

Comments of Dr. Dwight Culver, Clinical Professor of Medicine (Epidemiology), University of California at Irvine. (This comment was received after the close of the public comment period.)

The document recommends an Inhalation Reference Exposure Level (REL) of $3 \mu\text{g}/\text{m}^3$ (respirable; $\text{MMAD} \leq 10 \mu\text{m}$) for crystalline silica suspended in ambient air in California, in order to prevent the development of silicosis, a disease that leads to fibrotic scarring of the lungs that ultimately may be fatal. OEHHA has made this recommendation after reviewing most of the epidemiological studies that have been reported for working populations exposed to crystalline silica in mines and manufacturing plants. The recommendation is based on a risk assessment that relates dust exposure to the occurrence of x-ray changes in chest radiographs. The x-ray changes used in most cases indicate the presence of dust accumulation and fibrotic scarring in the lungs. OEHHA has used the reported frequency of these changes associated with the reported air concentrations of silica to calculate safe levels of exposure. Since the REL of $3 \mu\text{g}/\text{m}^3$ (crystalline silica) proposed by OEHHA is the same value as the average ambient quartz levels in U.S. metropolitan areas reported by the USEPA (USEPA, 1996), the bases for the recommendation should be examined carefully. The frequent exceedance of the REL that does occur in community air must not lead to public anxiety, unless there is solid factual basis for it.

There are three major generic problems associated with setting a REL of $3 \mu\text{g}/\text{m}^3$ that I would like to address in my comments. The first is the differing diagnostic criteria used in the available epidemiological studies; the second is the lack of precision in measurements of silica exposure (or dose) associated with diagnostic findings. These two uncertainties give very broad confidence limits to any estimate of a dose response relationship. The third problem is the selection of the PM_{10} mass fraction of airborne dust for a REL.

Comment 1. Diagnostic criteria. Regarding diagnostic criteria for silicosis, most epidemiological studies use a semi-quantitative reading of opacities seen in the chest x-ray to diagnose silicosis. The reading method designated, "ILO 1980 International Classification of Radiographs of the Pneumoconioses" is used for scoring opacities by shape, size, profusion and extent. In the diagnosis of silicosis, profusion of opacities, marginally increased over the normal lung, is scored 1/0 and is thought by some investigators to be the earliest indication of onset of silicosis. It is at this perceived level of profusion that experts at interpreting chest x-rays for silicosis, designated as "B readers", frequently disagree. Another characteristic of silicosis on x-ray is the shape of the opacities. Rounded opacities are thought to be typical of silicosis, however, some investigators believe that early in the course of silicosis irregular opacities can be caused by silica exposure. A problem associated with the use of irregular opacities as a marker of silicosis is the fact that ageing and cigarette smoking also cause an increased profusion of irregular opacities.

In the epidemiological studies of silicosis available, and most of them are cited in the OEHHA document, there are significant differences in methodology for establishing a diagnosis. These differences arise out of some investigators striving for more sensitivity in detecting disease while other investigators seek to avoid misclassification of cases and use

more conservative diagnostic criteria. Without an agreed-upon standard for diagnosis, the comparison of results from one study to the next will continue to produce discordant results.

Response. *The OEHHA chronic REL summary for crystalline silica highlighted the differences among the various studies. Overall, the diagnosis of silicosis has likely been underestimated in some studies due to limited follow-up (Muir et al., 1989; Rosenman et al., 1996; Hughes et al., 1998; Ng and Chan, 1994; LeGrand-Cattan et al. 1998). Nevertheless the data from four different cohorts (Hnizdo and Sluis-Cremer, 1993; Steenland and Brown, 1995; Hughes et al., 1998; Chen et al., 2001) indicate quite similar inhalation chronic RELs. In addition the key study for the REL calculation used the more definitive 1/1 as a cut-off for silicosis.*

Comment 2a. Exposure measurement. In the area of exposure measurement, there are a limited number of cohorts with exposures of a sufficient number of years that the disease has been able to develop fully. To find sufficiently aged cohorts, investigators have had to go back in time to the years when measurements of exposure were rare or not done and techniques for quantifying airborne concentrations of dust were primitive and the measurement of crystalline silica was in its infancy or absent. Much effort has been given to estimating cumulative silica exposures for these aged cohorts, but these estimates rest upon major and un-testable assumptions.

The review below takes the three studies upon which the OEHHA document's conclusions rest to highlight some of the difficulties and methodological differences among the studies. The other studies cited by OEHHA have similar or greater uncertainties associated with diagnosis of silicosis and estimates of silica exposure:

Hnizdo and Sluis-Cremer (1993): In this large South African gold mine study diagnosis of silicosis depended upon the finding of ILO category $\geq 1/1$ with rounded opacities. The cohort of gold miners from the period 1938 to 1991 was followed until the time of diagnosis or time of death. Exposure to dust was measured as particles per cubic meter by standard thermal precipitators in the early 1960s [Page-Shipp and Harris, 1972] in a random selection of mines. These count measures for particles in the 0.5 to 5.0 μm range were converted to mg/m^3 using an estimate of surface area. The authors then assumed that the dust in collected air samples contained 30% silica and used this figure to calculate silica air concentrations. Silica air concentration data estimated from these early 1960s samples were used to estimate work shift exposure and this information combined with the work records of each miner were used to calculate each miner's personal exposure.

Steenland and Brown (1995): In this study of South Dakota gold miners diagnosis of silicosis was made either by death certificate only (128) or cross-sectional radiographic surveys only (29) or both death certificate and x-ray (13). Silica exposure was measured in millions of particles per cubic foot of respirable dust and converted to mg/m^3 using a conversion factor of $10 \text{ mppcf} = 0.1 \text{ mg}/\text{m}^3$. Exposures were estimated by particle count measurements or by industrial hygienist judgment into 7 cumulative exposure categories, 0-0.2 to 4.0+ mg/m^3 years. The authors state, "There are several limitations to our estimation of exposure. One problem is the conversion of dust counts to gravimetric measurements (in this case $10 \text{ mppcf} = 0.1 \text{ mg}/\text{m}^3$), which may not be accurate. This conversion relies on an estimate of 13% silica

content of respirable dust. While this estimate was based on a relatively large number of samples (n = 82) collected in two different surveys, there was broad range of content in these samples (1% to 48%, SD = 9), and the percentage of respirable quartz may have differed in earlier days.”

Hughes et al. (1998): Diagnosis of silicosis in the diatomaceous earth industry was based on the judgment of at least 2 of 3 B readers who read an x-ray film to be positive, either for large opacities or for small irregular opacities of ILO profusion $\geq 1/0$. However, the authors infer that at 1/0 smoking effects or ageing could confound a diagnosis. As described in Checkoway et al. (1993), insufficient dust monitoring data precluded a direct quantification of the exposure-response trends. The dose surrogate used for crystalline silica was based on industrial hygiene judgments of differences in exposure intensity between jobs and over time, and estimates of the percentages of crystalline silica in the respirable fraction of the various diatomaceous earth materials. Good work-assignment records were available to the investigators.

The OEHHA document uses data from three of the cited epidemiological studies of workers, Hnizdo and Sluis-Cremer (1993), Steenland and Brown (1995) and Hughes et al (1998) and uses mathematical models to extrapolate risk to the general population. The extrapolations of the Hnizdo and Sluis-Cremer (1993) data did not take into account the uncertainties resulting from the fact that their thermal air sampler did not represent personal exposures (personal samples generally give significantly larger sample results than do stationary samplers) and that the 30% silica figure came from a random study of mines done in the "early 1960s although exposures started in the early 1940s. The extrapolations of the Steenland and Brown (1995) data apparently included the 5 cases of silicosis from the 0-0.2 mg/m^3 -years cumulative exposure group, of which Steenland and Brown state “These data suggest that some men get silicosis after brief exposure to low levels or, alternatively, that some of these men either were exposed to silica before or after working at the gold mine studied here or received short-term high exposure ignored by our job-exposure matrix.” The extrapolation of the Hughes et al. (1998) data ignores the fact that diagnosis of silicosis was based on ILO readings of 1/0 for irregular opacities, easily confounded by non-crystalline dust exposure and ignores the wide confidence limits the authors place around their relative risk estimate in the 1-3 mg/m^3 -year exposure category.

The data from these three studies, despite their major limitations form the bases for the OEHHA REL of 3 $\mu g/m^3$ (respirable; MMAD $\leq 10 \mu m$) for crystalline silica suspended in ambient air in California.

Response. *OEHHA staff agrees that these studies all have limitations. However, we have chosen for our key study what is considered the best study. The study by Hnizdo and Sluis-Cremer (1993) was long term including follow-up after the miners left the mines, had over 2000 subjects, showed a dose response curve for silicosis, use the more definitive ILO reading of $\geq 1/1$ as the basis for silicosis, included autopsy data, was able to detect a small incidence of silicosis (1.9%), and detected a NOAEL. Its shortcomings include the lack of exposure data from personal samplers and the uncertainty in the percent silica content of the mine dust.*

Comment 2b. The 3 $\mu\text{g}/\text{m}^3$ REL coincides with the level in the USEPA (1996) report statement that "direct sampling indicate that ambient quartz levels in U. S. metropolitan areas average around 3 $\mu\text{g}/\text{m}^3$ and generally do not exceed 8 $\mu\text{g}/\text{m}^3$." However, without confidence limits placed around the REL, the frequent exceedance above the 3 $\mu\text{g}/\text{m}^3$ that does occur can lead to public concern about an as-yet-unexplored and unreported public health threat. It should be kept in mind that the REL is the result of extrapolating very uncertain diagnostic data and frequently unreliable exposure measurement methodology using mathematical models that have little or no empirical foundation. Park et al. (2002), also cited in the OEHHA document, in discussing their own data (although they used LDOC as a surrogate for silicosis) state that "If the linear exposure-response for LDOC extends to concentrations of exposure to silica in the range of 0.001=0.005 $\mu\text{g}/\text{m}^3$ (sic), which includes ambient exposure concentrations, our findings would suggest considerable risks to the population due to air pollution. Although this may be the case for lung cancer, for LDOC and silicosis low dose linearity has not been established and the data from this study are inadequate to test that hypothesis."

Response. *The chronic REL is not a bright line (a definitive threshold) for the presence or absence of adverse health effects. Chronic RELs are concentrations at or below which adverse health effects are not likely to occur in the general human population. The USEPA defines a Reference Concentration as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." OEHHA uses a similar definition for chronic RELs in the Technical Support Documents for the Air Toxics Hot Spots Program. The more the ambient concentration is in excess of the REL, the greater the possibility of an adverse health effect. Air Districts are responsible for regulatory activities using the Reference Exposure levels, and are advised to contact OEHHA about the importance of exceedances of RELs on a case-by-case basis. A hazard index of 5 would be of more concern in a schoolyard than in a Park and Ride Lot. A hazard index of 5 would be more of concern for a REL in which the total Uncertainty Factor (UF) was 1 (a REL based on effects in sensitive humans) than a REL that used a UF of 3000. Since the total UF used for silica was 3, a hazard index of 5 would be scrutinized. As indicated in the summary the current workplace standard of 50 $\mu\text{g}/\text{m}^3$ does not appear adequate to prevent silicosis in workers and some have called for its lowering. Although called Threshold Limit Values, the ACGIH definition does not claim that these are no-effect levels, and adverse health effects are seen in some workers at many TLVs. The chronic REL is meant to protect the general population, not just healthy workers. (Note: Park et al. (2002) give a range for concentrations of silica of 0.001-0.005 mg/m^3 , which is equal to 1-5 $\mu\text{g}/\text{m}^3$.)*

Comment 3. Mass fraction. A final concern with the OEHHA document is the fact that the definition of the REL is in terms of a respirable particle size fraction that is $\leq 10 \mu\text{m}$ diameter. All of the epidemiological studies cited in the document normalized their respirable air sample results to a respirable mass fraction, the definition for which is a particle size distribution with a median cut point of 4 μm aerodynamic diameter. Particles above 5 μm mass median aerodynamic diameter are not considered respirable (USEPA, 1996, P 3-27). Since it is the particulate mass fraction with a median cut point of 4 μm that best represents a threat to the gas exchange region of the lung, where silica particles have their damaging effect (CD 7708. ISO, Geneva, 1991), it is reasonable to control exposures to this active mass

fraction rather than the PM10 mass fraction. A REL of 3 µg/m³, respirable, based on the same mass fraction (median cut point of 4 µm aerodynamic diameter) used by the occupational studies from which OEHHA derived its risk estimate would be a more rational approach and would not encroach so closely on present ambient silica levels. This might avoid producing the public anxiety that be caused by the present recommendation.

Response. *OEHHA staff agrees that the silica particles should be ‘respirable’. California EPA usually defines ‘respirable’ as particles 10 µm or less in MMAD. However, following public comment and discussion by the Scientific Review Panel, OEHHA now concludes that since the chronic REL is based on occupational silica exposures, the REL should be specified as applicable to concentrations of particles having a size range (and reactivity) similar to those measured in the occupational studies. Thus for the specific purposes of this chronic REL “respirable” is defined by the occupational sampling method, most recently described in NIOSH (2003)].*

Comment 4. In the meantime, if OEHHA has a real concern for the occurrence of silicosis in the general population, resulting from existing ambient exposures, OEHHA should urge the California Department of Health (Services) to undertake hypothesis-testing epidemiological studies among the populations of California, especially where high ambient silica levels do exist, such as Riverside, California {Pellizzari et al. (1992)}. This should be done before taking any action on the present REL recommendation.

Response. *OEHHA staff is not concerned about the occurrence of silicosis at ambient concentrations of silica. The definition of a chronic REL is a level at or below which adverse health effects are not anticipated. Staff used average ambient levels as a “check” against the chronic REL because there is no evidence of silicosis in the general population of California from exposure to ambient levels of silica. In fact, it was part of the rationale for using a smaller cumulative uncertainty factor (UF) in generating the proposed chronic REL. Furthermore, the REL is being generated to evaluate offsite impacts from industrial processes that emit particulate crystalline silica, where concentrations would exceed background ambient levels. It should be noted that the REL was generated from human data with a relatively small uncertainty factor.*

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