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INTRODUCTION

The following are the combined responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for asbestos, based on the pre-release review draft. Changes have already been made in response to these comments, and have been incorporated into the draft posted on the OEHHA website. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

United States Environmental Protection Agency (U.S. EPA)

Comment 1. “The study (Cemerick, 1977) used to calculate the noncarcinogenic PHG raises a number of questions: The endpoint used to identify the LOAEL (kidney effects and hypertension from oral exposure) may lack biological plausibility, the number of animals used in the study is too small and, therefore, may lack quantal plausibility, [pulmonary] Hypertension, as a potential effect from asbestos exposure, has been associated only with inhalation exposure.”

Response 1: The Cemerick (1977) study has both strengths and weaknesses, as do all of the studies found in the available literature on the non-cancer effects of asbestos. The Cemerick (1977) study was chosen because the route of exposure was via drinking water and was of subchronic duration (three months). A number of human studies have reported that occupational exposure to asbestos has been linked to adverse effects on the kidney, and in particular, to an increased risk of renal cell carcinoma (RCC) (Van Poppel et al., 2000; Mattioli et al., 2002; Pesch et al., 2000). In the Mattioli et al. (2002) study, after adjusting for cigarette smoking and alcohol intake, a significant matched odds ratio (OR) was found for RCC and asbestos exposure in males (OR, 7.11; 95 percent CI, 1.46-34.51). Pesch et al. (2000), in their case-control study on occupational risk factors for RCC, concluded that there is evidence for a gender-specific susceptibility of the kidneys to nephrocarcinogens. In contrast to many genitourinary malignancies, there are very little data available in the scientific literature concerning premalignant alterations in the kidney (e.g. intratubular neoplasia), and there are no data on the epidemiology of premalignant lesions of the kidney. Some relationship between adverse kidney effects (RCC) and hypertension has also been observed (Robles et al., 1999; Van Poppel et al., 2000). Other researchers (Gibel et al., 1976) have reported statistically significant increases in malignant tumors of the kidney in rats fed an asbestos filter material (20 mg/day) containing fifty-three percent chrysotile asbestos. Thus in light of the known associations between asbestos exposure and kidney effects in humans, OEHHA does not consider the kidney/hypertension effects seen in the Cemerick (1977) study to be “implausible,” and this may in fact represent an early event following exposure to ingested asbestos.

Comment 2. “It is unclear how the dose/LOAEL of 107 mg/kg-day (1x10^12 fibers/kg-day) for nephrotoxicity used to calculate the PHG was obtained (page 22 and page 49).”

Response 2. The LOAEL of 107 mg/kg-day in the Cemerick (1977) study was calculated in the following manner: according to the study methodology used, a suspension of asbestos fibers in drinking water was prepared by shaking 2.5 g of chrysotile asbestos in 500 mL of water; this was allowed to settle for 30 minutes and the top 250 mL, which contained about 9.4x10^9 (1 mg) fibers/mL was drawn off (the technique of Pontefract and Cunningham, 1973). U.S. EPA (1988c) has estimated that
mature male Wistar rats consume 32 mL/day of drinking water, and females 25 mL/day. Thus, for male Wistar rats, a LOAEL of 107 mg/kg-day for kidney effects was calculated according to the following equation:

$$\frac{1 \text{ mg/mL asbestos} \times 32 \text{ mL/day}}{0.3 \text{ kg (bodyweight at start of exposure)}} = 107 \text{ mg/kg-day}$$

The LOAEL for female Wistar rats was calculated as follows:

$$\frac{1 \text{ mg/mL asbestos} \times 25 \text{ mL/day}}{0.15 \text{ kg (bodyweight at start of exposure)}} = 167 \text{ mg/kg-day}$$

These calculations are shown in the revised PHG document.

Comment 3: “It is an exceptionally onerous task identifying noncancer adverse effects for oral exposure to asbestos. The available oral studies show that asbestos exposure does not cause any significant noncancer health effects - even in the gastrointestinal tract - at exposures up to 500-830 mg/kg/day (ATSDR 1995). But as stated on page 49 of this document, the value of 7.1 MFL or 7.1 x 106 fibers/L, used by the EPA’s Office of Water as the MCL for asbestos (long range fiber, fiber >10 µ), provides the most credible value for the estimating the human risk of oral exposures to asbestos in drinking water. Although this value is based on cancer effects (NTP 1985), it is appropriate for use for noncancer effects since the development of benign gastrointestinal polyps is a threshold event and the most sensitive adverse effects associated with oral exposure to asbestos.”

Response 3: With regard to the noncancer adverse effects of asbestos, there are many data gaps. In many instances, the effect of oral asbestos exposure on individual tissues/organ systems has not been studied. No studies were located regarding the respiratory, cardiovascular, musculoskeletal, hepatic, endocrine, dermal, ocular, metabolic or other systemic effects in animals after oral exposure to asbestos.

Additionally, most controlled drinking water asbestos studies utilize asbestos fibers in deionized water suspensions, which may differ from the water humans are exposed to at the tap. Organic and inorganic chemicals clearly can bind to asbestos fibers. In vivo studies have shown that ingested amphibole fibers are genotoxic (e.g., Varga et al., 1996a,b). Inhalation studies clearly demonstrate the role of adsorbed polycyclic aromatic hydrocarbons in asbestos carcinogenesis (Hammond et al., 1979). The large surface area of the fibers creates the possibility of co-genotoxic action with adsorbed water-borne organics. Studies by Varga et al. (1998, 1999) have demonstrated that asbestos fibers are able to adsorb benzo[a]pyrene molecules from aqueous solutions, and consider potential co-genotoxicity of these materials. At present, data are inadequate to fully address this possible tumorigenic mechanism. Hence, many of the existing oral exposure studies may not provide an accurate estimation of real world exposure to asbestos. Asbestos fibers contained in drinking water do penetrate the GI tract and cross the placenta. Additional targeted research is needed to elucidate the biological and toxicological significance, if any, of these effects.
Comments from University of California, Irvine

Comment 1: “Calculation of the PHG non-carcinogenic effect was based on a single study (Cemerikic, 1977) of 7 male and 7 female rats and 10 male and 7 female control rats exposed to a single dose level of $1 \times 10^{12}$ f/kg/day for up to 15 weeks. This dose was determined to be a LOAEL based on the presence of red blood cells and hyaline casts in the urine sediment of 4 of the 7 male rats and none of the 7 female rats. For risk assessment purposes this effect was selected as a LOAEL for non-carcinogenic effect and default non-biologically based uncertainty factors of 3000 were applied to give a public health concentration of $2.4 \times 10^9$ f/L. This evaluation is unsatisfactory for the following reasons: 1) OEHHA based the evaluation on 7 rats from a single-dose animal study, 2) no human studies were considered, 3) the quality of the rat study selected for the evaluation was not discussed, 4) there was no dose-response measurement in the rat study used, 5) the results from the rat study show no significant effect in female rats and only effect on only 4 of 7 male rats, 6) the exposure levels used for this rat experiment were extremely high ($1 \times 10^{12}$ f/kg/day compared to the expected human exposures in drinking water, and 7) the end point of effect was red cells and hyaline casts in the urine sediment, which is a rather weak basis for diagnosing renal toxicity.”

Response 1: As was mentioned in the responses to the first reviewer, the Cemerikic (1977) study in rats has both strengths and weaknesses, as do all of the studies found in the available literature on the non-cancer effects of asbestos. The Cemerikic (1977) study was chosen because the route of exposure was via drinking water and was of subchronic duration (3 months). It is not the case that no human studies were considered. It is an exceptionally onerous (and hypothetical) task to reconstruct exposures from ecological studies. All of the epidemiological studies have limitations that prevent their being used as other than suggestive or supportive studies with regard to (ingested) asbestos exposure and adverse health effects, which was the focus of this document. The NTP (1995) study used to derive the PHG for cancer effects also used only one dose (and hence no dose response was possible). U.S EPA and ATSDR concluded that the NTP (1995) study is the most appropriate basis for a risk estimate to determine safe drinking water levels of asbestos. Several other animal studies have reported gender differences following oral exposure to asbestos (NTP, 1985; McConnell et al., 1983a, 1983b), and gender-related differences in the manifestation of asbestos-related disease have been observed in humans (Delfino et al., 1995). This is not an uncommon finding in scientific research studies, and does not serve to negate the reported findings in the Cemerikic (1977) study. As to the exposure concentrations used in the Cemerikic (1977) study, the study design of nearly all toxicology studies entails the use of doses/concentrations that are higher than would be expected from environmental exposures, with the idea of showing a treatment-related effect. These findings are then extrapolated using current risk assessment methodologies to lower level exposures. Given the biopersistence of asbestos fibers in the body, and the possibility of co-exposure to asbestos from other sources in addition to drinking water (e.g., diet, air, soil), the true extent of human environmental exposure to asbestos is unknown. In the calculation of the non-cancer PHG number, as it was assumed that other sources of asbestos would be significant, a relative source contribution of 20 percent for drinking water was chosen.
Comment 2: “Calculation of the PHG-carcinogenic effect risk estimate in this draft document is based on the occurrence of benign polyps in 9 rats out of a group of 250 in a single dose study of lifetime feeding exposure. It would appear far better for California OEHHA to re-evaluate the information contained in the human epidemiological studies including the five cohort studies used in the evaluation of the NAS in 1983. The casual dismissal of epidemiologic studies based on their lack of statistical power and other excuses of their inadequacies does not justify OEHHA’s use of 9/250 rats from one rat study based on a single dose level of $1.13 \times 10^{10}$ fibers/kg body weight/day in which the end point did not include cancer, to estimate human risk of cancer in California.”

Response 2: Two separate authoritative bodies, U.S. EPA and ATSDR, have chosen the NTP (1995) study in rats as the most appropriate basis for a risk estimate of oral exposure to asbestos. The NTP (1995) study is an excellent study, well conducted, and with sufficient statistical power to conduct a thorough analysis. Benign epithelial neoplasms, like those seen in the NTP (1985) study, are an uncommon occurrence in 2-year carcinogenesis studies, and are therefore considered an important treatment-related finding. The benign epithelial neoplasms seen in the NTP (1985) study are considered precursor lesions of colon cancer. The association is strengthened by the fact that other investigators have reported an increase in colon-associated lesions (neoplastic and non-neoplastic) in rats fed chrysotile asbestos in their diet (Donham et al., 1980), and in rats administered amosite asbestos by gavage (Ward et al., 1980). Data from human studies have similarly reported elevated rates of cancers of the digestive tract (Conforti et al., 1981) and small intestine (Polissar et al., 1982) in association with chrysotile asbestos exposure. Taken together, this represents a weight of evidence approach that could not be demonstrated using human studies alone.

Comment 3: “It would be useful if OEHHA provided information about which of these fibers and in what concentrations occur in California waters by geographic location….”

Response 3: Data available from the California Department of Health Services (CDHS) Drinking Water Program on contaminants in public water systems do not specify fiber type, though the drinking water supplies of some regions of northern California are known to be contaminated with chrysotile asbestos (Bales et al., 1984), and chrysotile asbestos is the most common form of asbestos found in California soils.

Comment 4: “The document needs to include data and discussion on GI tract cancer incidence rates by geographic area in California [presumably for showing the contribution of asbestos-contaminated drinking water to the GI cancer burden].”

Response 4: This is a good suggestion. However, relating GI tract cancer incidence rates specifically to asbestos represents a complicated undertaking, and analyzing population-based data for this express purpose may not be able to reveal any correlation. The environmental factors most common to gastric cancers, including the stomach and small intestine, are smoking, alcohol consumption, nitrates, radiation and salty foods. There is
also an association between gastric ulcers (infectious agents) and gastric cancer. These risk factors would likely confound any effort to separate out the contribution from asbestos in drinking water to gastric cancer on a population basis. In this regard, epidemiological studies where there is a demonstrated exposure to asbestos, even if the precise exposure levels are not known, are more likely to reliably reveal any relationship between asbestos and gastric cancers, as many of the potential confounders can be controlled for in the study design. Therefore no additional statistical analyses of gastrointestinal cancer rates were carried out for the PHG document.

Comments from University of California, Davis

Comment 1: “The proposal of OEHHA for PHG of asbestos in the drinking water of 7 MFL seems to be reasonable, however, a length of the fiber size should also be stated within this summary to eliminate any confusion on what fibers, based on length, should be included in this PHG.”

Response 1: The asbestos PHG document has been changed to reflect the fact that the 7.1 MFL value relates specifically to asbestos fibers that exceed 10 µm in length.

Comment 2: “Calculation of the PHG for non-carcinogenic effects follows a formula that appears to be highly plausible and well thought out. I would concur with this estimation [of 2.4 x 10⁹ fibers/L] based on the data provided in the document.”

Response 2: Comment noted.

Comments from University of California, Davis

Comment 1: “The document is almost totally silent on relative potency, geographic distribution or kinetics of different fiber types of asbestos. While regulatory agencies may treat all asbestos fibers similarly, there is a large body of data suggesting greater carcinogenic potency of amphibole fibers and the report should address this in appropriate sections. For example, while California has large natural deposits of serpentine asbestos, some of these areas also have contamination with naturally occurring tremolite asbestos which may represent a more serious carcinogenic hazard from oral ingestion (or inhalation). Similarly, it is known that amphibole fibers preferentially persist in the body, and it is plausible that they are also preferentially ingested after inhalation exposure. Any data on selective fiber type ingestion after inhalation exposure should be addressed. That may affect the potency estimates that are derived from the studies that extrapolate from modeled ingestion of inhaled fibers.”

Response 1: Where specificity of fiber type and length was discussed in the scientific research studies, it was included in the text of the PHG document. Data available from the California Department of Health Services (DHS) Drinking Water Program on
contaminants in public water systems do not specify fiber type, though the drinking water supplies of some regions of northern California are known to be contaminated with chrysotile asbestos (Bales et al., 1984). Most of the gastrointestinal penetration studies entail exposures to chrysotile asbestos, the most common form of asbestos contaminant found in water, food, and beverages. Your comments on fiber type will be shared with DHS for their consideration in their water monitoring program.

Comment 2: “In various places in the document it is stated that human studies of ingested asbestos have yielded “conflicting” or “equivocal” results. I think that a more precise wording could be found for these summary statements. For example, “human studies of ingested asbestos do not show results indicating a carcinogenic effect of ingested asbestos”, or perhaps “human studies of ingested asbestos do not meet criteria for a causal association of ingested asbestos exposure and cancer.””

Response 2: We have attempted to evaluate hazard identification and dose-response separately. Our conclusion is that the overall data are suggestive but do not show a causal relationship. It is commonplace to use terminology such as conflicting or equivocal results when summarizing a group of scientific studies, some of which reported a strong or (statistically) significant association between asbestos exposure and an adverse effect, and some of which found a weaker association, or none at all. It would be an inaccurate characterization of the overall data to say that “human studies of ingested asbestos do not show results indicating a carcinogenic effect.” In fact, as stated in the PHG document, a number of epidemiological studies have reported increases, some statistically significant, in cancer death or tumor incidence rates at one or more tissue sites in populations exposed to elevated levels of asbestos in their drinking water. Kanarek et al. (1980) have noted that there were relatively consistent findings for stomach and pancreatic cancer among the (human) studies. The difficulty arises when attempting to use these studies for risk assessment purposes, as most are ecological, and therefore the dose/concentration of asbestos exposure is not known.

Comment 3: “The section on soil contamination should be expanded. For example, is there a difference between Northern (where most natural asbestos is located) and Southern California? What about local sources? The geologists refer to serpentine rock as “ultramafic”. I suggest a geologist review the document for accuracy in describing the environmental occurrence of asbestos.”

Response 3: A description of the location of asbestos sources is outside the scope of the PHG document. Your comments will be shared with the Department of Health Services for their consideration of characterization of drinking water by a geologist. Based on the information available to us, most of the asbestos found in California is chrysotile asbestos. The California Geologic Survey (CGS), formerly the California Department of Mines and Geology, has developed maps to show where asbestos is likely to occur. Specifically, the maps show areas of ultramafic (serpentine) rock in the state, which is where asbestos is usually found. They do not map asbestos deposits. The maps do not provide information on the types of fibers likely to occur at any given location. The CGS
may be able to provide some estimate of the relative frequencies of the different fiber types in California.

REFERENCES


