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M E M O R A N D U M

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DATE: July 5, 2001

SUBJECT: PROPOSED ACTION LEVEL FOR CARBON DISULFIDE

Staff of the Office of Environmental Health Hazard Assessment (OEHHA) have reviewed your Department's proposed action level of 770 ug/L for carbon disulfide, derived from the U.S. Environmental Protection Agency's (U.S. EPA) Integrated Risk Information System's (IRIS) Carbon Disulfide document, revised September 1, 1990. The proposed action level is based on U.S. EPA's chronic oral reference dose (RfD) of 0.1 mg/kg-day (based on inhalation data) (U.S. EPA, 1995). OEHHA does not concur with this proposed action level for carbon disulfide, and recommends that the action level be set at 160 ug/L.

Carbon disulfide is a colorless liquid that evaporates readily at room temperature and has a sweet ether-like odor. In nature, small amounts of carbon disulfide are found in gases emitted from marshes and volcanoes and certain soil microorganisms. Carbon disulfide will rapidly evaporate from surface waters, and in air will break down into simpler substances within days to a few weeks. While carbon disulfide is highly lipophilic, it is not known to bioaccumulate, principally because it is quickly exhaled unchanged, with the remaining portion being metabolized *in vivo* to other compounds including carbon

dioxide, dithiocarbamates, and thiazolidinones (Snyderwine and Hunter, 1987; Beauchamp et al., 1983; McKenna and DiStefano, 1977; Cohen et al., 1958).

The primary commercial use of carbon disulfide is in the viscose rayon industry where it is used as a critical component in the manufacture of synthetic fibers. Carbon disulfide also is used in the production of cellophane and carbon tetrachloride and in a variety of other industrial processes, including vulcanization of rubber, production of resins, plywood, metal recovery from waste water, and brightening metals in electroplating. Previously, carbon disulfide was used routinely in combination with carbon tetrachloride for the fumigation of grains to exterminate insects and rodents. However, in the late 1980's, all pesticides containing carbon disulfide as an active ingredient were cancelled by U.S. EPA (U.S. EPA, 1999).

In our review of the scientific literature, we concluded that the underlying basis for the value proposed by the Department of Health Services is inadequate. The study upon which U.S. EPA based its chronic oral exposure reference dose (RfD) is an inhalation study that examined the developmental effects of carbon disulfide exposure in two species of animals at two dose levels and established a no-observed-adverse-effect level (NOAEL) of 20 ppm (Hardin et al., 1981). OEHHA considers this a less desirable study upon which to base an action level, because human exposure data are available which offer a more appropriate basis for the development of a health-protective value (Johnson et al., 1993).

Several governmental agencies including U.S. EPA, the Agency for Toxic Substances and Registry (ATSDR), and Environment Canada have conducted evaluations on the human health effects of carbon disulfide exposure. ATSDR has set an acute-duration oral Minimum Risk Level (MRL) for carbon disulfide at 0.01 mg/kg-day (ATSDR, 1996). ATSDR based this value on the Masuda et al. (1986) study in which male mice were exposed to single oral doses of 0, 3, 30 or 300 mg/kg carbon disulfide to determine its effects on liver microsomal drug-metabolizing enzymes. The study found that the hepatic microsomal cytochrome P-450 content and drug metabolizing enzyme activities were rapidly decreased, reached their lowest levels at one hour, then gradually returned to control levels within 24 hours. A concurrent subacute study illustrated that this pattern of enzyme decrement and recovery continued even when animals were given daily oral doses of carbon disulfide at 0, 30 and 300 mg/kg-day for two weeks. ATSDR designated 3 mg/kg as the lowest-observed-adverse-effects level (LOAEL), but stated that it demonstrated a minimal effect since the inhibition of enzyme activities was selective and reversible. To calculate an acute oral MRL, they used an uncertainty factor of 300 to account for extrapolation from animals to humans (10), differences in sensitivity among humans (10), and to extrapolate from a minimal LOAEL to a NOAEL (3). Because this study does not identify effects associated with long term exposure to carbon disulfide, OEHHA considers this an inadequate study upon which to base an action level.

ATSDR has also established a chronic-duration inhalation MRL based on an occupational epidemiologic study conducted by Johnson et al. (1983). To determine the effects

of carbon disulfide exposure on the human peripheral nervous system, this study compared a cohort of male viscose rayon workers exposed to carbon disulfide to a group of non-exposed artificial fiber plant workers located on the same premises. The mean exposure period was 12.1 years, and individuals were divided into three groups based on their previous exposure histories, job descriptions, and current carbon disulfide levels established by eight-hour personal monitors. The median carbon disulfide level for the comparison group was 0.2 ppm while the exposed groups had median levels of 1.4, 4.1, and 7.6 ppm. Each exposure group was tested using surface electrodes to measure maximum motor conduction velocity (MCV) in the ulnar and peroneal nerves, and sensory nerve conduction velocity (SCV) in the sural nerve. The peroneal MCV decreased in a dose-dependent manner with increasing carbon disulfide exposure levels, and the decrease was statistically significant at the highest concentration in comparison to the control group. However, since the MCV decrease was within the range of clinically normal values, the authors (and ATSDR) considered these effects indicative of minimal neurotoxicity. Using the LOAEL of 7.6 ppm, ATSDR derived the chronic inhalation MRL of 0.3 ppm by applying a total uncertainty factor of 30 to account for a minimal LOAEL (3), and for human variability (10). ATSDR did not, however, adjust the exposure duration from occupational to continuous exposure conditions, which would have resulted in a LOAEL of 1.8 ppm and an MRL of 0.06 ppm.

Similarly, U.S. EPA has set a chronic inhalation reference concentration (RfC) of 0.7 mg/m^3 (0.2 ppm) using the Johnson et al. (1983) study. To derive this concentration, U.S. EPA obtained the individual data from the study and accounted for the effects of age on nerve conduction velocity (U.S. EPA, 1995). Using individual average exposure as the independent variable, a benchmark concentration (BMC) of 55.1 mg/m^3 (17.7 ppm) was obtained which reflects a 10 percent relative adverse response rate. This BMC was multiplied by 10/20 (inhalation volume adjustment) and 5/7 (days per week) to adjust from the intermittent exposure under occupational conditions to continuous exposure. The resultant duration-adjusted BMC of 19.7 mg/m^3 (6.3 ppm), identified as the LOAEL, was divided by an uncertainty factor of 30 to extrapolate from human data to sensitive populations (3), and to both account for database deficiencies, including concern for possible developmental effects at low levels and to extrapolate to a lifetime exposure (10). U.S. EPA concluded that the identified LOAEL represented minimal neurotoxicity.

Environment Canada recently evaluated the Johnson study and set a Tolerable Concentration (TC) for carbon disulfide of 0.1 mg/m^3 (Environment Canada, 2000). Canada's TC is defined as "the level to which it is believed a person may be exposed daily over a lifetime without deleterious effects." Therefore, it is comparable to U.S. EPA's RfC. However, Environment Canada set its BMC to reflect a 5 percent excess risk of an abnormal response. The resultant BMC of 20 mg/m^3 (6.3 ppm) was duration adjusted by multiples of 8/24 (hours per day) and 5/7 (days per week) to obtain a continuous exposure value of 5.0 mg/m^3 (1.6 ppm). This duration-adjusted BMC was divided by an uncertainty factor

of 50 to account for sensitive populations (10) and potential neurobehavioral effects (5). Environment Canada also noted that the effects reported by Johnson are of minimal neurotoxic consequence.

Other epidemiologic studies indicate that increased vascular atherosclerotic changes and a higher incidence of mortality from coronary heart disease are associated with chronic inhalation exposure to carbon disulfide (Koteseva and DeBacquer, 2000; MacMahon and Monson, 1988; Tolonen et al., 1979; Tiller, et al., 1968). There is also evidence that prolonged inhalation exposure to carbon disulfide can result in adverse reproductive system effects in humans including toxemia of pregnancy and menstrual disorders (Cai and Bao, 1981; Zhou et al., 1988). However, these effects are associated with higher levels of carbon disulfide exposure (typically greater than 63 mg/m^3 [20 ppm]) than reported in the Johnson et al. study.

OEHHA concludes that the Johnson et al. study identifies the most sensitive endpoint at the lowest dose level and has chosen to base its action level recommendation on the benchmark concentration of 5.0 mg/m^3, as consistent with Environment Canada, representing a duration-adjusted 5 percent abnormal response level. OEHHA believes that Environment Canada's duration-adjusted BMC represents a more appropriate LOAEL than that developed by U.S. EPA and ATSDR. It is the most sensitive, health-protective value identified. Environment Canada notes that their LOAEL represents a minimal effect that could be characterized as preclinical.

To derive an action level for ingested carbon disulfide, OEHHA evaluated the literature on absorption rates of carbon disulfide from inhalation and ingestion. Human inhalation studies show that carbon disulfide is rapidly absorbed from the lungs. About 80 percent is retained during the first 15 minutes of exposure, decreasing to about 40 percent after 45 minutes and remaining at that level for the rest of the exposure period (Teisinger and Soucek, 1949). Animal studies also indicate that carbon disulfide is rapidly absorbed following inhalation exposure, with equilibrium being reached after 1.5-2.0 hours with approximately 70-80 percent of the inhaled carbon disulfide being absorbed (Toyama and Kusano, 1953). A study on absorption of orally administered carbon disulfide showed that an intragastric administration of 10 mg/kg of ^{14}C-carbon disulfide results in exhalation of 63 percent of the dose within four hours as unchanged carbon disulfide. This led the authors to conclude that the majority of ingested carbon disulfide is absorbed (DeMatteis and Seawright, 1973). These studies indicate that carbon disulfide is rapidly absorbed via both routes of exposure and reaches equilibrium rapidly. Further, they support the assumptions that inhalation absorption is 50 percent and oral absorption is 100 percent of the amounts administered. OEHHA has utilized these assumptions in our risk assessment. We also assumed that each worker breathes 20 m^3/day of air and weighs 70 kilograms. The resultant LOAEL for chronic oral exposure to carbon disulfide, based on the inhalation LOAEL from the study of Johnson et al. (1993), is calculated as follows:

(5 mg/m^3 x 20 m^3/day x 0.5) / 70 kg = 0.7 mg/kg-day

OEHHA applied an uncertainty factor of 30 to account for extrapolation from a minimal effect LOAEL to a NOAEL (3), and for variations in human sensitivity (10), including concern for possible developmental effects at low levels. OEHHA has determined that the 0.7 mg/kg-day LOAEL based on the occupational study by Johnson et al. (1993), and a total uncertainty factor of 30 are appropriate for deriving a public-health protective level for carbon disulfide, calculated as follows:

C = LOAEL x BW x RS / UF x DWC =
0.7 mg/kg-day x 70 kg x 0.2 / 30 x 2 L/day =
0.16 mg/L = 160 ug/L

where,

LOAEL = Lowest-Observed-Adverse-Effect Level (decreased motor conduction velocity, Johnson et al. 1993),
BW = adult human body weight,
RSC = relative source contribution,
UF = uncertainty factor, and
DWC = adult daily drinking water consumption.

The action level for carbon disulfide in drinking water is therefore suggested as 160 ug/L. The primary basis for OEHHA's recommendation of an action level of 160 ug/L for carbon disulfide is to provide protection from neurological damage. Human data suggest that low-level chronic exposure to carbon disulfide can diminish nerve conduction velocity in the peripheral nervous system. At higher exposures, human data show that increased nerve damage of the peripheral nervous system can occur. At such levels, there is also the potential of increased cardiovascular disease, including atherosclerotic changes, and a potential decrease in reproductive capability.

It should be noted that in 1989, carbon disulfide was listed by California's Science Advisory Panel as a developmental and male and female reproductive toxicant under Proposition 65 (OEHHA, 2000). At that time, OEHHA established an Acceptable Intake Level, otherwise known as a Safe Harbor Level, for ingested carbon disulfide at 600 ug/day. This level is meant to protect the development of the fetus and is based on the Hardin et al., 1981 study discussed above (OEHHA, 1994). The law that governs Proposition 65 requires OEHHA to use a developmental study (as opposed to the most sensitive endpoint identified), then divide the NOAEL by 1000 to derive the developmental effects Safe Harbor value. OEHHA recently reviewed the carbon disulfide Safe Harbor Level and found there is no new developmental toxicity data available that warrants a change to the existing value (Washburn, 2001).

OEHHA believes the proposed action level of 160 ug/L (ppb) of carbon disulfide is protective of human health given long term exposure for the following reasons. The most sensitive, significant endpoint has been selected to derive the action level, and to that a 30-fold uncertainty factor has been added. This uncertainty factor accounts for extrapolation from a minimal effect LOAEL to a NOAEL (3), and differences in human sensitivity (10).

Should you have any questions about this review, please contact me at (510) 622-3168.

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