CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
(PROPOSITION 65)

NOTICE TO INTERESTED PARTIES
October 4, 1996

December 4, 1996 Meeting of the
Science Advisory Board's
Developmental And Reproductive Toxicant Identification Committee

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) is the lead agency for the implementation of the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

The Developmental and Reproductive Toxicant (DART) Identification Committee of OEHHA's Science Advisory Board advises and assists OEHHA in compiling the list of chemicals known to the State to cause reproductive toxicity which is mandated by Health and Safety Code Section 25249.8. The Committee serves as the "State's qualified experts" for rendering an opinion as to whether a chemical has been clearly shown, through scientifically valid testing according to generally accepted principles, to cause reproductive toxicity.

A public meeting of this committee will be held on Wednesday, December 4, 1996, in the Auditorium at 744 P Street, Sacramento, California from 10:00 a.m. until all business has been conducted or until 5:00 p.m.

The draft agenda for this meeting is as follows:

I. STAFF REPORTS
   - A. Update on administrative listings
   - B. Public comments
   - C. Report on OEHHA evaluation of need for workshop on postnatal exposures
   - D. Public comments

II. INORGANIC ARSENIC
   - A. Staff overview of draft hazard identification document
   - B. Committee discussion of possible finding that inorganic arsenic has been clearly shown to be a reproductive toxicant
   - C. Public comments
   - D. Committee discussion and decision

OEHHA has gone to considerable effort to develop a clearly defined procedure for how chemicals enter into the Proposition 65 process and the steps for appropriate evaluation. By publishing this notice well in advance of the Committee meeting, OEHHA hopes to encourage scientific dialogue prior to consideration of chemicals by the Committee. It is OEHHA's intent that relevant scientific studies, and relevant interpretations and analyses of such studies, be made available early in the process of Proposition 65 consideration so that OEHHA staff can prepare materials for timely consideration by the Committee that accurately reflect the available data. The Committee prefers that information for its consideration be presented in writing prior to its meetings so that it can give due consideration to the material, and so that it can devote time at the meetings to discussions and clarifications, rather than to extensive oral testimony. To allow adequate time for the Committee to review comments on the draft priorities and data summaries, and the draft hazard identification documents for inorganic arsenic and cadmium, OEHHA requests that all submittals on these items be received at its office on or before November 20, 1996.

Background materials for the meeting, including the following, can be obtained by writing to the above address or by calling (916) 445-6900:

- *Procedure for Prioritizing Candidate Agents for Consideration Under Proposition 65 By the OEHHA Science Advisory Board* (Draft dated October 1996)
- Draft list of draft priorities and draft data summaries on prioritized chemicals (dated October 1996). [Chemicals for which draft data summaries have been prepared include: acrylamide (CASRN: 79-06-1), aldrin (CASRN: 309-00-2), 1,3-butadiene (CASRN: 106-99-0), carbamazepine (CASRN: 298-46-4), carbon tetrachloride (CASRN: 56-23-5), chlordane (CASRN: 57-74-9), DDT (CASRN: 50-29-3), ethylene dibromide (CASRN: 106-93-4), formaldehyde (CASRN: 50-00-0), heptachlor (CASRN: 76-44-8), methylene chloride (CASRN: 75-09-2), progesterone (CASRN: 57-83-0), 2,4,5-T butyl ester (CASRN: 93-79-8), trichloroethylene (CASRN: 79-01-6), and vinyl chloride (CASRN: 75-01-4) CASRN = Chemical Abstracts Service Registration Number].
- Draft hazard identification document on *Developmental and Reproductive Toxicity of Arsenic* (dated October 1996)
- Draft hazard identification document on *Developmental and Reproductive Toxicity of Cadmium* (dated October 1996)
- *Mechanisms for Removing Chemicals from the Proposition 65 List Based on Findings Made by "the State's Qualified Experts"* (Draft dated May 1996)

The above listed documents are also available from the Internet at the following address: http://www.calepa.cahwnet.gov/oehha/.

DRAFT: 10/4/96

VINYL CHLORIDE:
DEVELOPMENTAL/REPRODUCTIVE TOXICITY DATA SUMMARY

Vinyl chloride (formula C_2H_3Cl, CAS No. 75-01-4) is used almost entirely for manufacturing polyvinyl chloride (PVC). Some vinyl chloride is used as an intermediate in various chemical syntheses. Vinyl chloride is on the Proposition 65 list as a carcinogen.

Overview of Developmental/Reproductive Toxicity Concern

There is a **MEDIUM** level of developmental/reproductive toxicity concern over vinyl chloride due to associations between vinyl chloride exposure and birth defects in humans, and reports of damage to the testes in rats. Evaluation of possible confounding and multiple exposures in human studies is not possible at this level of review. Developmental toxicity studies in animals reported embryotoxicity and developmental delay, sometimes in association with maternal toxicity. All animal studies use the inhalation route, the most relevant route for humans.

Developmental toxicity

A number of epidemiological studies of malformations have been conducted in communities adjacent to PVC manufacturing facilities. Results are not entirely consistent and the early positive studies have been criticized for their design and statistical analysis. Animal studies demonstrate embryotoxicity, developmental delay and hematomas at the higher doses which are frequently also associated with maternal toxicity.

Female reproductive toxicity

Human information appears to be scattered and derived from small and incompletely reported studies. Apparently, no standard fertility studies (multigeneration or continuous breeding) have been conducted in animals.

Male reproductive toxicity

Impotence was reported in three studies of worker populations, and increased fetal loss was reported in the wives of workers at a polymerization plant. Animal studies indicate damage to testes with vinyl chloride inhalation, but general toxicity was not discussed. Reports of studies of dominant lethal effects were inconsistent in different secondary sources and no male fertility study was located for animals.

Overview of Exposure Concern

There is a **MEDIUM** level of concern over the extent of exposure. 97% of vinyl chloride is used in PVC manufacturing. The other 3% is in assorted chemical synthesis. Major exposures can occur in manufacturing or fabrication of PVC. General population exposure can occur from releases from landfills, prefabricators, and water treatment. Small amounts are released from PVC packaging and pipes. There is a "minute amount" in cigarette smoke. Little exposure from food occurs since 1974 regulations requiring "cleaner" (decreased monomer content) PVC. At two landfills in California, emissions were detected in the ambient air of nearby areas. Vinyl chloride is not produced in California. Two facilities in California use vinyl chloride to produce PVC. In California, surface waters were "generally free" of vinyl chloride, but half of 947 wells tested had detectable levels. Vinyl chloride is not expected to bioconcentrate or bioaccumulate. It degrades rapidly in air, but more slowly in other media.

Data on developmental and reproductive toxicity

NOTE: Unless otherwise indicated, all information, including the citation, is obtained from secondary sources. Full citations of all studies are not provided here.

Developmental toxicity in humans

1. Bao (1988), as cited in ATSDR.
   No effects were reported in pregnant workers in China exposed to 0.2-130.7 ppm vinyl chloride.
2. Edmonds *et al.* (1975), (1978), as cited in ATSDR, Schardein.
   No relationship was found between malformations and distance from plant or parental occupation in a second study in the same area as Infante *et al.*, 1976b.
3. Infante (1976), Infante *et al.* (1976b), as cited in ATSDR.
   Increased malformation rates (CNS, upper alimentary tract, genitals, club foot) were found in communities with vinyl chloride polymerization facilities compared to county and state averages.
4. Rosenman *et al.* (1989), as cited in ATSDR, HSDB, Schardein.
   The odds ratio for CNS defects was correlated with the amount of emissions from 2 polymerization facilities and also with the distance from the facilities. No overall increase in birth defects was detected in the community. It was concluded that the increase in CNS defects was probably associated with vinyl chloride emissions (HSDB)
5. Theriault *et al.* (1983), as cited in ATSDR, Schardein.
   There was an increased prevalence of malformations in a town with a polymerization facility vs. 3 matched control towns. Prevalence of malformation was correlated with seasonal changes in emissions but not with proximity to the plant or with parental occupation.

Developmental toxicity in animals

1. Bingham *et al.* (1979), as cited in Barlow and Sullivan.
   Rats were exposed by inhalation to 0, 600 or 6,000 ppm 4h/day on gd 9-21. Low birthweight was reported.
2. Mirkova *et al.* (1978), as cited in ATSDR, Barlow and Sullivan.
   Rats were exposed to 2.4 ppm by inhalation throughout gestation. Increased early postimplantation loss, fetal hematomas, and hydrocephaly with intracerebral hematoma were reported, but no statistics or information on maternal toxicity were provided.
3. Mirkova *et al.* (1978), as cited in ATSDR, Barlow and Sullivan.
   Rats were exposed by inhalation to 2.4 ppm vinyl chloride throughout gestation. Hepatotoxic effects in offspring including decreased bile enzyme activity, decreased bile secretion, and decreased cholic acid content were reported; increased hexobarbital sleep time was also reported in offspring. No information was provided concerning maternal toxicity or study methods.
4. Salnikova and Kitsovdkaya (1980), as cited in ATSDR, RTECS®, Reprotox™, Shepard's Catalog of Teratogenic Agents.
   Rats were exposed via inhalation to, 0, 1.9, or 13.9 ppm vinyl chloride, 4 h/day, throughout gestation. Alteration in blood vessel permeability, nervous system functional disturbance and other abnormalities were reported at 1.9 ppm. Maternal toxicity was reported at 13.9 ppm along with decreased erythrocyte count and urinary hippuric acid. Increased fetal hemorrhage was also seen at 1.9 and 13.9 ppm and fetal edema at 13.9 ppm. At 6 months postnatal, offspring had decreased hemoglobin and leukocytes, decreased nonreproductive organ weights, decreased ability to orient, and increased pentobarbitol sleep time.
5. Schwetz *et al.* (1975), John *et al.* (1977), (1981), as cited in ATSDR, RTECS®, Barlow and Sullivan, Schardein.
   a. Mice were exposed to 0, 50 or 500 ppm vinyl chloride by inhalation during embryogenesis (gd 6-15). Decreased litter size and fetal weight, delayed ossification, decreased maternal food consumption, decreased maternal weight gain and increased maternal mortality were reported.
   b. Rats and rabbits were exposed to 0, 500 or 2,500 ppm vinyl chloride during embryogenesis (gd 6-15 for

rats, gd 6-18 for rabbits). In rats, decreased fetal weight, decreased maternal food consumption, decreased maternal weight gain, increased maternal mortality, and dilated ureters (2500 ppm) were reported. In rabbits, litter size and maternal food consumption were affected.

6. Ungvary *et al.* (1978), as cited in RTECS®.
   Rats were exposed by inhalation to 1500 ppm, 24 h/day on gd 1-9. Postimplantation loss, altered growth, developmental delay, increased resorptions and increased maternal liver/body weight ratios were reported. Anopthalmia and micropthalmia were reported but these results were not statistically significant.

Female reproductive toxicity in humans

1. Bao (1988), Chinese, as cited in ATSDR.
   Pre-eclampsia was reported in Chinese workers exposed to 3.9-130.7 ppm.
2. Lindbohm *et al.* (1985), as cited in ATSDR.
   No increase in abortion was found in 44 plastics workers exposed to vinyl chloride, polyurethane and styrene.
3. Makarov (1984), Russian, as cited in ATSDR.
   Decreased "sexual function" was reported in women 41-50 years and in women exposed for >21 years to vinyl chloride. Menstrual irregularities were described with no effect on abortion. This study was confounded by acrylate exposure.

Female reproductive toxicity in animals

1. Ungvary *et al.* (1978), as cited in ATSDR, RTECS®.
   Rats were exposed by inhalation to 1500 ppm, 24 h/day on gd 1-9. The study found increased resorptions and preimplantation loss and increased maternal liver/body weight ratio.

Male reproductive toxicity in humans

1. Infante (1976), as cited in ATSDR, Reprotox™, Schardein.
   Increased fetal loss was reported in the wives of workers at a polymerization plant. The study has been criticized for statistics and methodology.
2. Lee and Harry (1974), as cited in ATSDR.
   In a case report, decreased testicular size was described in an exposed worker who died of angiosarcoma.
3. Makarov *et al.* (1984), as cited in ATSDR.
   A decrease in "sexual function" and reduced testosterone levels were reported in this study. Exposure to methyl methacrylate also occurred.
4. Suciu *et al.* (1975), as cited in ATSDR.
   Sexual impotence was reported in 24% of an exposed worker population. No further description of the study was provided.
5. Veltman *et al.* (1975), as cited in ATSDR.
   Male potency problems were reported in 20% of exposed workers. No further description of the study was provided.
6. Walker (1976), as cited in ATSDR.
   35% loss of libido, 8% impotence, and decreased testosterone production were reported. No further description of the study was provided.

Male reproductive toxicity in animals

1. Anderson *et al.* (1976), as cited in ATSDR, RTECS®, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan.
   In a dominant lethal study, male mice were exposed by inhalation to 30,000 ppm, 6 hr/day, for 5 days prior to

mating. One secondary source reported an effect on preimplantation loss (RTECS®), but another reported no pre or postimplantation loss and no fertility effect (ATSDR).

2. Bi *et al.* (1985), as cited in ATSDR.
   Rats were exposed by inhalation to 10, 100, 3000 ppm, for 6 h/day, 6 day/wk over 3, 6, 12 or 18 mos. Decreased relative testes weight was seen with 6 months of exposure and damage to testicular seminiferous tubules was seen with 12 mos exposure in the 100 and 3000 ppm groups.
3. Short (1977), as cited in RTECS®, Reprotox™, Shepard's Catalog of Teratogenic Agents, Barlow and Sullivan.
   In a dominant lethal study, rats were exposed by inhalation to 250 ppm vinyl chloride for 6 h/day, 55 d prior to mating. The vinyl chloride concentration in this study was also cited as 100 ppm. One secondary source (RTECS®) reported an effect on the female fertility index, but other secondary sources reported negative findings or no dominant level effect.
4. Sokal *et al.* (1980), as cited in ATSDR.
   Male rats were exposed via inhalation to 0, 50, 500, 20,000 ppm for 5 h/day, 5 days/wk, for 10 months. Morphological lesions in liver and testes and depression in body weight were reported at 500 ppm. Damage to spermatogenic epithelium and disorders of spermatogenesis were also mentioned.
5. Torkelson (1961), as cited in ATSDR.
   Rats, dogs, guinea pigs, and rabbits were exposed to 200 ppm 7 hr/day, 5 days/wk for 6 months (4.5 mos for rats). There were a small number of animals in each group. No effect on testes weight was found.

Other relevant data

Vinyl chloride is metabolized by alcohol dehydrogenase. Interactions with alcohol ingestion can occur (John (1977), Schwetz (1975), as cited in ATSDR).

Secondary Sources

ATSDR. (1993) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Vinyl Chloride.

Barlow S.M. and Sullivan F.M. (1982) *Reproductive Hazards of Industrial Chemicals*, Academic Press.

HSDB. Hazardous Substances Data Bank. National Library of Medicine. (TOMES APRIL 30, 1995)

Reprotox™. Dr. Anthony M. Scialli. (TOMES APRIL 30, 1996)

RTECS®. Registry of Toxic Effects of Chemical Substances. National Institute of Occupational Safety and Health. (TOMES APRIL 30, 1995)

Schardein J.L. (1993) *Chemically Induced Birth Defects*. Second Edition, Marcel Dekker.

Shepard's Catalog of Teratogenic Agents. Dr. Thomas H. Shepard. (TOMES APRIL 30, 1995)