" and "Inadequate" should be used because their meanings transcend the subject of carcinogenicity and are broadly applicable. Futhermore, it would be better if adequacy was assessed in these terms.

NEW PAGE

SPECIFIC COMMENTS

BOLD UNDERLINE

CONSUMER EXPOSURE IN CARS (Section 1.2, page 1, paragraph 1; Section 7.2.4, page 71, paragraph 3)

At the February, 1988 VI Technical Committee meeting Roy Gottesman mentioned that GM had conducted a study of VCM levels in new cars. We should make sure that this information is provided to EPA.

** GM STUDY NEEDS TO BE REFERENCED & DISCUSSED HERE **

PLASTIC PIPE LEACHING DRINKING WATER EXPOSURE (Section 1.2, page 1, paragraph 2; Section 1.3, page 2; Section 2.2.3.2, page 18, paragraph 2; Section 2.3.3.3, page 24, paragraph 2; Section 7.2.4, page 71, paragraph 2)

The VI has generated considerable data on the leaching from PVC pipe. I have asked Alan Olson (BFG) to prepare comments and provide the data.

CARCINOGENICITY AND OTHER DISEASE (Section 1.4, page 2, paragraph 1; Section 2.2.1.1, page 14, paragraph 1; Section 4.3.6.4)

The discussion of the types of disease and cancer caused by VCM is very misleading. The document states that "lower concentrations" cause "vinyl chloride disease" but fail to note that these effects are not of concern at present workplace and ambient concentrations. Furthermore, this section suggests that VCM can cause cancer of the "liver, brain, lung and possibly other organs." IARC Supplement 4 (1982) clearly states that "Vinyl chloride causes angiosarcoma of the liver" and distinguishes other tumor with lesser weight of evidence being "associated with".

A recent assessment of the data by the world-renowned epidemiologist Sir Richard Doll (1987) further supports this distinction. He notes that the evidence that VCM causes liver cancer, specifically angiosarcoma, is strong. However, the combined data on respiratory cancer fail to support an association of VCM and lung cancer. In the case of brain and lymphatic and hemopoietic cancers he indicates that the excesses are not statistically significant and that there is nothing to suggest that they are occupationally related.

EFFECTS ON OFFSPRING/DEVELOPMENTAL (Section 1.4, page 2, paragraph 1; Section 2.2.11, pages 13-14; Section 4.3.3.1; Section 4.4)

The profile on VCM fails to note that there is no evidence that VCM causes birth defects or reproductive effects but that it's only a concern from the point of view of potential transplacental carcinogenicity. The lack of focus on this conclusion or any conclusion may be due to the lack of consideration of key documents which are described in "Potential Effects of Vinyl Chloride on Human Offspring" (1987). Also, the absence of critical review has contributed to a misleading presentation.

It is also interesting to note that the discussion of developmental toxicity on page 13 appears to avoid the fact that "VCM did not cause significant embryonal or fetal toxicity and was not teratogenic in any of the species at the concentrations tested." (John et al, 1977) Based on these results it is incongruous that the document would espouse any NOAEL, not to mention one at 50 ppm. Unfortunately, there is no information provided to support the 0.7 ppm minimal risk level or the 50 ppm NOAEL. Such absence of detail and supporting rationale is a common deficiency in this document.

CANCER RISK ESTIMATES (Section 1.6.2, page 4; Section 2.2.1.1, pages 14-15)

Estimates of cancer risk are limited to those derived by EPA in 1985. Since risk estimates have been derived by others these should be identified and discussed. This is particularly important since some of these estimates (NHCH, 1987) differ by more than 2 orders

or magnitude from EPA. Furthermore, EPA has recently revealed the fact that it is now using new risk assessment procedures which have dramatically lessened risk estimates for many chemicals (Chemical Regulation Reporter, 1988).

GENOTOXICITY (Section 2.2.1.1.)

The ability of VC to induce mutations in human cells was examined in three separate, independent studies conducted by Funes-Craviato et.al. (1975), Ducatman et. al. (1975), and Purchase et. al. (1975) which all examined workplace exposure to VC. All three studies suffer from a number of flaws which includes lack of exposure data, inappropriate statistics, and no descriptions of how control groups were selected. The studies show a slight association between potential VC exposure and chromosomal breaks in lymphocytes. Two of the studies, Funes-Craviato Set. al. (1975), Ducatman et. al. (1975), actually found that the number of chromosomal aberrations were often lower among workers as length of employment increased. The last observation is significant since it suggests that metabolism and/or repair become active after extended periods of exposure. Because of all the information that is missing from these studies, it is hard to develop any conclusions on the relationship between VC exposure and chromosomal aberrations.

Workplace exposure and chromosomal aberrations among lymphocytes of male workers was also examined by Leonard et. al. (1977). The workers studied were employed in a VC facility in Belgium where there was no record of exposure levels. The authors assumed that employment during early exposure years was initially 500 ppm which

was eventually reduced to 10 ppm. Controls who were employed in the laboratory of the same facility and were assumed to be exposed to less than 1 ppm. An additional 10 controls were obtained from outside the factory and assumed to never have been exposed. The average of the number of aberrations per 100 cells was approximately the same for each group. Even though some specific chromosomal aberrations were found in the exposed group, the significance of the finding is questionable since each of those workers received regular radiologic examinations which would produce the same observations. Consequently, this study does not support the premise that VC causes mutations in human subjects.

Fleig and Thiess (1978) studied aberrations of lymphocyte chromosomes among workers at a BASF plant in Germany. The actual plant exposures have not been documented in this study, but they were reported to be comparable to the German workplace standard which was around 1,000 ppm in 1945 and decreased to 150 ppm in 1973. The subjects chosen in this study had overt signs of VC toxicity which included angiosarcoma of the liver, and the controls were carefully matched and took into account smoking, alcohol, vaccinations, and other medical problems or treatment. They reported that they could find no differences between the cases and controls with the exception of one case that was receiving chemotherapy for cancer. Their data was not able to demonstrate an increase in chromosome aberrations as a result of high level VC exposure in the workplace.

Vinyl chloride has been examined in a number of different laboratory studies with mice, rabbits, and rats. Studies were designed to examine mutational effects (changes in DNA) as well as teratogenic/ reproductive effects (birth defects, fertility, miscarriages, etc.).

An early study done by Anderson et. al. (1976) examined VC mutagenicity in fertile male mice using the DOMINANT LETHAL ASSAY. Their study exposed mice to VC for 6 hours per day for 5 days to concentrations of 3,000, 10,000, and 30,000 ppm. They were not able to find any mutagenic effects at any of the stages of spermatogenesis. To assure that their test system was functional, this study employed two known mutagens as positive controls (cyclophosphamide and ethly methane sulphonate) which did in fact give a positive response in their study. Therefore, the lack of mutagenic response from VC is indicative that VC is non-mutagenic rather than their test system lacks sensitivity.

The dominant lethal mutation study was later repeated by Himeno et. al. (1983) in CD-1 mice under two different exposure conditions. One group of mice was exposed for four hours per day during five consecutive days to 10,000 ppm of VC and the second group of mice was exposed for four hours per day, five days per week over a 10 week period to 5,000 ppm VC. This study, like the earlier study of Anderson et. al. (1976), was not able to demonstrate any dominant lethal type of mutations as a result of VC exposure, and this independently supports the observation that VC is non-mutagenic.

John et. al. (1981) examined the effects of VC exposure on the fetal development of mice, rabbits, and rats. All animals were exposed to 500 ppm VC for seven hours per day during the critical development

phase (organogenesis) for each species (days 6 to 15 for mice/rats and days 6 to 18 for rabbits). Some additional rats and rabbits were exposed to 2,500 ppm VC, and some additional mice were exposed to 50 to 500 ppm VC plus ethanol in their drinking water. At the high VC concentrations, there were some maternal deaths in mice, and some fetal body weights were lower for mice and rats treated with 500 ppm VC. Other than a depression in fetal weight in the high dose groups, there were no other apparent fetal changes. Quite surprisingly, fetal weights were unchanged from rats exposed to 2,500 ppm VC, and natural abortions in these particular rats were lower than the unexposed controls.

A similar study on teratogenicity was also carried out by John et. al. (1977) using mice, rabbits, and rats. Dose levels and exposures were similar to the previous study, but there was more emphasis placed upon concurrent ethanol treatment. The high dose of VC caused maternal toxicity in all species in addition to some embryonic death. The ethanol co-administration exaggerated all aspects of maternal toxicity in addition to decreased litter size, fetal weight, and fetal resorption. A number of skeletal defects were found with the co-administration of ethanol, but VC by itself was not teratogenic in mice, rabbits and rats. If anything the study emphasized the risks associated with ethanol consumption during pregnancy rather than indicating VC related problems.

Ungvary et. al. (1978) carried out a detailed study of VC exposure upon rats. In the first part of their experiments, the exposed rats on the 18th day of pregnancy to either 2,000, 7,000, or 12,000 ppm VC for 2.5 hours. They then detected and measured VC in maternal

blood, amniotic fluid, and fetal tissue which demonstrated that VC could be transferred to the fetus from the mother. In additional experiments they exposed rats to 1,500 ppm VC during different periods of pregnancy, and they were unable to produce teratological effects in the offspring. These results demonstrated that lack of teratological response in VC exposed rats were NOT due to the inability of VC to be transferred from the mother to the developing fetus.

All the animal studies cited above are remarkable in two important ways. First, some of the exposure levels of VC employed in the experiments were on the order of tens of thousands of ppm. Such exposures would only be encountered in the workplace under rare, isolated circumstances, and environmental exposure to such levels are not possible except in rare circumstances. Second, even though very high exposure levels were used in the animal studies, no mutations or birth defects could be detected. Substances known to give positive responses under similar conditions behaved as expected, so any lack of response to VC in the animal test systems could not be attributed to failure of the test systems. Rather, the more likely conclusion is that VC does not produce the anticipated adverse effects.

FDA REGULATIONS (Section 1.7, page 6; Section 2.2.3.1, page 18)

Statement of FDA regulations of food packaging is inaccurate. The FDA has recently proposed to amend the prior sanctions and regulations regarding vinyl food packaging to limit VCM to 5 to 50 ppb, not ppm. Also, there is no current official "action level" or "regulatory level" for VCM but there are manufacturer's voluntary guidelines.

EFFECTS ON OFFSPRING/REPRODUCTIVE (Section 2.2.1.1., page 14)

No reference is provided to indicate what animal data is being discussed. We assume this is Bi et al (1985). The authors fail either here or on page 50 to ask whether these observations are consistent with observations in other long-term studies. In fact, a review of the data indicates it is not (Maltoni and Mehlman, 1984).

More importantly, it should be noted that histopathologic organ changes are evidence of systemic changes even if they are found in reproductive tissues. Although observations of toxic effects in reproductive tissues would lead one to question whether the reproductive capacity of an animal might be compromised, it does not provide any evidence that a chemical is a reproductive toxin. In the case of VCM, the data indicates that VCM does not affect reproduction.

BIOLOGICAL MONITORING (Section 2.2.2, page 16, paragraph 3)

The authors note observations of elevated urinary coproporphyrin as a common finding associated with VCM-related liver disease and suggest it might be useful in population monitoring. What is not pointed out, however, is that while it is indicative of liver disease, it is not specific to VCM or chemical induced liver disease.

ADEQUACY OF DATA (Section 2.3.2.1, page 20)

Item 2 should note that while a potency factor or potency factors can be derived, the precision of those estimates is unknown.

The health effect and exposure route referred in Item 4 are unclear.

INTERACTIONS (Section 4.4)

The document fails to discuss the interaction of VCM and alcohol (i.e. metabolism and cancer in workers).

---

1. Drinking Water and Health, Vol. 4, National Academy Press, Washington, D.C., page 153.

2. Maltoni, C. and Mehlman, M.A. Experimental Research on Vinyl Chloride Carcinogenesis, Vol. II, Princeton Scientific Publishers, Inc. Princeton, New Jersey, 1984.