Comments to EPA Science Advisory Board Asbestos Committee

On

Office of Solid Waste and Emergency Response (OSWER) Proposed Approach for Estimation of Bin-Specific Cancer Potency Factors for Inhalation Exposure to Asbestos

By

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These comments include specific exposure assessment concerns with the OSWER approach, general concerns with risk assessment and regulatory policy, and some broader toxicological concerns regarding particle toxicity.

Previous analyses using largely the same methods and data as the proposed OSWER approach based on statistical modeling or generated relative potency estimates which diverged from those arising from direct observation in laboratory studies of fiber toxicity. Laboratory studies provide clear evidence that chrysotile is a more potent carcinogen than crocidolite and amosite. Previous users of this approach asserted that amphiboles are more potent than chrysotile.

An authoritative conclusion adopting the modeled relative toxicity for forms of asbestos would deeply affect the public health and agency determinations regarding many other substances. These include diesel particulate matter, carbon nanotubes and other nanoparticles, silica, other synthetic mineral fibers, welding fume and other metal oxides. Relative potency in laboratory studies has been an important and sometimes the sole guide to public health decision making.

It is important to remember that the criteria for determining whether all forms of asbestos are carcinogenic to humans have been satisfied, and are overwhelmingly recognized. These criteria include observations of exposure-response relationships for both lung cancer and mesothelioma for all mineral forms of asbestos. Obstacles to retrospective exposure assessment discussed below have been addressed for each form of asbestos in individual studies in particular worksites. However, similar obstacles to differential potency determinations are not likely to be overcome.

The OSWER proposed approach is a conclusion of differential potency based solely on modeled epidemiological data. In order to adopt such a conclusion, cancer risk assessment guidelines, including those adopted by EPA, would require:

a. Biological plausibility.

b. A conclusion that "chance, bias and confounding could be ruled out with reasonable confidence."

Laboratory and clinical studies do not provide biological plausibility for decreased relative potency of chrysotile. In fact, laboratory and clinical studies support the opposite conclusion.

Just as importantly, the exposure assessments in the epidemiology studies relied on in the model are so uncertain that chance, bias and confounding cannot be ruled out.

The key points are:

A. Uncertainty in exposure assessment prevents concluding differential potencies between asbestos fiber types.

1. General principles of exposure assessment in the industrial environment create a range of uncertainty around exposure and thus potency estimates. These general principles were not referenced in the document. The irreducible uncertainty around the estimate of exposure directly multiplies the uncertainty in potency values.

2. Potential bias and confounding in exposure assessment results are not addressed in the discussion of the OSWER approach.

3. Special considerations for asbestos air sampling enhance the general uncertainty of industrial hygiene data sets and increase the chance for bias and confounding, especially across process types.

B. The recommendations of the NAS Risk Assessment Committee for presenting the full range of risk assessment results have been ignored.

1. Model uncertainty in the OSWER approach arises from both selection among studies, especially excluding certain studies, and combining exposure assessments across processes. An equally plausible approach would be to compare potency of mineral types within an industry classification. Such an approach would flow from the plausible concern that exposure indices in mining reflect different aerosols than fiber counts in textile facilities.

2. Exclusion and inclusion of studies is a source of model uncertainty which creates different results. Therefore, the full calculation of potency values for various inclusion and exclusion selections should have been done.

C. The OSWER proposal is contrary to current developments in the carcinogenicity of inhaled particulates.

1. Alternatives to the “long thin fiber” potency hypothesis should have been explored or at least explained.

2. The fiber durability hypothesis supporting increased potency of amphiboles is not sufficient to support such a conclusion.

A. Uncertainty in exposure assessment prevents concluding differential potencies between asbestos fiber types.

Uncertainty in risk assessment derives from statistical uncertainty and model uncertainty. Risk assessments from laboratory data include the variance around the proportion of test subjects experiencing the effect, but the dose is considered to be known and precise. By contrast, a potency estimate derived from epidemiological data should include both effect uncertainty and the uncertainty in the dose. The OSWER approach does not address uncertainty in exposure and therefore dose.

1. General principles of exposure assessment in the industrial environment create a range of uncertainty around exposure and thus potency estimates. These general principles were not referenced in the document. The irreducible uncertainty around the estimate of exposure directly multiplies the uncertainty in potency values.

Historical exposure measurements referred to in retrospective human health studies were not collected to evaluate population exposures. These samples were collected to evaluate the hazards of specific operations by comparison to authoritative exposure limits or reference values, and possibly to assess maintenance or improvement of control measures. Knowledge of the properties of these data sets has evolved since the 1940's which should inform interpretation by statistical modelers and epidemiologists. Several key points are now recognized by the industrial hygiene profession.

- Exposures within a homogeneous exposure group vary substantially. A true homogeneous exposure group consists of employees performing the same tasks with the same equipment in the same period; as the group is extended in extent and time, the variation increases.
- A small number of samples will understate the average exposure.
- Variation is apportioned between worker-to-worker in identical environments, and from day-to-day for the same worker.
- Median exposure will be less than the average, divergence will increase with variability. This arises because routine exposures occur under the most prevalent control conditions, a process doesn't run all the time, but from time to time process upsets, breakdowns and blowouts create very large exposures which pull the average upwards.
- Exposures from a "well controlled" mechanized production process will vary by factor of 4 from high to low. For less controlled operations the exposure variation will be 8 to 16-fold.
- A minimum of 6 samples are needed to define whether two exposure conditions (homogeneous exposure groups at the same time, or the same group at different times) are likely the same or different.
- Additional samples improve knowledge of the average, but the variation remains the same.

- In technical terms, exposures appear log-normally distributed with a geometric standard deviation of at least two and frequently larger than two. Geometric standard deviations as high as 6 have been reported in mobile job titles.
- Area samples tend to overstate the median personal exposure, because employees don't remain in the work area all the time, retreating to low exposed areas for breaks.
- Area samples are the best measure of trend.
- Area samples understate the average personal exposure, because employees work closer to the source, but mostly because of intermittent high exposure tasks.
- In manufacturing, about 20% of hourly employees are assigned to maintenance tasks; these involve a combination of substantially lower exposures outside the production area, and substantially higher exposures during breakdowns, process upsets, blow outs and maintenance tasks with controls bypassed or removed.
- In manufacturing, about 30% of hourly employees are assigned to non-monotask jobs such as mechanical material handling. Aside from cleaners, these job assignments tend to have lower exposures.
- Thus, historical exposure assessment data typically don't apply to 50% or more of the hourly workforce.

These general considerations would apply with more force to aerosol exposure than to vapor phase exposure, and with even more force to asbestos as discussed below.

In simple language, the true exposure over a small and similar exposure group varies by a factor of 4 around the most likely value derived from an exposure data set; for a larger and more diverse group the uncertainty in the true value is may be 8 or 10 fold. Potency is not significantly different if the upper limit of the potency in a chrysotile population overlaps the lower limit in an amosite population.

2. Potential bias and confounding in exposure assessment results are not addressed in the discussion of the OSWER approach.

Two contrasting biases may be present in historical exposure data.

- Repeated samples are collected in known low exposure situations, or under optimum control conditions, to demonstrate safety to employees or public health agencies. This would underestimate the true population exposure distribution.
- Samples are collected on a worst first basis to identify control opportunities. This would overestimate true population exposure distribution.

Bias in sampling strategy is more likely consistent within a single workplace or employer, but even there may change with time. Bias between employers and industries is very likely different. There is no evidence for an assessment of the potential impact of sampling strategy bias in the decision documents.

Confounding would arise from the association of a particular sampling strategy bias or aerosol distribution with a particular industry type or fiber type.

3. Special considerations for asbestos air sampling enhance the general uncertainty of industrial hygiene data sets and increase the chance for bias and confounding, especially across process types.

Exposure monitoring for asbestos poses additional uncertainties for dose reconstruction or comparison across process types. Counts of particles, fibers or structures are not the exposure; these measures are indices of exposure to a complex aerosol mixture which varies with industrial process and likely time.

Airborne fibers vary by diameter and length. Counting methods all ignore small fibers and granular particulate matter. Very likely an impinger-counted particle or a Phase Contrast Microscopic fiber (some invisible to impinger counts) or a Transmission Electron Microscopic structure (some invisible to PCM counts) reflect materially different aerosol exposures in a mine and mill operation than an asbestos textile, cement or friction products plant.

Airborne asbestos fibers are a part of a complex mixture generated by mechanical action on a matrix of materials. The effect of the severity of mechanical handling on fiber size distribution is unclear for a single mineral type and across mineral types. Fibers may differ from granular particles; little is known about changes in length and diameter of fibrous particles with increasingly severe mechanical processing. For granular particles, more severe handling (for example, concrete saw vs. sledge hammer) generates a greater portion of respirable (fine and ultrafine) particles. The document is silent on the impact of process type on aerosol characteristics in mining and milling.

Some efforts at translating PCM fiber counts to TEM structure counts have been made by reanalyzing archived filters for PCM collection and analysis. This is not feasible for earlier particle counts. For PCM to TEM translation, each unit process would have to be represented, and each of for each of the HEG's within a process an exposure distribution with attendant variance would have to be generated.

It is plausible that mining and milling operations generate fewer thin fibers because of less handling of pure asbestos coarse fibers, and less severe handling compared to textile operations. Fewer short fibers and cleavage fragments would also be expected. These differences in fiber size distribution (relative to a single measure particle count) may account for contrasting outcome results between these two industries. This argues for separate assessments by industry.

In a mining-milling operation, large chunks of rock are blasted from an open pit mine, loaded in transporters, dumped in a crusher to free the fibrous asbestos from other rock. Pellets of rock are shaken to separate heavy rock from lighter fibrous materials conveyed pneumatically to a classifier for separation by gross fiber characteristics, then conveyed again to a bagging operation. What was in the rock goes into the bag, which then is sent downstream.

The longest gross fibers command the highest price and are used for asbestos textile applications. It would appear the object of the process is the most gentle processing for preservation of gross fiber length. The apparent heavy equipment used in processing does not equate to high mechanical stress concentration applies to the coarse fiber product.

In asbestos textile manufacture, bulk asbestos is conditioned, then carded, spun and woven. Mechanical force is applied directly to the bulk asbestos product in creating the final product which is yarn and woven fabric. Friable asbestos may also be released during the processing of the product.

In asbestos cement manufacture, bulk asbestos is debagged, conditioned and then mixed to form a slurry which is then cast and processed. It would appear that friable asbestos would be generated from the product through use of powered equipment. Compared to friction products manufacture, asbestos cement manufacture would be expected to create larger articles to which greater mechanical force concentration is required for whatever finishing (cutting and drilling) activities take place.

In friction products manufacture, bulk asbestos is debagged directly into mixers for formulation of the ultimate product. For drum brakes (and likely clutch plates), the mixture is a slurry with resin which is cast, cured, trimmed and drilled. For disc brakes, an asbestos-resin dry mixture is created, then formed in a briquetting press, cured, trimmed and drilled. Prior to the 1980's, most production was drum brakes, which by process is more easily controlled than the newer disc brakes. Articles created for application to cars and light trucks were smaller in size than those for heavy trucks and aircraft.

For all these industry types processes and methods changed with time; likely the application of mechanical force to asbestos containing material would have changed with time, causing a qualitative change in aerosol. For friction products manufacture, the shift from drum to disc brakes would have caused a substantial shift in aerosol characteristics.

B. The recommendations of the NAS Risk Assessment Committee for presenting the full range of risk assessment results have been ignored.

1. Model uncertainty in the OSWER approach arises from both selection among studies, especially excluding certain studies, and combining exposure assessments across processes. An equally plausible approach would be to compare potency of mineral types within an industry classification. Such an approach would flow from the plausible concern

that exposure indices in mining reflect different aerosols than fiber counts in textile facilities.

The NAS Committee recommended that the risk assessor furnish a risk manager with the full range of alternative results, along with a recommendation for the choice. Range reflects statistical uncertainty, which may be calculated, but also model uncertainty which does not follow any particular distribution. An important form of model uncertainty is the grouping of studies. In this case the modelers enumerate some alternative data choices, but only calculate one risk value based on their choice of model. Instead the full calculation should have been for each alternative grouping of studies.

2. Exclusion and inclusion of studies is a source of model uncertainty which creates different results. Therefore, the full calculation of potency values for various inclusion and exclusion selections should have been done.

This flows from the recommendation of the NAS committee to present the risk manager with all plausible alternatives. In this instance, the risk manager should be able to choose whether EPA prefers a potency model that excludes the Selikoff studies but includes the Quebec Mining cohort, or involves some other collection of studies. It is clear that potency estimates vary substantially based on which studies are included or excluded, and that the general direction of these exclusions was clear to modelers before they started.

A comparison of quantitative potency values with fiber type, in contrast to qualitative impressions that the variation would narrow or widen with different assumptions, ties the hands of the risk manager to the single quantitative result. Again, conclusion needed as to why this is bad.

C. The OSWER proposal is contrary to current developments in the carcinogenicity of inhaled particulates.

There is no consensus on a mechanism by which asbestos fibers induce cancer. Without a robust biological mechanism for the proximate process, hypotheses about fiber length and persistence are suggestions to explain observations, and don't resolve the apparent reverse order of potency between that observed in the laboratory and inferred from epidemiology.

1. Alternatives to the "long thin fiber" potency hypothesis should have been explored or at least explained.

The review ignores our new understanding of the respiratory cancer hazard posed by granular durable particles. The OSWER grouping ("bins") of fiber exposures emphasizing long, thin fibers recaptulates and assumes to be correct the "Stanton Hypothesis," which suggested that the toxicity of asbestos arose predominantly from interaction long fibers with tissues. The Stanton Hypothesis was proposed in 1972. It derives from the time when asbestos was known to cause fibrosis and lung cancer, while silica was "known" to cause only fibrosis and not lung cancer. However, the most authoritative organization for classification of carcinogenic risk, the International Agency for Research Against

Cancer, concluded in 1997 that it is “known” that silica is a human carcinogen. This was based on literally dozens of studies in people combined with laboratory evidence similar to that available for asbestos. Thus, the entire framework that long fibers are uniquely potent in causing respiratory cancer has been contradicted.

Similarly, IARC classifies diesel particulate matter as probably carcinogenic to humans Other durable particles, including titanium dioxide and carbon black are also carcinogenic in rats and therefore “possibly” carcinogenic to humans., carcinogen.

Similarly, the discussion of risk of fibers v. cleavage fragments could be amplified by discussion of the new understanding of the hazards of nanometer particles. Short thin fibers penetrate into the systemic circulation? An 0.1 micron short fiber particle is a nanoparticle with penetrating properties, if penetration is governed by the end diameter, not the length. Not sure this is helpful, relevant or comprehensible.

2. The fiber durability hypothesis supporting increased potency of amphiboles is not sufficient to support a conclusion.

The claim that greater durability of amphibole fibers predicts greater potency is an after the fact observation, not a reliable basis for concluding that greater potency is biologically determined. The predominant exposure pattern for asbestos toxicity is repeated exposure over time. If fibers are degraded or cleared from the respiratory system at a rate similar to deposition, the concentration of fibers in the system will eventually achieve a steady state. If disappearance from tissue is slow in comparison to deposition, the concentration will increase until exposure stops. Concentration will decline only after exposure is stopped.

It is plausible that lesser concentrations of chrysotile at autopsy of asbestos victims compared to amphiboles reflect disappearance after the initiation of the cancer process. A greater rate of disintegration of chrysotile suggests greater interaction with tissue, plausibly suggesting a mechanism for increased potency.