State of Oregon
Department of Environmental Quality

Response to Scientific Peer Review

On October 3, 2016, the Oregon Health Authority (OHA) and Oregon Department of Environmental Quality (DEQ) (collectively referred to as Oregon agencies) submitted a document proposing 24-hour screening levels for 15 air toxics to a group of five independent experts in the field of toxicology for their peer review. On October 12, 2016, Oregon agencies submitted a revised version of the proposal. The only change between the original and revised version of the proposal was a modification to how total chromium would be addressed. The next section explains the difference between the original and revised proposals in more detail.

The experts selected by Oregon agencies for peer review are Bruce Hope, Ph.D. retired DEQ and CH2MHill and member of Air Toxics Science Advisory Committee; Fredrick Berman, DVM, Ph.D. with Oregon Health Sciences University's Toxicology Information Center; Julie Wroble[1], Toxicologist EPA Region 10; Michael Stewart[2], Ph.D., Environmental Protection Specialist with EPA's Office of Air Quality Planning and Standards; William Lambert, Ph.D. Epidemiologist, Oregon Health Sciences University and chair of Air Toxics Science Advisory Committee.

Reviewers' general comments coalesced around two substantive themes addressed in following sections. The first theme that emerged was the need to be clearer about the purpose and intended uses of these short-term guideline values and what exceedances will mean. The second substantive theme was concern about using chronic toxicity values unmodified as 24-hour screening levels. Other than these two themes, comments were generally supportive of the approach taken by Oregon agencies. Remaining reviewer comments have all either been incorporated into the proposal for public comment or are discussed in the last section of this document.

Difference between Original (October 3, 2016) and revised (October 12, 2016) Proposals

The original proposal included a proposed 24-hour screening level specifically for total chromium. This proposal was based on a 6 to 1 ratio of total chromium to hexavalent chromium from a specific study used by the United States Environmental Protection Agency (EPA) to derive their inhalation unit risk

[1] The views expressed by Julie Wroble in her comments are hers, and do not represent the official views or policies of the U.S. EPA.

[2] The views expressed by Michael Stewart in his comments are his, and do not represent the official views or policies of the U.S. EPA.

estimate for cancer risk associated with hexavalent chromium. The modified version of the proposal from October 12, 2016 replaced the 24-hour screening level for total chromium with a guidance to apply the 24-hour screening level for hexavalent chromium to total chromium measurements. The guidance further directed that total chromium measurement in exceedance of the 24-hour screening level for hexavalent chromium should trigger additional monitoring that speciates hexavalent chromium. Regulatory and other response decisions should be reserved until speciated monitoring can determine whether the 24-hour screening level for hexavalent chromium is being exceeded.

Clarification of Intended Use and Purpose of Short-term Guideline Concentrations (SGCs)

Some reviewers expressed the need to better define the intended purpose and use of the originally proposed "24-hour screening levels." In response to this comment, Oregon agencies have renamed these toxicity values Short-term Guideline Concentrations (SGCs) to shift away from a strict adherence to a single monitoring result with a 24-hour averaging time. There is considerable variability in the degree of uncertainty and exposure periods studied in the derivation of each of these SGCs by other authoritative bodies. Therefore, it is appropriate to de-emphasize a specific averaging time that applies to all of the SGCs, but rather to describe these values as screening-level guidelines for a range of averaging times from 24-hours to several days depending on the toxic chemical and professional judgment. SGCs are not designed to guide decisions about evacuation or other emergency responses nor should they be considered "never to exceed" values from a regulatory perspective. However, they are intended to trigger closer investigation, consideration for prioritized or expedited health assessments, and to guide Oregon agencies in developing conclusions about health risks related to short-term exposures at these levels. Language to clarify this intended purpose and name change have been added to the proposal for public comment.

Use of Chronic Toxicity Values as Short-Term Guideline Concentrations

A few reviewers expressed concern about using toxicity values designed to be used as annual averages unmodified as SGCs. The substance of the scientific argument against doing so is that "…it is not at all clear whether there is any kind of a dose-response relationship that would permit a short-term (24-hour or acute) exposure and a chronic exposure to yield the same response over the same time interval." This argument is consistent with Haber's Rule that a much higher concentration is required to cause the same effect over a short exposure interval than over a longer one. In the case of cobalt, for which we applied a 24-hour averaging time to a chronic toxicity value, Oregon agencies agree and have removed it from the list of air toxics with SGCs.

However, Oregon agencies would posit that there are health endpoints and air toxics that pose exceptions to this rule. For example, developmental malformations and immune sensitization are both chronic health endpoints that have been used as the basis for chronic health guideline values but that can be caused by relatively short durations of exposure. In many cases, chronic toxicity values are derived by agencies based on toxicological studies that are not designed to determine the minimum exposure period necessary to cause the effect at a given exposure level.

This is the basis for ATSDR's decision to use 5 ng/m^3 as the non-cancer minimal risk level for both intermediate (14-364 day) exposures and chronic (365 days or longer) exposures for hexavalent chromium. The critical study was an occupational study where workers had been in the exposure environment for periods ranging from a little over a month to several years. While effects were

measured during the time period the researchers were involved, it isn't clear whether the measured effects began on the workers' 2nd day of work or required the full 6 months or several years to develop.

Methyl Ethyl Ketone. Lifetime and annual averaging times for endpoints related to developmental events that occur during a 3-month trimester, or even a two week critical window, are less protective than applying a shorter averaging time that better matches the exposure period in the underlying toxicological study. The reference concentration (RfC) for methyl ethyl ketone (MEK) is a good example of this principle. The chronic RfC for MEK is based on a developmental study in which pregnant mice were exposed during gestational days 6-15, which resulted in skeletal malformations in the offspring. EPA did not apply any factors to adjust the averaging time from this ten-day exposure result to a chronic averaging time for the RfC. The evidence from the critical study used to develop the chronic RfC indicates that a short-term (ten-day) exposure during a critical developmental window, can result in a permanent effect. Developmental stages last longer in humans than in mice, however, the study was not designed to look for critical effect windows shorter than the 10-day gestational period selected. It is biologically plausible that the true critical period was only one or two of the days within that 10-day window. Based on this evidence for a chronic/permanent health outcome following a short-term exposure, Oregon will retain the EPA RfC for MEK as an SGC.

Lead. The National Ambient Air Quality Standard for lead is based on a 3-month rolling average (not an annual average). From this perspective, applying an annual averaging time to the NAAQS for lead is less protective than the NAAQS as it is applied by EPA. Given the adjusted definition of SGCs, Oregon will retain the NAAQS for lead as an SGC. This SGC will still be slightly conservative relative to EPA's 3 month rolling average, but this is appropriate given the severity of the health effects associated with lead exposure for children in terms of permanent IQ decrements.

Manganese. The originally proposed 24-hour screening level for manganese was identical to the Oregon ABC, which was based on an RfC developed by the California Office of Environmental Health Hazard Assessment (OEHHA). The critical study (Roels 1992) is an epidemiological study of occupationally exposed workers with neurological effects as the critical endpoint. The duration of exposure in the critical study ranged from 0.2 – 17.7 years. OEHHA applied an uncertainty factor (the square root of ten) to extrapolate from subchronic to chronic exposures. This study was not designed to determine the minimum exposure duration necessary to cause the neurological changes measured as the critical endpoint.

While the critical study did not evaluate neurodevelopmental endpoints in children, supporting studies cited by OEHHA indicate that manganese has the potential to impair neurodevelopment. OEHHA applied additional uncertainty factors to address this potential. Because of the potential for manganese to permanently impair brain development during short-term critical windows of exposure, Oregon agencies will retain a modified version of OEHHA's RfC as a SGC. The modification is to eliminate the uncertainty factor added to extrapolate from subchronic to chronic exposure, which means multiplying the OEHHA RfC by the square root of ten. This modification brings the value into alignment with ATSDR's chronic MRL for manganese.

Beryllium. In the case of beryllium, the critical endpoint of concern is development of a chronic granulomatous disorder (chronic beryllium disease or CBC) that is mediated by an adaptive immune response directed against self-antigens that are modified by the beryllium molecule. While chances of developing this disorder increase with length of exposure to beryllium, an adaptive immune response only requires 4-7 days to form. Once formed an adaptive immune sensitivity is a chronic condition. Thus,

it is biologically plausible for a short-term, low-level exposure to result in a chronic, long-term health effect. Indeed, the IRIS summary document for EPA's RfC states that no adjustment from subchronic to chronic averaging times was applied because, "… the occurrence of CBD does not appear to be related to exposure duration." For a sensitive individual, it is biologically plausible that a single exposure over a critical threshold could lead to sensitization leading to CBD. Therefore, Oregon will retain the EPA's RfC for beryllium as an SGC.

Chemical-Specific Comments and Responses

Arsenic

Comment: The exposure duration for the arsenic value is 4 hours/day during a critical window of development. Should we be concerned about exposures at this level for 24 hours? Should an extra safety factor be added to the value or do the current uncertainty factors account for this?

Response: Thank you for this comment as it raises a good point. Based on other comments as discussed above, Oregon agencies have shifted away from a strict 24-hour averaging time for the application of these proposed SGCs. So there is room for flexibility in how to interpret exceedances of these SGCs based on the exposure durations in the critical study and level of certainty around SGCs for each air toxic.

There is uncertainty extrapolating consecutive 4 hour exposures over 4 days to either a 1 hour averaging time or a 24-hour averaging time, though the 1 hour averaging time is more protective. Developmental windows are much shorter in mice than in humans, so it is possible that a longer exposure period during the same developmental phase would be required in humans than in mice to cause the same effect. The total exposure time in the study was 16 hours, which is closer to 24 hours than 1, so it is difficult to know which averaging time is ultimately most appropriate. The total uncertainty factor for this value is 1,000 and is most likely adequate to compensate for the uncertainty around difference in averaging time between 1, 4, 16, and 24 hours. From a practical perspective, Oregon agencies are unlikely to acquire monitoring data integrated over less time than 24 hours. Oregon agencies plan to retain the OEHHA acute REL as the SGC as it stands.

Hydrogen sulfide

Comment: This level is above the odor threshold, which could be a problem in terms of sensitive populations who may suffer psychosomatic effects. I would almost prefer the lower value used by agencies that consider mean odor threshold as the point of departure. Not sure how this would affect paper mill operations if a lower screening level were used. Nevertheless, the value selected should be protective.

Response: Odor threshold and odor related effects are important for public health. The difficulty in using them in this setting is the wide range in odor perception and severity of odor-related health symptoms across the population. All odor issues have a subjective component that is difficult to relate to toxicological outcomes. Oregon DEQ does have a complaint-driven odor nuisance strategy that can be applied to any facility for any odor where sufficient complaints are registered. With this strategy as a back drop, Oregon agencies have chosen not to consider odor threshold as a basis for SGCs, preferring to rely on measurable toxicological outcomes.

Hexavalent Chromium

Comment: With respect to hexavalent chrome, [Oregon agencies are] proposing to use the chromic acid ATSDR intermediate (15 to 365 day) MRL as a 24-hour health screening value. Notably, the chromic acid MRL is approximately 60 times more conservative than the ATSDR [intermediate] MRL for particulate hexavalent chrome. In situations where [Oregon agencies] need to monitor for hexavalent chromium, to the extent it is possible, I recommend seeking information about the potential sources of chromium influencing the monitor and then determining which of these two ATSDR intermediate MRLs is most appropriate to use as a screening value. It very well may be that certain industries and their associated processes are much more likely to emit a certain type of hexavalent chrome…

Response: Oregon agencies agree with this comment and will have separate SGCs for the two forms of hexavalent chromium (chromic acid mist and dichromate particulate). Monitoring is not able to differentiate between the two forms, however agencies can work together on a case-by-case basis to understand the source and the most likely form of hexavalent chromium in the monitoring location. That will allow for application of the most appropriate SGC.

Naphthalene

Comment: Is there a need to find a value protective of acute poisoning in neonates (hemolytic anemia) as referred to in EPA's IRIS profile for naphthalene (Section 4.7.1)? The NTP study is more recent than the one on which the 24-hour recommended value is based, but may not address the short-term effects.

Response: The difficulty with the hemolytic anemia endpoint for naphthalene is that the effect has not been replicated in animal studies in a way that quantified dose response, and the cases where hemolytic anemia has occurred in humans have always been in settings where levels of naphthalene were not measured in a timely way. The best documented example is a case where several infants were wrapped in blankets that had been stored in moth balls and many of them developed hemolytic anemia and some died. Naphthalene was identified as the causative agent, and inhalation was identified as the critical route of exposure. However, there were no measurements of air concentrations taken at the time, which makes it impossible to develop a quantitative dose response for this effect.