DRAFT MEETING SUMMARY

Second Meeting of the Health Expert Advisory Committee (HEAC) for Development of Permissible Exposure Limits for Airborne Contaminants in the Workplace California Code of Regulations, Title 8, Section 5155

November 2, 2007
Elihu Harris State Building
1515 Clay Street
Oakland, California

HEAC Members in attendance

Mike	Cooper	Exponent
Will	Forest	Santa Cruz County Public Health Dept.
Michael	Kleinman	U.C. Irvine
Bob	Ku	SafeBridge Consultants
Patrick	Owens	Shell Oil Martinez Refinery
Patty	Quinlan	UCSF Occupational Health Clinic
Julia	Quint	Independent
Susan	Ripple	Dow Chemical Company
Mark	Stelljes	SLR International
James	Unmack	Unmack Corporation

Public and Interested Party attendees

Heather	Borman	State Compensation Insurance Fund
Juli	Broyles	California Advocates
Steve	Derman	MediShare
Dan	Leacox	Greenberg Traurig law firm
Barbara	Materna	Occupational Health Branch Calif. Dept of Public Health
Marcie	McLean	Retired
Jane	Murphy	Phylmar Regulatory Roundtable
Dan	Napier	DNA Industrial Hygiene
Olivera	Radovanovic	Unmack Everett Environmental
John	Sacco	CalPASC, CCMCA, AGC of CA, MIA, CCNSIG
Dennis	Shusterman	HESIS

Cal/OSHA Staff

Bob Barish (meeting chair), Steve Smith, Tom Mitchell, Bob Nakamura, Mike Horowitz

Meeting Summary

Bob Barish opened the meeting by welcoming HEAC members and interested parties. The agenda for the meeting was reviewed and everyone in the room introduced themselves. Bob Barish asked if there were any comments on the draft minutes for the first HEAC meeting held August 21, 2007. One attendee noted that the minutes had only recently been posted and so asked for more time to review and comment on them. Bob Barish said that there was no specific time limit for correcting or clarifying the minutes, but that if possible, comments should be sent to him by the end of November.

Bob Barish reviewed the substances that would be the subject of the day's discussion: dichloroacetic acid, hydrogen fluoride, n-methyl pyrrolidone, and hydrogen chloride if time.

Dichloroacetic acid

HEAC member Susan Ripple presented her review of dichloroacetic acid (DCA). She said that since dichloroacetic acid is used as a therapeutic agent it's acute effects are well-studied in humans. She noted that DCA has also been of interest to the public health community because it is generated in drinking water as a byproduct of chlorination.

Susan referred to the assessment template document she had constructed, reviewing the basis for the ACGIH TLV of 0.5 ppm (8-hour TWA) and the U.S. EPA non-cancer reference dose calculation. Susan said that DCA had been found to induce liver cancer in mouse drinking water studies, but that IARC and ACGIH had not classified it as a human carcinogen. Her assessment document for DCA suggested that although several agencies have assessed the risk of cancer, the most current review by EPA IRIS review 2004 states that there is unknown risk of cancer in humans, even though IARC 2004 designated it as possibly carcinogenic to humans (Group 2B). She suggested therefore that it would be inappropriate to recommend a PEL based on the cancer endpoint when there is not a clear threshold in humans.

Julia Quint thanked Susan Ripple for the thorough job she'd done on the assessment document, but said she thought that the PEL for DCA should address cancer risk since it is on the Proposition 65 list as being "known to the State of California to cause cancer," is given a 2B classification by IARC as "Possibly carcinogenic to humans," and the EPA IRIS document discusses evidence of carcinogenicity.

Mark Stelljes asked if OEHHA had published a cancer slope factor for DCA. Sara Hoover said that OEHHA is currently working on a cancer slope factor for DCA for purposes of developing a Public Health Goal (PHG) for drinking water. Julia Quint said the EPA IRIS document assessment contained a cancer slope factor that could be used. Sara Hoover said that OEHHA is evaluating the DeAngelo (1999) cancer bioassay in male mice, which is the same one that was used in the U.S. EPA document, for use in the risk assessment being conducted under the PHG program. She noted further that OEHHA applies risk assessment methodology that is very similar to that of U.S. EPA, so she considered it likely that the slope factor that OEHHA derives will be consistent with U.S. EPA. Julia Quint suggested that the Committee use the U.S. EPA cancer slope factor noted in Susan Ripple's document to calculate cancer risk for DCA.

There was discussion of how to apply cancer risk assessments in PEL development. Julia Quint noted this has been a frequent issue in Cal/OSHA PEL development work over the years. She noted the committee working in

1997 developed a policy statement indicating that the PELs did not address cancer risk assessment. *(**NOTE 1**: A copy of this statement from the Initial Statement of Reasons for a previous 5155 rulemaking is provided at the end of these minutes.)*

Julia Quint said that even if Cal/OSHA did not adopt a PEL based on cancer risk, where it has been recognized by an agency such as EPA or OEHHA, or on a list such as Proposition 65, it would seem appropriate to at least have a footnote stating that the chemical is a carcinogen, as was done in 2006 for glutaraldehyde. Julia Quint and others said that EPA, IARC, and OEHHA all follow the same approach to evaluating the carcinogenicity of chemicals, with ACGIH as the outlier by comparison.

Bob Ku expressed concern with how to adopt a PEL based on prevention of cancer as opposed to noncancer effects. He noted that ACGIH for DCA did assign an A3 designation (Confirmed Animal Carcinogen with Unknown Relevance to Humans).

There was then discussion about how to calculate the exposure level associated with a 1 in 1,000 cancer risk level based on the oral cancer slope factor of U.S. EPA. Sara Hoover went to the whiteboard and showed one method for how to use the slope factor to estimate the cancer risk associated with the ACGIH TLV for DCA of 0.5 ppm.

She said the U.S. EPA oral slope factor is 0.05 $(mg/kg\text{-}day)^{-1}$. To derive a unit risk factor from an oral slope factor, a default approach that is often applied is:

$0.05\ (mg/kg\text{-}day)^{-1} \times 20\ m^3/day \times 1/70\ kg = 0.014\ (mg/m^3)^{-1}$

To estimate the cancer risk associated with the TLV of 0.5 ppm (which was reported by ACGIH to be equal to 2.6 mg/m^3), the following approach which accounts for a worker exposure scenario can be taken:

$2.6\ mg/m^3 \times 0.014\ (mg/m^3)^{-1} \times 8\ hr/24\ hr \times 5\ d/7\ d \times 50\ wk/52\ wk \times 40\ yr/70\ yr$

The above approach produces a cancer risk of 0.00485, or approximately 5 excess cancer cases in 1,000 exposed workers.

If the worker is assumed to have a heavier breathing rate, the calculation would be as follows:

$2.6\ mg/m^3 \times 0.014\ (mg/m^3)^{-1} \times 10\ m^3/20\ m^3 \times 5\ d/7\ d \times 50\ wk/52\ wk \times 40\ yr/70\ yr$

With the heavier breathing rate, the cancer risk increases to 0.00729, or approximately 7 excess cancer cases in 1,000 exposed workers.

So, if a TLV of 0.5 ppm yields a cancer risk of 5 in 1,000 or 7 in 1,000 then a PEL associated with a cancer risk of 1 in 1,000 would be either 0.1 ppm or 0.07 ppm, depending on whether the heavier breathing rate for workers is used.

Sara Hoover noted that this default approach for using an oral slope factor to estimate cancer risks associated with the inhalation route does not take into account potential differences between the oral and inhalation routes of exposure. For example, a simple pharmacokinetic difference that could be considered is the absorption rate by each route. If the absorption rate by the oral route was 100% for DCA, but the absorption rate for the inhalation route was only 50%, the risks reported above would be lowered by 50%. She recommended that these issues be reviewed for the DCA case.

Sara Hoover noted further that current methodology for cancer risk assessment does not typically account for

sensitive subpopulations as is done in non-cancer risk assessments, so the only adjustment needed in using a cancer slope factor or unit risk value from OEHHA or U.S. EPA is to adjust for worker exposures appropriately.

Mike Cooper suggested that 0.1 ppm for 1/1,000 increased risk is a number that is reasonably close to Susan Ripple's initial suggestion of 0.5 ppm which is the ACGIH TLV. Patty Quinlan said that if the cancer data and quantitative risk assessment is available they should be used and the resulting number looked at as a possible PEL recommendation. Susan Ripple questioned whether a PEL should be set on an endpoint (in this case cancer) for which there is not any human data. Dan Leacox said he was concerned that a single number recommendation would not adequately communicate the uncertainty inherent in the recommendation.

Dan Napier said it is important to look at the biopersistence in the human body of the substances being considered. Sara Hoover said that trying to take this factor into account involves pharmacokinetic modeling. She thought it likely that there would be insufficient data to assess the pharmacokinetics of DCA, and that doing pharmacokinetic modeling would be beyond the resources of the Committee. Dan Napier suggested that the assessment template document for each substance should at least address if such data was found.

Jim Unmack questioned the use of the U.S. EPA cancer oral slope factor of 0.05 since it appeared to be rounded up from a smaller number. Sara Hoover said that U.S. EPA slope factors are only expressed to one significant figure whereas OEHHA goes to two significant figures in its published slope factors.

Bob Ku suggested that application of a safety factor of 300 to the non-cancer LOAEL of Cicmanec (1991) yielded a value almost identical to the 0.1 ppm calculated above based on cancer risk.

Sara Hoover said that it might be worth applying the OEHHA noncancer risk assessment approach to DCA to see if it produces a similar result.

HESIS item

Barabara Materna, Chief of the Occupational Health Branch in the California Department of Public Health, introduced Dennis Shusterman, an occupational physician, as the new Chief of HESIS. He replaces Julia Quint who recently retired from HESIS.

LUNCH BREAK

After the lunch break Sara Hoover noted that differences in absorption between oral administration and inhalation can be taken into account with adjustment factors if appropriate data are available. Based on her technical assistance to Cal/OSHA on the proposed PEL for methyl methacrylate during the last 5155 PEL update process, Julia Quint commented on the importance of applying pharmacokinetic data in the assessments when it is available and of good quality.

Hydrogen Fluoride

Mike Cooper presented the assessment document for hydrogen fluoride (HF). He and Richard Cohen who was not able to attend the meeting were the team for HF.

Mike Cooper said that, as indicated in the assessment document, the basis for lowering the TLV in 2005 was the study of Lund (1999), based on an increase of CD3 cells in bronchioalveolar lavage fluid taken from human

subjects after inhalation of HF. He said that an increase of CD3 cells indicates an inflammatory response and that with a LOAEL in the study at approximately 0.7 ppm, the TLV was set at 0.5 ppm as an 8-hour TWA.

Mike Cooper went on to note that OEHHA established an acute Reference Exposure Level (A-REL) for HF of 0.3 ppm based primarily on the one-hour exposure study of Lund (1997). He said that a value of 2 ppm Ceiling would be near or below most of the LOAEL levels for irritation observed in a number of studies noted in the assessment document.

He said that OEHHA established a chronic inhalation REL (C-REL) of 0.04 ppm based on the study of Derryberry (1963) of workers in a fertilizer plant. Mike Cooper noted, and there was discussion of, the question of the clinical significance of the findings of the health effects noted in the Derryberry study. He suggested that with uncertainty about the significance of the effects noted in the Derryberry study, he and Richard Cohen applied an intraspecies uncertainty factor of 3, rather than the 10 used by OEHHA, resulting in a possible PEL recommendation of 0.4 ppm (8-hour TWA), close to the TLV of 0.5 ppm.

Based on the above, the assessment of Mike Cooper and Richard Cohen made an initial recommendation for a revised PEL for HF of 0.5 ppm 8-hour TWA, and a STEL of 2 ppm.

Julia Quint said that the 8-hour TLV of 0.5 ppm was very close to the LOAEL in Lund (1999) of 0.7 ppm, and so might be too high for the PEL. Dennis Shusterman said that colleagues at the University of Washington had done some related research and he would provide the reference to Mike Cooper. With regard to the clinical significance of increased CD-3 cells in bronchiolar lavage, as well as the effects in Derryberry, Mark Stelljes said it is important to differentiate between Lowest Observed Adverse Effect Level (LOAEL) and Lowest Observed Effect Level (LOEL). There was general agreement that the committee should be working from LOAEL's, ie adverse effect levels, and not simply levels causing any measurable effect even if not potentially harmful.

Bob Ku asked about details of Lund (1999) and (1997) studies, including exposure durations of the test subjects. Julia Quint asked Mike Cooper how the suggestion for a STEL of 2 ppm was reached. She also asked about the exposure times in the studies on which the STEL recommendation was based.

Mike Cooper responded that the existing Cal/OSHA STEL of 6 ppm is clearly too high based on studies noted in the assessment document. He said it was less clear exactly where the STEL should be set. Will Forest said it appeared a STEL of 2ppm would exceed the LOAEL values for acute effects in several of the studies cited in the assessment.

There was discussion about the need for a STEL for HF. Mike Cooper noted most of the acid gasses with PELs have STEL or Ceiling values. Susan Ripple said that STEL and Ceiling values are important to protect against irritant effects. Dennis Shusterman said a STEL can be important to protect against severe short-term effects. Sara Hoover and Dennis Shusterman noted the difficulty of converting from 1 hour exposures to a 15-minute PEL STEL. There ensued discussion of the exact exposure durations and effect measurement sequences in the studies used to suggest the STEL. There was agreement that the exposure durations on which the STEL suggestion was based should be clarified in the assessment document.

Julia Quint suggested focusing the rationale for the full-shift PEL on the findings of Lund (1999). She thought that the subclinical findings of Derrberry (1963) should not be a significant part of the rationale for the suggested PEL. She suggested further that the assessment document should clarify the clinical significance of the finding of increase in CD3 cells in bronchiolar lavage after exposure to HF. Sara Hoover noted that whereas Derrberry (1963) contained a NOAEL, in Lund (1999) there was an effect seen at the lowest level of exposure thus yielding a LOAEL. Bob Ku noted that the exposures in Lund (1999) were short term but that the study results were being used to provide the basis for a full-shift exposure limit. Julia Quint said that if the increase in CD3 cells in Lund

(1999) is clinically significant it suggests the 0.5 ppm suggested PEL may not be adequately protective.

Sara Hoover asked if a complete literature search had been done on HF? Mike Cooper said that it had, that he and

Sara Hoover asked if a complete literature search had been done on HF? Mike Cooper that he and Richard Cohen had done literature searches in both ExPUBs and Micromedex Tomes. Approximately 40 studies were deemed relevant from this search and these were used in the assessment. Susan Ripple asked if the draft assessment document for HF listed all of the references obtained and looked at. Mark Stelljes suggested that assessment documents should list all studies obtained and reviewed even if they are not used as the basis or support for the PEL recommended or other conclusions reached.

N-Methyl Pyrrolidone (NMP)

Julia Quint presented her assessment document for N-methyl pyrrolidone. She noted that this chemical is sold commercially in a number of different forms (eg. pastes, gels, sprays etc.) and that it has a diverse and growing number of uses including paint stripping, cleaning in the electronics industry, as a pesticide carrier and for graffiti removal. She said there is no ACGIH TLV for n-methyl pyrrolidone but there is an AIHA WEEL (Workplace Environmental Exposure Level Guide) of 10 ppm as an 8-hour TWA. She said the WEEL document focused on four studies which they concluded suggested a NOAEL of 100 ppm. It was unclear, however, whether the WEEL of 10 ppm for NMP was based on applying a safety factor of 10 to the 100 ppm NOAEL since this was not specified in the document. Based on information presented in the WEEL document, she concluded that the four studies generated NOAELs of 90 ppm and 50 ppm, and LOALs of .150 ppm and 165 ppm. She said the basis for the recommendation was not entirely clear to her from reading the WEEL document. Susan Ripple who is a member of the WEEL Committee said the 10 ppm WEEL was based on the committee's judgement rather than a formal risk assessment. She said the WEEL Committee is currently reviewing its process for making exposure level recommendations.

Julia Quint referred to page 4 of the draft assessment document for her calculation of a recommended PEL of 1 ppm based on a NOAEL of 50 ppm in Solomon et al. (1995), one of the studies reviewed in the WEEL document. She said she applied the risk assessment procedure published in the OEHHA guideline for non-cancer risk assessment (http://www.oehha.ca.gov/air/chronic_rels/pdf/relsP32k.pdf), made adjustments for occupational versus environmental exposure, and used safety factors of 3 for interspecies uncertainty and 10 for intraspecies variability, yielding a recommended PEL of 1 ppm.

Mark Stelljes asked about the reference to Federal OSHA at the top of page 3 in the draft NMP assessment document regarding uncertainty factors. Julia Quint said it referred to a statement in the Federal Register detailing Federal OSHA's approach to a risk assessment done for glycol ethers (the Federal Register reference is listed in the draft assessment document). Julia Quint said she tried to use an approach to the assessment consistent with that used or adopted by other relevant agencies. She pointed out that the 10-fold safety factor for intraspecies variability was consistent with the approach used by Federal OSHA in their quantitative risk assessment for the proposed glycol ether standard.

Julia Quint said that because NMP is relatively non-volatile and is easily absorbed through the skin the PEL should include a requirement for biological monitoring. She noted that ACGIH had adopted a Biological Exposure Index (BEI) based on the AIHA WEEL of 10 ppm, but she had not recommended a particular biological exposure limit in the assessment document.

Mark Stelljes noted from page 2 of the draft assessment that no US regulatory agency had adopted an occupational exposure limit for NMP. Mark Stelljes also said that only Japan in the list of countries on page 2 of the draft assessment document had a limit as low as the 1 ppm suggested in Julia Quint's assessment. He said he didn't want to end up with Cal/OSHA having PELs that would be consistently and significantly less than those in other countries. Julia Quint responded that she had no information on the scientific basis of the NMP PELs developed by the other countries, nor the dates of their adoption. She said also that the goal of the HEAC was to recommend health-based PELs derived from scientific evaluations of the data. Sara Hoover noted that recommendations of HEAC are not PELs but rather the committee's recommendation for the health based level that the Division will then put through the risk management phase of the process. Therefore she said HEAC recommendations should not be compared with PELs of other countries which have presumably been through the risk assessment process.

Bob Ku asked Julia Quint about the toxicology studies on NMP on which she based her calculations if they involved whole body or nose only exposure, in light of the fact that NMP can be readily absorbed as a vapor through intact skin. Julia Quint produced a copy of the study, noted that NMP vapor was administered to the test animals in a chamber, and provided a copy to Bob Ku for further review

There was extensive discussion of additional details of the studies referred to in Julia Quint's assessment document for NMP. There was also discussion about the idea of establishing a biological exposure limit as ACGIH had done in order to enable assessment and control of skin exposures. Susan Ripple asked if there is a precedent in Cal/OSHA regulations for biological monitoring requirements. Julia Quint said that the comprehensive standards for a number of substances including lead and methylene chloride contain requirements for biological monitoring triggered by airborne action levels. She noted that she did not recommend a specific biological exposure limit but suggested that one be set to control the exposure dose based upon the PEL decided upon, analogous to the approach taken by ACGIH which set their BEI based upon the AIHA WEEL of 10 ppm.

Mike Cooper noted that Julia Quint's assessment did not include data on effects from human studies. Julia Quint responded that there have not been any epidemiologic studies to date on the reproductive effects of NMP which appears to be the most sensitive endpoint. She noted that all of the metabolic processes relevant to NMP that are seen in animal studies also occur in humans. Will Forest noted that very few epidemiologic studies have been done on multi-generational developmental and reproductive effects of chemicals because of their difficulty and expense. Susan Ripple said that there is uncertainty about the similarity of the gestation process in humans and test animals so it is necessary to make conservative assumptions in determining the health-based recommendation.

Conclusion

Bob Barish said that for the first meeting of this newly formed committee for PELs he was very impressed with the presentations and the discussion.

There was discussion of planning for the January 29, 2008 meeting, for which four new substances were scheduled for discussion. There was general agreement by committee members that on January 28 the first item of business should be follow-on to today's discussion. There was agreement that the presenters of today's substances would work on modifying their assessment documents in light of the day's discussion in preparation for further consideration and possible ratification at the January 29 meeting. It was also agreed that hydrogen chloride scheduled to be presented at today's meeting would be postponed for its initial presentation January 29, and that of the four substances originally scheduled for presentation at that meeting only sulfuric acid, and toluene if time, would have their initial presentation.

Patty Quinlan and Jane Murphy also asked to have an update at the next meeting on the list of substances to be considered in this round of PEL development.

Mark Stelljes said that he was encouraged by the day's meeting in terms of working out how committee members will work through substances in future meetings. He was optimistic that the process would go more smoothly as time and practice with work on individual substances progressed.

Bob Barish said the next meeting after January was tentatively planned for mid to late April. He thanked the presenters for their work on the individual substances discussed and all in attendance for their participation and adjourned the meeting.

END

***NOTE 1*:**

Cal/OSHA PEL Advisory Committee 1997 Carcinogen Position Statement and preceeding explanation from Initial Statement of Reasons for 8 CCR 5155 rulemaking with Cal/OSHA Standards Board public hearing on May 11, 2000:

http://www.dir.ca.gov/oshsb/aircontaminant2.html **Initial Statement of Reasons**
http://www.dir.ca.gov/oshsb/aircontaminant0.html **Rulemaking web page for May 11, 2000 hearing**

In many cases the Committee's recommendations agreed with the rationale and limits set by the ACGIH, in other cases the Committee made recommendations not in agreement with the ACGIH limits, and in some cases the Committee used a different basis than that used by the ACGIH. The Committee's recommendations were made on the basis of consensus of opinion of the members. The Committee spent a considerable amount of time during Committee meetings discussing a class of substances regulated by Section 5155 which are considered by other authoritative bodies such as the World Health Organization's International Agency for Research on Cancer as suspect or actual human carcinogens. The Committee members wanted it made clear that the recommendations they were making should not be assumed to adequately control this aspect of risk for many of the substances considered. Summaries of the discussion of this issue can be found in the Committee meeting minutes on the following dates 9/15/97, 9/29/97, and 11/07/97. The Committee stated its position on this issue in the following statement:

The Airborne Contaminants Advisory Committee
carcinogen position statement

This substance has been identified by the International Agency for Research on Cancer as a carcinogen (Group 2B or higher). The exposure limits recommended have been primarily set on the basis of other types of toxic results, damage or interference with organ systems, irritation, respiratory problems, etc. Quantitative risk assessments can be used to estimate risks of cancer at various exposure levels in order to set a Permissible Exposure Limit. No such risk assessments have been conducted by this committee. Currently, neither the Division of Occupational Safety and Health nor the Occupational Safety and Health Standards Board have standard methods for performing these assessments or a useful criterion against which limits might be set. Cal/OSHA should reconsider the Permissible Exposure Limit proposed here if such a carcinogen guideline policy is adopted and appropriate resources can be allocated for an occupational risk assessment for this substance.