Sixth Meeting of the Health Effects Advisory Committee (HEAC) for Permissible Exposure Limits for Airborne Contaminants in the Workplace California Code of Regulations, Title 8, Section 5155
March 6, 2018
Elihu Harris State Building
1515 Clay Street Oakland, California

HEAC Members present

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Will Forest, MPH, Santa Cruz County Department of Public Health (Epidemiology/Toxicology)

Robert Harrison, MD, MPH, School of Medicine, University of California, San Francisco, CA (Occupational Medicine)

Sarah Janssen, MD, PhD, MPH, Occupational Medicine Department, Kaiser Permanente, San Francisco, CA (Occupational Medicine)

Patrick Owens, MSPH, CIH, Shell Oil Martinez Refinery, Martinez, CA (Industrial Hygiene)

Mark Stelljes, PhD, SLR International Corp., Martinez, CA (Toxicology)

James Unmack, CIH, Unmack Corp., San Pedro, CA (Industrial Hygiene)

Michael Bates, MS, PhD, UC Berkeley (Toxicology)

Kent E. Pinkerton, PhD, UC Davis (Pathology/Inhalation Toxicology)

Public and Interested Parties

Erica Stewart, Kaiser Permanente
Dan Leacox, Leacox and Associates
Bob Nocco, Chevron
John Martinelli, Forensic Analytical Consulting
David Woodard, East Bay Municipal Utility District
Mike Marzano, Union Sanitary District
Harvard R. Fong, CA Dept. of Pesticide Regulation
Kashyap Thakore, Toxicologist, California Department of Public Health, HESIS
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Russell Johnson, Associated Building Contractors
Emma Wilson, CDPR
Jim Kegebein, Kegebein Consulting
Ben Schanker, UCSF Environmental Medicine
Stewart Holm, Forestry Council
Alex Holmes, Holmes Western Oil Corporation
Michael Geyer, KERNTEC Industries
Paul Sotti, Asphalt Institute

John Schweitter, American Composites Mfgers Assoc.
Willie Rivera, CA Independent Petroleum Association
Sharon Callahan, Andeavor
Ray Ehrlich, Styrene Information and Research Center
Courtney Mizutani, Mizutani Environmental

Elisa Koski, Cal/OSHA Standards Board Staff

Division of Occupational Safety & Health

Garrett Keating, Chris Kirkham, Eric Berg, Kevin Graulich and Mike Horowitz

Chris Kirkham opened the meeting, introducing himself as the newly appointed successor to the retired Steve Smith. Kirkham spoke of his experience and long interest in Permissible Exposure Limits (PELs).

Garrett Keating said that handouts for the meeting included, in addition to the summaries and priority list from the website [https://www.dir.ca.gov/dosh/DoshReg/5155Meetings.html], supplemental materials on the table at the back of the room. He stated the agenda provided for morning discussion of hydrogen sulfide (H2S), then manganese and then, 2-butoxyethylethanol (2BEE) and 2-butoxyethylacetate (2BEA). After lunch would see methyl isobutyl ketone (MIBK), and tert-Butyl acetate (TBAC) discussions and finally PEL prioritization for 2018.

Hydrogen Sulfide

Keating summarized the prior H2S deliberations. A PEL of 1 ppm based on lactate accumulation had been proposed, but withdrawn as this was a subclinical effect. A PEL of 5 ppm is now proposed based on eye irritation. Many references to H2S eye effects have no exposure information. Van Horne, the rayon spinner study, does have good controls and well-characterized exposure. The study has exposure to both H2S and Carbon Disulfide (CS2), which is another eye irritant. The literature has several studies reporting eye irritation as a qualitative effect from mixed chemical exposures, but in the Van Horne study, it is possible to conclude that the H2S was the main cause of the eye effects.

Mike Cooper said a five-fold CS2 concentration reduction was less than an order of magnitude so wasn't it still possible that CS2 caused or contributed to the eye irritation? Keating said that in the Van Horne study there were virtually no reports of eye irritation when the sole chemical exposure was high concentrations of CS2. With lower concentrations of CS2 at 100 ppm and H2S exposures at 6 ppm, eye effects were reported. With CS2 concentration remaining at 100 ppm but H2S reduced to 3 ppm, no eye effects were reported. From this Keating concluded that exposure to 6 ppm of H2S is the primary cause of eye irritation in VanHorne.

Cooper said Keating has done a lot of work on the H2S recommendation, and had brought the clarity that the committee has been looking for.

Bates asked who composed the unexposed group. Other workers at the plant, explained Keating, with no adjustment for sex. Bates asked if the eye irritation noted in the Van Horne studies could potentially be due to an age difference between the exposed and unexposed groups, if there was a difference in ages of the two groups. Age is associated with changes to the eye that may tend to increase sensitivity, Bates said. Keating agreed to look into that possibility and to send Bates a copy of the Van Horne studies.

Michael Geyer said if a PEL is to be changed, a better basis is needed. Irritation is weak and there's an age issue, he said. Compared to eye effects from anhydrous ammonia, where a mechanism for the damage is known.

Without a mechanism explaining the purported eye irritation, the proposal is weak, lacking foundation.

Keating, acknowledged that in switching health endpoints from lactate production to eye irritation, he had not included a mechanism of action in the summary. The sulfhydryl molecule is the reactive chemical group that causes the damage to tissues and cells. He promised to add that basic information to the document.

Referencing his comment letter sent Cal/OSHA concerning feasibility of a lowered PEL for H2S, Russell Johnson said the new proposed PEL was much better than 1 ppm. But even this proposed PEL would cause more alarms to go off and more people would have to wear respirators. Older workers may not be medically qualified to wear respirators, adversely affecting availability of the most skilled workers in the oil and gas industry.

Alex Holmes said that in the petroleum industry the lower PEL will indeed cause more alarms. The industry will comply but a new PEL of 5 ppm, it should be explained as significant reason. Not like eye irritation where there is no noticeable effect or it is considered by the workforce to be a nuisance.

Mark Stelljes said the purpose of the alarm was to alert workers to an increasing chemical concentration. He asked how workers could conceive an alarm going off as a nuisance.

Holmes explained it is harder to convince workers of the risk at the alarm level if they do not feel the adverse effect.

Will Forest said engineering controls are the first line of defense, so you should be controlling to the appropriate level.

Holmes noted that the petroleum industry work was outside. We service wells, and it would not always be practical for engineering controls to be fully successful in such circumstances. But we do put in engineering controls for well servicing, and we still get alarms. I just want to go back to our people with evidence of the necessity for lowering the PEL to 5 ppm.

Keating said the study relied upon was a study specifically looking at this effect. There is also a study of a geothermal plant with full time H2S direct reading air monitors (supplemental materials). Very few exceedances were seen in a full year. Few readings above 8 or 10 were recorded.

Holmes said few exceedances over 10 ppm H2S was also the experience of his plant.

Dan Leacox said that if a petroleum employer is getting alarms but workers are not experiencing any ill effects, it is only human nature that workers may begin to disregard the alarms. The more often the alarms go off, the bigger challenge this may become.

Patrick Owens asked Holmes if they do a signs and symptoms check when an H2S alarm goes off.

Holmes said no, because of the remote location of the facilities, we try to get the workers away from the exposure. Workers don air-purifying respirators when alarms occur, H2S levels tend to drop after the alarm sounds. There is quick dissipation of H2S emissions which are intermittent in any case.

Keating noted a STEL level is also proposed. Did Holmes have any experience monitoring for 15 minute intervals during such alarm events? Holmes said it was not practical to sample when a leak happens, and since the wellheads are outdoors, there is quick dissipation of the H2S released.

Robert Harrison asked if anyone had experience with operations utilizing the ACGIH TLV of 1 ppm.

Geyer said no, and he had been a consultant for the oil and gas industry and other outdoor activities like construction and sanitary landfills for 30 years. These environments are not a continuous process like the rayon site; oil and gas, construction, you have puffs and whiffs. All may have hits at 60 to 90 ppm, but unless you have a data logging device, you have no idea of the duration or amplitude of the exposure. Yes, people will after a while consider the alarms to be nuisance alarms if they go off frequently. I know a person at an asphalt plant. A worker was passing a tank when the relief valve on the top of the tank released H2S. The worker passed out, woke up a little later. But I have not heard of anyone complaining about eye irritation. In construction, oil and gas, everybody wears the alarms set at 10 ppm. If the alarm goes off for these folks go on supplied air. Engineering controls are not always applicable in the field. For work in storm drains, you might expect more of a continuous H2S emission source. 5 ppm will be a challenge; again, workers wear personal alarms: they are not data logging.

Keating asked Kirkham if Cal/OSHA had data on employee eye irritation or short-term exposure levels. Kirkham explained that employers have to assess the possibility of exceeding STELs. During an inspection, an enforcement officer may or may not have a chance to physically assess the possibility of STEL exceedance.

Geyer spoke to the difficulty of knowing when a short-term exposure might occur; sampling gold standard--if you know some frequency or periodicity, you can be there with sampling equipment. If the timing of a release event is unknown, there is not a sampling program out there that is going to catch it. Fortunately, there is a lot of data logging equipment out there that can capture that.

Stelljes said he had been on the North Slope around oil wells with H2S exposures. There are large signs that say "possible H2S source." Therefore, if you are going into one of those areas you put on a personal alarm. But there are other areas where more constant monitoring is done. Therefore, I would argue a little with the idea that potential for H2S exposures are a complete unknown. It is not impossible to do reasonable sampling.

Holmes said they try very hard not to have leaks, even when people with thermal imaging cameras are present. What Stelljes is talking about are pressurized gas situations, where you have a relief valve that might burp. But we are trying to reduce leaks, to comply with air quality management requirements.

Owens asked why the 10 ppm alarm setting was chosen, and what would it be lowered to if the PEL went down.

Holmes said it was just the standard practice to use 10 ppm as the alarm setting. We tell people that when the alarm sounds they should get out, put on respirators, etc.

Kirkham said this use of 10 ppm as an alarm set point was akin to a Ceiling.

Leacox said changing the PEL and alarm set point is disrupting a very, very reliable practice.

Geyer said the 10 ppm alarm set point was ingrained, at this point.

Stuart Holms said ½ of a PEL is generally seen as an Action Limit. Since half of the OSHA Ceiling Limit of 20 is 10, the alarm set point of 10 the industry is using is equivalent to an Action Limit.

Mike Marzano said the waste water industry practice was to get out when the alarm at 10 ppm sounds. We clear the area, make sure it is safe, we ventilate—whatever we need to do. In the draft document's discussion of economic impact, the claim is made that costs can be offset by reductions in workers comp claims. Do we have

workers comp claims, injuries, exposures?

Harrison said the proposal is to lower the PEL to 10 ppm. What I've heard is that you are already setting your H2S alarms at 10. That's no change; the PEL is an 8 hour time weighted average (TWA).

Stelljes said what he was concerned about were the puffs, which really compares as a STEL, not a TWA. So with an alarm set at 10, they are already protecting against a those puffs. It is up to the regulated community as to what they want to adjust their H2S meters.

Geyer said best practices is you don't exceed 50% of an exposure limit like a STEL.

Cooper said we are discussing outdoor transient exposures of 15 seconds, not 15-minute STEL exposures.

Geyer said a 15 second exposure could be really high.

Keating said you do want to have an alarm from a detection and compliance standpoint. For certain operations an alarm at 10 would be adequate.

Geyer said if you set the PEL at 5 [and the alarm is at 10], how will you ever know you are exceeding the PEL?

Cooper noted the PEL is an 8 hour time-weighted average. You could have five bursts of 15 seconds and easily be over the PEL of 5 ppm.

Geyer said workers work all day, and could accumulate an over PEL exposure from such bursts.

Owens said that with the alarm set for 10, theoretically there could be a 6 ppm exposure all day without the worker having a signal to stop work.

Stelljes said constant exposures of 6 ppm do not occur in these outdoor work locations.

Leacox said the proposal is just up against a very, very workable established practice.

Owens said high exposures are not the average.

Stelljes asked either Russell Johnson or Willie Rivera. In your comments, you say the act of reducing the PEL from 10 to 5 would lead to a $10 million cost for fire protective clothing?

Johnson said it is just an example of feasibility and the cost associated with dealing with the H2S, items that would have to be brought in or acquired to do the job, not for the PEL.

Stelljes said so the $10 million cost is just an example, not specifically associated with the PEL reduction. Johnson said correct.

Forest said, in relation to the expressed concern about increased numbers of alarms, we do not set the alarms, just the PELs. There is nothing in dropping the PEL to 5 that would require you to lower the setting for your alarms to 5. The STEL is dropping from 20 to 10. Is this a standard practice of half a level?

Leacox said it is a happy coincidence that the current PEL is one-half the current STEL; if you never go over ten, you're good.

Forest said the alarms are currently set for an excursion, not the PEL. The reason we have alarms is because of the excursion. Alarms do not have to be changed just because it is an historical practice for them to be set at half the PEL.

Cooper noted that half of a PEL is often set as a concern level.

Johnson said our members' agreement with the companies is they follow the standard operating procedures.

Keating said it was time to move to the next agenda topic. I will meet with Bates to discuss the Van Horne study and will add text about the irritation mechanism of H2S. I do not see any need to bring this back to the committee. We have had a lot of input on feasibility that the Division will address during final rulemaking.

Manganese

Keating said the proposed PEL had been revised from 0.01 milligrams/cubic meter (mg/m^3) respirable to 0.02 mg/m^3. Last meeting saw a fair amount of comments on feasibility and after discussion with some committee members, an uncertainty factor for pre-natal effects was removed from the PEL calculation. Keating referred to the handout. This document focuses on the toxicokinetic uncertainty factor used. In summary, much of the knowledge of health effects of manganese comes from smelter studies. Exposure in smelters is from micron-sized particles, which are arguably less bioavailable than sub-micron manganese particles from welding. Particles from welding have a much finer particle size distribution. The first figure in the handout shows a new pharmacokinetic model that shows as the concentration gets above 10 $\mu g/m^3$, brain levels of manganese start to rise. The flat line is normal manganese concentration from dietary sources. Manganese is an essential metal, unlike aluminum or lead. So the body has mechanisms to obtain, sequester and excrete Mn.

The next key figure, on page 2, are plots of manganese concentration in blood and welding fume. Note the deflection point in blood Mn levels at 10 $\mu g/m^3$ [= 0.01 mg/m^3]. Above approximately 0.01 mg/m^3 a different slope in the blood manganese level is seen. In the top figure, NHANES data for the average US male blood manganese concentration is shown. Below 10 $\mu g/m^3$, there is very little difference between the average male and welders. As Mn concentration exceeds 10 $\mu g/m^3$, the slope of the blood Mn increases. Again, this is an inflection point around 10 $\mu g/m^3$. The lower figure is based upon plasma manganese levels, as opposed to levels in whole blood. So at 25 $\mu g/m^3$respirable manganese you see the inflection point in this graph.

The last figures are on particle size; welding fume is well below 0.5 microns. These are two workplace studies of different welding methods. Particles with mean aerodynamic diameter below 5 µm are deposited in the alveoli. Total average mean diameter of the welding fume is 0.36 µm, but that includes steel cutting which have a diameter of 5 microns similar to what you might see in smelters, which have a larger particle distribution. Then in study 2, highlighted boxes show samples below 4 microns for various welding techniques. Then 0.5, 0.4, 0.24 µm —the submicron particle sizes in that fraction. Lastly, are tables characterizing Mn exposures and MRI brain and blood Mn levels in welders and alloy smelter workers. Blood levels are higher in welders than smelter workers despite lower exposure by a factor of 10. Smelter workers are in turn higher than controls. Welders have accumulated a higher level of manganese in a shorter period of time with a lower concentration.

Stelljes did not understand the first Table. It looks like the airborne concentration for welders is higher than for smelter workers.

Keating referred to the table. The blood levels are higher in the smelters but not in proportion to the much higher Mn exposure (concentration and years), the smelters received. Keating pointed out T1, T2 signal

intensity in the bottom table. Brain manganese concentration is higher in the welders even though smelter workers exposure was of greater intensity. Keating noted this is the only comparative study of Mn levels in welders and smelters he could find.

Stelljes suggested this means that blood levels may not predict brain concentrations.

Keating said this is true but what is important to this is related to the inflection point on brain Mn. Manganese gets in the blood and is then transported to the brain, a cumulative process. Manganese has a half-life of 60 days. This is why for welding studies they look at the cumulative exposure index, CEI. Years of welding, the concentration, the type of activity and possible co-exposures.

Cooper said on the first part of the Table T-1, T-2, are controls roughly the same as for the welders?
Keating said these are mechanical MRI measurement of lesions in the cortex. Welders are significantly different—lower, with higher measurement depending upon the type of measurement.

Stelljes said this was slower transmission.
Keating said these measurements are consistent with higher manganese concentration.

Bates said the inflection point in diagram 2, if you look at the horizontal log scale with a couple of standard deviations around it, you will find many of these are within the normal range. It is squished up, so the difference between 1 and 10 is the same as between 10 and 100. Just by visualizing, I am not totally convinced that the inflection point is actually 10. It could be somewhere between 10 and 100. [Forest interjected that the text below says that.]

Keating said "inflection point" is a term in the literature, and while 10 has been mentioned, others cite a range of 10 – 100 $\mu g/m^{3.}$

Owens asked if the first graph used respirable data. Keating says it was, and he thought the data came from the Roels study that looked at particles of five microns, but many particles were smaller. Keating said the exact location of the inflection point was not crucial. The utility of this data was it supports the uncertainty factor utilized to calculate the new proposed PEL of 0.02 mg/m^3.

Leacox said the decision should be put off on behalf of steel and ironworkers until the data from a bay bridge exposure study which looks at feasibility as well as exposure could be included; the study should be completed by September.

Geyer said welding fume was personal of interest to him as he has a child studying to be a high-end welder. He noted there are synergistic effects caused by some of the diverse metals generated by welding. The atomic weight of manganese is similar to that of iron and nickel. Especially when consumable rod is used, you get exposure from a plethora of metals. I encourage the committee to focus on welding and Parkinsons-like disease but I think manganese is just a piece of the puzzle, given synergistic effects. Smelters are more of a homogeneous environment compared to use of consumable rod with high exposure to other metals.

Harrison said the proposed manganese PEL resulted from feasibility and engineering control issues. Controlling manganese exposures would also control exposures to other metals. Without looking at the PELs for other metals, the proposed manganese PEL would have a beneficial effect.

Geyer said yes and no. One thing I have learned by taking a lot of samples is that this may be true in a fixed environment with build-in controls but exposure is harder to predict and control in a construction environment

such as the construction of Diablo Canyon nuclear plant. For a lot of construction, I see personal protective equipment (PPE) being a mitigating factor. Engineering controls that work in the controlled environment, like a snorkel ventilation device, may not work when you are welding in the narrow corner of a construction project.

Johnson said, as mentioned last meeting, we have a welding lab in Bakersfield where ABC teaches welding procedures to ironworkers. We have serious feasibility concerns with the new PEL. One is, in the field, welding often is performed in confined spaces. Respiratory protection is necessary, and a lower PEL would mean a tougher respiratory protection program would need to be implemented. This would mean pushing some of your best, most experienced, welders out of the workforce. Our ABC welders average in their mid- to late-40's.

Owens asked if Johnson saw a problem with powered air purifying respirator (PAPR) use. Johnson said he did not know enough technically.

Keating said there is considerable information on welding processes and the conditions under which welding is done. There is merit in compiling data on welding fume to assist the feasibility assessment. Oregon OSHA recently contacted us looking for a data set on welding fume. Many publications have data sets. Germany has a PEL of 0.02 mg/m^3 for some years now and is confronting this issue. Although manganese has come before HEAC four times, I think the feasibility issues deserve a concentrated look on our part.

Harrison said he agreed. It was worth getting the data. Hopefully this feasibility review can wrap up in September.

Cooper said this separating out the feasibility from the toxicological could go on forever. He expects the feasibility discussion will come up again during formal rulemaking.

Keating agreed that health effects are supposed to be the bulk of HEAC discussion, and said unless the models are revised, I do not foresee the need to go more into the health effects.

Horowitz clarified that the Division is being asked to allow a little time before we push forward to rulemaking.

Leacox said he agreed, expecting that the data from the ironworkers he mentioned by September would certainly be the last input. He understood, from last December's meeting, that HEAC would entertain at least some feasibility discussion.

Eric Berg said the Division will take the feasibility input, although it is not HEAC's primary function.
Geyer said 25 to 35% of the welders from whom he collects samples are smokers.

2-Butoxyethyl acetate and 2-Butoxyethanol (2BEA and 2BE)

Keating said the previous recommendation was 1 ppm derived by using a human equivalent dose and using an uncertainty factor of 10 to account for human variability. No animal intraspecies factor was used. The committee questioned if the 10 UF should be utilized. The in vitro studies on 2-BE hemolysis took blood from a range of humans—elderly, children, people with known blood conditions – and observed a human variability factor at 3. From a range of estimates, I came up with 3.5, which I've rounded up to 5. The human study (Haufroid) looked at hematocrit and other blood markers in a population of workers exposed for 5 to 7 years to 0.7 ppm 2BE. The workers had a significant decrease of hematocrit of about 3%. Nonetheless, this was still within the range of hematocrit in the population. In the table, the hematocrit, hemoglobin, RBC count and other parameters for males from the NHANES survey are reported. Keating calculated a BE exposure that would exceed the NHANES range this way: 0.7 ppm 2BE caused a 3% reduction in hematocrit in that worker

population. A 12% hematocrit reduction is required to fall out of the NHANES (2011-2012) range. Multiply 0.7 by 4 (12/3) to get a 2BE concentration of 2.8. Some in the NHANES range are likely anemic individuals. Patrick asked what the clinical hematocrit values are— Keating said 39 to 52 is the hematocrit range. The PEL recommendation is based upon the method using Haufroid: extrapolation of the human reference concentration and application of the uncertainty factor. The other calculation was for discussion.

Stelljes said the two methods verge to about the same number though coming at the problem from opposite directions.
Keating said currently we are at a PEL of 20 ppm with a new PEL recommendation for 5 ppm [for both chemicals].
Bates said 3% change is usually in the range of experimental error in many human studies. So 3% does not mean anything. Keating said he considered that and the controls don't show that variation. Bates asked if this was subject variation or something real. 3% is not a lot of change. A minimal change epidemiologically, particularly since the sample group was only 30. Keating suggested the variation Bates referred to was already accounted for by the range of hematocrit. Horowitz said the article's abstract states the 3% is statistically significant.
Bates said that had surprised him, as generally you would need a sample size of more than 30 in each group to demonstrate statistical significance. He questioned the statistics without seeing the original paper.

Keating said he would review this. The PEL estimate is spelled out on page 8. The second study doesn't detract but doesn't add much either. As Stelljes said, it is a different approach to estimate the number.
Bates said the range was 40.6 to 41.4. It seems not credible; the P value does not seem right to me, maybe a statistical error. I'd say the same for the other one, but not as strongly. Stelljes said it was surprising to him as well.
Keating said this will be reviewed. He said he could bring this issue back to the full committee or discuss with select members, or strike reference to the study in the document. But the questions do not fundamentally effect the recommendation of 5. The real basis of the PEL recommendation is benchmark dose model of rat data and applied uncertainty factor.

Bates said it was best to leave the study out, but he was happy to look at any paper. Keating said he would send it to him.

Erica Stewart said the PEL change might have a large impact for hospitals. Two studies by Bellows, at U Mass, Lowell, quantify exposures for 2BE used by hospitals in cleaning as ranging between 5 and 20 ppm.

Keating noted that EU REACH has extensive 2BE exposure scenarios. This document represents information for two chemicals, 2BE and 2BEA. Although they are toxicologically equivalent, we will have two separate PELs for the Title 8 Table AC-1.

For the purposes of discussion, we reviewed the alcohol (2-BE) because the acetate rapidly metabolizes to the alcohol. For California usage data, we have surveyed the CERS database. There 137 employers reporting 2BE usage and 135 reporting 2BEA usage. The CERS database reports the average daily amount of the chemicals. Some report use of both, and some cleansers use mixtures of both as an ingredient, but what struck me was the larger percentages of 2BEA in the products. Since the two are toxicologically equivalent, 2BEA is essentially exposure to 2-BE. I don't know if the 2BEA would be detected by the 2BE sampling method.

Unless further issues are raised, I would like to conclude further discussion of these two chemicals.

Bates asked about the reference to beryllium in the economic analysis section of the document. Beryllium is abbreviated BE, so this could be confused with 2BE.

Kevin Graulich said this was not a mistaken use of beryllium. Rather it was for comparison purposes with federal OSHA estimates of cost data for adherence to a new PEL in its beryllium rulemaking package.
Harrison supported the PEL recommendation and closure of discussion on 2BE and 2BEA. Forest seconded Harrison's support.

Lunch Break

After the break, Keating said this afternoon we will discuss prioritization of additional chemicals—we want to pick 10 a year from our list of 200. But first we'll talk about MIBK.

Methyl-isobutyl ketone (MIBK)

Keating said MIBK has over 1000 users in the CERS database. Like some other compounds, MIBK produces unique tumors in male rats attributed to alpha-2u-globulin (A2G). Chemicals that cause A2G in male rats operate via a well-documented mechanism and are not genotoxic. Tumors caused by A2G are considered not relevant to humans. There are a set of 7 criteria for determine the relevance of A2G to humans which are bolded in the handout. That is the point of today's discussion: how to assess chemicals on our list with differing levels of this evidence. How should they be brought to the committee and how much effort expended to evaluate this kind of evidence?

Stelljes said the EPA has done some of this evidentiary analysis and in depth review and determined that specific endpoint was not relevant for humans even though a chemical might have other effects that could be relevant. In all the IRIS (EPA's Integrated Risk Information System) reports I can recall, this particular endpoint for rats is omitted as a human endpoint.

Bob Nocco asked if gasoline was another example. Stelljes said yes, there are multiple examples.

Keating said he had not looked at it comprehensively. The MIBK draft circulated at the last meeting indicated that it does cause A2G. Tert-butyl acetate (TBAC) is a suspect A2G mechanism currently under review by IRIS and OEHHA. The two questions on MIBK are its neurotoxicity and the severity of the tumor formation via the A2G mechanism. On page 2 of the handout I suggest criteria to guide HEAC discussions: A2G, CPN/RTT dose response, other tumor sites, genotoxicity and mode of action. The occurrence of the A2G protein is the first necessary criteria. If the mechanism is acknowledged, other endpoints are evaluated —for example you can look for tumors in the female.

Harrison said that if your point is the effect in studies is unique to males, pathologists can make a determination.

Stelljes said you do not do the determination in a vacuum. There are other critical endpoints in the rat studies that can be used for risk assessment. Keating said a great deal depends on a proper assessment of A2G. Would a subcommittee working with me want to focus on this to look at each chemical's A2G effect on a case-by-case basis and decide yes or no if it is a relevant endpoint?

Stelljes says he agrees it has to be case-by-case determination utilizing the weight of evidence in each study but he thought the whole committee should weigh in. Keating said a subcommittee could relay its conclusions to the larger committee and let the larger committee decide. I'd like to work first with a few committee members. That would be my choice, but it would mean a little more advance effort for some subcommittee participants.

Cooper asked if the subcommittee would look at critical endpoints or was that one of several things that might be considered. Keating said sometimes it is the only critical endpoint. Forest said typically it's a carcinogen at

other sites. Stelljes said typically it is whether a chemical is a carcinogen or not.

Keating said that the A2G mechanism is carcinogenic in rats. In the case of TBAC, IRIS found the available data too nonspecific or conflicting to consider the tumors relevant to humans. OEHHA determined the A2G mechanism did not account for the rat tumors and therefore considered the tumors relevant to humans. Stelljes said that kind of decision bothers him when the weight of evidence is negative and then you take the one positive study and go with that. I'd like to see a more objective evaluation of this data.

Keating said in the table in the handout, limonene is a classic A2G carcinogen. Incidence, severity and the tumors increase with dose, which you would expect. You see the tumors show up in males but no response in females. The next case is TCP. It doesn't have that dose response but it has the highest kidney tumors of any chemical in the table. It is not an A2G carcinogen, but is genotoxic. The other chemicals we will consider are TBAC, MIBK, benzyl quinone, chloroprene, benzophenone, furfural alcohol. Keating said that while genotoxicity is important evidence, there are other mechanisms of carcinogenicity. I rely on IRIS, OEHHA and other agency carcinogenicity determinations.

Stelljes said an example of a chemical with very good IRIS summary is chloroform which has a threshold of carcinogenicity. Below a certain dose, there is none, but above that, cancer appears. Chloroform is the only chemical I am aware of that is regulated both ways based upon concentration, as a carcinogen and a non-carcinogen. It's not an A2G mechanism, but in terms of evaluating the weight of evidence for determining if a chemical is a non-genotoxic carcinogen, it's a good example.

Keating said he will continue working on PEL derivation for MIBK, which is in progress, and TBAC, which is on our P-1 list but I'd like to involve subcommittees on some of these key questions.

Bates asked if the example involved strain-specific exposures and results.

Keating said the Fischer rat was used for testing of chemicals for RTT. Stelljes said he wasn't sure, and would have to go back and look. Keating said it was definitely a well-established mechanism in at least one of the four or five strains of Fischer rat generally used for these tests.

Kent Pinkerton asked if the tumors appeared after a long period of time. Stelljes said these are NTP-type, two-year lifetime exposure studies. Keating said what is unique about A2G is that it does not occur in female rats. It occurs within weeks of exposure, triggering irritation and hyperproliferation that suggests a non-genotoxic process. You have to look for A2G early, and then track the kidney pathology. Some studies will only have the two-year data and have suggestive pathology but won't have sufficient A2G proof. Going forward I want to evaluate this with MIBK and TBAC and will update HEAC at the next meeting.

Pinkerton said Keating asked about Alan Buckpitt at UC Davis; I could contact him.

Keating said Buckpitt had questions about oxidative damage by TBAC. He certainly has an understanding of the method and data that I don't have.

Harrison supported the proposal going forward but wanted a reminder on how chemicals got on the P1 and P2 priority lists—what was the criteria.

Keating said the criteria were difference between the PEL and TLV, usage, certain health endpoints, HESIS recommendations, and some chemicals were inherited.

Saeher Muzaffar explained the HESIS draft PEL for TBAC based upon excess cancer risk. The current PEL is 200. For a 1/1000 risk, the PEL would be 0.8 ppm, while a 1/10000 risk works out to be 0.08 ppm. OEHHA found that TBAC did not meet the A2G carcinogenicity test. Stelljes asked if OEHHA had looked at non-cancer endpoints.

Keating replied that with TBAC, IRIS did use other endpoints, like kidney weight. IRIS did not use the rat data. The TBAC work in progress, but I will define these two chemicals, with again, any volunteers from the committee.

Prioritization

Keating said there are over 400 chemicals in Title 8, some half of which may need review of their PELs. Manganese and aluminum are off the list now. Today BEA will come off. That opens space for chemicals to be elevated. I sent the list to committee members to solicit suggestions. There are four on the list we haven't started yet. The right hand column of the list compares the PELs to the current TLVs. Keating also discussed the status of the work on H2S, and peracetic acid. As a general rule, chemicals whose current PELs are 10 or more times the current TLV are good candidates for addition to the Priority 1 list. In addition, the chemicals on the current list marked 2 with no existing PELs are good candidates to be added to the P1 list. [The committee then reviewed pages 7 and 8 of the prioritization handout. Keating explained the columns and notations in the tables on those pages.] We can proceed with P1 as listed, Keating said.

Muzaffar next explained the HESIS position on chemical prioritization as presented in their risk prioritization handout. HESIS recommendations are risk-based. Many don't have PELs, and many are derived from Proposition 65 listings. Several of HESIS recommendations from last year were adopted by HEAC. Four new chemicals are recommended for this year. HESIS first looked at 81 chemicals this year, narrowed the candidate chemicals to 28, then 21, and then finally selected the four listed on the back page of the handout.

--Parachlorobenzotriflouride (PCBTF) is the first one. There is a recent NTP study indicating a concern for cancer in rats and mice. There are also liver, lung and reproductive concerns. The CERS database shows usage at 30,000 gallons per day with 1700 listed locations of use. It is often used in auto body shops. One SDS suggested an appropriate OEL would be 20 ppm.
--Diesel exhaust is a lung cancer concern
--Di-isodecyl phthalate (DIDP) is a plasticizer for polyvinyl chloride, especially in wire and cable applications. It is also used as a lubricant and in paints and coatings.
--leather dust

Stelljes asked, since DIDP is a phthalate, doesn't it belong to the broader phthalate community of chemicals that we list as needing to be developed by a special committee? Keating said it could still be separately evaluated; it didn't have to be evaluated as a member of a chemical class. Muzaffar noted that the Consumer Product Safety Commission has performed a lot of review of DIDP.

Owens asked if the leather dust listing correlated with a risk for skin exposure and health effects.
Keating commented that the HESIS list chemicals don't have PELs. He said former HEAC member Linda Morse had pointed to NIOSH studies of airborne phthalate exposures.

Harrison said that if he had to vote for one chemical, it would be diesel, hands down. Epidemiological and toxicological evidence is enormous. We won't have trouble finding the literature. Kirkham noted that MSHA (US Mine Safety and Health Administration) has one for underground miners. Forest asked how MSHA measures it. Kirkham said it was measured as elemental carbon. Harrison said developing a diesel PEL would be path breaking and a lot of work.

Harvard Fong said the Department of Pesticide Regulations had reviewed the priority list. We suggest that agricultural chemicals within DPR jurisdiction that are no longer in used in California like parathion should be dropped from the list. Other chemicals that remain in agricultural use, should be moved to a lower priority. DPR has a unit evaluating health effects of those agricultural chemicals still in use. Keating agreed to go through the list and follow this DPR recommendation. Fong acknowledged there are some chemicals like sulfur dioxide that have dual agricultural and non-agricultural uses. Keating said we would keep that in mind and make a determination ourselves.

Stuart Holm asked about turpentine, which has been mentioned as a possible P1 chemical. Is it gum turpentine, wood turpentine or mineral turpentine? Keating said he would have to look at the CAS number. Holm said the wood and paper industries makes a lot of turpentine—so much you wouldn't believe. It's a base chemical for a lot of things. Keating said there is animal data on irritation effects. It's also a sensitizer. I'm not anticipating a large toxicology review for turpentine. Stelljes said the handout says there are 98 CERS users of turpentine, 154 reports. Keating said he would look into turpentine and phthalate reports.

Harrison said we haven't systematically gone through the inhalation sensitizers. For example, phthalates clearly cause work related asthma. Holms mentioned that there were two Consumer Product Safety Commission reports on phthalates. Keating said we don't have to do turpentine singly but could do it with the chemical class. Harrison said that's just another approach; there are about 250 sensitizers. Years ago we matched these 250 chemicals with their PELs and determined which ones did not have an adjustment for the evidence of work related asthma. We then prioritized those based upon their potential for occupational exposure. We did this about ten years ago with Steve Smith, with the Sensitizing Committee. You must have the list. Keating said we could bring these back next meeting or discuss off line. So unless there is other input, we will stay with turpentine, sulfur dioxide (SO2), benzophenone, TBAC. Two possible 2018 ACGIH TLV adoptions relate to updating our STELs. Chlorine gas and butane. Looking at these would be more of an update than a full review.

Cooper said we have a long list. Is the idea to put a list out there that says 2018? Keating said exactly, as Priority 1. One purpose of the list is to alert stakeholders what is coming to HEAC, what will likely be reviewed by HEAC in the next 12 months.

Forest asked what the reason is for prioritizing the HESIS recommended PCBTF for P-1. Likely carcinogen? Keating said yes, there is a lot of cancer data for PCBTF and it's a VOC. Forest added it is near the top of the CERS list. Muzaffar said HESIS would be evaluating PCBTF and would be developing an estimate for a PEL.

Cooper asked for the updated P-1 list to be put on one piece of paper separate from the full list of lower prioritized chemicals. Keating said that was the last agenda item. Any other concerns?

Bates said he sometimes has difficulty reading through the list of summarized studies on the committee draft documents. I would like to see a clear separation between the toxicology and the epidemiology. Often they are co-mingled. I'd also like to see a summary table of key features, one line that summarizes the study. And a different summary table for toxicology and epidemiology. Stelljes agreed. Summary tables are used in the ATSDR Tox Profiles. A one-line summary for each key study. A LOAEL, a NOAEL, what's the endpoint. So you don't have to read through all the different paragraphs to find what you need. Bates said otherwise you have to keep things in your head, reading from one to the other to the other. You can see which study you should focus on if you have a summary table. Stelljes agreed that separating epidemiology and toxicology in separate tables is a good idea. Bates said there are many models of summary tables that could be adopted as templates. We don't have to stick to them rigidly. But they're very helpful to see key features on one page. Bates said he could provide a suggested template for epi studies. You still need the narrative sections as well. The table brings it all

together.
Stelljes said many benchmark dose studies really rely upon summary tables. Cooper said do the tables for something current, like H2S. Bates said maybe you will have to have different tables for different health effects. Don't rewrite existing documents, just insert tables. Stelljes said that's sort of the approach he is suggesting for revising existing documents. You could look at summary documents prepared by Julia Quint for the last HEAC committee for good examples.

Muzaffar noted the NIOSH REL for carbon nanotubes. Cooper said recent information on potential health effects from titanium dioxide nanoparticle exposure from 3D printing is also relevant. Keating said with functionalized nanoparticles the question about toxicity is difficult. Is it the particle or the attached substance?
Stelljes said its complex. Maybe both aspects contribute.

Stewart wondered if surface area or weight was more significant for causing toxic effects.
Stelljes said the surface area of the particles is important. Sometimes the surface is designed to protect the stuff inside until it gets where it's supposed to go. Then the outer compartment separates. So there are two sets of particles, the outer chemical, and then you've got the actual target compound inside. Both could have their own effects. Quite complex.

Owens said that solubility, especially in the case of engineered metal nanoparticles, is a big factor in the toxicity of the nanoparticle. But there is not a lot of epidemiology showing occupational exposure. Toxicologically, however, we can determine the effects of solubility, surface, electric charge and number (density).
Stelljes said another toxic effect can be heat of reaction at the reaction sites, but I agree.
Pinkerton said that carbon nanotubes were fibrous, but not as toxic as asbestos. A factor in toxicity of carbon nanotubes is how much aerosolization of the fibers occurs.

Stelljes said it was premature to consider carbon nanotubes for a priority this year.

The committee next discussed dates for the next meeting, settling on June 5th, 2018. The meeting adjourned at 4:12 pm.