Airborne Contaminants Advisory Committee

Draft 2001 to 2004 Minutes

May 4, 2001 Meeting

Attendees: Carl Foreman, Rick Kelly, Dagmar Fung, Craig Steinmaus, Mike Cooper, Richard Cohen, Patricia Quinlan, Jeff Jones, Will Forest, Bruce Wallace, Bob Nakamura.

Bruce Wallace welcomed those attending and called the meeting to order. He noted that Stephen Gomez was not able to attend due to a family emergency, and Allan Smith is out of the country. He asked everyone to introduce themselves.

Bruce W. gave an overview of the history of the "5155" Committee which was started in the mid-70's. Jeff Jones added that in the early 80's the intent was to convene every two or three years as needed to review the ACGIH changes. At that time, there was little comprehensive review of the data or ACGIH documentation, it was mostly a summary adoption or rejection of the listed items. The TLVs were viewed as the industry standards, and considered on that basis. In the 90's there was much more of a focus on reviewing the background information.

Bruce W. continued with the general goals and expectations for these meetings. The primary goal is to propose changes to the Board that will best promote the health and safety of California employees. The expectations are that the committee follows a democratic process and that the views expressed and recommendations made be those of the members.

Bruce W. gave an overview of the rulemaking process as differing from Federal rulemaking. In California, there is an independent Standards Board that adopts standards on the basis of proposals developed by the Board staff itself for many safety issues, or by the Division (DOSH) for occupational health issues. Before Cal/OSHA there was a Division of Industrial Safety in the Dept. of Industrial Relations, and an Occupational Health Branch in the State Health Department. 1980, or so, the industrial hygienists in OHB were transferred into DOSH. They were the main occupational health resource in the program, and consequently, the Division has had the responsibility for occupational health standards development.

The rulemaking process starts with a proposal, developed in this case with and advisory committee, along with a rationale for the recommended changes. The Division staff will convert this into the specific rulemaking documents such as the Informative Digest, which describes the changes and the effect of the changes. An Initial Statement of Reasons is also developed, which states the purpose of the changes and the reasons that the changes are necessary to achieve that purpose. The Standards Board staff reviews these documents for conformance with code requirements and sends them to the Office of Administrative Law and formally publishes a public notice. This is the start of the 45-day public comment period. A public hearing is normally held near the end of the period. All comments received are responded to by explaining why a change to the proposal is not necessary, or describing the change, which will be made in response to the comment. A substantive change requires an additional 15-day comment period followed by a response to additional comments received. Richard Cohen asked what a substantive change would be. Bruce W. answered that it would be based on how much it differed from the description of the proposal in the Informative Digest. In the worst case, very extensive changes would require that the whole process be restarted. Mike Cooper asked if the records from the last rulemaking for 5155 are available. Bruce W. replied that he would send him the relevant documents.

Richard C. asked how this committee's work would be sent to notice, and what was the impetus for convening this committee? Bruce W. replied that there is a California Labor Code provision that directs the Division to evaluate hazards, develop and propose health standards regardless of Federal OSHA activity. Jeff J. asked if there were substances on the last list that were not reviewed or completed, which were on this new list. Bruce W. replied that there might be, but only if the ACGIH had a recent change for it.

Bruce W. continued with describing the committee organization of the last committee. The last committee rotated the chairman between members. The Chairman's responsibility was to coordinate the agenda with Bruce W. and run the meeting. No one objected to this approach.

There was a general discussion of publishing announcements for meetings and status on the committee as member or observer/interested party (voting or nonvoting). Richard C. described in detail the process of dividing

the work that was followed by the last committee. There were teams of two members who did the review and research for a part of the list. This avoided the whole group having to try to prioritize the entire list. Will Forest discussed the role of HESIS. They have a continuing contract with the UC library that provides a lot of research capability. They also expect to have an epidemiologist on staff soon. Dr. Cone is also available to provide some assistance but he has other duties too, as chief of OHB. The HESIS chief is Julia Quint, who is a toxicologist. Their mandate is to conduct research and make recommendations concerning occupational health issues to Cal/OSHA. During the last committee process, they were able to find current literature on specific items that the committee identified to try to set a no effect level. He would be able to provide similar support for this committee. Jeff J. added that HESIS took the role of filling gaps in the ACGIH content and conclusions where data was lacking. Bruce W. noted that had been considerable difficulty getting some of the reference papers in the ACGIH documents in the last round. Mike Cooper asked if there were attempts to get data from corporations that should have a lot of data. Bruce W. responded that it was rare to get such information. Rick Kelly asked if that referred to medical data or air monitoring data since medical confidentiality is of great concern now. Mr. Cooper noted that he was thinking more about air sampling to demonstrate feasibility. Will F. noted that the most likely information that would be supplied would demonstrate the unfeasibility of achieving control levels, as in the example of chromium. Craig Steinmaus asked if the committee is to base the recommendations solely on health issues or to consider cost as well. Bruce W. responded that the health issues are the primary consideration. There can be some consideration of feasibility in terms of the existence of engineering controls, but PPE is allowed to be used to supplement these controls. The example of MTBE was discussed briefly.

Patricia Quinlan noted that there were several on the list that are also have current proposals by the ACGIH (the 2001 list) and recommended reviewing them in terms of the current review rather than the 1997 list to preclude further review in a couple of years. Richard C. concurred but noted that the ACGIH material should be viewed as the basis for the review, and not the limiting factor for the committee. There was general agreement with this.

Patricia Q. identified beryllium, molybdenum, 1-hexene, and 2butoxyethanol as the substances she saw on the 2001 list.
Will F. recommended adding chromium to the list for the committee since it has become a very public issue (via Erin Brockovich) and identified by HESIS for years. It should be reviewed even if no recommendation is made. There was a general discussion of adding to the list. Bruce W. said that other substances can be added, but the documentation of any recommendation made would need to be more extensive to make up the lack of ACGIH information.

Richard C. asked about the substances that were identified by the last committee as probable carcinogens but had not been evaluated with a cancer risk model. The committee, with its limited resources, could not apply the cancer risk model and added to their recommendations a note expressing that concern. Bruce W. responded that he would get the statement from the last committee for this group's reference (see Att #1). It would be very difficult to institute the significant change of adding a carcinogen designation to the list of PELs. Another way to approach that might be to use the Director's list, as that list has one trigger based on a substance being classified by IARC as an animal or human carcinogen. Mike C. asked if there are links to the BLS data that can be used for this review. There are some industries that are required to do the reports and these might show an increase in the exposures, or their effects. Bruce W. replied that there probably would not be a direct way to tie the data to exposure levels. Rick K. added that he had tried to do that and only got the "coarse" data. Bruce W. said he would check with DLSR to see if something useful is available. Richard C. added that when there was no scientifically based review process to follow, it would be preferable to find a data driven process, like finding a NOEL value first, and work from there. Will F. agreed. The Feds have a longer assessment process because they use a formal risk assessment procedure. He recommended that the committee use one and offered to help design a procedure and find models that are used by others in DHS for air or water assessments of the same substances that appear on this list. Richard C. supported this idea. Craig S. offered to write a protocol since he had done one for arsenic. Mike C. recommended creating the assessment by group characteristics. Will F. added that there are formal and practical risk assessments that can be considered.

Rick K. returned to Patricia's suggestion to review the latest ACGIH draft document for substances already on the list. Bruce W. said that he didn't see any problem with including these draft documents and agreed to find and distribute them to the committee. There was a discussion of buylcellosolve noting how widespread it has become in consumer products.

Richard C. suggested that a subcommittee be formed to explore the risk assessment issue with Will F. and Craig S. before the next meeting, and develop one that the group can review at the next meeting. Mike C. asked what

criteria were used in the last committee process. Bruce W. replied that there were substances where the research was so sparse or indirect that group had to resort to "back of the envelope" type approaches. Richard C. added that for almost half, there were no established NOELs. He noted that there is more information available via the Internet now than before. Patricia Q. asked if there were any petitions to include substances on the current list. Bruce W. replied that the closest thing to a petition was a request made to the Board two years ago to do an extensive review of gluteraldehyde, but there were no formal petitions to the Standards Board. Richard C. observed that there should be an interest in this activity by industry groups, and asked if many of the listed changes differ greatly from Federal OSHA regs, and if there is current rulemaking such as for Be? Bruce W. replied that Federal OSHA has not recovered yet from its total involvement with ergonomics. The last time they changed the PELs, there was immediate reaction, mostly unfavorable, and the political climate for Federal activity seems particularly unfavorable now.

Will F. suggested that the committee form teams, an IH with a medical member as much as possible. Bruce W. agreed and further suggested groups have a new member with someone that had been on the last committee. He also advised the group that one of the members unable to attend, Stephen Gomez, is a toxicologist in the pharmaceutical industry. The groups: Quinlan and Steinmaus; Fung and Gomez; Cohen and Cooper; and Foreman and Kelly. Patricia Q. suggested that each group conduct reviews of two substances for the next meeting, without the risk assessment procedures, to expedite the process. There was general agreement with this. The group divided up the entire list (see Att #2).

Bruce W. noted that the Labor Code gives a fairly broad description of the considerations in setting exposure limits, so there are few real constraints on the committee. Basically, you need to make reasonable case with evidence to support it. If the protocol for risk assessment doesn't work for some specific substance, a judgment call can be justified instead. The issues are severable; one snag does not necessarily drag down another substance with it. Jeff J. noted that the ACGIH is still considered the strongest organization out there, so if they have made a compelling case, go with it. Jeff J. added that the ACGIH were the consensus standards originally adopted by Fed OSHA. Richard C. cautioned that there are specific cases that are not good such as asbestos, noise, the lead BEI, which were or still are behind the current state of research.

Bruce W. asked the groups to email the substances chosen for the next meeting at least one to two weeks before the next meeting so that they can get on the agenda in time for other member's consideration. Will F. suggested reviewing Benzene in terms of an older ACGIH documentation that was an excellent example of an assessment. The group agreed that they would like to see the older documentation. There was also a decision to take up the issue of Benzene and Refractory Ceramic Fibers as a project for the whole group.

Next meeting: June 22, 10 am, 455 Golden Gate, 10th fl, SF. Carl Forman agreed to chair the next meeting.

Meeting adjourned

Airborne Contaminants Advisory Committee

Draft Minutes

June 22, 2001 Meeting

Bruce Wallace called the meeting to order, four members present: Carl Foreman, Dagmar Fung, Craig Steinmaus, and Pat Quinlan. Others present: Steve Smith, Bob Nakamura, Mohammed Shaykzadeh
Bruce Wallace announced that Rick Kelly was ill and could not attend.

Carl Foreman began as chair for this meeting.

First agenda item: Review of the minutes for the May 4 meeting; Carl F. noted two errors, page 2 “and” and on Page 4, butyl is misspelled.

Carl F, reviewing the agenda, noted that the discussion of Beryllium would be postponed since Rick Kelly is ill. Next meeting date, to be confirmed with the rest when they arrived is scheduled for September 21.

Craig Steinmaus and Patricia Quinlan began their reviews with Molybdenum. Craig S. passed out a handout for the group. There were two forms of the element to consider, the soluble compounds and the insoluble materials. with much more concern over the soluble form. The ACGIH proposal is to establish a 0.5 mg/M3 respirable and a carcinogen designation (A2). There is really only one human study (Droste) to support the A2 designation. The study includes reports and links to jobs; OR=2.1. Craig S. found no flaws in the study. There was an elevated OR in conjunction with chromium but not as a big confounder. There was also a possible effect from smoking but this is considered. Job task is considered as well. There were a wide range of industries included.
Of the animal data, the best study was done by Chan. Referring to table 4: 10 mg produced lung cancer in mice. Also produced in rats with a higher level. These show toxic effects, not the LC.
Bruce W. asked if this referred to the oxides, and Patricia replied that it did. The metal value was adjusted to be consistent with other similar substances (PNOC’s at 10 inhalable, 3 respirable). The trioxides and other solubles are of main concern. Craig S. concluded that the A2 classification is justified but they could not find a NOEL. The Chan study produces the LOL, but what safety factor should be used? Could use a factor of 10 which produces a level of .01.
Patrica Q. added that if you look at the reference list, #7 and #8 are really the same data but 7 is the NTP review which has the Chan data. Other studies are from the 60’s or even earlier.
Craig S. added that a search of medline and toxline did not show other references.
Will Forest noted that typically researchers look at cancer as a non-threshold endpoint and the risk assessment is based on projection.
Patricia Q. said they could not find one, though there could be. The group should definitely adopt the 0.5 from the ACGIH. The issue is whether to go lower or not. What would justify setting it lower?
Craig S noted that they ignored the mouse data and Patricia Q. added that they used a 20x factor instead. Craig S. added that the ACGIH set a NOEL of 10, but it is really a LOL.
(at this point, there was a brief interruption when a visitor, Robert Chrisansen, arrived).
Patricia Q. noted that the evaluation did not discuss common levels observed as other evaluations have; this had no exposure data review.
Will F. said that HESIS almost certainly has the NTP report.
Patricia Q. noted that the question would be if the data is not different from the Chan report.
Will F. responded that the standard NTP report will group the rat and mouse data by male and female, and it would include the explicit opinion of the reviewers.
Patricia Q. hoped that would make it more clear.
Will F. added that there is usually a review of 8 pages or so that might be worth reading.
Patricia Q. noted that they had tried to get the NTP data online, but could not.
Bruce W. asked what might account for the mice data being ignored?
Craig S. thought it might be if mice and rats have different respiratory rates.
Will F. agreed and added that the respiratory systems are very different physiologically.
Bruce W. observed that the data seemed to show a reverse dose-response.
Will F. agreed that the data anomalies might be explained in the NTP report.
Bruce W. asked about the metaplasia data.
Craig S. replied that 10 was the NOEL.
Patricia Q. added that 10 was the NOEL but they found the effects at 30.
Will F. added that metaplasia is generally considered a pre-cancerous state.
Craig S. referred to page 5 of the report, last sentence: NOEL of 10 for chronic alveolar inflammation.
Patricia Q. said that they seemed to make an adjustment for the hours of exposure, but it didn’t make complete sense.
Bruce W. agreed; the way they seem to have done it was to reduce the weight to 5 and use a factor of 10 to get 0.5.
Will F. added that the odd thing was to ignore the mouse data, pick 10 for one NOEL, and not the LOEL.
Craig S. concurred that if there was a big problem, it should have appeared in the Chan research.
Will F. suggested that the ATSDR might be useful since it is a fairly detailed report, cites relevant literature, and though it does not include a risk assessment it might lead to other evaluations.
Dagmar Fung summarizing, there is evidence to support lowering it, but there should be more data to establish the actual limit.
Carl F. agreed and concurred that there is some inconsistency.

Move on to the insoluble form.
Bruce W. called attention to table 2; it shows chronic inflammation and on the next page discusses results in which they cite #7 and #8; are there useful references there?
Patricia Q. replied that they could not find the NIH documentation which might give more justification for the numbers chosen. There was only one epidemiological study. The Droste research was the most relevant. Recommendation is to accept the 10 and 3 since there is no other data suggesting greater toxicity, and the change would be consistent with their overall approach to use these values for all similar substances.
Will F. disagreed, the proposal makes no sense. 10 inhalable is much more lax than 10 total.
Bruce W. added that the idea of introducing a value based on a different sampling method (inhalable sizing) would require reviewing all the similar materials (with total dust limits). Cyclones are similar to the new sampler, and there is not a lot of data comparing the new sampler with the standard 37 mm cassette results.
Patricia Q. suggested leaving it at 10 total dust.
Will F. noted that the last committee in its review of silica, added the 3 but left it at 10 total dust.
Patricia Q. asked how it could not have been changed?
Steve Smith and Will F. responded that it was not.
Patricia Q. agreed to 10 total, but there should be a formal conclusion. Does the group want to get the report from the website and review the ATSDR report?
There was general concurrence. Will F. would check next week.
Carl F. noted that lacking a quorum, the decision would have to await the arrival of another member.
As stands, the recommendation for the insoluble is 10 total and 3 respirable.

Next, Cumene. (Handout)
Patricia Q. reported on this proposal; to delete the Skin notation, no change to the TLV.
History: TLV 50 ppm from 1967 to the present. Skin notation added in 1967. In 1967 STEL of 85 added, removed in 1986. This had information on exposures: 1 ppm to 5.8 ppm. No reports on human health effects. There were three articles on animal studies referencing 8 toxic reports. There was a 1951 report discussing the toxicity, and a 1990 AmJournIndMed reporting moderate irritation to the eye and skin in rats and rabbits.
Craig S. added there was no study of toxic dermal exposure except an LD50.
Patricia Q. continued with Table 1 on page 2; oral toxicity; looking at the second to last column, there is a “4” undefined; means 4 of 10. The other study is by Wolfe, no concentration reported but effect of moderate irritation and necrosis.
Craig S. added that there is no indication if it was absorbed in toxic amounts.
Patricia Q. concurred and added the logic for this evaluation is on page 5. There was an EPA reference that they could not find.
Patricia Q. concluded that there doesn’t seem to be any conclusive support for dropping the Skin notation.
Craig S. added that the dermal levels seemed high.
Patricia Q. also noted that the definition of the Skin designation includes acute animal toxicity data.
Bruce W. asked if this follows from the range finding data?
Will F. commented that the California definition for Skin differs from the TLV, and Dagmar F. commented that the California definition appeared looser.
Patricia Q. suggested that since it has “may” in the definition, it should be left alone.
Mike Cooper arrived.
Craig S. noted that given the chemical/physical properties it could be absorbed.
Mike C. asked if TOSCA data was available.
Will F. replied that it might be. The summary information includes LD50 data. The dermal LD50 is higher but not by more than a factor of 2, so there seems to be a dermal effect.
Rich Cohen arrived.
Craig S. asked the group if they would like to vote now or get some more data?
Patricia Q. added the point to the discussion that the Federal regs have the Skin notation, so the effectiveness issue is introduced if the committee wants to delete Skin, especially when there seems to be no reason to do so. Programmatically, the Cumene issue is minor.
Rich C. asked, if the Feds retain the Skin, isn’t this a moot issue?
The group agreed that it pretty much did, but Steve Smith pointed out that they could try to argue equivalent effectiveness.
Bruce W. added that no change requires no justification.
Will F. noted that there is not likely to be much skin contact anyway.
Carl F. asked for a vote, and the decision was to not drop the Skin designation (unanimous by members present).

Maleic Anhydride

Patricia Q. distributed a handout sheet and informed the group that the ACGIH lowered the TLV to 0.1 and added a sensitizer designation.
Dagmar F. asked if the PELs included a SEN designation as well?
Bruce W. replied that they do not.
Patricia Q. noted the focus would be on adopting the TLV value.
Bruce W. pointed out that a footnote warning of the sensitizing hazard could be added, but none of the other known sensitizers have such a footnote either.
Patricia Q. agreed that there are a lot of substances in the TLV list with the SEN.
Continuing, she noted that there are a lot of references in the review. The Jarvis study, ref. 22, reported asthmatic responses, and a Russian study showed conjunctivial effects at a LOEL of .22. Reference 20 listed numerous effects but did not specify the levels of exposure.
Craig S. added that there is nothing obvious, but the ranges are listed.
Patricia Q. continued with a case reported by Lee of occupational asthma, found by bronchial testing in a factory, at a level of 8 mg/M3 (2ppm) by inspirable particulate mass testing; and with provocative testing positive with dust readings of 0.2 and 0.02. At 20 minutes exposure time, the response dropped to 45% of normal. An animal study showed that at .25, there was ocular and nasal irritation. Their committee reported that Australia adopted 0.25, and reviewed other standards. Evidence supports going to 0.1 or lower, and it is clearly a potential sensitizer. The decision to go to .1 with observed effects at .27 is not justified, and there is no useful data from the factory study.
Mike C. asked if the factory produced maleic anhydride?
Patricia Q. replied no, it was a polyester resin factory. If you look at the studies, the anhydride studies often focus on sensitization, more than with phthalic anhydride, but there is nothing to support that conclusion.
Craig S. noted that .25 is the NOEL. The Russian study suggests a NOEL at .22, and a German review sets the irritation threshold at 0.05 ppm in reference #9.
Mike C. asked what the detection level is, guessed it to be 0.1. Noted it would be useful to know how the material is used.
Rich C. discussed a sensory study that took .03 x the dose of irritation to get a correlation with the TLV.
Craig S. asked if the group thought it worthwhile to try to get the Russian study?
Will F. noted that only the summary was likely to be in English.
Rich C. was skeptical that the article would be available at all. As for the PEL, there doesn't seem to be any question about adopting at least the 0.1. The SEN designation is an entire issue by itself.
This led to a general discussion of the SEN designation. Will F. thought it should be in the MSDS already. Craig S. noted that Reference 9 chose .05 and the German MAC documentation might produce another reference. Rich C. was asked what he thought. He suggested going with 0.1. Patricia Q. agreed but noted that it may not be low enough. Craig S. noted a detection level issue below that and recommended going with 0.1 unless somebody finds more definitive information. Discussion by the group concluded that the German reference might be their review of the MAC values, or it might just have a table with that value.
Carl F. asked if the group concurred to adopt 0.1 now, unless something conclusive is found?
There was no objection to this proposal
Bruce W. suggested that if they found problems at the PEL, there is justification to at least go to 0.1,
Will F. agreed to try to get the reference.

Lunch break.

Confirmed next meeting date: September 21. After that, tentative: November 9th.
Carl F. asked Dagmar F. to go ahead with acrolein.

Acrolein.
Dagmar F. reported that there was enough evidence to support a Ceiling of 0.1 ppm. Toxline articles reported irritant effects that support a 0.3 STEL. But, they found a NOEL indicating that 0.1 is not low enough, so there is difficulty in setting a PEL. Also, they recommend a Skin designation as designated in the TLV list. The response to the chemical is similar to the anhydrides. Data showed that at .06 there is eye irritation, and at 0.13 there is nasal irritation in humans.
Craig S. asked if they just want to remove the TLV?
Dagmar F. replied that the intent is to not allow anything over the Ceiling.
Mike C. asked what the rationale for just the Ceiling would be?
Rich C. replied that it emphasizes the irritant effect levels.
Dagmar F. continued that their recommendation is to accept the Ceiling of 0.1, add the Skin designation, and find a PEL below 0.1. she also noted there are tissue changes below 0.7.

Rich C. noted that there were reports of emphysema and gross pathologies in animals at 0.22 which seem pretty significant.
Mike C. asked what the IDLH is? A report associated 10 ppm with fatalities.
Will F. responded that the book shows that 150 ppm for 10 minutes is an IDLH.
Craig S. asked if there wasn't an uncertainty factor as with molybdenum?
Will F. commented that based on the rodent irritation, .03 would be the level to control irritant effects, why recommend 0.1?
Bruce W. responded that his guess would be that the rationale assumes that a very low average level would have to be achieved to allow for a ceiling of 0.1.
Mike C. asked what the Federal level is, answer 0.1; and NIOSH recommends a level of 2 for IDLH.
Rich C. suggested a PEL of .03.
Will F. responded that the Ceiling of 0.1 is probably more protective.
Rich C. replied that he meant in addition to the Ceiling.
Mike C. asked what was in the table, .03?
Rich C. replied that the only number below .1 that correlated with concern was .03, which was calculated from the exposure level at which 50% of the animals showed the effect.
Carl F. asked if the group wants to see reference 14?
Craig S. added what about #45, the NIOSH reference?
Will F. noted that there is a reference to the OSHA PEL, probably the 89 version, which should mean that NIOSH has not looked at it.
Mike C. asked about references 39 and 40.
Rich C. suggested holding off on the .03 issue until after the discussion of risk assessments, and go ahead with a decision on the 0.1 Ceiling.
Mike C. asked if the 0.1 is base no a NOEL calculation? and asked if there was other data?
Craig S. replied that there was a LOEL of 0.22.
Rich C. added that was the lowest point, but it is still very serious.
Mike C. asked if the effect was reversible, like eye irritation?
Rich C. thought it was.
Craig S. suggested that Will F. try to get one reference.
There was a short discussion of 0.9 suggested by Mike C..
Will F. suggested considering the Skin designation. He added that if there was a very high correlation, it doesn't have to be a very toxic effect.
Rich C. added it can be absorbed and that is likely to lead to toxicity. Would be good to review the original article.
Bruce W. thought there were two articles.
Mike C. suggested the ACGIH review.
Bruce W. noted that it did not show very good grounds for support.
Mike C. asked if it was just the ACGIH, and not the State (DHS) or Feds?
General reply was yes.
Craig S. suggested doing a search on medline or toxline.

Carl F. summarized that the group would recommend the 0.1 Ceiling pending more information.

Carl asked Dagmar if she could do the next substance, (Stephen Gomez had done that review)
DOP.
Patricia Q. asked if the proposal for the phthalate is to remove the STEL?
Mike C. wanted to know if there was a basis for the original STEL?
Bruce W. responded that this is a substance without a ceiling, and from the note in the TLV booklet, not found to have a toxic effect.
Mike C. noted that then is nothing to trigger the removal of the STEL or supporting criteria to keep it.
Carl F. replied that by applying the formula, you calculate 10. (5155(c)(2)(B))
Dagmar F. added that their assessment was that the level was fine, but she doesn't have the notes they made.
Rich C. asked if there was any reason to have the STEL? Did they just use the formula?
Bruce W. responded that you would want to look at the acute effect reports.
Mike C. asked if the basis was acute or subchronic; if acute, there would have been an acute assessment. He wanted to clarify if there are acute effects.
Will F. replied that it is a mild irritant.
Dagmar F. noted that she and her partner had tried to get article #10 but could not. Will F. thought he could get it, and added that it may be teratogenic and a liver toxin, but lowering the level is a separate issue.
Rich C. noted that they already have a Ceiling, the default of 10.

Mike C. asked if everyone agrees with 10?
Carl F. suggested taking out the STEL and going with the 10 mg which is derived from the formula.
There was no objection to this proposal.
Mike C. asked where the formula had come from?
Bruce W. thought that it probably came from the federal adoption of the 1969 TLVs.

Carl F. asked the group to move on to the risk assessment discussion.

Rich C. described the approach he uses for his clients to develop a NOEL for establishing an exposure limit.
First thing is to search databases. Any dose response data can be used.
Need to find a dose value, and a daily dose value. Also need to get the pathology to figure out the end point.
Finally, requirement to get the time of the effect.
If we can find the toxico-kinetic data, get it, especially the half-life. Then extrapolate the dose: if animal data, choose a human model. To reflect size of current workforce, choose 50 (smaller people), and in terms of surface area, you use 1.3 M^2.
Then, have to work with safety factors and

safety factor

Classify each according to the outcome: NOEL: 1.0
non life threat TD_{low}: 10
Toxic effect no TD: 100
cancer:100
animal: another 10

Dose: divided by another 10; accounts for total inspired air.

Many substances do not have inhalation data, have to use factor of 10 M^3 for the respiration. With oral exposure, only some % reaches the bloodstream, but by inhalation, close to 100 % reaches circulation. The assumptions are what can be easily challenged. But this makes the process easier and you have a history of how you reached the decision.
Mike C. asked about the differences between oral and gauvage dosage.
Rich C. replied that is one of the things you have to decide in the process.
Mike C. asked what else affects the oral?
Rich C. replied that there are other factors such as the transit of the substance through the esophogeal tissues.
Will F. commented that this procedure will be very helpful with this project, and there are more concrete factors that can be incorporated.
Craig S. agreed it would be good to use this for other evaluations.
Rich C. continued, after that part, how do you get to a TLV?

Example: TD(low) human, 5mg/duration gives you 5 divided by 10 for .5.
Then, animal: median value, range, # studies
Human: 4week
" :4-12 week
" : 12+ week

Craig S. asked why not just the number instead of the median?
Rich C. responded that it depends on the effect. Hard to pull it all out. Hardest to get the documents for a group.
Craig S. raised two issues, what is the safety factor, and how to evaluate a study for validity.
Carl F. responded that this process parallels analysis of work environments and target populations.
Mike C. asked Will to explain the nonstandard approach.
Will F. responded that the nature of the effect is not considered until the management stage. It is important to differentiate from risk assessment; this allows people to argue the science. Would not include the nature of the end point until after the assessment.
Craig S. asked if the process already used safety factors?
Will F. responded that the 10X actually has some basis in reality, reflects the probability of the effect at lower levels. Risk managers don't talk about different factors for types of endpoints. They take it into account but not in a stated numerical way. Risk assessment looks at each endpoint, for example, setting a number for cancer and irritation. In this process, regulate cancer for sensitivity, get a numerical value for the level of risk for the endpoint, then select the endpoint of the effect that is the most protective.
Craig S. commented that if you set standard for cancer, you want to be safer.

Will F. replied that cancer is a special case; that is a non-threshold endpoint, use a different calculation instead. Invariably, the number for cancer protects against everything else.
Craig S. asked, okay, then what about cancer?
Rich C. replied that if cancer is the endpoint, separate that out.
Will F. agreed, cancer needs to be done separately. Choose a level of acceptable risk, and with that, you can calculate the limit. The risk management is the hard part, for example, Benzene.
Mohamade Shaykzadeh asked if a safety factor of 1000 isn't what is used in Prop 65?
Will F. replied that Prop 65 was done taking into account cancer and reproductive effects and the number is basically 1/100,000 for a lifetime risk. The reproductive safety factor was set at 1,000 from the NOEL arbitrarily. This group should consider a cancer number like 1/100,000.
Craig S. asked if the group should choose the value, and if so, what number?
Mike C. noted that there may not be numbers for all the listed substances, but this gives a way to approach it.
Rich C. added that choosing one endpoint based on effect provides a flexible way to decide.
Dagmar F. noted that today, the Ceiling was an issue.
Will F. suggested using a factor of 10.
Rich C. added that the uncertainties with cancer, animal data, etc. should be discussed. In the last committee, the cancer issue remained inconclusive. The public expects everything to be considered.
Will F. noted that the good thing about cancer research is that someone has generally done a risk assessment.
Craig S. asked if that meant there would be two separate evaluations?
Cancer can be done as a linear extrapolation.
Bruce W. suggested that Will F. find risk assessments for anything on the list, if he could.
Mike C. suggested dividing the list into those with RA's and then work on non-carcinogens first because the carcinogens are already pretty much done.
Patricia Q. asked to clarify if they were referring mostly to IARC?
Will F. said that if someone has done a formal risk assessment, it can be treated like a carcinogen.
Rich C. suggested that the group divides up whatever risk assessments that Will could find, and generate proposals for each one.
Craig S. asked about different research methods; it might be better to get the data from these assessments and do the straight line derivations ourselves.
Will F. agreed that the straight line is often most protective, and the group may have to do that. If so the calculations should be done with a determined risk level.
Craig S. suggested asking for the participation of Allan Smith (UC, last committee) who supports straight line derivations.
Will F. responded that no one can prove that one model is the best; low exposure level evaluations are affected by the models applied. Maybe at 1/1,000, the model doesn't matter. He agreed to try to find formal RA's for everything on the current list.
Patricia Q. reminded Bruce W. about getting copies of the AIHA article (Sept. 93, p488).
She wanted to summarize decisions from this meeting: Skin designation retained for Cumene, Molybdenum: 10 total and 3 respirable. Acrolein: support proposal pending data review. The other items were not completed.
Bruce needs a month lead time to distribute information.
Patricia Q. will chair the next meeting.
Meeting adjourned.

Airborne Contaminants Advisory Committee

Draft Minutes

Sept 21, 2001 Meeting

Attending: Patricia Quinlan, Richard Cohen, Will Forest, Mike Cooper, Dagmar Fung, Craig Steinmaus (PM), Bruce Wallace, Bob Nakamura

The meeting was brought to order by Bruce Wallace. He announced that Carl Foreman was unable to attend because of unforeseen circumstances. Also, Rick Kelly has withdrawn from participation due to illness. There was a general discussion about adding new members to the committee based on some original members not being able to

participate. The consensus was that there would be difficulty getting a quorum at future meetings, increased work level for remaining members, and that two new members should be recruited.

Bruce W. discussed the agenda. The first item was the minutes from the last meeting. The visitor who was interested in the Beryllium issue had not been listed as an attendee, so the minutes need to include that at the top. No other problems were noted.

Patricia Quinlan began as chair of this meeting with the items from the last meeting that were open .
Bruce W. referred to a new list of the substances for review. This list (List-4) has corrected footnotes but is otherwise unchanged from the previous list that was emailed to the committee. Bruce noted that Acrolein should show that "Skin" was added to the TLV on page 4.
Patricia asked if that was pending a lower value? Will responded that he had emailed the information that people had asked for shortly after the last meeting. Patrica summarized: 0.13 mg. was found in the German reference, but Will F. had recommended not using it. She asked if the group therefore wanted to agree to the ceiling limit of 0.1 ppm and Skin notation? Consensus, yes. And, was there a need for further action on Acrolein? Consensus, no. There was a suggestion to make the last column on the page the completed date.
Patricia asked about DOP. Bruce said that there seemed to be no basis for the original STEL, this was discussed briefly, and the minutes from the last meeting were reviewed. There was no objection to removing the STEL with 10 as a default. Patricia added that her notes showed that the decision was to eliminate the STEL and asked if that was the consensus now? The group agreed that removing the STEL was the recommendation.
Patricia referred to page 3, and Beryllium, suggesting that the substance list should show the 2000 proposed change of .0002 mg and not the last one so that the issue will not remain for the next committee. (The group acknowledged that this issue had been raised before). In 1997, the change was to raise the STEL to 0.010 mg. In 2000 the TLV notice reduced The TLV to .0002 mg and the STEL was eliminated. There is also a SEN designation proposed for the TLV. She asked Bruce W. if there was anything else on page 3 to review, and he said there was not, but he would update the Be listing to reflect the notice of intended change.
Patricia moved on to page 1 and Cumene. She summarized that the new information found did not support removing the Skin notation, and asked if the recommendation not to remove the Skin should stand. There was general agreement to not recommend a change for Cumene.
Maleic anhydride: the recommendation at the last meeting was to lower the PEL to 0.1 ppm. The group at the last meeting had hoped to find an actual NOEL in the literature. The German MAC information was found, but Craig Steinmaus had reported that he hadn't found it useful. Patricia proposed leaving the recommendation at 0.1 ppm. This was acceptable to committee.
Molybdenum, the current status is that there is no decision on a recommendation for the soluble compounds.

New business:
Allyl alcohol. Dagmar F. suggested reordering the columns on the substance list by starting with the existing PELs, followed by the TLV information. Bruce agreed to make this change to the list. Richard Cohen distributed a handout on Allyl alcohol. The ACGIH change was to drop the TLV to 0.5 from 2.0 and delete the STEL. Richard had applied his risk assessment process to the information on animal and human data he found, and listed the TWA exposures (on the handout). He found that the human data was only anecdotal and not useful. He also found an EPA recommendation that discussed a dose, but had little about cancer or reproductive information.
Patricia asked about the ACGIH value.
Richard said that he had used the formulas previously discussed and applied the safety factors that are shown on the second page of the handout (backside) that reflect the volume and ventilation rate, and derived an extrapolated value that is in the last column as ppm.
Patricia asked about RTECs and Richard said it was part of the references. She also asked what LCLO denoted. lowest concentration, lethal outcome.
Mike C. wanted to review the calculation:
Richard said that he had done the calculation shortly after the last meeting, so he needed to review the calculation while Mike wrote it out on the wall board.
Richard used the second line of animal data as an example, the LC for the rat of 165 ppm, which was a four hour test.

$$\frac{165\text{ppm}}{(1000)\ (10)\ (2)} = .008$$

LC 50 animal four hour adjustment

He also noted that an LC is automatically animal data. So, the .008 should be the human NOEL estimate for an eight hour exposure.
Will noted that the LC 50 should be the least desirable data to be relied on, and Mike asked if that was because there is better NOEL data? Will said it was.
Mike recommended that there should be a hierarchy for using data as:
Human, NOAEL, NOAL, and LC 50.
TCLO: RTEC, lowest value with significant adverse effect.
LCLO: Lethal Concentration, Lowest observed. Will noted that there can be human LCLO data from accident reports, and if it is an irreversible effect, it is not "low".
Patricia asked if severe irritation was SF=10 and the lethal was SF=1000? Yes.
Patricia asked what RfD EPA meant? Rich said it is an EPA environmental level.
Will asked if the NOEL in the study was the water data? Yes. Mike added that the EPA has done that with other substances with a conversion formula when there is no other data to use.
Richard said that the ACGIH made their recommendation based on the sensory irritation reported in the paper that was discussed at the last meeting, and applied a safety factor. The only chronic data that he found was from Torkelson.
Bruce added that this had resulted in the 0.2 ppm. Richard responded that the ACGIH is based only on irritation (at 0.5); this is an analogy because it is irritant data. The human data is very soft. Torkelson had the only specific data.
Bruce asked what was the effect Torkelson's NOEL at 2 ppm didn't see?
Richard replied that there did not seem to be a specific effect in the pathology.
Will added that the EPA reported liver and kidney damage, but Richard said those effects were at higher exposures. There were two different effect levels, 2 and 7. 7 produced the kidney and liver effects. Will suggested that meant the 2 is the NOEL for liver and kidney effects then. Richard continued that he had with 5 of 10 human subjects, there was no irritation so he suggested a Ceiling of 5, but that was 1959. Can take the EPA data and multiply by the differentiation in time, and get about .05.
Patricia noted that in the first paragraph, ocular and respiratory effects were correlated to the TLV, but with the RD 50, can't find it in the research paper, what is it?
Will responded that the RD 50 is the decrease in the breathing rate by 50%. This is a more severe effect than simple irritation since it means that the atmosphere was very unpleasant for the animal to breathe. Patricia added that the data is hard to derive, so is the suggestion to use 2 ppm NOAEL? Yes. That was the calculation.
Will added that it was worth mentioning that the data in section 2 and 3 is all irritation. The EPA used drinking water with a liver/kidney endpoint that set a lower level than the irritation data. The group needs to choose what is the most sensitive endpoint. The good thing about the water data is shows how much is in the body.
Richard said that it is possible to convert the EPA level by applying a work exposure factor. This gives .05, which is even lower.
Will F. noted that their value is also probably based on a lifetime exposure, not the working span. Richard said they apply 1000 where he used 100. Will added that the EPA has standard risk assessment factors. Richard noted that it caused reduced food intake based on organ weights, and this produced 0.5.
Mike C. asked the group if there was a significant difference between 0.5 and 0.2? Isn't it more prudent as a defensible decision to consider them the same in the absence of data? Is there an error bar to show that there is no significant overlap, and a real distinction? Richard said no, the confidence level will move up and down with the criteria selected.
There was a discussion of the ACGIH basis for setting the TLV at 0.5 and the method used by Richard. Will F. thought that there would not be a significant difference in the level of protection between a 0.2 and 0.5 level given the processes used to make the estimate.
Richard said that he would not object to recommending 0.5 ppm given the differences were not large. There was a consensus to recommend 0.5 ppm.

Next item Propane:
Mike C. stated that the TLV of 2500 seems based on O2 depletion or a percentage of the LEL. The LC 50 is based on ACGIH review, and is convoluted but summarized on the handout. The reversible animal effect is cardiac sensitization. The human data shows only one good study. Propane was found in venous blood. There is no LC 50 except for mouse and rat data. For several gases, there is an implication that 10% of the LEL was chosen, though it seems odd. The problem is that the value is higher than the IDLH published by NIOSH, which has significant implications, and applies to other asphyxiants. This would need a complete review. His recommendation is to leave the current PEL alone pending further data.
Richard asked about the history. Mike replied that the ACGIH had 1000. Bruce said the current PEL is 1000.
Patricia recommended not changing the current PEL. Mike responded that he thought it might be inappropriate. Is it

health based? No, but shouldn't it be health based? Bruce noted that the footnote for the PEL says it is based on the fire and asphyxiation problems. Will added that since the Federal is also 1000, it would be really difficult to raise the CA PEL. Bruce replied that it is possible, but it needs a very strong basis to justify it. Mike responded that he is comfortable with the footnote specifying that it is not derived from toxicity. His concern is that there would be implications when employees must be notified about their exposures. There was some general discussion about how this might apply in such a case.
Dagmar asked Mike about the inhalation study. Will noted that finding a substance present in the blood is not necessarily a sign of toxicity. Mike responded that there were objective symptoms found by physical examination. Richard said he would be concerned if there was disagreement between FedOSHA and Cal/OSHA. Bruce replied that the Federal PEL is 1000 but it does not have a footnote which describes the basis. There weren't any objections to recommending no change for Propane.

Lunch break

Bruce W. asked to get a copy of the Torkelson study that was the basis for the Allyl alcohol recommendation. Richard gave Bruce a copy. Will suggested including the EPA document. Bruce said that he really only needed the one study, but he will consider that.
Patricia called for selection of the next meeting date. The next meeting scheduled for November 9th, 10 AM. The following date is tentatively scheduled for January 11.
Craig Steinmaus arrived and was briefed on the morning decisions. He suggested that Michael Bates might be a good candidate for the committee.

The topics for the next meeting:
Patricia/Craig: dichloroproprionic acid; pentyl acetate; and triglycidyltriazanone.
Richard/Mike: acetone with Mike and 2-butoxyethanol.
Dagmar: ethyltertbutyl ether; and propylene oxide.
Will noted that there should be a lot of data on Dagmar's items since they are widely used or studied.

Patricia asked Richard to begin with Beryllium since Carl could not be here.
Richard noted that he has been involved with finding recent literature. He started with the history of its standard setting. Be was first considered to be a problem in 1943. In 1949 the AEC became involved and paid for some research because there were problems in Be plants. The first standard, 2ug/M^3 (8 hr twa) and 25ug/M^3 (peak) is known as the Taxicab Standard because it was developed by the authors while they were riding a taxi together. They knew that Hg, Pb posed certain toxic effects that were somewhat the same as Be, so they based their standard on the proportionate difference in the atomic weight of Be. Bruce noted that it was a density type of consideration, and Richard agreed and added that the justifications actually came after that.
Effects: 25 ug/M^3 is now considered able to cause acute Berylliosis. One study found nine cases in a geographic cluster living within ¾ miles of the factory. Only one further away case had indirect contact with the factory by washing contaminated clothes. The others had no association other than residence. Air data at the houses found about .01 ug/M^3, with a range of .004 to 0.1 The AEC also decided that since there were no acute cases in the factories, the chronic cases were at 10 or higher, and they used the outdoor median. With time, the cases were fewer as the plants got cleaner. In the 60's and 70's, there were low numbers of cases. IARC gave it a carcinogen ranking of group 2b in the 80's but now it is group 1. There are more recent cases of occupational settings at 2ug/M^3 or below, with the chronic disease. The environmental data still stands for outside the plant.
There is a paper from Public Citizen (given out) the requests that Federal OSHA adopt a lower limit. Richard proposed the environmental value modified for the workweek as a start for the review since the animal data is not so clear. Richard asked if Carl had sent any documents. Carl had not. The past standard was totally by analogy.
Craig had questions about the epidemiological data.
Richard replied that McMahon had blasted the epi data, but it actually seems consistent. The major issue is the number, 0.2 ug/M^3, protective enough?
Craig noted that he didn't think there was really enough exposure data; even Livermore has little data. Mike thought there was industry data somewhere. Richard replied that Henry Hardy used to make reports in 1952, but it was stopped. Bruce pointed out that the Eisenbud data is on page 14 (or its own, 83). Richard added that the exposures are fairly limited. Bruce asked if there was community data and Dagmar said it was on page 85. Richard concluded that it would be hard to make a decision today. He had thought that Carl was going to be here. Patricia added that the journal has an article on Be comparing the historic and current standards, done by Mark Kolanz and Kostenbach. Also by Brush and Wellman. Will F. suggested there should be a no-significance risk level available at Cal EPA.
Patricia asked if there should be a Toxline search or review of EPA data. Bruce added that there are a couple of articles done by C. Kreiss who was doing a follow-up on some of the people found in the 40's and 50's. Richard said

they were able to diagnose cases. Patricia referred to page 11 of the Public Citizen handout that has a review of literature and exposures in the Breathing zone. Also, the JOEM reported .13 ug/M^3 and .14 ug/M^3 above it.
MCA: .01 on page 7, in B, non-exposed workers, and this came from the 49 standard. Richard thought he could get the original article with the household data tables. Then he will review with Carl to see if there have been more studies found that are relevant. Did Carl have more for today? Bruce responded that he wasn't sure. Will F. was asked to get any Prop. 65 data.
Patricia asked for clarification. Richard said that he wants to gather the data including environmental and do the risk assessment in this process. He doubts that there is data on the follow-up to the environmental data. The group needs references #3, from OSHA, and 29 by Yoshida (Craig has it). Patricia suggested that everyone should have the same articles so the information that everyone needs should be identified. Richard said that #29 has low dose data. The group should see the 49 standard as well. Will offered to try to get the articles.
Bruce suggested that the ACGIH references 35 and 36 should be reviewed by the group also. Patricia asked the group if there are more articles that are needed.
Will noted that he first did a simple Toxline search. He can look for more risk assessments and review articles.
Patricia said this is a somewhat confusing situation and asked Bruce if Carl would remain as the member working on this substance? Bruce will check with Carl and distribute the papers he gets.

Next item returning to soluble Molybdenum
Craig Steinmaus said that the data presented at the last meeting (Chan et. al.) could extablish a LOEL of 10mg/M^3 in mice for outcomes other than carcinoma. This can be seen in Table 4 Alveolar/bronchiolar epith. metaplasia, in both male and female mice. This would result in a limit of 0.1 mg/M^3 based on a ten fold reduction due to animal->human, and another ten fold reduction because it is a LOEL and not a NOAEL. The committee agreed to recommend 0.1 mg/M^3 as a respirable limit on this basis.
meeting adjourned.

10/3/01

Airborne Contaminants Advisory Committee

Draft Minutes

November 9, 2001 Meeting

Committee members present: Tim Roberts, Dagmar Fung, Richard Cohen, Robert Ku, Mike Cooper, Craig Steinmaus(pm), Allan Smith (alt), and Patricia Quinlan
Otheres present: Will Forest, Deborah Gold, Bruce Wallace

Bruce Wallace called the meeting to order. He distributed the agenda and a document "Community Exposure to Beryllium." Bruce stated that he did not mail the article prior to the meeting because he had been expecting to receive more articles on Beryllium. Richard Cohen asked who he had been expecting articles from. Bruce said they were listed in the minutes. Will Forest said that it had not been in his notes to provide any materials. Tim Roberts asked if there was a limit to the timeframe to discuss the issue. Answer: no. Tim said that because he works at Lawrence Livermore, he probably has good access to the Beryllium information.

Bruce introduced two new members of the committee, Tim Roberts from Lawrence Livermore National Laboratory, and Robert Ku from SafeBridge Consultants, which does a lot of work on toxicology based health and safety, primarily in pharmaceutical research and development. Robert added that his company does a lot of general health and safety consulting, in both research and manufacturing.

The remaining committee members introduced themselves.

Review of minutes from the last meeting:

Richard Cohen asked if the minutes said they would take up Beryllium at this meeting. Bruce replied that there had been a wide-ranging discussion of an article Richard had put out, and they had concluded the group needed various references. Bruce read from the previous minutes. He said he assumed the reference mentioned was 1949, not reference #49. Richard replied yes. Bruce said the implication was that there would be a general distribution of papers, and then they would take a serious look at the issue.

Patricia Quinlan asked about Carl Foreman. Bruce said that Carl had been involved with the OES on anthrax in support of local agencies. Patricia said that Carl and Rich had taken on beryllium, and asked if someone else should be on the subcommittee. [Allan Smith arrived] Bruce said that Carl had given him the impression that he was still willing to work on this substance. Tim Roberts said that he has taken over from Rick Kelly, and has access to the same information as Rick had. Richard said that Craig Steinmaus knew a lot about this issue. Allan said that Craig has worked on beryllium quite a lot, he has published on it and done studies. Allan said he was sorry he hadn't been able to participate more in this committee, he has had conflicting meetings, but he is happy to help.

Bruce said the task is to find someone to coordinate this topic, and act as a focal point. Tim said that he would do that. Bruce said that the committee needs a common base from which to work, and to prepare well in advance. This is a high profile issue. [Mike Cooper arrived]. Will said to be sure to talk to Alan, Rich, Craig and Carl. Bruce said that the previous meeting's minutes had a list of materials people were interested in. Will said that the minutes say that he would get specific articles, but all he remembers is saying that he would look for risk assessments. He said that Bruce should give him a list of the articles they need. Bruce said he would do that, and he would mail copies of any articles he received to the committee.

Allan and Mike Cooper introduced themselves. Bruce asked if there were any objections to approving the minutes, there were none. He said that members could let him know later if there were any objections. Patricia asked if the agenda could be changed to accommodate the schedules of people who had indicated that they needed to leave early. Agenda was modified to make Propylene oxide first.

Propylene Oxide:

Dagmar Fung distributed a summary sheet on propylene oxide (PO). The current PEL is 20 ppm, it is proposed to lower it to 2 ppm. According to the ACGIH it is a sensitizer and an A3 carcinogen. IARC lists it as a possible carcinogen, and NIOSH lists it as an occupational carcinogen. Richard said that it is an IARC 2B carcinogen associated with nasal cancer. Will was asked if he could get the two human studies. The ACGIH recommendation is based mainly on reference #36, which established a NOAEL in rats of 50 and below, for non-neoplastic changes. Robert said that utilizing the risk assessment equation, you would calculate a 5 ppm exposure level. The 2ppm proposal doesn't really consider a cancer endpoint. He said that subcommittee wasn't able to obtain the original reference. As described in the ACGIH document it was a study which looked at genotoxicity and cellular proliferation, but then characterized the "no-effects" level as for non-cancer endpoints. It appears to have been a study designed to study cancer endpoints. Dagmar Fung asked Will if he had gotten reference #36. Will said he hadn't. He had asked for the PO documentation(ACGIH), and hadn't gotten it. Patricia said it was dated 3/10/00. Bruce made him a copy. Tim asked if the proposal was from the committee, or if it was the ACGIH proposal. Dagmar responded it was the ACGIH proposal. She said they wanted other human data, such as the Current Intelligence Bulletin #51 from NIOSH. Will said they would need to look through the Bulletin to see what it was relying on. He has the risk assessment data from EPA's IRIS data base, and other data. Dagmar said that's what they were asking for. Robert said they also wanted reference #79, which said that concentrations from 0.6 to 12ppm reduced the capacity of cellular repair mechanisms. Will said he will probably need to check it out of the library and lend it to the committee. Tim said that the Bulletin was available on-line. Dagmar said they really want to backtrack to references, and this is one of the few articles with documentation below 2 ppm.

Richard asked what was the ACGIH rationale. Dagmar responded that they had used reference #36. Bruce said it shows a 2001 adoption, but it is a draft document. Patricia said it changed in 99, and then in 2000 they noticed a change from 5 to 2, with a sensitizer and A3 notation, and in 2001, adopted 2 ppm, and the sensitizer and A3 notations. Richard asked if they based it on reference #36, how did they get from a NOAEL of 50 to a recommendation of 2. Patricia asked if they had divided by 10 for species? Robert said they didn't provide a rationale. Richard said they needed to see the reference. Robert said he looked at studies regarding the mechanism, which indicated that propylene oxide should be less potent than ethylene oxide, so the PEL should be higher than ETO. Richard said there is usually nothing specific from ACGIH regarding the values they select. He said he prefers 5, because they can document that. Will said that they probably went lower because it is a 2B carcinogen, and employer's can probably meet the 2ppm limit. Richard said it was only a 2B and asked if there was

any data showing the same toxico-kinetics as ETO. Robert said it acts at the site of contact, the nasal epithelium, similar to ETO. There is a detoxifying mechanism similar to formaldehyde, and maybe ETO. There are studies which look at the relative potency of ETO and PO to bind to DNA at a cellular level.

Richard asked if the assumption is that PO will behave as ETO. Mike and Robert responded yes, but maybe not as potent. Allan asked what the TLV is for ETO. Bruce said that the ACGIH is 1 ppm for ETO. Mike said that NIOSH is 0.1 for ETO. Bruce said that Cal/OSHA is 1 ppm ETO. Patricia said that Cal/OSHA had a vertical standard, 5220, for ETO, and asked if federal OSHA also has a vertical standard. The committee members had several separate conversations.

Richard asked if 2 was low enough. There appears to be convincing evidence of PO carcinogenicity. There seems to be convincing mechanistic evidence. Dagmar and Robert didn't consider the cancer endpoint. Forest said that he has several risk assessments, from EPA, IRIS. He just got them last week, and hasn't looked at it. The NTP is a qualitative assessment, that it is carcinogenic. OEHHA and Cal/EPA have an acute reference exposure level, which is 3 mg/m3, on the order of 1 ppm. Allan asked what the context is for the reference limit. Will said it is a 1-hour exposure, it is not something you would expect to be adopted in the workplace, because it is based on the sensitive individual.

Robert said the IRIS reference concentration is 0.03 mg/m3, which is approximately equal to 0.01 ppm. Bruce said that was a couple of orders of magnitude below what the committee is contemplating. Robert said that the IRIS value is based on public health risk. Dagmar said it is based on 24 hour exposure. Allan asked how the number is derived. Robert said that they identified a NOAEL and divided by 100. Will said that IRIS has different reference values based on routes and endpoints. There is a cancer potency endpoint. IRIS has difference reference concentrations corresponding to difference acceptable risks. A 10E-6 cancer risk corresponds to 0.1 ug/L (oral in drinking water), which is probably lower than the reference concentration. There are different approaches to cancer and non-cancer endpoints. Bruce asked if the 10E-6 is a lifetime risk at 1 L/day. Robert said that if you ingested 0.1 ug/L, with the assumption that you consume 2 L/day, there is a 1/1 million incremental risk of cancer. Bruce asked if nasal mucosa weren't the target organ. Will said there are various numbers. For chronic inhalation, the number is 0.03 ug/m3. Robert said there were a series of numbers for inhalation.

Richard asked if the NIOSH was 0.1. Mike said that was for ETO. Tim said there is no safe level in NIOSH, no threshold. Robert said that for cancer risk IRIS uses the multi-stage linear model, which has no threshold. But information in the ACGIH documentation indicates there may be a threshold. There may be enough of a detoxification mechanism to handle low levels of PO. Allan asked what the breakdown product is. He said that sometimes what appears to be a "threshold" is only inadequate data at lower doses. He asked if there is more than one paper. Robert said that several studies talk about it from a mechanistic standpoint. The documentation doesn't talk much about the mechanism, or what product binds to the DNA. It's not a novel mechanism, it's fairly well recognized. He thought maybe the NIOSH reference which talks about the DNA repair might be useful.

Will said this brings the committee back to the question regarding how to handle carcinogens. There are risk assessments. The committee needs to decide on acceptable risk. What is an acceptable risk in the workplace? Robert said that the documentation states that OSHA policy is 10 E-3. Richard said, that's not what they've done, on asbestos it's lower. Bruce said that the asbestos PEL had been set in a lengthy appeals court process. They couldn't hit the 10E-3 target. The benzene decision says that a risk that is greater than 10E-3 is not acceptable. OSHA couldn't sample that low, to achieve a limit corresponding to 10E-3, so they added the automatic controls for certain classes of work. Tim said that workers have to be provided with higher levels of protection in different kinds of work. Allan said that the average cancer risk is 1 to 2 in 100 in current workplace standards. If you wanted to lower the risk, you might be able to target a 1/1000 risk. 1/10000 may be too abrupt. You need a systematic approach and a policy decision. The NTP study shows at 400 ppm of PO, 10/50 were effected. That's 1/1000 at 2 ppm, by simple linear extrapolation. You can do a very simple calculation. You need to look at published risk assessments. The committee agreed last year to develop a systematic approach. Bruce said that they had agreed to do it, if resources were available. Will said they have risk assessments for some substances, with numbers. Bruce said that if they took the EPA risk assessment, with a very low 10E-6 risk, and then found the level for 10E-3, that might be an approach. Allan said he is working on an article on this subject, 1/1 million is ludicrous, and dangerous to public health. You need to tackle the larger risks, the 1/1000 risk. Diesel exhaust is 1/1000; going to 1/1 million isn't a good policy, or even 1/100,000 like in California. Bruce said that if there is a risk assessment for 1/1million risk, and we recycle it to 1/1000, people may say that is no good, it gives inadequate protection. Richard said that in the past we didn't take into account cancer endpoints, but neither employers nor workers know that. Allan said that our process is transparent compared to ACGIH, which doesn't open itself up for dispute. But being

more open puts you in the hot seat. Looking at the PO cancer risk under the current proposal would be considerably lower than the current risk for more substances, if you use a simple linear extrapolation. Will said it would be better to use the cancer risk data from IRIS. He asked OEHAA if you can do 1/1000 or 1/10000 for workplaces -- they use a linearized multi-stage model, so 10 times the exposure presumes 10 times the risk. It's probably relatively accurate in this range. He read the following values for risk:
Risk24 hour concentration
10E-40.03mg/m3
10E-50.003 mg/m3
10E-60.0003 mg/m3
10E-30.3mg/m3
Further calculating for reducing the exposure to 8 hours, leaves 0.3mg/m3*1/0.238 = 1.3mg/m3; the 1/0.238 represents 168/40. At 1 ppm/2.38 mg, this would be 0.53 ppm for a 1/1000 risk.

Will said the numbers are based on animal testing with a factor of 10. Bruce asked if it was still linear at 1/1000. Will said that it was more likely accurate at this end than at 1/1million.

Tim asked if extrapolating to higher risks takes into account repair mechanisms. Will said that repair mechanisms were more likely to be effective at the 1/1milion risk dose levels. Patricia asked if we had decided on 1/1000. Richard said this was for illustration. Allan said that the risk for most substances is 1%, except for those with standards adopted after the benzene decision. Will said that the ones where the number was set after 1980 are more protective than the broad range of carcinogens. Robert said a paper in 1987 showed OSHA's new approach to risk assessment tended to address a 1/1000 risk. Patricia asked if he was saying that the current ETO PEL is less than a 1/1000 risk? Will replied that it was probably set with 1/1000 as a goal, and they probably didn't meet that goal.

Patricia said that she would be curious to see how OSHA came up with 1 ppm for ETO. ETO is an A2 vs. PO as an A3. PO is a less potent carcinogen. She said she would be interested in seeing the risk assessment data for ETO. Will said he thinks that OSHA currently strives for a 1/1000 risk, but doesn't always get there. Allan said that the risk for all carcinogens is 2/100. Often cancer is entirely ignored in establishing the PELs. It is important to start where the risk is. Address the higher risk substances, before trying to reduce the risk on a substance to one in 10,000. If they were to propose 1 ppm for PO, that calls into question the PEL for ETO. Bruce said that it may be that OSHA used risk assessment data that differed from the EPA risk assessment. Will said that he is confident OSHA used a 5-10/1000 level for ETO. Patricia and Bruce said that the information would be in the preamble. Bruce said that he can get the preamble for the federal ETO standard. Will said that they should look at the preambles for carcinogens which were regulated in the past 20 years, including methylene chloride, ethylene oxide, benzene, and cadmium. Tim said that the asbestos standard was 2.8/1000. Will asked if there was a standard for perchloroethylene, but the response was that there wasn't. Patricia said she would like to see the numbers they came up with. Obviously, we can't go to 1/1million, but she would like to see what the numbers were in setting these standards. Bruce said that asbestos wouldn't be useful because of the additional work practice requirements.

Allan offered his group to review the risk assessment criteria that OSHA used for the recent standards. He said that all of them had ended up in court. One doesn't necessarily want to do that. There's a battle between those who want a 1/1million standard, and others who want much higher risks. You can end up shooting yourself in the foot if you drastically reduce risks. Patricia said it would be useful to know what the risks are, whether or not we agree. If we try to go down below the ordinary, to go orders of magnitude lower than what's already out there. The ACGIH is going down 10-fold in this recommendation on PO. We should look at whether we are proposing to go down another 10-fold.

Mike said that 0.3 is only on a 24-hour day basis. The fraction is inverted to modify it 168/40. Tim said that the calculation works out to 0.5 ppm. There's only one significant figure. Mike said that it was still a ways away from 2 ppm. The E-3 calculation was written on the board as (0.3 mg/m3)(168/40)(1ppm/2.38).

Tim said that the benzene decision allowed OSHA to look at feasibility. Richard said that our job is to determine the toxicology. Let the Standards Board deal with the feasibility issues. Robert said that the EPA benchmark dose approach doesn't presume an acceptable risk. It's done on a case by case basis. Allan said that the bench mark dose projects from levels determined from studies to pose a 1/100 or a 1/10 risk. Then they add a safety margin. The EPA way out of the 1/1million risk assessment is to switch methods. The problem isn't so much with the method as with the 1/1million target. The public wouldn't find a risk of 1/100 to be acceptable. You wouldn't get much argument in taking another 1/10 safety factor. Richard said that if Dagmar had taken a 1/10 additional safety factor

to the 5 ppm, they would have ended up at 0.5 ppm for PO. Will said it's not that different from Allan's approach to start at the 10/50 risk level, and then adjust. Allan said the animals were exposed to 400 ppm on a pattern that is more similar to workers -- for 8 hours/day, 5 days per week. Will said it was probably 6 hours per day. Allan agreed. Tim said the handout said 3 hours per day -- reference #23. Allan said it was easier to work out workplace risks from animal data -- they usually use adult animals, whereas in IRIS risk assessments they deal with developmental issues in young animals. He said that if Craig agrees, he would work on a simplified OSHA approach. Richard said that he had prepared something which Craig had looked at.

Patricia asked if there was any resolution on PO. Richard said they had come to 0.5 two different ways. He asked if the committee wanted to wait for Allan's analysis to finalize the recommendation. Mike asked if this was based on the A2 rating, and people responded that it was an IARC 2B, and an ACGIH A3. Richard said that he puts in a 10 safety factor for a carcinogen.

Allan said that the problem with the NOAEL is that it depends on the number of animals in the study. The more animals, the lower the no effect level. The benchmark is better; it's the level of 1/100 risk. Richard said he would be happy if Allan or Craig wants to massage his proposal. He just wants there to be a systematic approach. Allan said that they could say that if there is no human data, extrapolate to the 1/100 animal risk, then take a 10 safety factor. He asked if that is sufficient safety. It would clearly be progress. Mike said that if there were human data, they should take that. Allan said that if there is actually evidence of cancer in humans, this approach might not be sufficiently conservative. He would propose that you find the concentration with a 1/100 risk, and then decide on the safety margin. Using 1/100 risk as a benchmark, it doesn't require much extrapolation. The study usually involves 50 animals. Those arguing for 1/10 say that's sure, then use a larger safety factor. You generally end up with the same results, because the function is very linear at that point. Mike said he likes having a systematic approach.

Allan said that he didn't incorporate a species conversion factor, for example a 4 from rat to human. Will said he also didn't factor in the difference for 6 to 8 hours exposure. Allan said that the species conversion makes a big difference, it's based on body surface area, and metabolic rate. The metabolic rate makes a difference if the substance has the effects when it is activated. It is not so important if it has to be deactivated. He said that they teach a course on risk assessment. He will pull the information together for the next meeting. He asked if they needed to reach a decision today. Patricia said that they did not. All members agreed that defining a methodology was more important. Richard said that it would be best if they could come back with something relatively simple. Allan said he would ask his colleagues and report back to the next meeting. He asked when the next meeting was. Bruce said January 11th.

Robert said that they should look at ETO in discussing PO. Bruce said he would find the ETO OSHA risk assessment. Patricia asked if they had the OEHHA risk assessment. She referred to an e-mail from Will saying he had identified OEHHA risk assessments for 10 compounds. Forest said that the OEHHA risk assessment for chronic PO exposure was based on IRIS 1995 inhalation reference concentration of 0.009 ppm, based on hyperplastic changes in the respiratory epithelium. That may be a more sensitive endpoint than cancer. Patricia said that 0.009 sounds like a 1/1million risk. Will said it was ambient, 24/7, full population, more sensitive endpoint than cancer. It is based on a LOEL of 30 ppm for degenerative and hyperplastic changes. Then adjusted by a factor of 3 for interspecies variation, 10 for intraspecies, and 3 for a LOEL vs. a NOAEL. Allan said that this includes babies, etc. Will said it was based on the Kuper study, the same as IRIS, reference #33 in the ACGIH documentation. Tim asked if they were thinking of nasal cancer for PO. He asked if they were factoring in that rats are obligate nasal breathers. Will said there was no reason to do so. People breathe primarily through their noses at non-irritating levels. Bruce said that he would get the OSHA preamble for ETO and find what they considered to be the acceptable level of risk. The OSHA risk assessment for ETO, to compare it to PO. Alan and Craig will come up with a process for risk assessment for carcinogens. Bruce asked if the committee wanted to table PO pending development of this process.

Richard said that the group wanted to see the ETO risk assessment. We came up with a number for PO, for a 1/1000 risk. If OSHA was also shooting for 1/1000 with ETO, it doesn't make sense. They have 1 ppm for ETO. We have 0.5 ppm for a less potent chemical. Allan said that this is an estimate for a worker who spends 8 hours/day at the PEL. Workers aren't all exposed to that risk. He asked if Bruce was getting the ETO OSHA risk assessment. Bruce said that he would. Allan said he would get information regarding overall cancer risk, and propose a simplistic approach they can use for the data. Richard said that they won't all get the same numbers, but they can use the same approach. Allan said that PO is tabled till then. Richard said it is mostly finished, but one more number is needed. Allan said they need to take existing standards and risk estimates for those substances outside of OSHA, to come up with a reasonable safety factor, to avoid drastic changes. Richard said that Allan should come up with

the safety margin. Allan said that puts them on the hot seat. Richard said that the committee would take the heat as a group, but was relying on Allan's expertise. Robert said he thinks the EPA deliberately left out safety factors in discussing benchmarks because they also need to take into account how much of the population is exposed, and how robust the data is. Allan noted that the EPA had held back on arsenic. When they reviewed the data they found the actual risk to be above the benchmark. So they had to revise the whole risk assessment. Robert said that the same thing had happened with dioxins -- the background levels were too high. Allan said that the recommendation from WHO was 1 ng/kg/day. Two-thirds of the population was above this, so they revised the recommendation higher. But at least the process was transparent.

Richard passed out a summary sheet on ethylene glycol monobutyl ether (2-Butoxyethanol) (EGBE). Bruce noted that it was now noon, and asked if they wanted to take a lunch break. Patricia suggested that they plan for future substances for the next meetings right after they return from lunch. She also suggested discussing the proposal for cancer risk assessment at the next meeting.

Lunch

The committee reconvened at 1:00 p.m. The committee confirmed that the next meeting is scheduled for January 11, 2002 at 10:00 a.m. The committee scheduled the following meeting for March 1, 2002 at 10:00 a.m. Bruce noted that Mike hadn't returned, and suggested that the March 1 date remain tentative until they hear from him. He also noted that Carl isn't here. Bruce agreed to attempt to find a room in the Oakland State Building for January.

Bruce asked which items to put on the agenda for next time. Patricia asked when they would take up Beryllium. Bruce said he would like to post a specific notice for that. It was agreed to put it on the agenda for March, and Bruce will get a bigger room for that meeting. Patricia asked if Allan and Craig could have the carcinogen risk assessment information for the January meeting. Allan said they could. Patricia asked what other substances would be on the agenda. Dagmar said that if they had the carcinogen discussion in January in the a.m., they could also finish the PO discussion then. They could do ethyl tert-butyl ether (ETBE) in January as well. Most of the literature is on MTBE; they have had trouble finding articles on ETBE. Robert said that some of the ACGIH documentation citations were apparently abstracts. Will said that he had the abstracts Dagmar had requested. The pages he gave her have 12 abstracts on MTBE and ETBE. He hasn't seen the journal that the abstracts came from. He doesn't know if they were from a conference. He can get the journal. He said that these abstracts are the worst sources to look at in terms of evaluating a substance. The ACGIH neither provides a comprehensive list of references, nor an intelligent subset. Patricia asked Dagmar if they wanted to do other substances in their group? Dagmar said she would do the Vinylidene chloride (VC) and Vinylidene fluoride (VF). One is just dropping the STEL. For the January meeting, Dagmar and Robert subcommittee will prepare: PO, ETBE, VC, and VF.

Bruce said that glutaraldehyde is assigned to Tim Robert' and Carl Foreman. There are interested people in health care, who should be notified when glutaraldehyde is coming up. Patricia said that octane and pentane are just issues of deleting STELs. Bruce said they did propane last time. Tim said they would do octane and pentane next time. Richard said that he hadn't talked with Mike, but assumes Mike will continue with ketones, since he has already done acetone. Richard will do n-butyl acrylate for next time. [Mike returned]. Mike said he would do diethyl ketone for next time. Patricia said she is ready to do dichloropropionic acid today, and will put off pentyl acetate to the next meeting. Craig wanted to put off until next time the discussion of 1,3,5 Triglycidyl-s-triazinetrione, because it is more complicated. She asked about hexachlorobenzene. Bruce said that hexachlorobenzene is an obsolete pesticide, which may be encountered in some hazardous waste scenarios. Patricia noted it was not on her copy of the 5155 table. It is supposed to be an A3 animal carcinogen. Bruce found it on his copy of the table. She can prepare it for discussion at the next meeting. Mike said the 3/1 meeting in Oakland was okay with him. Richard Cohen will chair the next meeting.(Jan 11)

Ethylene glycol monobutyl ether (2-Butoxyethanol) (EGBE):

Richard said that the current PEL is 25 ppm with a skin notation. The ACGIH proposal is to delete the skin notation, and lower the PEL to 20 ppm. He read through the summary sheet he provided. He noted that the notation Low following TD/LC is an error, and should be crossed out. He said that he had reviewed the studies and the ACGIH documentation, and the summary is on the sheet. He extrapolated from the study does, and applied a 10 safety factor. He noted that the notation "Low" is incorrect for the safety factor of 100 Toxic Dose/Lethal Concentration. He reviewed the extrapolation considerations. The extrapolated doses are in the far right hand column of the table on the summary sheet. There are no cancer end points. The cancer data is soft. There is no reproductive data. The most problematic effect was the Hanfroid study, which showed a slight decrease in hemoglobin at 0.6 ppm. This is

troubling. Although the study classified it as a NOAEL, it s clearly a lower effect level. Other limits are the NIOSH REL of 5 ppm, CICAD at 11.3 ppm, and EPA at 11.3 ppm. This number is below all of the regulatory limits. He agrees with deleting the skin notation, skin absorption is not a significant route of exposure. In terms of the PEL, there is no support for 20. Levels should be well below 5. He recommends going with the NIOSH REL of 5, although one could easily argue for a lower level. The effect in the Hanfroid study was subclinical. Mike asked if it was reversible. Richard said that the effects of glycol ethers are usually reversible. The Hanfroid study found a 3.3% decreased hematocrit, significant at 0.03. Craig said that was not a very large effect, and Richard agreed. Craig asked how good the exposure assessment was. Richard said he didn't know, he would like to see the full article. The citation is Haufroid V, Thirion F, Mertens P. Biological monitoring of workers exposed to low levels of 2-butoxyethanol. International Archives of Occupational and Environmental Health 70(4):232-6. Patricia said she thought she could get the article on line.

Richard said that even if you didn't consider that study, the numbers are much lower than 20. You could argue for a PEL of 5 ppm based on other studies. In the Johanson study, 7 volunteers performed light exercise on a bicycle for two hours. The abstract doesn't mention the end point. Allan looked at the abstract and agreed there was no mention of the endpoint, only a discussion of toxicokinetics. Robert said that the Carpenter study noticed immediate irritation, and some nausea and headache over 4 hours. He noted it is a 1956 study. He asked whether an adjustment needed to be made for exposure time if the endpoint is irritation. Richard said he factors that in. He got 10 ppm as an extrapolated dose from the Carpenter study by dividing 200 by 2 (for time) and by 10 for low effect. He adjusted for time in the Johanson study by dividing 20 by 4 to get 5 ppm. Robert said that without the time adjustment, both would be 20. Richard said it seemed like they need to look at the Hanfroid study. He said that CICAD means Concise International Chemical Assessment Document, and it is based on NIOSH and ATSDR data. CICAD came up with 11.3ppm. Allan asked how ACGIH got from the 25 current to 20. He read from the ACGIH document that the 20 was for harmonization. Bruce said that the CICAD and EPA values are really in mg/m3. EPA is 13 mg/m3, CICAD is 13.1 mg/m3. 13/4.83 is approximately 3 ppm. If you then multiple by 4.2, the value is probably harmonized. Tim asked if the values from the Johanson and Carpenter studies are based on irritation, whether they shouldn't be kept at 20? Richard said yes, if it was looked at only in terms of irritation. Bruce said that they should leave it alone if they're only going from 25 to 20. Richard said that they should look at the Hanfroid study, which is based on the effects on red blood cells. Clearly NIOSH and EPA are taking it to lower levels. There is a red cell concern with glycol ethers. Patricia said that she would get the article and e-mail it.

Craig said he was concerned that the animal studies show lower levels in multiple species, but the human values are higher. Richard said he would rely on human data. Will said the animal studies were all blood effects. Craig asked if Richard would rely on the human data, even though the animal data was from multiple species. Richard said he supported removing the skin notation because it is not an important route. Will said that there was a hemolysis effect. Richard said there was some effect on cell membranes. Craig noted that the Hanfroid study agrees with the animal studies. Richard said if you removed the 10 safety factor in the extrapolated dose from the animal studies, you would still get a number around the NIOSH REL. The NTP study is pretty low -- it found a measurable adverse effect at 31 ppm. Allan said that if those effects are real, it is a concern. Hanfroid only looked at humans.

Will says he frequently sees a claim made that humans are less sensitive to hemolytic effects than animals. But where are the human studies the claim is based on. Richard said he had done a literature search, including medline and toxline, and looked at the references cited by ACGIH. This is all he found. Will said that there must be more human studies for that claim to be specifically and flatly stated. Allan said not, that one person wishfully makes a statement, and everyone repeats it. Will said there must be more data. Richard said that he would look again, and suggested that Will could also look. Allan read the statement in the ACGIH documentation, which referred to a statement from Carpenter that people were not as effected, but also stated that 3/4 of the studies showed systemic effects. Will said he would like to be thorough in reviewing human data, and he will work on finding other studies. Allan read from the ACGIH documentation that stated there was a minimal potential of hemolysis in humans as compared to rats, based on models. He said it was worth looking further into the issue. Will said that in animals, hematologic effects are clearly the sensitive endpoints. He said there must be more to the claims regarding less effect in humans. Patricia will e-mail the Hanfroid study. Will will look for more human data. The discussion will conclude at the next meeting.

Acetone:

Mike passed out a summary sheet on Acetone and a printout from the IRIS database. He said that the current PEL is 750 ppm, with a 3000 ceiling and a 1000 STEL. The federal PEL is 1000 ppm. The ACGIH suggestion is 500 ppm TWA, 750 STEL. He reviewed material on the summary sheet. The NIOSH IDLH level is based on 10% of the

LEL. He said the animal data look like pretty good numbers. The ACGIH ranks its carcinogenicity as A4. There are 17 human studies in the ACGIH documentation, summarized on pages 14 and 15 of the documentation. The endpoints include irritation hematopoetic, immunological, and neurological. Referring to his summary sheet, he said that some end points occur at 200-300 ppm. He also called attention to the Nelson study, which showed that 200 ppm was the highest concentration volunteers could tolerate for an 8 hour period. He called attention to the table on the summary sheet showing that other countries have lower PELs. He referred to page 17 of the ACGIH documentation, calling attention to the observation that complaints of odor and irritation were increased as subjects entered the chamber at 500 ppm. Below 200 ppm effects are arguable. There is a reasonable case for reducing the PEL to 500 ppm. His conclusion was that the committee should consider a 250 ppm PEL, with at 500 ppm STEL, and at a minimum reduce the PEL to 500, with a 750 STEL.

Mike continued that data from human studies show significant effects below and above 250. On average there are systemic and neurological effects detected at 250 ppm. Regarding animal studies, if you use the formula to correct for an animal study, and to account for work hours, the LOEL's from animals are around 210. This is a factor of two different from the ACGIH limit. He wanted to get the study from the British Royal Society of Chemistry, cited on p. 19 of the ACGIH documentation, which recommended a PEL of 250 ppm.

Patricia said that the documentation showed effects at 200, and that the ACGIH recommendation for a 500 ppm TLV made no sense in light of this documentation. Mike said the ACGIH said the combined weight of evidence supported that value. Patricia said that they say that effects at less than 200 ppm are arguable. Allan said that the 1978 NIOSH REL recommendation was for 250 ppm. Will said there is probably a good rationale for 250, the RELs are generally well rationalized. Allan read from the documentation that discussed 250 based on the 1943 Nelson study. Craig said that the ACGIH documentation calls effects below 200 ppm questionable. Patricia responded that they don't argue with the effects shown at 250, but then they come up with a recommendation for 500. Mike read from the documentation that 500 ppm is higher than the majority could tolerate. He said that the PEL should be put at 200. Allan asked what are current exposure levels. Richard said that when he goes to workplaces, they are usually less than 200 ppm. But people in the 200 ppm range can be symptomatic. Patients he has seen were well below the PEL, but they were sick. Tim said there is a high variability of exposure during the day. The 8 hour TWA isn't very relevant, there are often a series of peak exposures. Patricia said we shouldn't set the standard at 500, if it is irritating at 500. Mike referred to the ACGIH documentation, citing Nelson that a 3-5 minute exposure at 500 ppm produces respiratory irritation. Another cited study showed 2 minutes to 4 hours at greater than 900 ppm for throat and lung irritation. Another study found throat and nose irritation at 901 ppm, 8 hours/day. There was another study, 6 hours per day, at 250 ppm, which showed nose and throat irritation. Will said that the problem is that these are effect levels, without a NOAEL. There are no NOAELs given for neurological endpoints. There was a 3-5 minute NOAEL at 200 ppm, but the rest of the reported values are effect levels. Mike said that it was tough to justify 500 ppm. Will said that you shouldn't average in effect levels. Richard said that acetone and isopropyl alcohol are very widely used. Employees and employers view them as not toxic. They're used like grape juice. There is some synergy in liver toxicity between ketones and alcohols. Many studies show exposure to solvents in general increase the risk of miscarriage and there is one new study relating these exposures to birth defects.

Craig said that he wanted to go below 500, but the question is how much. Allan asked if any workplaces currently exceed 250 as a TWA. He asked if going to 100 would be a problem. Mike responded that acetone is widely used. Exposures are usually intermittent. For example there are peak exposures during wipe cleaning, and then zero for the rest of the time. It would be hard to hit 250 on an 8 hour basis. Even 100 would be easy to meet as an 8 hour TWA. The STEL is more important. He suggested 500 based on the nose and eye irritation. Richard said that in his experience in biotech and electronics exposures are rarely over 50. Mike said that in his experience exposures in those industries and in aerospace are rarely over 50. But in some applications such as the installation of flooring materials, they are higher. Tim said there were also higher exposures in boat building. Mike said he would like to go below 500. 250 could be justified based on the Nelson study, reference #64, and on the Matsushita 1969 study, reference #65. Bruce said that #65 is a better justification, because it shows a change in reaction time, which is a safety hazard in operating equipment. Mike said that #66 gives one of two cited NOAELs. Mike said that 250 ppm for 5.25 hours is a NOAEL. 500 is a LOEL. One 1975 study of reproductive endpoints of 1000 ppm for 7.5 hours, shows a shortened menstrual cycle (#68).

Richard said that if the committee picks 250, it will harmonize with NIOSH. Allan referred to p.13 of the ACGIH documentation, which found reproductive effects in Russian factory workers at lower levels. Mike said there were other reasons for a 250 ppm TWA, including that one study found complaints of odor ant irritation at 250 ppm were slight, when compared to exposure at 500. Richard said that the recommendation should have a good basis. Allan asked why we don't see more complaints, if exposure levels can't be tolerated. Mike said exposures were not

usually at those levels. Allan asked what a safe level should be. He suggested that 100 ppm might be appropriate. Mike said that some industries could be enhanced by realizing that the PEL is 250, rather than 750.

Allan said the documentation for the committee's recommendation of a 250 PEL should say that the argument in the committee wasn't about 250 versus 500, but whether 250 is low enough. Mike said he would like to find out if there have been violations of the acetone PEL. Patricia said she would also like that information, and asked if it was available from the OSHA data base. Mike said that the literature shows irritation at 250 ppm. Bruce said the references #65 and #66 show significant problems at 500, such as increased reaction times. Allan said that the Toxicological Review of Selected Chemicals quotes Dr. Raleigh's characterization that dizziness, nausea and irritation are no impairments of health. In 1989, claims that dizziness didn't matter were rejected, because of the increased risk of accidents in the workplace. Richard said that there are no subtle indicators for CNS damage that occurs after 11 years. There are problems with long term neurotoxicity, and the only early signs are symptoms like headache and nausea. Robert said that employing the extrapolation matrix to the cited studies would have resulted in recommending much lower levels. Allan said that the documentation should reflect that 250 represents a higher recommendation, rather than a lower one.

Richard said that the problem is peak levels. Mike said it is easy to get high peaks due to the high vapor pressure of acetone. Richard said that we might need a ceiling. Bruce said there is currently a 3000 ppm ceiling. Allan asked what a ceiling limit is, in practice. Patricia said that it is often measured by a direct reading instrument or Draeger tube. Richard asked about a 500 ppm ceiling, since they won't be taking the TWA very low. The irritation level is really relative to a ceiling level. Tim said there might be a strong reaction from industry with a very low ceiling. Mike said that the use of nail polish remover might put you momentarily over a 500 ceiling. Allan suggested going to the 250 8 hour TWA. Mike said if you punched the numbers through the risk assessment equation, you could get into the teens for the PEL. Richard suggested a ceiling of 1000, a STEL of 500, and a PEL of 250. Will said the justification for those numbers would be easy, the documentation shows irritation in 3-5 minutes at 250, not 500. Mike asked if you need a STEL if you have a ceiling. He would be happy with a ceiling and a PEL. Robert said that without a STEL you could have close to a ceiling for an hour -- you need a STEL to control those exposures.

Bruce asked if the committee was prepared to recommend a TWA of 250, a STEL of 500, and a ceiling of 1000? Richard said there is a feasibility concern regarding the 1000. He said that the committee had significant concerns that 250 isn't low enough, based on the studies summarized on the handout. Also, the risk assessment calculations would indicate a lower limit. Tim said that adverse effects include delayed visual reaction time. Richard said that the proposed limits are to protect against CNS and mucosal irritation effects. Reaction time is a CNS irritant effect. Bruce said that reaction time is a measured effect references #65 and #66. Mike said one of the problems with going to 100 is that we don't have the full articles, which are in Japanese. Richard said that the 250 is also justified in terms of the NIOSH REL, and the Japan, Sweden, and UK recommendations, and the NIOSH criteria document.
[Allan and Richard left at 3:00]
See below for final discussion of Acetone

2,2-Dichloropropionic Acid (DCPA)

Patricia passed out a summary sheet regarding DCPA. The ACGIH has recommended changing the TLV-TWA from 1 ppm to 5 mg/m3. 1 ppm is really 5.8 mg/m3. The change is recommended because the problem is the magnesium and sodium salts, including the herbicide dalapon. These are water soluble salts. There is no different information toxicity. There is no discussion of toxic effects in the field study cited in the documentation, which looked at blood levels and half-life. ACGIH's logic for proposing the change to mg/m3 is that a ppm exposure limit is not appropriate for a substance which mostly occurs as a liquid aerosol. The ACGIH proposal is for inhalable particulate mass (IPM). The IPM has a higher cut off than ACGIH respirable mass. Respirable mass is 50% of 4 micron particles. IPM is 87% for 5 micron particles. The ACGIH TLV proposal is defined in terms of this sample. ACGIH respirable fraction used to use a 50% cut-off at 3.5 microns, but it was changed to a 4micron cut-off. Tim said that he has done sampling for the inspirable fraction, but never side by side with respirable. Patricia said that when you change from a total mass standard to respirable mass, you potentially increase the total mass level. The only sampling method for this substance is a partially validated NIOSH method for the vapor. She said that we could change the standard, but it doesn't mean that we can analyze for the salt. Tim said that you could collect droplets of mist on silica gel. Patricia said there is no method for analyzing for the salts. Mike asked if it was a liquid. Patricia said that the salts are solids. Will said that the acid is liquid. Patricia said that in the commercial product, the salts

are suspended in liquid, and are in the ionized form. She said that dalapon is applied in water. Tim asked what the commercial names are for this product. Patricia responded: Dalapon, Ratapon, and Dowpon. It is a herbicide.

Page 2 of the handout contains a formula which applies the safety factor. Mike asked if the dose was mg/kg/day. Robert said the study is a two year feeding study. Craig asked if it was 90 days or two years. The ACGIH documentation refers to a sub-chronic 97 day diet study, and a chronic effect level at 50 mg/kg/day for 2 years. Robert said the ACGIH cites a NOAEL of 115 mg/kg/day. Will said that they shouldn't make any calculation based on the ACGIH documentation, since they don't know what the ACGIH used as a basis. Robert said that it may not be appropriate to look at inhalation limitations based on a feeding study. A feeding study is almost a bolus study. Will said this could be a bolus dose. They could have been feeding daily 5 days/week, or every day, but it doesn't say. There could be a correction for 24 hours and 5 vs. 7 days. Bruce said there is also a problem with the cited 115 mg/kg/day vs. 50. The only actual study appears to be reference #4. Patricia said most of the other references aren't studies. Only #4 and #6 are, and #4 is the key. Bruce said that #4 is dogs and rats. Patricia said #12 is an unpublished report. In reality, the only change being proposed is from ppm to mg/m3.

Bruce said that the other reality is that DPR is the primary regulator for pesticides. We have jurisdiction over manufacturing and certain other exposures. Patricia said that Cal/OSHA doesn't have a definition for inspirable particulate mass. Bruce said we do not distinguish between IPM and total mass. Will asked if for other substances, we don't express PELs both as ppm and mg/m3? Bruce said we currently have an exposure limit of 6 mg/m3. Patricia said this only would lower it by 1 mg/m3, and get rid of the ppm limit. She suggested leaving it alone and ignoring it. The change isn't worth the time. She proposed keeping the PEL as it is. Mike said that even is you used a correction factor, there would be no big change. Bruce asked if there were any objection to taking no action. There was no objection.
Acetone cont.
Craig said that the next item on the agenda would take some time. Patricia and Mike noted that the committee had resolved acetone and dichloropropionic acid. Bruce said that he will have to write a statement of reasons at some point. He asked if it was true that reference #65 had not been translated from Japanese. If so, he may need more information, that someone could read. Mike suggested that he pull the Nelson study. Bruce said that the issues of reaction time and chemical imbalances are stronger. Mike said that there are a ton of animal studies. Patricia suggested using the NIOSH criteria document instead of the untranslated Japanese reference. It's available on the web and the CD ROM. Will suggested that people provide documents prior to the next meeting, including the summary sheets, so that people can consider them. He suggested that people e-mail to each other. Bruce distributed an updated contact list for the committee. The meeting adjourned at 3:45.

11-29-01

Airborne Contaminants Advisory Committee

Draft Minutes

January 11, 2002 Meeting

Members present: Patricia Quinlan, Craig Steinmaus, Tim Roberts, Robert Ku, Richard Cohen (chair), , Mike Cooper.
Others present: Bruce Wallace, Will Forest, D. Gold, and Bob Nakamura.

Articles distributed prior to the meeting: Yoshida, A Study on the Beryllium Lymphocyte Transformation Test and the Beryllium Levels in Working Environment; Kreiss, Risks of beryllium disease related to work processes at a metal, alloy and oxide production plant; Kreiss, Machining Risk of Beryllium Disease and Sensitization With Median Exposures Below 2 ug/m3.

Review of minutes:
Richard C. asked for any comments or corrections on the minutes. He noted there was a spelling error on p. 7, 5th line, "does" should be "dose." Patricia Quinlan noted that the requested article on 2-butoxy ethanol which is referred to in the minutes has been provided. There were no further comments on the minutes, and the minutes were accepted by consensus.

Bruce Wallace said that Carl Foreman is not coming. He said he did not have information regarding other people who weren't there. Robert Ku said he had sent Dagmar Fung a couple of e-mails this week. Richard C. noted that there was at least one member present per sub-committee, and the committee agreed to proceed.

Ethylene glycol monobutyl ether 2-butoxyethanol:
Richard C. said that he had distributed a new cover sheet for 2-butoxy ethanol. The 5th column shows the dose for the effect. He also has provided the Haufroid article, which is the only human study he could find on heme effects. Will Forrest said that he had found in vitro studies on human cells, which seem to provide a basis for the distinction the ACGIH documentation had made between hemolysis effects in humans and animals. Richard C. said that the question last time was why the distinction between human and animal heme effects. He said that the in vitro studies involved placing human and animal blood cells into 2-butoxyethanol. The human cells had much less lysis. This is consistent with the ACGIH claim. He noted that the Haufroid study had not found a lot of difference between the exposed and unexposed group, but it was slightly lower, on all three measures, although only the hematocrit was statistically significant. The study could be classified as a "no effect" study, or a very low effect. The exposure levels in this study are quite a bit lower than the ACGIH recommendation. The average concentration was 0.6 ppm. Even if the committee accepted the study as a no effect level, it's still quite a bit lower than the ACGIH recommendation. He suggests a 5 ppm limit.

Will F. noted that ACGIH was proposing going to 20 ppm. Richard C. said that the ACGIH recommendation was to go from 25 to 20, in order to be consistent with other limits. He suggests 5 ppm based on this data. It is also consistent with the NIOSH recommendation. Will F. asked if the data in table 3 of the Haufroid study was really statistically different, since there was less than 2/3 of a standard deviation between the values for exposed and control groups. Richard C. said that there's a p-value given, and they did a t-test. The difference is not a big deal clinically, but all three of the major indices - red blood cells, hematocrit, and MCHC are all lower. Even if you were to say that it's not a meaningful difference, and even if 0.6 ppm is taken as a no effect level, he's concerned about going too much higher. Will F. said that this study was not done at the same exposure levels as the animal studies, since 0.6 ppm is a significantly lower dose than the doses in the animal studies. He said that the Haufroid study involved a negligible exposure that doesn't cause effects in animals, and that the study found marginal effects. Bruce W. asked what the Johanson article said. Richard C. replied that that study was on irritant effects. Will F. said that he's sure that the Haufroid study was conducted with the best of intentions, but that he believed that the findings were an artifact. He said that the exposure is of no consequence, and that if it were true, it would show that animals are less sensitive on this endpoint than humans, which is not consistent with other data.

Richard C. asked if the committee though the difference on three indices are real, or an artifact. Bruce W. said that if it's real, it's still sub-clinical. He asked when a response is unacceptable. He said that excessively sensitive measurements are not necessarily evidence of an harmful effect, unless there is a long-term health consequence. Will F. said that he would not discount the study on that basis. If there is an actual effect, it should be taken seriously. But he discounts the study, because it conflicts with the in vitro data. Craig Steinmaus said that there really aren't three independent effects, it's really one effect measured 3 different ways.

Richard C. asked if they should go with the ACGIH recommendation of 20 ppm. Bruce W. said that the reason the ACGIH was proposing to change from 25 to 20 was to align with the European standards; it wasn't a health-based rationale. Richard C. said that when he did an extrapolation from the animal studies, he ended up at slightly less than 5 ppm. Craig S. said that the animal studies are low-effect studies, which show effects at 20. Patricia Q. noted there was a laboratory human study. Bruce W. added the participants were engaged in mild exercise, pedaling a bicycle. Richard C. said the study only looked at toxicokinetics. There were volunteers exposed at 20 ppm. The study reported no effects. In his calculations, he made the assumption that 20 ppm was a no effects level. Patricia Q. said that there was only one dose in the study. She asked if Richard had gone from 20 to 5 based on a two-hour study, versus an 8-hour exposure. She said that they didn't know if they had exposed the volunteers at 40, if they would have detected an effect, which would mean that the recommended exposure level would be considerably lower. Robert K. asked if the ACGIH had described the rationale for 25. Richard C., reviewing the ACGIH document, said that the TLV was based on irritant effects, from a 1956 study, an old study. It references Johanson. Toxicokinetic studies are not looking for effects. Craig S. asked if the 1956 Carpenter study had looked at heme effects? The committee had a brief discussion regarding the ACGIH documentation. Richard C. asked if there were any proposals. Robert K. said that the ACGIH change from 25 to 20 is based on irritation, and asked if the committee is proposing a change based on another effect.

Craig S. asked if we know that the human red blood cells are less susceptible. Will F. said that there was pretty much no effect in vitro on human red blood cells. One study looked at the RBCs of 10 mammalian species in vitro.

Five had very clear increases in RBC size, which is what happens, when the cells are susceptible to lysis. Five basically remained the same as control. Humans were in the no effect group, whereas the baboon was not. Mice had dramatically more effect than rats. They found negligible to no effects in human cells. Tim Roberts asked what the EPA limit is. Richard C. said the EPA recommendation is 11.3 ppm. Tim R. asked what the basis is for that EPA recommendation. Will F. said that there are two references in this article to human poisonings with hemolytic anemia. He didn't notice the references before, but he can look them up today, and see if the doses involved are relevant to the committee. Richard C. said that the EPA recommendation is based on animal data. Patricia Q. said that they didn't have any information from NIOSH regarding the documentation of their recommendation. Will F. said that NIOSH didn't always do a criteria document. Patricia Q. said that it's a 1982 REL. Will F. said that NIOSH would have something on line, they don't make RELs without a basis. Patricia Q. said that the ACGIH didn't even give references for NIOSH, normally they reverence a criteria document. The ACGIH documentation mentions a 1998 NIOSH document. The information is probably in something NIOSH did on glycol ethers, but it may not be a separate document. She asked if the committee hadn't reviewed a huge document on glycol ethers a couple of committees ago, with George Chi, which had caused them to recommend lowering EGME to 2 or 5. Robert K. said that the 2001 ACGIH updated documentation shows a 1999 NIOSH criteria document, and a document dated 3-13-00. Richard C. asked if they wanted Will F. to get the case reports. Craig S. asked how often do you get good dose data from a case report. Patricia Q. said that she feels more comfortable going lower than 20. The study on heme is 0.6, but the Johanson study would lead to 5 ppm. She would like more support regarding whatever recommendation the committee makes.

Richard C. said that they could recommend 10 ppm, based on the Carpenter study. Will F. offered to look for the NIOSH documentation. Tim R. said it was a 1998 or 1999 document. Patricia Q. said the recommendation was 5 in both. Richard C. said that the committee could recommend 10, based on the Carpenter study, unless case reports or the NIOSH documents provide support for other levels. Tim R. said that Carpenter was really at 200 ppm. If irritation is the endpoint, it's difficult to extrapolate the dose. Richard C. said that the Carpenter study really doesn't help that much. Bruce W. said that if the committee accepted the Carpenter study, the recommendation would be 20. Craig S. said that they were not basing it solely on Carpenter, but on the other data points as well. [Mike Cooper arrived at 11:00] Richard C. asked if there is a proposal to go with 10 unless there is further data. Bruce W. asked what the basis of the recommendation is. Richard C. said the preponderance of the evidence, and the diversity of the data. Will F. added that the recommendation is also based on the consistency of effects. Bruce W. said that the Carpenter study was a good basis. Craig S. said that the Carpenter study of 200, with a safety factor of 10, plus another safety factor for animals. The committee agreed to recommend 10 ppm, unless the additional documentation provided conflicting information.

n-Butyl Acrylate:
Richard C. said that the ACGIH proposed 2 ppm for n-butyl acrylate because of a no-effect level at 25, with a safety factor of 10. He pulled abstracts to the referenced studies, and looked at them. His gut feeling was that the recommendation was okay. He didn't do an extrapolation. The main issue on acrylates is sensitization. Cancer and reproductive endpoints are not significant. IARC categorizes it as Class 3. Will F. asked if Richard had prepared a handout. Richard C. said that he had not prepared a handout. He said that the OSHA limit is 10 ppm and NIOSH is 10 ppm. Germany is the only other place at 2 ppm. Patricia Q. asked is the ACGIH is listing it as a sensitizer. Richard C. said yes. Bruce W. asked if asthma is a concern with all acrylates. Richard C. said that it probably was. He searched for human studies, and didn't find any western ones. There are some in Russian, which he didn't get. Russian studies often don't meet western criteria. Patricia Q. read from the ACGIH documentation that it showed skin sensitization, and cross sensitization with other acrylates. There was a report of a skin reaction to residual on the frame of eyeglasses. Richard C. said that he didn't pull the studies on skin. Patricia Q. asked what is the "neurotic disturbances," reported in the ACGIH documentation. Richard C. said that those were eastern block reports. The studies are different there, and they have different ways of drawing scientific conclusions. Will F. said that the eastern block countries don't do science the way we do science, and he generally didn't find their stuff useful. Patricia Q. said that it looked like the rest of the ACGIH references are skin effects, not systemic. Richard C. said that he couldn't find anything systemic, other than the two Russian studies. What they were saying seemed consistent with the studies he did pull up. The ACGIH recommendation also seemed consistent. W.Forest asked if he had looked at the Merkle article - the reference a NOEL and he wonders if a LOEL was reported as well. Bruce W. said that would be many orders of magnitude away if the NOEL is 25. Will F. said that a LOEL could be 50, which would result in a different recommendation. He said he could check in the library for that article today.

Richard C. said he had pulled information from Repro Tox - it was not teratogenic in rats at levels that didn't cause maternal effects. He said hat he recommended they go with the ACGIH recommendations. Shepherd had doses at 25, 135, and 250. 135 and 250 caused maternal toxicity but no fetal effects in surviving fetuses. He took 25 as a

NOEL, and got to 2. Mike Cooper asked if there was any recommendation for a short-term limit. Richard C. said that the 2 ppm was a TWA. Mike C. said that they had considered the issue before. Richard C. said there was no STEL recommendation, until there was additional data. Mike C. said that NIOSH has no short-term limit, but it looked like Sweden did. Richard C. said he just didn't deal with a STEL. Patricia Q. said that the ACGIH is tending to remove STEL's. Bruce W. said that STELs were originally put in based on rules-of-thumb. Mike C. said that based on 5155, 4 would be the STEL. Bruce W. said that the note that Mike C. was referring to is a kind of a backward requirement - it's not considered dangerous if exposures are kept below it. But the enforcement burden is different than for a specific STEL. Richard C. said that it is a sensitizer, and that they should keep the 4, not go any higher. He asked if there was a consensus for a 2 ppm PEL. There was no disagreement.

Diethyl Ketone:
Mike C. handed out a summary sheet and pages from the NIOSH document on ketones. He said that California is currently 200 ppm. The Federal PEL was vacated. ACGIH currently has a TWA of 200, and a STEL of 300; The NIOSH REL is 200 ppm, with no STEL. He suggested adding a STEL of 300, which is lower than the default level. Diethyl Ketone is an irritant, and causes narcosis. It causes effects on the skin, eye, and mucous membranes, and is analogous to other ketones. He referred to the LC Lo, LD Lo, and LD50's reported on the summary sheet. The ACGIH recommendations are based on treating the ketones as a homologous series. Under the ACGIH recommendations acetone is 250, MEK is 200, on down to methyl-n-butyl ketone, which is 1 ppm, based on neuropathy. The human data is based on volunteer studies, which indicate that more carbons means more toxicity and more irritation. There's not a lot of data, most of it is at 200 ppm. There's not much rationale for the UK 250 STEL. The numbers are based on analogy. He suggested approving 300 as a ceiling so that the ceiling is lower than the 5155 default STEL. Using the risk assessment formula, based on the rat LCLo, the calculation would be about 20 ppm, which is an order of magnitude lower than the TLV. Richard C. asked what the conversion was between ppm and mg/m3. Patricia Q. said that 200 ppm = 705 mg/m3. Mike C. said that they don't have human volunteer data for diethylketone regarding how much people can stand. There aren't a lot of studies regarding a rationale for lowering the STEL. The ACGIH rationale seems reasonable. Clearly, other ketones are better studied. Will F. said that the major concern is axonal neuropathy. Mike C. said that it wasn't a concern with this compound, it's a concern with methyl n-butyl ketone. Bruce W. said that methyl n-butyl ketone is the n-hexane metabolite. Patricia Q. asked if MEK also caused peripheral neuropathy. Richard C. said no. Mike C. said that his proposal would put it at the same level as MEK. Robert K. said that he doesn't follow the argument ACGIH is making regarding the homologous series, and asked Mike to elaborate. Mike C. said that ACGIH didn't give more details. He directed people to look at NIOSH Table III-1, the column "Highest Satisfactory Concentration." Patricia Q. said that the data was old, from 1973. Mike C. said that the NIOSH document is 1978. Mike C. said that he went through the TOMES Plus system. The only piece he found for diethyl ketone is on the front page of his handout. Med Tox doesn't give diethyl ketone. Robert K. asked if the ketones listed have STEL's. Mike C. said that acetone did, that the committee had discussed it at the last meeting. Bruce W. said that the committee had recommended a 250 TWA, 500 STEL. Mike C. asked if MEK has a STEL. Patricia Q. and Mike C. responded that the STEL is 300. Patricia Q. said that NIOSH also gives MEK a STEL of 300. Robert K. asked if the TLVs or STELS are going up or down with the homologous series. Mike C. said that as you add carbons the toxicity increases, so the limits are going down. Robert K. said that this compound is C4. But there's a C5 both above and below it, so he was trying to understand what ACGIH meant. Bruce W. said that the last one is methyl n-butyl ketone, so throw that out of the series. Bruce W. asked what is EENT? Mike C. said eye, ear, nose and throat. Mike C. said that as you get more carbons, the TLV decreases. We're ranking it right with MEK. Robert K. asked if his recommendation is 300 ppm STEL. Mike C. said that right now, the STEL is 1.5 times 200, which is the same. This just points it out. D. Gold said that a STEL calculated based on the note is not enforceable in the same way as an explicit STEL. Mike C. asked if this made it more enforceable than the recommendations in the note. D. Gold: yes. Robert K. pointed out that Mike Cooper's document said that it recommended approving a "ceiling." Mike C. said that should have been STEL. Richard C. asked if the committee agreed with recommending the 300 ppm STEL. There were no objections. Richard C. said that the committee had accepted that recommendation.

Patricia Q. asked, while we're on the issue of ketones, why the committee had gotten the data on acetone from inspections. Bruce W. replied that she had requested it. He recalled they had some feasibility questions. He had provided some IMIS data. Patricia Q. said that mostly it showed 100-200 ppm. D. Gold said there were a few with 750.

Triglycicyl

1,3,5 Triglycicyl-s-triazinetrione (TGIC):

Craig S. provided a handout on TGIC. He said that this substance is mostly associated with resin powder coating. The exposure is inhalation. He summarized the animal studies in the handout -- the two most important were references 15 and 41. He tried to get the one from Batelle (reference 15), he went to the web site but it's not on the web site. There was a statement on the website which said that most of their reports are not available to the public. Reference 41 is from Navartis and the report is not available. Richard C. said that if someone's doing a study, it should be available. Craig S. said that the two major animal studies are in bold on the hand out -- a subchronic study in dogs and a reproductive study in mice. It was assessed as a chemotherapeutic agent, so there are drug trials, which are summarized on the third page of the handout. Four are listed in the ACGIH documentation. In the Neidhart and Dombernowsky studies the effects were primarily hematologic and nausea and vomiting. The table lists the doses that effected leukocyte counts. There was suppression at 52 mg/m2. He converted it for a LOEL. The Dombernowsky study reported 60 mg/m2 was the start of effects. Robert K. asked if the drugs were given IV. Craig S. replied yes. Will F. asked if the dosage unit was per square meter of body surface area. Craig S. said yes. Bruce W. said that there was an equation for converting mg/m2 to mg/kg. Craig S. said that for weight 70 kg, for height 68 inches, there's an average body surface area of 1.83m2. A 70 g man has 1.83 m2 surface area, then you use 1.83/70, to get a conversion factor. Then you multiple the dose per square meter by 0.026 to get the average dose. The ACGIH took the same studies and did their own conversion.
Richard C. said those are standard assumptions. Patricia Q. asked why they give the dose in mg/m2. Robert K. said that for anti-neoplastics, the dose correlates better for surface area than for body weight. Will F. said there is a very steep dose response curve for anti-neoplastics, so it's important to get an accurate dose. Patricia Q. asked if surface area was only used for neoplastics. Richard C. said that generally, pharmaceutical dose is in mg/kg. Will F. said that the EPA uses something similar to body surface area.

Craig S. said that the four major studies are bolded. In dogs the LOEL was 0.8 mg/kg. In mice, there was a reproductive NOEL of about 2.5. The human data showed a NOEL of about 0.8. When converted from mg/kg to mg/m3, 0.8 came out 5 mg/m3. The dog study LOEL of 0.8 converted to 5.6 mg/m3. Richard C. said the mouse study was already inhalation, 2.5 NOEL, and 7.8-10 was the LOEL. All studies have pretty consistent data points. He has a NOEL of 5 mg/m2. ACGIH cites a mouse reproductive study, so you should add a safety factor for reproductive endpoints. Craig S. said that if you add a 10 safety factor for repro, 10 for LOEL, you get 0.05 mg/m3. For a NOEL, you could argue for 0.025, or one half. Robert K. asked what were the rationales for the safety factors. Craig S. replied 10 for subchronic as compared to chronic, 10 for animal, 10 for repro. Richard C. said we're using 2 safety factors for 3 things. Do we know anything regarding the half-life of TGIC? Craig S. said that it was very short. Will F. asked how this compares to other anti-nepotistic agents. Richard C. added that the FDA regulated them. Richard C. said that he has developed NOEL's for many anti-neoplastic agents. Robert K. said that a lot of exposure limits set by industry for these agents are lower than 50 ug/m3. Will F. said that he had thought that. Richard C. said there's not much data here.

Bruce W. said TGIC was never put into use as a chemotherapeutic agent. Patricia Q. said that it was used in powder coating. Bruce W. said that the process involved spraying the material on, and baking it to melt it on. It is used as a substitute for porcelain and gives a hard coat. Tim R. said it is also used on custom cars. Bruce W. said that employee exposures are very high. Employees are potentially in a cloud. Tim R. said they are definitely in a cloud. He said they had a small operation, and it's hard to analyze the exposures. The TGIC is less than one percent of the mix. Their operation is infrequent and of short duration. You can't use traditional ventilation system to control the powder. Patricia Q. asked if Tim R. was saying that you can't analyze exposures. Tim R. said no, but that their operation is hard to analyze because of the small scale. Craig S. asked what the detection limits are. Tim R. said that it can be detected at the TLV, but that their operation is very short duration. Patricia Q. said it was a filter method. Tim R. said you use a treated filter, and then desorb it.

Craig S. asked if there is an option of adding a sensitizer designation. Patricia Q. said that the ACGIH has a sensitizer designation, but that Cal/OSHA doesn't. Bruce W. said that we could start a sensitizer designation, but it would have to be case by case. You would have to define what it meant. Patricia Q. said we don't have this designation. Bruce W. said that the only place with an analogous designation is the director's list. It is possible to determine the source for an entry on the list, for example IARC. For example, there's no way currently to know a reproductive hazard from the standard. Patricia Q., unless it's mentioned in the standard, for example in the medical appendix to the lead standard. We've already discussed a sensitizer, but it won't come up in our list. Richard C. said that his suggestion is to consider all end points, including endocrine disrupter, sensitizer, reproductive hazard, etc. in defining the limit. Will F. said that if the PEL is protective against sensitization, it doesn't matter whether it is listed as a sensitizer. Richard C. asked if this particular compound is a sensitizer. Craig S. said that it is both a skin and respiratory sensitizer in case reports. Will F. asked if anyone is knowledgeable regarding Prop 65 and this regarding sperm toxicity. Bruce W. said that in terms of Cal/OSHA, Prop 65 is mainly a hazard communications

issue, the employer must warn employees. Richard C. said that the Prop 65 designation comes from the state list, not the PEL. Bruce W. said that there is a mention of Prop 65 in the hazcom standard. Richard C. said it doesn't apply to substances not on the list.

Craig S. said that the proposal is to adopt the ACGIH TLV of 50 ug. Robert K. asked if the mouse study said how long the exposure was. Craig S. said the only information he has is in the ACGIH documentation: 6 hours/day, 5 days per week. Will F. asked how many weeks. Craig S. said that it doesn't say. The study is referred to on p. 5 of the ACGIH documentation. Will F. said that his sheet says 7.8-10 mg, but that's not on p. 5. Craig S. said that it's on p. 10, the first paragraph. W. Forest asked if that was the same study. Craig S. said that it doesn't say that, but it's the only such study mentioned. Will F. said that a dominant lethal study isn't the same as a chromosomal aberration study, so he doesn't think it's the same study. Craig S. said he had just assumed it was the same study. Will F. said they could have looked at more than one thing in the study. He said that there is also a mention of sperm cell toxicity. He said that it was common for alkylating, anti-neoplastic agents to also be reproductive hazards. He said that he has no information that they should treat this agent less stringently than similar agents, which are usually worked with in lab hoods. Patricia Q. asked if there are PELs for other alkylating agents. Richard C. said that he creates occupational exposure limits for manufacturers. If necessary, he adds another safety factor. Bruce W. said that in absolute value, it's a very low level. Patricia Q. said that cadmium is 2, and beryllium is also very low. Richard C. said that the lowest he's recommended is for an endotoxin, which was 30 ng/m3. Tim R. said that they regulate one compound in femtograms, which is 10 E-15. Robert K. said he agrees with the concerns Will F. raised. Also, the human studies are for 5 day regimens, usually followed by three weeks of no dosage, because of the toxicity.

Richard C. proposed a 10 safety factor for animal, a 10 safety factor for short term exposure studies, a 10 fold for carcinogen, which could be used to justify 10E-3 rather than 10E-2. Mike C. asked if adding another factor of 10 would place them below the limit of detection. Tim R. said that he didn't know. Mike C. said that would be his only concern. Tim R. asked if they should use a health based number. Mike C. said you can't publish what you can't measure. Will F. said there are well established reasons for doing that, it pushes the technology. Richard C. said that it is the committee's function to make recommendations to the Standards Board. The Board deals with feasibility and other issues. Robert K. said that there are ways of analyzing which are routinely used in industry, at lower levels than 0.01 ug. For example, they use ELISA and radio immunoassay. For some compounds, there are already methods for analysis in blood, and those methods can be adapted for air, which is an easier medium. Mike C. asked if an additional safety factor is what is on the table. Richard C. responded that what he's hearing is that the group would be more comfortable with a 10E-3 safety factor. Tim R. asked if there is any information regarding the uptake rate from inhalation. Will F. said that it's a solid, and would most likely be directly absorbed. Tim R. said that depends on how inert it is. Patricia Q. said it causes contact dermatitis. TGIC has stronger patch test results than TGIC in powder coatings. Richard C. said that there's an LOEL death at 100 mg/m3. If you applied safety factors it would be 1 ug. That's two safety factors to get to NOEL, one for animals, one for alkylating, and another for cancer/repro. This information also suggests that inhalation reason for concern, there's an LC 50 in mice at 2000 mg/m3.

Patricia Q. asked how they size the particle in inhalation studies of rats. She asked what "nose only" meant. She can see it for gases or vapors, but what about the respiratory tract. Robert K. said that in nose only, only the nose of the animal is exposed. If the animal were in a chamber, there would be other routes of exposure, such as ingestion. Will F. said that in the ordinary studies, the animal is just exposed in the chamber. Patricia Q. said that she could see that, but what about other inhalation. Tim R. said that rats are obligate nasal breathers. He said that he could find the OEL's for other anti-neoplastic agents. Richard C. said that would only give a range. He asked if there were any analogous compounds. Robert K. said there were three epoxides in this molecule, which would suggest that it's cancer causing. He asked if it would change their approach if they assumed it was cancer causing. Will F. said he is concerned that it causes cancer, that's why he's reluctant to go along with the ACGIH approach. Richard C. said that TGIC was used in situation where cytoxin is ineffective, and cytoxin is one of the strongest anti-neoplastic agents. Robert K., if you assume it's an alkylating agent, how would that change the risk assessment method. Will F. said that the risk assessment for alkylating agents is done by multi-stage modeling, not by safety factors. Richard C. asked if there was enough data for that approach. Will F. and Craig S. responded that there was not enough data to do that. Will F. said that he was concerned because it is a probably carcinogen and a reproductive hazard. Craig S. said that there are two separate studies to base it on. The low effective dose is 10. 2.5 and 7.8 are NOELs. Will F. said that you would then add a safety factor of 20 or 200. Richard C. said that it sounded like they were back to traditional safety factors, and did they want 2 or 3 orders of magnitude. Craig S. said that in looking at this, he didn't consider data on similar agents; now, thinking about it, he would add another safety factor. Will F. said that if other agents are controlled more stringently, he would lower the limit. Robert K. said that they are controlled more stringently in the pharmaceutical industry. Richard C. said that he advises a client who uses alkylating agents in

bulk. They work in total isolation, like BL4, total encapsulating suit and glove box. That's how industry deals with it. Mike C. asked if they are looking at adding another safety factor, is that 10 or a different number. Robert K. said that he would be comfortable with 10. Craig S. said 10 would be reasonable. Patricia Q. said that would be 5 ug/m3. Richard C. said that he sees consensus on 5. There was no disagreement.

Lunch break

There was a general discussion of how to arrange subjects for the coming meetings, and the best way to schedule the carcinogen meeting and the beryllium meeting.

Tim R. suggested spitting the Be issues between carcinogenicity and the PEL; the former discussion would affect the latter. Bruce W. suggested separating the two discussions since they could both be lengthy. Richard C. suggested discussing the carcinogen issue along with some of the other List items, and devote an entire meeting to Be. He asked if Tim R. and/or Craig S. had word from Allan, and they said they had. Patricia Q. read from her notes that Allan had offered to review the OSHA process. Bruce replied, so do the cancer risk and include some other substance if possible.
Dates: next meeting is March 1 in Oakland, after that is May 10 in SF. Chairs: Craig will do the next, and Mike will chair in May.

Will noted that he had done research on butyl acrylate; the article people wanted didn't look useful. He also looked up TGIC, found an international document for chemical safety: no carcinogen data but it is listed as a mutagen. He also found a criteria document for butoxy ethanol which showed the basis for the 5ppm from animal hematologic effects, no human data. So if the group thinks blood is not an issue, don't rely on it.
Richard C. asked, so that means, no change?
Will: right, Also, there were 2 poisoning cases, window cleaner ingestion, that were not helpful. Humans are less sensitive than in the in vitro tests.

Robert K. noted that he did a critique of cancer risk assessments, but did not include the OSHA analysis. Richard C. asked him to coordinate the discussion with Craig.

Pentyl acetate:

Patricia Q.: before they were regulated, there were 3 isomers of pentyl acetate (handout) and two different PELs recommended. (the summary sheet needs to be corrected).

The TLVs:	n-amyl:	100
	Sec-amyl	125
	Isoamyl	100

Bruce reviewed the current CA PELs. Patricia Q. noted some of the commercial uses: photographic solutions, paints, cellulose solvents. Patricia Q. reviewed symptoms, referred to the summary sheet. Current concern is for the throat discomfort at 100, so the issue is whether to go below 50; she did not do a conversion.
Mike asked if that meant using the rat LD50? Richard C. suggested an RD 50 when there is a 500 ppm NOAEL. Patricia Q. referred to page 4 of the documentation at the bottom, discusses using 0.3 X rd50 >>43-47 ppm. Is anyone familiar with the RD50? Bruce: it referred to a respiratory depression chart. The data mentioned discomfort at 200 (pentyl). Patricia Q.: so if there is a slight discomfort at 100, is a 2X or 3X decrease appropriate? There was discussion of the use of iso with respirator fit-testing. Richard C.: found an odor threshold of 3 ppm in the documentation. Patricia Q.: so 50 may be okay, but the easiest path is to just adopt it. Richard C. suggested going along with their proposal; there are only irritation symptoms, and the only effect shows in the RD50, so it doesn't seem to be a problem. He wondered if there was direct experience in the group. Mike and Tim R. said they did not use it. Patricia Q. asked if the group proposed to accept the ACGIH, and there was general concurrence.

Richard C. asked to move on to pentane and octane.

Octane:
Tim R. presented a handout for octane, with a summary and the ACGIH data. He also did a Medline and Toxline search but found nothing new had been done for years. The basis is on the handout, and there was some information from the 20's under Patty and Yan. This morning there was discussion of old evaluations; this is a similar case. This is also one where the STEL does not seem to be supported. Mike asked if the IDLH is supposed to really be 10% of the LEL? Tim R. responded that the old IDLH was 5,000 based on irritation and impairment of self-rescue; it has a relatively low toxicity. The new IDLH is 10%, because NIOSH wanted to use 10% of LEL for

many substances in 1994. Bruce noted that the former was 50% of the LEL which seemed odd, even with continuous monitoring of the process. Tim R. agreed that it was a new philosophy. The discussion of human effects showed a narcotic effect at 10,000, the LEL. Mike asked if the group thought that 300 is appropriate? Tim R. replied that it is based on some individual reports of irritation, and the REL is 75. Richard C. noted there is no specific reference for 300 and they also argue for 50, but ended up with 300. Bruce pointed out some mouse data. Robert K. found that there was a statement of 2X the potency of heptane. Richard C. noted that it almost seems that it only matters to find the no effect level; you know at 8,000 you fall asleep, but that's all it shows. Robert K. asked if the committee should evaluate all issues? And the answer was yes. Tim R. responded that he had only looked for the data for the STEL. Mike asked if they knew why the NIOSH REL is 75? (no one knew for sure) Tim R. noted that from the LEL factor, isn't the Ceiling 1,000? Bruce replied that it could be 2000, but it gets to be more of a safety issue. Richard C. asked if there is a Cal/OSHA Ceiling? Answer: no. Bruce said there is a large burden to prove it, eg. Industry standards. But when there is a STEL, it is presumed there is a harmful effect, and easier to defend. Patricia Q. noted that it could be left as is, that has been done with other substances. Will noted that it does not seem like a chemical of concern. Richard C. suggested there was not enough data to take action. Mike thought that there would be no appreciable problem with the values that would be derived using the STEL (1000). Asked about Heptane? There is a 500 STEL for heptane. Tim R. noted that there may have been some reason for the STEL since they were popular then. Will added that if you cancel one or the other, cancel the PEL which is more likely to have an immediate effect. Patricia responded that the way the STEL is defined, you need a PEL. its better to leave it alone, this also deals with acute exposure like a spill anyway. Bruce: controlling this also means indirect control of benzene. Will thought there was no need to spend a lot of time on this. Patricia Q. made a motion to leave it as is. Mike asked about propane. Reply was no change; they had gone for raising the TLV to 2500 ppm. Committee voted to recommend no change, as Patricia Q. had proposed.

Mike asked if there was access to the NIOSH documentation for the REL. Tim R. said he has it in the Alkanes criteria document. He also noted the literature makes a distinction between the n and the iso forms. Richard C. asked if pentane was another one? Tim R. said yes, this was Carl's and it seems to be very similar. Mike noted the odor threshold is not as well defined and asked if there was information on the 5000 ppm? Richard C. suggested putting it off until next meeting.

Ethyl tert-butyl ether:
Robert K. presented ETBE. There is not much data, more on MTBE. Seems that there is a proposal of 5ppm for ETBE, and the basis is a paper by Neeland, study of 8 people, exposed at different levels with testing between exposures. Levels were 0,5,25, and 50 ppm. They did light exercise, tested for irritation and pulmonary effects. Found no chemical effects but slight pulmonary function effect: FVC at 25-50 compared to the readings at 0 and 5. Concluded there was impairment of function possibly within human variation expected. But, this seems to be the basis for the TLV. Richard C. said that the issue is the significance and statistical relevance of the PFT. Robert K. added that the ACGIH set it at 5. He looked at MTBE, found that the same group did the experiment, but the MTBE (40) seems to be based on animal studies (kidney) and not the PFT work The PFT experiment was done with MTBE but the decrement was marginal. So it seems that the ETBE shouldn't be so much lower than the MTBE. Mike responded but there is no data to set it. Robert K. recommended setting it at 20. Patricia Q. asked if this was from the FEV1? Tim R. asked if that was the only difference from the MTBE? Patricia Q. noted that MTBE also had reproductive effects. Robert K. said there was no comparable data for ETBE. For subchronic and acute, there is 400, the same as MTBE. Richard C. noted the decrement is not very large, and Craig noted that there is no dose response to be seen. Will added that looking at an earlier draft, there is a significant difference that is not necessarily related to exposure levels. Richard C. added that the PFT is not really meaningful; looks like less change in flow than parenchymal expect the opposite from the deeper cavity. Also, they say it "might be used". Bruce said yes, but if it is used, it will in huge quantities. Richard C. added that a breathing test for smelling something funny is not a blind study. Mike asked if he see changes in the FEV1? Richard C. replied that it changed a little. Robert K. agreed; the same people were exposed for the test. Richard C. said it seems that there will be a large use. Robert K. said is seems there is more concern for ETBE, but that is the only real basis. Mike asked if ETBE wouldn't be studied more if used? General response was not necessarily. Richard C. noted that if you use 100 as a safety factor, it goes to 20-50. Robert K. added that the animal study had a 500 NOEL. Richard C. said, then it goes to 50. Robert K. responded that the MTBE has a factor of 10, so they weren't consistent. Richard C. said if you use the NOEL, drop it to 5, MTBE started with 400 and went to 40. Mike said it would be nice to be consistent. Craig noted the group is not always consistent with ACGIH either. Robert K. thought 5 was more reasonable than no level. Richard C. noted that the proposals are 5 and 20. Will said it is easier to set a limit before the economic interests develop. Bruce noted that 5 would be easier to defend in rulemaking. Robert K. opted for 5. Mike asked what they would have done with MTBE? Gone to 5? Robert K. responded that his impression is that they put if closer to an

effect level than what is practiced today. Probably would have gone to ten now. Richard C. noted there seems to be reasons to go with 5, any objections? There were none.

Bruce suggested setting up a list of substances for the next meeting.
Group 1: flour dust
Group 2: ethyl buty ketone (Mike) or methyl methacrylate (Rich)
Group 3: dinitro toluene and pentane
Group 4: propylene oxide.
Robert K. noted that vinylidene chloride/fluoride is based on relative potency, and he looked only at the STEL issue.
Meeting adjourned.

Airborne Contaminants Advisory Committee

Draft Minutes

March 1, 2002 Meeting

Attendees: Mike Cooper, Will Forest, Richard Cohen, Patricia Quinlan, Craig Steinmaus, Robert Ku, Dagmar Fung, Bruce Wallace, Bob Nakamura

Bruce Wallace announced before the start of the meeting that Carl Foreman is ill and Tim had notified Bruce that he would be unable to attend today.

Craig Steinmaus is chair for this meeting and called the meeting to order. He first asked for corrections to the minutes from the last meeting (see corrected copy, file name minutes5-2.doc).

Dagmar asked for copies of the Beryllium documents distributed at the last meeting, Bruce agreed to mail them. Changes to the agenda were noted. The following substances on the agenda would not be discussed: flour dust , pentane, and DNT.

Patricia suggested going through the list of substances, and the committee agreed. Craig distributed two papers on risk assessment methodology. One describes the process used by Allan Smith. Patricia asked about the Be articles and Craig responded that there are more complete articles available, and he had mailed about 15 to Tim Roberts. Bruce said he would try to get them from Tim and distribute them to the members. Patricia continued that she had found that the Applied Industrial Hygiene issue from May 2,000 that has articles on Be and asked if the others want copies. The one headed “Topics” is fairly basic. Robert Ku he had made a comparison of the original EPA cancer risk guidelines versus the revision that was made in the mid-90’s for a presentation he had made in 1997. The newer approach is still a draft, and not adopted by the EPA. Bruce asked if this was the bench-mark approach. Robert replied yes, the EPA wants to harmonize with bench marks but they still use a linear method for genotoxic chemicals. So there are genotoxic versus non-genotoxic carcinogens. Will noted that bench-marking doesn’t get away from the rest of the evaluation. Robert replied that it gets close to a NOEL but at that point it needs a decision as to the safety factor. Bruce noted that a safety factor always has to be decided. Robert added that for customizing the risk assessment, it puts the burden on the risk manager in each situation, and that is where it stands.

Craig asked where the group wants to go from here? He suggested asking Allan to go to the next meeting to explain his rationale. Mike Cooper asked if he could make a proposal for a more concrete discussion, and Craig said he could. Will asked if there were more sources? Will responded that OEEHA has offered to come and discuss risk assessments that they have done. Mike asked if they would review the proposal and Will said they could. The group wants to get it first. Will added that the difficulty here is not the RA since the choices for data are there, but the hard part is the management and selecting the risk level. Craig asked what the OSHA risk level is. Bruce replied that he reviewed the vertical standards, and all were in the range of one per thousand. Will said that he had researched all the standards set by OSHA since 1980 and found all were close, 1to 12 per thousand; all stated a risk level, and none was below one per thousand.

Craig proposed that everyone consider risk levels before the next meeting. Bruce asked if OEEHA would work with this methodology for their risk assessments? How does it mesh with Allan’s? Will responded that they are basically the same, use the same method, but some judgements are going to be different, and that will produce different numbers. Bruce asked then can they get numbers for one in a hundred, thousand, ten thousand, etc.? Will said they can. Bruce asked, so you just decide what is an acceptable risk? Will said yes. Mike wanted to clarify that the OSHA mark Is one per thousand. Bruce replied that they start with the risk at the current exposure level and compare that that risk which would result from the change. Will added that they give an explicit number. Richard

said, that's fine, use one per thousand as part of the recommendations. Craig asked if the OEEHA reviews covered the whole list and was told that it was only some of the carcinogens. The group reviewed the OEEHA list and Will noted that there are some non-carcinogens included.

Robert said that he knew of a document that discusses various government risk levels, OSHA included written by Joe Rodericks in 1987, and it is the only he knows. Mike thought it would be something the group would want to cite. Bruce agreed and added that many of the OSHA documents refer to the Benzene decision of the Supreme Court regarding significant risk. This established that risk above one in a one per thousand is significant, agency discretion lies between one in a thousand and a billion, and anything less than one per billion is insignificant. Mike asked what year that would have been, and Will replied that it was around 1980. Bruce added that each vertical standard has a legal reference, and it seems the decision was late 70's or early 80's, but each preamble has a section called "significance of risk". Mike asked if they used the term "unacceptable". Will responded that they call it "significant risk". Mike wanted to clarify, that one per thousand is acceptable. Bruce responded that it wasn't exactly put that way, but that is where it ends up. Craig suggested finishing this discussion at the next meeting and moving on to ethyl Butyl ketone.

ethyl Butyl ketone:
Mike Cooper provided a one page handout. He reviewed the proposal, which is add an STEL of 75; there is no STEL or Ceiling. The compound is pretty well detected in air. The IDLH was lowered to 1000 because of a 1949 animal study. It is normally found in urine, and is a food additive on the GRAS list. Notable in the animal studies: 1949, Smith, found that at 4,000, all test animals died. At 2,000, all survived. Other studies indicate no neurotoxic effects at 700 by inhalation. No reproductive effects have been shown. Most regulatory limits are at 50 for a PEL, and only the UK has a STEL of 100. The ACGIH logic is based on an analogy to isobutyl ketone (referred to table on handout). Last January the group discussed diethyl ketone and picked the C4. The Smith study shows an LD on the second page to an adjusted dose of 408 ppm. This is the basis for going to 1,000. In this case, proposal is based on homologous values, and suggested going for the 75 STEL. There is no evidence to suggest irritation, and no controversy. There is not much human data. The exposures of concern would be the industrial manufacturing mode or food processing. This matches with the NIOSH review of MIBK since they seem to be similar chemicals. Bruce asked what human effects are shown. Mike replied that there is just irritation. The 1978 Ketone criteria document is the source of that data. This was used to set the Ceiling for diethyl ketone at the last meeting. There is also a good NIOSH detection method. Patricia Quinlan proposed recommending the 75 ppm STEL, there was no objection to the proposal.

methyl methacrylate:
Richard Cohen noted the current PEL is 100ppm and the TLV is 50 and noted that it is used in plexiglass production. It is interesting to see that it is used in surgery in acrylate glues when there is generally poor ventilation in a surgery. He noted that there are ACGIH-listed animal studies, and the human data are from abstracts and Gosselin and Ellenhorn are from HMSB (HSDB?). Bruce noted that the chart shows lethal animal doses at 41 and 48 (dogs and mice). Richard continued that the human data shows that it is unlikely to be a carcinogen or reproductive hazard, but it is clearly a sensitizer. For sensitization the pulmonary route is questionable, probably an infrequent source, though there would be some activity. The dose response did not account for that. In the human studies, irritant effects appear. Jcychowski did a flow rate study. The human data makes it clear that it needs to be below 100 but it is murky about being below 50. The Netherlands went to 5 based on Russian data, but most countries have set a level of 100.

Mike asked what the NIOSH rationale was. The general response was that no one got it since it had no change recommended. Richard said the data can support going to 50; there were clearly effects below 100 (means) with one report (Mizumuna) showing irritant effects at 6. The fluctuation suggests an effect below 100 also. There may be inadequate data, most of it is occupational. Because of the relatively low pulmonary potential, inhalation is not a serious threat; the problem is dermal exposure. Will noted that the problem is that the FDA banned it as a fingernail cosmetic product. It is most likely that it was due to skin exposure, but it is hard to put an inhalation context to that decision. It is highly allergenic, so does that mean a pulmonary problem? Richard responded that yes, one study showed that 3ppm caused pulmonary obstruction, but the confounder was that it was present with styrene even though the styrene levels were low. Also, people complained with a mean exposure of 6 in the Mizunuma study. This makes it hard to set the limits. Mike asked if the nail salon people (with problems) also had pulmonary effects. Will replied that they tended not to though this may be because the shops are mostly small operations. By 1987, it was prohibited. Patricia noted that it is still used in prostheses and in dental materials. Richard replied that could be a valid point and asked Will to get the Mizunuma and Jcyrychowski articles. Patricia agreed that she would like to see them also. Mike suggested consideration of the 5ppm NOEL result in the Blagodatin study too. The group

concurred that they want to see why there are contradictions, maybe there are other factors involved. Richard noted that on the information sheet, HA means headache and GU means genital urinary. Richard and Will plan to get the articles for the rest of the group. Will also noted that sensitization is consistent with the fact that a fraction of the population seems susceptible. Final decision on this is tabled.

Propylene oxide:
Dagmar Fung noted that the issue at the last meeting seemed to be that the 2 ppm level seemed adequate, but carcinogenicity had not been considered, and the group wanted to compare it with ethylene oxide. She found the criteria document and found the animal data supported the conclusion but the human data did not because the effect of the EtO could not be isolated. There was one human carcinogen study, but EtO was present. The sensitization factor is based on 3 studies. One human study showed that all were sensitized and confirmed by patch testing. Patricia noted that she had an article showing contact dermatitis with Propylene oxide. Mike added that there is a note in the guideline done by NIOSH shows the limit of analysis is 8ppm, should a level below minimum detection be used here? Craig replied that previously, the point was made that setting a standard can drive the technology. Dagmar noted that this is so with Prop 65. Mike asked about the study showing effects below 20, is that the one confounded by EtO? Craig noted that the group has to be careful about studies with confounders. Mike added that he would like to distinguish the situations where there is a pure effect or not. Will thought it doubtful that the ACGIH would use data with non-quantifiable outcomes. Bruce added that this issue came up before. He suggested acknowledging that the rationale supports 2ppm and change it later if carcinogenicity data comes to light. Richard thought that ACGIH must have taken a position on the issue. Patricia found that the NIOSH detection limit says 8, but not when that was reported. She added that there may be a lower limit now with better techniques, and she asked if it is in IARC? Dagmar found that it is 2B. Patricia found that EPA calls it B2, which means a probable human, and the ACGIH designation is A3

Craig asked for clarification. Mike noted that the proposal for 2 is supported by animal and human endpoints below 20, is that so? Dagmar replied that it was; a reduced capacity for DNA repair (according to the NIOSH document). Robert noted that they looked at the workers exposed from 0.6 to 12 ppm and lymphocyte effects, and found 23 workers had DNA synthesis inhibited. Craig added that NIOSH refers to 5 human epidemiological studies, but some of them may have EtO present. Mike asked if the DNA effect is significant? Richard replied that it is really not known. Craig added that the effect has significant implications. Will added that the EPA says that it suggests mutagenicity. Rich agreed that this was more likely than not. Will said that there is some evidence for that and it is clearly analogous to the EtO effect. Robert noted that this was mentioned. OEEHA came up with 0.92 ppm for the general public and a non-cancer endpoint. The listed uncertainty factor cumulatively is 100, the difference results from that. Mike asked Craig what would make the 2 or the 20 acceptable? Craig replied that he didn't know, but the DNA effect shows that 20 is too high. Bruce noted that the ACGIH says it exhibits 3-5 less potency than EtO on sister chromatid exchange, and if this is correct, this would be in the right relationship with the EtO limit. Richard asked if that was a cancer RA, and Robert said it was not. Richard suggested staying with 2 for now, and see if other information is found. Patricia wanted to confirm that the OEEHA RA's are not only for cancer, and Will said that was correct. Robert noted that two meetings past, numbers for the risk assessments were expressed as one in ten thousand, one in one hundred thousand, and one in a million. Will responded that the OEEHA numbers were 30 mcg for one in 10K, and 300 mcg for one in 1K so it works out to 0.7ppm. Robert said it was not clear that PO should be considered a carcinogen. Will responded that there is clear animal data for mutagenicity which is clearly analogous to carcinogenicity, but there is no human data. Also, epoxides tend to be highly DNA reactive. The EPA considers it a probably carcinogen, and it is on the Prop. 65 list. Robert asked if it should be considered a carcinogen on that basis? Mike felt that different conclusions could be drawn from the data. Craig thought it seemed carcinogenic. Richard added that deciding it is not would disagree with the NTP (and Prop 65), and that the NTP conclusions are well-respected. Mike asked what the "R" notation in the NTP meant and Patricia answered that it means reasonably anticipated to be carcinogenic. In the NTP data, "K" means known. Mike said, that he agrees with Richard to support the NTP decision, and the NIOSH data has similar implications but considering a carcinogen calls for a different number. Robert read the EtO study, and you have to assume that the EtO study is correct to accept the PO decision.
Richard asked if the EPA made the evaluation as a 24 or 8 hour exposure? Mike asked if that would make it 2, and the general response was no. Bruce noted that if you assume that the EtO decision is good, and that PO is less potent, it suggests that something is wrong with the RA because the OSHA limit conflicts with EPA's. The OSHA number is 1ppm and the EPA is much less, so if it is less potent, it is inconsistent. Mike asked by what factor? Rich said it was 4.3. Bruce said there is still a contradiction. Richard asked if the potency was based on carcinogenicity? Bruce replied that it was based on the sister chromatid exchange. Will said there was an eightfold difference, which would be 0.8ppm. Craig said, so round it to 1ppm? Richard said yes, it seems the SCE data may be sketchy. Mike suggested then 1ppm is defensible, and the others agreed. Bruce asked what argument should be made in support.

Richard responded that the committee supports the NTP carcinogenicity evaluation, and the IRIS-EPA risk assessment of 1994. The committee calculated the difference between the life-time exposure basis that they used versus the working exposure (8 hour basis) calculation, and used the one per thousand risk level for the assessment.

lunch break

Vinylidene chloride:
Robert had looked for the basis of the TLV and STEL and found that the TLV is based on a 1986 rat inhalation study producing reversible liver changes. 5 ppm was chosen on that basis, but there is no rationale given. ACGIH noted that humans are less susceptible by metabolic calculation; the reactive intermediates only become a problem after the depletion of the glutathiones that detoxify them. There was a substantial discussion about the possible carcinogenicity, citing 12 studies, one of which had positive results. Robert reviewed these conclusions, including IARC and believes that the carcinogenicity is not confirmed. It seems that it is hard to separate the mechanism and the effect; it the exposure is high enough, can trigger the mechanisms. The question is if exposures can be carcinogenic, but there is no data, and there are extrapolations. Assuming that humans are less susceptible, and that the animal effects are transient, the ACGIH chose 5, and this seems reasonable. For the STEL, there are not many studies of acute toxicity. One in 1979 by Anderson on rat mortality showed that from 100-200 there is increased mortality, and at 100, no mortality. This may be the basis for the STEL starting point, but he could not get to the 20 from that basis, and there seems to be inadequate support. Richard asked about setting it at 100? Patricia asked why the Cal/OSHA STEL is at 1ppm? She proposed to leave it as is. Bruce responded that it seems curious, but he doesn't know the history. Richard asked why work on that (supporting Patricia's proposal)? Patricia replied that it was on the list simply because ACGIH had made a change. But why did it go down and then up? It was agreed by the group to leave that as is and go to the next. Bruce asked if the group wants it to be researched, but there was not much interest in this.

Vinylidene fluoride:
The proposal is to set it at 500ppm. There is little information. For the acute effects, it seems to be 100X less toxic than vinylidene chloride. A study in Stockholm found that at exposure for 8 hours/5 days, over 14 weeks. There was initial increased pre-neoplastic changes as an enzyme deficient hepatic foci, but after 10 weeks, there were no foci (effect required longer exposure). A 1979 study by Filser indicated that the metabolism of VF is about 100 times slower than vinyl and vinylidene chloride. There is no rationale given for the 500 ppm TLV. It was probably set by taking the 5 of vinylidene chloride and applying the 100 fold sensitivity difference. Looking at the vinyl chloride, it was at 5ppm but was lowered to 1 ppm.

Mike noted that NIOSH has 1 and 5. Patricia asked that since there is no criteria document, where do the numbers come from? Will had a list of 1998 NIOSH recommendations. Will said he would try to find the 1998 document, and noted that the vinyl chloride potency related also to peak exposures. Patricia responded that it refers back to the VC standard which is at 1 ppm and 5 ppm, but that may not be justified. It seems better to use 100. Will said the group should look at the NIOSH rationale. Richard asked if this was their best data? Robert replied that yes, and it seems to be based on metabolism. Mike asked if the half-life doesn't suggest that it is around longer? Will responded that it could be a two-phase process, the toxin is created and then converted to excretable material, and then it would depend on the relative rate of the two reactions. Robert added that it is mostly exhaled at higher concentrations, and at lower concentrations, there is metabolism. Will noted that one step would be 100 times slower, and the epoxide metabolite is probably the slow step. Mike asked if we can assume that detoxification and excretion in the urine is fast? Richard replied that you cannot assume that. Some chlorides metabolize to unstable states, but there are epoxides here of unknown stability. Robert added that if the production is a slower rate, it is probable that the detoxification rate is not overwhelmed. With VC, even if the rate is 100 times faster, the detoxification may keep up. If not, there may be DNA binding and so forth. This is why he recommended 100. Will and Patricia wanted to see the NIOSH information first since vinyl chloride is now recommended to be controlled to the lowest feasible concentration. Craig recommended that this should be tabled until the next meeting.

Next meeting dates, tentatively: May 3rd in SF, and June 10 in SF.
Next time, finish methyl methacrylate and vinylidene fluoride and a discussion of risk assessment. With vinyl chloride, the Feds have a STEL of 5, so that is off the list tentatively. Flour dust is on, and maybe ethyl cyano acrylate by Richard. Robert Ku may do vinyl fluoride and bromide, and will discuss risk assessment. Also possibly on the schedule is methyl n butyl ketone.

In June, Beryllium. Bruce will get articles distributed including the paper on acceptable risk by Robert.

Richard asked if Tim is doing the Be review and Patricia said the whole group is supposed to review it. General consensus was that Tim should chair that meeting.

Meeting adjourned.

Airborne Contaminants Advisory Committee

Minutes

May 3, 2002 Meeting

Attending:
Mike Cooper, Carl Foreman, Tim Roberts, Richard Cohen, Patricia Quinlan, Craig Steinmaus, Robert Ku, Dagmar Fung, Allan Smith, Deborah Gold, Bob Nakamura, Julia Quint, Melanie Marty, Andrew Salmon

Mike Cooper is chair for this meeting, and called the meeting to order. Since there were several people from OEHHA, self introductions were made by the group. It was noted that Bruce Wallace had a family situation that required him to be absent, and that Will Forest was ill.

Agenda: Mike noted that the next meeting date was tentatively June 10 in San Francisco, and that another date needed to be set for September. These would be discussed just before or just after lunch. Mike also suggested having a brief review of the non-carcinogen risk assessment approach developed by Richard Cohen for those who hadn't attended before. Then Allan could discuss carcinogen risk assessment and setting risk levels.

Julia Quint distributed a handout showing risk estimates from completed risk assessments by OEHHA. (see Att-1.tif)
Mike welcomed OEHHA visitors to the meeting and noted that the committee is still in the process of refining the methods that would be the basis for many of the decisions for the list of substances.
Mike also checked other proposed items for the agenda, flour dust, vinylidene fluoride. Bob Ku replied that he had not received the vinylidene chloride papers he needed, including Cal/OSHA information. No one had any unusual time constraints for the day.

The minutes were reviewed. It was noted that it would be easier to see corrected minutes as strike-through and underline. Bob Ku pointed out one error in the discussion of vinylidene chloride, it should say metabolic <u>activation</u> not calculation. No other problems were noted, and the minutes were approved with this correction.

Mike asked Richard Cohen to review the approach for doing the non-cancer assessments.
Richard summarized the process: (see Att-2.tif) To generalize, we try to find the no effect dose by going to the studies, both animal and human, and calculate a daily dose for the study. Then you factor in the variables such as body weight, skin surface area, etc. Apply factors to adjust the daily dose based on an assessment of the severity of the effect. For example, minor health effects, 10, potentially lethal effects, 100, and reproductive or cancer, 1000. Also apply a factor for animal data of 10(interspecies factor). Apply the human ventilatory factor daily volume is 10 cubic meters to get air concentrations. This takes judgement of the effect's severity and what the committee wants to choose based on the different factors.

Mike noted, we choose the PEL to fit the estimated NOAEL and apply the second box of information to get the factor. Craig added that the problem is finding the data to establish the NOAEL because we find a lot of exceptions. Mike suggested applying those in the middle box. Richard responded that it was okay to have a variance factor for exceptions.

Deborah noted that Bruce Wallace was drafting the Initial Statement of Reasons for the substances that depart from the ACGIH. For example, with butoxyethanol, there was a question about the time adjustment factor (4 hr study to 8 hr exposure) when the endpoint was irritation. Mike responded that though the ACGIH is one source, it is not the only source for the data. Richard added that the idea is not to decide if we like the ACGIH write-up but to choose a good value and we know that Bruce is concerned with the justification.

Melanie Marty noted that they use a bench mark process, a regression analysis, and the standard procedure is to use a 95% lower bound, and find the 5%. Andrew Salmon said EPA has a software package to do that, and they use it. Richard noted that the committee would need someone (other than the members) to collect the data and run it. Andrew responded that they have done a lot of it. Mike asked if there are matches with our list. Andrew replied that it doesn't

match but there is a degree of overlap. Different exposures also have a derivation based on NOAEL methodology which parallels this approach but if the only endpoint is lethality, there is a 10X factor. This methodology is not used for cancer, and we don't have a specific factor for reproductive effects, but Prop 65 has a 1000X factor. There is a default factor of 10 for animal data (interspecies); this may be replaced by another method from the EPA.

Mike wanted to know if the table developed by OEHHA was based on the no significant risk part of prop 65. Melanie replied that it was not Prop 65 work, it is from the air toxics program. Andrew added that it was more general assessment. Richard asked how this all could move forward? Julia responded that HESIS doesn't have the personnel to do all the list, but they can start matching the list for non cancer endpoints with the ones where OEHHA has risk assessments done, and then OEHHA can run those. For the ones that they didn't do, they would have to work on getting the resources. Craig asked if there are formal documents for OEHHA risk assessments? Melanie said there are, and they have been public and peer reviewed. Julia added that the EPA has some too.

Bob Ku had a specific question on the benchmark process, is the decision on the point of departure LED 10 or 05? Melanie responded that it is generally LED 05, but if there is a lot of data, some times you can use LED 01.
Andrew added that actually there are 2 factors, statistically, it is set at the low end range of observable data, then consider the properties of that for the exposed population and severity of the effect in choosing the point of departure. The LED 05 is fairly consistent with the NOAEL, but there are a number of cases where there are severe effects that this would not be the case. The underlying animal approach is the same. The EPA approach is a generic method.

Allan asked that since the animal dose points are fixed, but the human are not, how do you use both? Andrew replied that in theory, the point should be in line with the co fitting routine.

Mike wanted to recap; there seems to be an offer to run some of the data? Melanie responded, yes, Julia agreed to refer the requests to OEHHA. Mike noted there are 12 on the handout, will this involve only the carcinogens, and can the data be available for the next meeting? Julia said that it probably could be done, she would check with Will (Forest). Mike added that this would include Be, and asked about the second set that OEHHA didn't do. Julia replied that some are done by the EPA, but the others may not be possible to run. Mike asked if the OEHHA reports had summaries? Melanie replied that some are but many are not, and not all have summaries. Mike added that the group puts the non-carcinogens on a one page summary for discussion, and often have to try to find the data that is referenced. Andrew responded that most of their RA's have one page tables that list the source data and the calculations used. Mike noted that it would be great if there was a way to incorporate the data to be used with that presentation.
Richard noted that Will has done some of that already. Julia and Melanie thought they could do it. Mike concluded that it would help reach a goal of consistency.

Andrew said that some of the information can be found on their website, and the name of the publication is the Air Toxics Hot Spot Risk Assessment. The EPA document is called the Bench Mark Methodology. Deborah suggested that if he has information, he should send it to Bruce for forwarding to the committee. Mike added that if OEHHA has information on the chemicals that the committee has already reviewed, we would like to see them to see if there is some consistency.

Next agenda item, carcinogen risk assessment.

Allan Smith began with a general discussion of NOEL and LOEL issues:
When you graph the test animal response to the dose, you can find the no-response point on the graph. The validity of the data depends on the dose chosen and the size of the study. For example, if you assume a 1% response, you could use 30 animals you would likely see no response, but if you used 100 animals, you expect to see a response, and with 1000, it would be very certain. So, the no effect point is really a moving target that is inherent with the dose and size of the study. Small study results can easily be reversed by subsequent larger studies. For this reason, Allan didn't support the use of NOEL. ACGIH just seems to find the lowest level with response and sets it there. With respect to carcinogens and non-carcinogens, why do it this way? It is a moving target.

With cancer, a reason that extrapolation to very low doses is done is the possibility of a single change in DNA triggering the disease. But now, many have concluded that the one hit theory isn't correct. Another problem with extrapolating risks to very low levels, 10e-6 or 10e-5, is that for many exposures, control at these levels is a practical impossibility. Many risks in industrial settings are often many orders away from these risk levels and closer to 10e-2. The lack of understanding the causal mechanisms led to arguments as to which models best fit the actual risk in the extrapolation zone. Complex models were developed which could make the curve hook around all over the place. Allen said that when he came to the US in the early 80s he found the idea of calculating that one in a million will die as a point estimate

appalling, you need to describe it as uncertainty, and that risk is a range of values. In 87, Taylor started the benchmark dose idea that does not use linear extrapolation, which tries to find a given response rate and adds a safety margin. For example, TD10 could mean that 10 % of the animals could get tumors. Independently and at about the same time it was suggested going to TD01 for epidemological studies. Another problem is that when OSHA did the extrapolation type risk assessments and showed that the existing risks were 1/100, they were almost always taken to court with long delays.

So, the ACGIH approach is not good, and you need to show how these numbers were reached. The EPA seems to be using a bench mark approach but then combines some of the extrapolation concept by doing a straight line from the point of departure, rather than directly applying a safety factor. The two methods can achieve the same result, but the safety factor cannot be argued against scientifically and the straight line can.

Regarding the OEHHA summary: The good part of the review approach is to provide a comparison of risks, and then you can prioritize what should be done. The idea was to identify the highest risks and see what could be done about them. Allan thought that it was not as important to set a single level of acceptable risk as it was to direct available efforts to the highest existing risks. Allan asked for OEHHA comment.

Melanie cautioned that some of the risk assessments that were used to generate the table were old and that they used the linearized multi-stage model. If you use the LED10 of the new EPA approach for comparison, it is usually within a factor of 2.
Andrew added that both use the same basic data. In both CALEPA and the EPA, the assumption is that carcinogen data should be linearly extrapolated towards the zero effect. The best support for this extrapolation is genotoxic carcinogens, for example aflatoxin, data was linear nearer the zero point, including genetic damage at exposures below those at which tumors are seen, actually support this extrapolation. The linear extrapolation is not a mythical beast, it is a plausible interpretation for the ones where you can see effects at low dose. It can be used as a criterion to rank the health risk. This is the preferred methodology for the genotoxic carcinogens. There are some exceptions. If the linear assumption is made, the sort of dose responses seen are asymptotic to straight line, so it doesn't seem to matter a lot which point of departure is chosen, and this limits debate on this point.

Mike asked how this could be converted into a reasonable approach for this committee to take to establish PELs, etc.? Allan responded that as a goal for an occupational health standard, he would, to put something on the table, recommend use of a safety factor of 10 with a 1% departure, or 50 with a 5% departure. We have often heard that one in ten thousand is unachievable but if you say that you have chosen one in a thousand, you get criticized. The point is to make it overt.

Richard replied that there will be criticism anyway, but Bruce thought that Federal OSHA used one in a thousand as a goal; is there a simple way to apply that?
Mike noted the example of benzene. Allan responded that the goal of 1 in 1000 and the use of a safety factor of 10 for one in a hundred are not exactly the same. Melanie noted that Will reviewed the benzene analysis, and Julia said that the data from the Feds showed 1 or 2 per thousand, but she thought the EPA analysis was different. The carcinogen RA's are not systematic.

Richard continued that a process could be used for the ones with credible risk assessments to recommend a PEL at 10e-3. For the others without a risk assessment which are suspect carcinogens (IARC 2b), how can those be done? Craig asked how easy was to use the EPA software. Andrew replied that you have to find reliable animal data. Allan asked about epi data. Andrew said that any epi data needs more thought, and depends on how well the study was done. Normally, the additive and multiplicative models were used while the animal data is relatively straightforward. Richard responded that human studies are valuable also for pointing out nuances in the exposures.
Mike asked what had been done by the previous committee?

Richard replied that they made a statement that was a disclaimer, but it was never published in the regulations anyway. Allan thought the committee should get volunteers to run the animal data. Andrew noted that for IARC 2a and 2b they have data, there are one or two exceptions. Bob K asked if there were OEHHA RAs for vinyl bromide or fluoride, and noted that there were positive long term studies for cancer. Andrew said there was one for the vinyl bromide. Richard suggested that they send a list of the ones that have reliable data. Allan cautioned that it was not safe to assume even with the software that the process would be easy. It might be better to ask the Standards Board to make a request to OEHHA. Andrew said that the software still requires judgments to be made.

Mike wanted to recap:

The basic picture is for a carcinogen with a risk assessment, use one per thousand for a PEL. Without a risk assessment, for IARC 2a&b, review the OEHHA /EPA risk assessments, list the the substances that are on the list without OEHHA or EPA risk assessments, apply a judgement factor or use the OEHHA linear extrapolation to get a one per thousand PEL.

Andrew said there are some substances where the CA definition effects the evaluations beyond IARC 2a and b, for example diesel, and may go beyond Prop 65. Considering the air contaminants, IARC looks at occupational exposures and lacks quantitative data descriptions. Mike asked if the committee could get a white paper on this? Andrew said that it is already written and online. Mike said the committee needs to focus on how HESIS would define IARC vs. California prop 65 substances, and there is a need to define the lowest endpoint. Andrew replied that IARC 1, 2a&b are included in Prop 65. Mike asked how far OEHHA has gotten with identifying the no effect risk levels from Prop 65? Andrew said the lowest was 1 in 100,000. Some of these are used in the Hot Spots program. Most air districts use public notice process for one in a hundred thousand, and one in ten thousand triggers action by them (as part of the stationary sources program).

Discussion of Mike's graphic outline.(see Att-3.tif)
Mike wanted to discuss this as an approach. Andrew said that OEHHA normally used the extrapolation approach and did not routinely apply direct safety factors. If this committee choose extrapolation then OEHHA would be in a better position to support the recommendations. Allan said he is uneasy with running software with just animal studies, even if there are only animal studies to consider, it is a big job to analyze them to pick the best study or combine them for the risk estimate. Melanie replied that that would be a lot of work, but if they are available, they can provide assistance. Mike gave Andrew some of the summaries the committee had already done. Allan noted that Pub Med is a good source with a good search engine. Carl added that if you are paying for the service, you can get access to the whole article. Mike asked if it would be helpful to the committee to have these models presented, or should there be more discussion?

Deborah asked if OEHHA and the EPA have not done a RA, are there other sources, like NIOSH? Melanie looked at the list, and said there are 2 in progress, silica and styrene. Five do not, but they are probably considered carcinogens: Bis 2 dimethylamino ethyl ether, allyl glycidyl ether, refractory ceramics, asphalt fumes and coal dust.
Mike said the committee would like to have a comparison of the 54 on the list to identify which are carcinogens, and show the non-carcinogens, including a methodology description. Bob K asked if the EPA policy is to use linear extrapolation? Andrew replied that it is the EPA's default, they allow use of a margin of exposure if there are indications that response is not linear. New guidelines are being drafted. Years ago, California used a margin of exposure type of approach that recommended a factor of 10,000 for the environmental exposure for carcinogens. They also used a parallel analysis for MTBE (alternative for comparison) and the issue was that most would say 1000, or 10000 for the general population, from the point of departure of animal data, but the epi data might be different. Melanie added that the most recent draft says nothing on the margin of exposure. Allan noted that by this approach, the cancer risk might be lower, the recent draft is very confusing. Bob K added that the older draft leaves the margin of exposure open, leaves it to the manager. Andrew noted that the manager had to look how that was defined, and select the margin. Allan added that the new wording leads back to a committee decision, and so is more arbitrary.
Melanie responded that some of this may be a result of turf fighting.

Dagmar suggested a brief recap:
The committee would receive carcinogen RAs from OEHHA if available, and if there is no RA, HESIS would attempt to find something equivalent. For the non-carcinogens, use Richard Cohen's method with adjustments. Mike noted that HESIS would provide assessments that are already done. Julia said she would see if there are other RAs, and establish that there are no available risk assessments that could be used.

Bob K said that in the case of vinyl chloride(Bob and Dagmars substance) the OEHHA estimate is 26 per thousand, how do you justify a PEL that is much higher, 1/1000 compared to 26/1000. Allan responded that with vinyl chloride, OEHHA based its estimate on animal data, but the human data shows the risk much lower, this is not usually the case, so if human studies are done they need to be considered to test the plausibility of the animal based estimate. Andrew added that in that case, there was metabolic saturation, the potency was higher at lower doses. The saturation effect was considered with butadiene. Most of the evaluations have more consistent results. Allan responded that you cant have an estimate of the risk that is far higher than the actual occurrence in the same industry, so you need to check out the human data.
Richard said that this would provide credible data but the committee still has to evaluate the data, and it will not produce a number for the committee. Mike suggested listing out 10 critical points for each substance. (See Att-4.tif) Melanie said that most of the documents have shorter summaries with critical data. Also, Allan's point is well taken, especially when the research is not current. Andrew added that the recent reports consider environmental data, and consider the

saturation effect. There is also data (vinyl chloride) in the low-dose range where there is no saturation assumption. When looking at the occupational risk you are looking at levels where the saturation effect is important. Patricia asked Allan to review the vinyl chloride analysis, and Allan said he would try. Andrew added that the animal data is more available, it is best to use the human data and apply the pharmacokinetic mechanisms.

Mike proposed using the approaches that were presented, and the committee agreed. He thanked OEHHA for their assistance, and their participation at this meeting.

1220: Lunch, return to be 130

Discussion of the next meeting, date changed to June 17, location San Francisco or Oakland (committee preference Oakland). The next meeting after is tentatively set in the first week of September, September 13, and will probably be the glutaraldehyde review. Patricia asked for the committee to be able to see any petition or correspondence that was made to the Board regarding glutaraldehyde.
For the June 17th meeting, the main subject will be beryllium, but Tim suggested having other substances prepared as a backup. He also noted that the original plan was to have two sessions for Be, one for cancer issues, the other for the general toxicity, and asked for comments on this. Richard suggested starting with the non-carcinogenic discussion. (Someone asked if there were Federal standards and Tim said there is a Federal action level of 0.2ug/M^3) Mike noted that consensus was to proceed that way and asked if Patricia was ready to discuss flour dust. Patricia replied that she was.
Getting back to Be, Richard thought there would not be a risk assessment for cancer. Allan suggested that Craig could do that, and Craig agreed. Patricia suggested contacting Lee Newman or John Balmes also. Bob Ku asked if the Federal data is online? Tim said it is, at the DOE site, under 10CFR850. Richard noted they did the first standard. Patricia noted that many of the patients that they find with the exposure (positive LPT) do not know where or how they were exposed. Tim responded that the issue may be the particle size.
Mike returned to the meeting plan: the morning will be the non-carcinogen, the afternoon will have a carcinogen discussion. He asked if Brush Wellman should be notified, and the group said they should be. He asked Tim if he knew anyone with experience at Lockheed, but Tim did not. Patricia asked Deborah about unions, and Deborah suggested IAMAW. Mike added that the committee also wants copies of any glutaraldehyde documents making a request or petition to the Board.

Patricia said she would like to review flour dust, and may need to recalculate the assessment; the real issue is the difference between inhalable particulate as opposed to respirable, and how significant the difference is. Patricia said that Bruce had looked into it and had seen a problem with using inhalable as the basis for the PEL. Deborah noted that the last session had a sampling method for fiberglass included, so it seems appropriate if desired. Deborah said she would check this with Bruce. Tim asked about ozone with three different criteria for work levels (heavy, medium, or light), how would this work in enforcement? Patricia responded that there is also a sensitization issue. She asked if anyone has dealt much with inhalable particulate measurement? Tim replied that there is no good comparison, just use the numbers reported. Patricia asked how to use that with the OSHA standards; one report says there is a twofold difference from the respirable. Tim said that their (LLNL) data supports that. Patricia responded that there are about 30 studies of flour dust without inhalable data, how can that be supported by DOSH enforcement?

Mike moved the meeting on to methyl methacrylate.
Richard referred to an updated summary sheets, and explained that the value 18 which was written in was the median level in the group which had more of the symptoms.
Richard said that a Polish study measuring pulmonary obstruction, had a median level at 5. He found significantly lower exposure levels from other studies, including a rat inhalation study with subchronic effects. Human olfactory dysfunction is reported at 5. It is also a strong sensitizer, so another question is if these studies indicate a need to go below 5. Mike asked if 15 or 5 were each put through the equation, do you get a lower final number? Richard said you do; other standards have other conclusions, one choosing 5. It is hard to justify a standard above 20, unless those studies are to be thrown out. Mike asked if it is a skin sensitizer in the ACGIH? Dagmar found that it is. Richard continued that in the Mizunuma study, 5 could be argued as the no effect level. Mike noted that this would go on Bruce's list of divergent conclusions, so is there evidence to support a different conclusion? Richard replied that is hard to say, they did find a NOEL report of more than 5. Allan asked if these discounted low levels of styrene? Richard replied, if anything, throw those out. In the high exposure group at 18ppm, 5 was reported as no effect. (There was a question about headaches). He continued that the Mizunuma effects were somewhat subjective; there were 32 males, at high and low levels. The Polish study had 454 subjects and 600 controls. NIOSH discusses a range of 4-100ppm. Craig asked about the French study that had tighter range. Richard replied that they used spirometry. Mike asked if the current recommendation was 20? Richard replied that yes, most of them are in the 20 range. Mike asked if the human data was occupational, and

Richard said it was. Mike asked if the EPA data compared the exposed and unexposed, and Craig said it did just the exposed. The symptom rate is always higher but not statistically so. Mike asked if there should be a safety factor and Richard said it was not needed with the human data. Bob K asked if there was detail on the sampling method, but there was not. Richard continued that the other reason for concern is that these are sensitizers. Mike said there should be confirmation; some things are listed with undocumented effects, and that could be a concern. He asked if the studies normalized for smoking, and they were. He asked about the main expiratory flow, and Richard and Craig said it was statistically lower. Allan asked if a smoking effect would show, and they said it would. Craig recommended 20 ppm based on the French, Polish, and Japanese studies. There was no opposition to this recommendation, but the committee wanted to get a copy of the French study.

Ethyl cyanoacrylate.
Richard said there is scant data that justifies the reduction to 0.2ppm, and not much data overall. The rationale is to base it on the data for methyl, and the issue is mostly the pulmonary effect. There is no pharmacokinetic data, but it is probably hydrolyzed to formaldehyde. The case histories do not have much supporting data.
Patricia noted that there was a case of exposure to someone making surgical equipment who developed asthma, but he worked outside of the area where it was actually used. Mike asked if the Goodman study was done around 1985, but Richard was not sure. Patricia asked if it is still in nail material, and the general response was yes. Richard added that the status is that it is probably a sensitizer, and there is not much else showing a reason to disagree with the ACGIH.
Allan asked if the proposal was based on analogy to methyl and suggested reviewing methyl first.
Mike proposed adopting 0.2 pending the review of the methyl data, and this was generally accepted. Richard also has methyl, and he will try to get the Goodman study.

Pentane:
The issue is removing the STEL of 750. Carl went through Toxnet and looked for inhalation studies, found one where it was found in breast milk, nothing provided a basis for dropping the STEL. Tim added that the documentation was confusing because some references to irritation were not well supported. Carl added that in one report, irritation was reported from skin contact, but the irritation stopped after 15 minutes. Allan asked why the STEL was so close to the PEL in the first place? Miked asked if it was the 10% of the LEL, and it was not. Allan added that Octane had a similar relation between the STEL and PEL. No one knew why. Patricia asked if it was an anesthetic at 5000, and the answer was it is close to that. Mike asked if there were decreased cognitive effects, but there were not. He continued that there was general agreement to remove the STEL, and he wanted to be sure that the committee had a copy of the their handout from the previous meeting.

DNT:
The proposal is to go from 0.15 to 0.20, and it is at .15 based on the risk of heart disease. For carcinogenicity, the ACGIH changed it from A2 to A3 (unknown human implications). The old standard was based on methemoglobinemia; he has more data if people want, but the interesting quote is “no significant decrease in protection between 0.15 and 0.2” . So the overall implication is that inhalation is less significant than skin absorption. Mike asked if IARC changed their standard on it? Patricia said no, this is just the ACGIH designation. Dagmar asked if there is currently a Skin designation in the Cal/OSHA PELs, and it was found to be for the 2-4 isomer at 0.15, no STEL. Patricia noted that if you accept it, it would be 1.7/1000, which raises it to 0.2. Carl added that the NIOSH statement about using the lowest feasible level could refer to a dog study that supports 0.2. Tim said he found in Medetext a statement that no increase in cancer cases is documented. Mike noted that the IARC 2b differentiates between the 2-4, 2-6, and 3-5 isomers. Allan noted that the OEHHA table suggests a level of .086 ug/m3. Patricia proposed leaving it alone unless there is some support to lower it, and disregard raising it. Tim said he will get the OccMed letter. Patricia said there is also a 1993 JOM article on ammunition workers looking at cancer and cardiac mortality, an epi study. Allan wants to look at that report, and discussed it briefly with Patricia. The consensus was to not recommend a change pending additional information.

Vinylidene chloride is postponed to Sept. 13. Carl Foreman agreed to chair the next meeting.

Meeting adjourned.

6-19-02

Attending:
Mike Cooper, Carl Foreman, Tim Roberts, Richard Cohen, Patricia Quinlan, Craig Steinmaus, Robert Ku, Dagmar Fung, Deborah Gold, Bruce Wallace, George Fulton, Gene Murphey, Marc Kolanz, Will Forest, Steve Smith, Karron Power, Steve Burastero, Jeff Lomax

Bruce Wallace called the meeting to order at 10:15. All present introduced themselves. Carl Foreman, chair for this meeting, began with a discussion of the agenda. Tim Roberts said that Steve Burastero, who is with the Beryllium Medical surveillance Program at LLNL would be attending after lunch and would make a short presentation on this program after lunch. Tim also suggested that George Fulton's presentation be moved up on the agenda, as he would not be able to attend after lunch.

Review of the minutes of the May 3 minutes:
Patricia Quinlan suggested that the comments on the May 3 minutes by Will Forest be reviewed. These comments were emailed to the committee members on 5-22-02. It was noted that the diagram referred to at the top of page 2 was missing, i.e. not in Bob Nakamura's notes. Mike Cooper and Richard Cohen agreed to try and recreate the diagram for the minutes. It was also suggested that on page 5, the second sentence after "Mike wanted to recap:" be clarified by adding a reference to risk assessments by OEHHA and EPA and list the exceptions where IARC 1, 2A&B substances were on the list but did not have associated risk assessments. There was a recommendation to delete the second sentence of the third paragraph on page 5. On page 6 second paragraph, delete quartz and styrene from third sentence, change 52 to 54 in the fourth sentence, change the word "form" to "from" in the eighth sentence. On page 7, change the reference to the Federal PEL to an action level at 0.2 ug/m3. On page 8 second sentence, change "IMAW" to "IAMAW" and delete the reference to TME near the bottom of the page. On page 9 under DNT, change the "if" to "it" in the second sentence. The minutes were approved subject to the above changes.

Mike recommended extracting action items and unresolved issues from the minutes and listing them separately so that they would not be overlooked. Examples were cited including "inhalable" dust limits vs "total" dust limits, and light, medium, and heavy work attributes of the TLV for ozone. Bruce agreed to create a separate list and circulate it before the next meeting.

Beryllium:
Tim Roberts introduced George Fulton from the LLNL beryllium program. George began with a summary of the history of the Lawrence Livermore Lab. and its beryllium program. (copies of George's overhead slides were distributed) Beryllium was described as essential to nuclear devices and that it had been present at the laboratory since its beginning. The beryllium program has evolved since the first exposure guideline in 1949 to an extensive program covering all aspects of exposure control. 10 CFR 850 is applicable to the laboratory as it is a DOE contractor. George described the experience of the DOE complex at Rocky Flats plant (124 CBD, and 329 sensitizations) and the Y-12 plant in Oakridge Tennessee (45 CBD, and 119 sensitizations). The LLNL experience with > 1300 current and former employees is 1 CBD and 31 sensitizations. Of personal samples made at LLNL, typical levels were non-detect, the peak measurement was 1 ug/m3. The current detection limit is 0.02 ug/m3. LLNL uses 2 ug/m3 as an exposure limit and 0.2 ug/m3 as the action level under 10 CFR 850. Most of the significant requirements of 10 CFR 850 are triggered by the action level which is a defacto PEL. Richard Cohen asked how the 0.2 ug/m3 was chosen by DOE. George said he did not know how it was derived. George said that the personnel that had been sensitized had not been associated with high exposure level measurements, but that they had been in jobs with potential for peak exposures. The DOE rule sets a surface contamination limit of 3 ug/100 cm2. DOE has established a case registry, but it is not accessible to researchers. Tim Roberts provided the following web sites for the LLNL Be program and a symposium sponsored by DOE, NIOSH, and National Jewish Medical Center: http://tis.eh.doe.gov/be/ and http://www.ornl.gov/meetings/beryllium/poster.pdf . George described some recent research by Michael McCawley into particle size distribution and number of particles per unit volume as an exposure measure. George also recommended the DOE beryllium web site as a good resource for recent information. George estimated that with approximately 15 IHs and Dr Burastero, the LLNL program costs about one million/year. Richard asked if there had been any association between Be exposure and lung cancer. George said that there had been one case, but the person had been a long term smoker.

Lunch break

Marc Kolanz began his presentation and distributed copies of his power point slides. Marc described his 21 year history with Brush Wellman and that he had had many conversations with early researchers such as Merril Eisenbud. During

the early 90's he had tried to provide input into the ACGIH TLV committee regarding beryllium with little success. The TLV committee eventually agreed to co-sponsor a symposium on beryllium in 1999. In may 2001 the papers from that symposium were published in the ACGIH journal. Marc referred to the Cardiff study by Jim Johnson. They found that the Cardiff plant was in compliance with the 2 ug limit 97% of the time. Marc then described the uses and production processes of beryllium, beryllium ceramics and alloys.

Marc described the two forms of beryllium disease, acute (ABD) and chronic (CBD). The acute form is associated with exposure to soluble rather than insoluble forms. The acute disease has been associated with exposures to beryllium salts and low fired beryllium oxide. The acute form has not been seen since the late 60's. The chronic form was diagnosed before the late 80's by individual symptoms, shortness of breath, chest xray, and reduced lung function. In the late 80's sensitization tests and other diagnostic tests were developed that could detect the disease without clinical symptoms. Marc referred to a chart showing cumulative incidence of CBD that showed increases in the rates of incidence in the late 80's and early 90's. He noted that the increased rates coincided with the introduction of the new diagnostics. Patricia asked if the 90's incidence that was labeled BLPT was just sensitization and not CBD. Marc said that these cases included granulomas as well as sensitization. Marc said that the cases are diagnosed at several centers, and that there are slight differences in the criteria used to make the diagnosis. Richard said the there had been a Be case registry that had fallen into disuse, and that for the last 20 years there hasn't been a central collection point for information. Marc said that the original registry combined chronic and acute cases and used different criteria for diagnosis.

Tim asked if the DOE and Cardiff facilities could be compared. Marc said that the Cardiff employees were monitored with traditional techniques, and the exposure controls and level of air monitoring at the Cardiff plant were superior to those at the Rocky Flats facility. Marc thought that it was remarkable that Cardiff only had one case of CBD in thirty five years of operation, a record that no other facility has equaled. Marc referred to the slide showing the results of the Brush Wellman surveillance program. He noted the areas of a plant where the cases were most prevalent, the oxide and fluoride areas, had similar air concentrations to those with fewer cases. There was a suggestion by Kreiss that the difference might indicate that mass concentration might not be the best exposure measurement metric. Mark said that there have been investigations of skin exposures and other routes of entry, including direct entry from cuts on hands. Particle size seems to stand out as an indicator, small particle size was found at the Elmore plant in the oxide and fluoride areas and those areas had the greatest incidence. This points to ultrafine particles (< 1.0 um). The current efforts at controlling exposure are emphasizing work practice, as engineering controls are near the limits of what can be done.

Marc discussed a slide showing the results of split BLPT samples analyzed by different labs. This slide shows that the results had varied between labs and within labs over time. BLPT tests have shown a 67-100% predictive value for granulomas for employees with >5 yrs exposure, but doesn't predict well for shorter periods. There have also been cases where positive BLPT status has changed, 10 of 18 tested negative after 7 years.

Marc described current research including joint projects with NIOSH. NIOSH is collecting very detailed work histories and combining that with Brush Wellman sampling data. This will be analyzed according to particle size. There are also "skin stripping" studies being conducted at the Elmore plant. The studies remove fine layers of skin to evaluate penetration of the skin. There has been emphasis on studying the experience of new employees which has been made easier with newer diagnostic techniques. Animal studies are being performed trying to demonstrate sensitization in mice.

Carl asked if there were questions for Marc at the end of the presentation.

Mike asked what recommendation he would make for a proposal. Marc said that you would need to decide on the endpoint to protect against. Sensitization is the most sensitive end point. The Cardiff study shows that exposures well below 2 ug/m3 can protect against clinical disease. This is not the case for the Redding facility, where similar levels produced subclinical CBD. There is a need to decide the critical endpoint. Tim asked if "inhalable" vs. "total dust" sampling had been explored. Marc thought that moving toward inhalable was not indicated because the studies are pointing the other way, toward fine particles. Bob Ku asked if there had been studies of beryllium levels in blood. Marc said that Brush Wellman had done a poster presentation at Society of Tocxicology in 1999. Blood levels were very difficult to analyze, and were a poor predictor. This approach was not followed up. Will Forrest asked if there were any studies which show correlation between total dust measurements to respirable fractions. Marc said that this is very form and process dependent, and could not be generalized across processes. Mike asked what the current Brush Wellman detection limit was. Marc said he thought it was 0.006 ug/m3.

Tim Roberts introduced Stephen Burastero who is managing the beryllium medical surveillance program at LLNL. His program follows current workers at LLNL. Former workers are being followed by an organization at Oakridge. His current worker results show 8 of 360 sensitized, and three workers were offered medical removal. There was one marginal case of CBD diagnosed from this group. Participation in the program was initially relatively low and when results of sensitization came out more workers participated, including those at Site 300. This is the explosives test area near Altamont. Among former workers, 37 of 1200 were found to be sensitized. Of the 37, 17 have had follow-up exams and 1 of the 17 was diagnosed with CBD. Most of the personal samples have been very low (non detect), and the highest observed was 1 ug/m3. Steve emphasized that the ratio of CBD to sensitization at LLNL was low compared to rates reported at other facilities (Rocky Flats). Steve said that there have been suggestions that total Be lung burden may be associated with progression to CBD. Steve thought that the pulmonary community had been focusing on immunology and that the role of lung burden on the development of CBD has not been adequately considered. This could account for the difference between Rocky Flats and LLNL. A case control study could shed some light on this. Steve also said that there was ongoing research into skin sensitization through direct penetration of insoluble material, and that possible effects on mucus membranes of the mouth and nose should be considered. Steve thought that the variability seen in LPT tests now is less than that seen in the early 90s. Steve said that they had not seen the reversals that Marc had described in LPT results. Steve also thought that improvements in medical imaging could allow the detection of small granulomas. Steve said that if lung burden was a factor in CBD then chelation might be an effective therapy.

Questions:
Bob Ku asked if skin sensitization was a result of direct contact with skin cells or based on absorption into blood stream. Steve said that this was difficult to resolve, and described a possible two step process where there was sensitization by skin, but that the disease would not be promoted without a lung burden. Steve also said that the mouth and nose mucus membranes could be involved in the sensitization while protecting the lung from direct exposure, but that this has not been investigated. Tim asked Steve if Dr. Newman was still estimating rates of progression from sensitization to CBD of about 10%. Steve said that he still makes the same estimate. Steve said that this was from old cohorts with higher exposure including Rocky Flats, and a ceramic plant. Steve said that this does not seem to be the case with LLNL.

Patricia said that there were many other workers in aerospace employment who were not likely to be in such and as extensive a program as the DOE or Wellman programs. She asked if the petitions to Federal OSHA were just for a change to air levels or for a comprehensive program. Marc said that there had been two petitions, one had been turned down, and little had happened with the other. It was his understanding that a vertical standard unlike existing ones was being discussed by OSHA standards staff, but there have been changes at OSHA so it is uncertain what would happen. Marc said that given Brush Wellman's experience that they would not support just a change to the air levels because this would not be sufficient to prevent disease, a comprehensive program similar to the DOE program would be supported.

Planning for future meetings:
Next meetings Sept. 13, Oakland was confirmed as next meeting date/place.
The substances for that meeting are: Glutaraldehyde, Flour dust, Vinylidene chloride, finish DNT. Richard agreed to chair.
The following meeting is planned for Nov. 1
Patricia recommended that the group try to add substances to this list during the summer so that we could make better progress, as it will be a long time to the next meeting.
Bruce agreed to pole the members for additional substances about one month before the next meeting.

Returning to Beryllium:
Tim Roberts asked how we should proceed, and were there any proposals.
Dagmar asked about the timeline for the NIOSH research to be completed. Marc said the planned to completion date is end of next summer. Richard distributed a summary sheet and noted that the OSHA PEL was incorrect; it should be 2 ug/m3 not 2mg/m3. Richard said that two additional lines should be added for LLNL and for the Cardiff study with median exposures around 0.02 ug for LLNL and 0.1 ug for Cardiff. Richard said that the summary is intended to focus primarily on chronic beryllium disease and the associated median air levels. Bob Ku asked what Will Forest had found from his research of the various regulatory agencies (Calif.). Mike asked if Will could also comment about the cancer risk for beryllium. Will said that the cancer risk normally drives the limit to very low levels, but that does not seem to be the case here due to the sensitization reaction from beryllium. Mike said that the cancer risk estimate(for 1/1000 risk) from OEHHA seemed to be in the area being considered for the air exposure limits. Will referred to a document for OEHHA's chronic toxicity inhalation reference exposure level. Will said that he had not studied it. Will said that the reference exposure level was 0.007 ug/m3 to control CBD and sensitization. This could be converted to an occupational level by multiplying by 7.665. This would be based on 8/24 hours, 250 days work vs 365 per year, and 40 yrs working vs

70 yr life. Would result in an occupational level about 0.05 ug/m3. Mike asked how the 0.007ug/m3 was derived. Will said that it was normally derived using a benchmark dose process. Richard thought that reducing the limit to 0.2ug/m3 was justified, but the question remained as to whether a lower level was needed. Tim thought that given the possibility that excursions above the limit could produce sensitization and perhaps CBD, that a ceiling limit should be considered. Will Forest pointed out the potential difficulty of conversions between "inhalable", "total dust", and "respirable fraction"; and that the ACGIH recommends an "inhalable" limit. There was discussion of this and there was an agreement that the total dust limit was the most practical way to describe the limit, based on the bulk of research using this measurement. Tim said that the LLNL monitoring data had been based on total dust measurements. Marc said that recent studies had used a ten stage "Moody" impactor as a particle size selector, the "Marple" impactor, and total particle counters. Richard thought that this committee was not going to be able to resolve the particle size issue. Bruce said that he thought that two studies, the Yosheda and Kreiss studies were targeted at showing risk at levels below 2 ug/m3.

Will, after looking at the OEHHA chronic toxicity summary, said the basis of the reference exposure level was the 1996 Kreiss study of the beryllia ceramics plant (This is the Tucson plant described in Marc's slides). The median exposure of sensitized workers at the plant, 0.55 ug/m3, was used as a LOAEL and several uncertainty factors were use to derive the reference level, 0.007 ug/m3. Bob Ku asked how the air monitoring was done. Marc said it was at the B. W. Tucson plant. The sampling was done with high volume samplers, and together with job time/motion studies, "daily weighted averages" were calculated. There was some personal sampling done. Marc pointed out that the Yoshida study had been done with area samples as required by Japanese law, this should be considered when comparing those results to results based on personal samples. Mike asked what sampling was used at the Cardiff plant. Marc said that both were used, a quarter million lapel samples, and a half million area samples. Mike cooper said that this would suggest a 0.1 ug/m3 as a no effect level based on personel samples. Tim asked if the majority of exposures at the Cardiff plant were to beryllium metal and wouldn't oxide exposures be considered more hazardous. Marc responded that the majority of exposures at the Cardiff plant were to the metal, and that it was thought that the hazard ranking was beryllium oxide, beryllium metal, berylium compounds, followed by beryllium copper alloys. Mike suggested considering a ceiling limit as was suggested earlier by Tim and asked if there were any data that could be used to support a ceiling value of 0.2 ug/m3 to prevent sensitization. Bob Ku said that he thought that the Kreiss paper had observed 4% sensitization at exposures between 0.1 and 0.6 ug/m3. Mike referred to the 1996 Kreiss study's large range of measured exposure levels 0-1931 ug/m3, and asked of there were any studies which could be used to show that there were no sensitizations where peak exposures were below 0.2ug/m3. Richard suggested that the LLNL data could be used. Tim said that there had been an exposure of 1.0 ug/m3 and that he didn't think that the data was comprehensive enough to support a revised limit. Richard referred to two old community exposure studies, Eisenbud 1949 and Lieben 1969, and said that these could be used to support a limit of 0.1 ug/m3 and should not be discounted. These studies observed clinical CBD at exposure levels that extrapolate to near 0.1 ug/m3. There was a discussion of the difficulty of measuring a ceiling/peak values. Marc commented that the shortest sample time was ~ 3 min with a 300 liter/min pump. Patricia thought that it would be difficult to detect anything with a 15 min sample at 2 l/min. Richard thought that if the goal was to protect against sensitization, then levels will need to go a lot lower than the 0.1 level. Yoshida describes 0.01 ug/m3 as a NOEL for sensitization based on area samples. Marc said that he had had a discussion with Eisenbud and that he had rexamined his 1949 data and estimated a 0.2 ug/m3 NOEL at 3/4 mile from plant vs the 0.1 ug/m3 cited in his original paper. Bob Ku asked if the committee agreed with the ACGIH statement (in the TLV documentation) that the the limit of 0.2 ug/m3 should control sensitization below 3 to 4%. Will Forest said that the ACGIH limit was as the "inhalable fraction" and that would not be comparable to a total dust standard. Bob said that the study that was used as a basis for the recomendation was the Kreiss study and that study was based on total dust. Bob said that his question was if the 3 to 4% rate was appropriate. There was a discussion of background rates for sensitization with no known exposure. Marc said that while there weren't any published studies, testing labs had seen about 6 out of 500 test positive in control groups, a background rate of about 1%. Marc said that there were speculative theories to account for this: dental prosthesis, one had played with broken florescent tubes as a child. Brush Wellman had looked into studing this and estimated the cost at 0.5 million.

Will asked if there was a consensus that the current limit is not sufficiently protective. There was general agreement that this was the case. Will asked a follow up: Is there anybody here who thinks that we as a group have the skills to determine a level that is protective for something that is a sensitizer and may have an unorthodox exposure response curve? Bruce said that the question might be whether there was anyone anywhere who had the skills, and thought that such a question didn't get you very far to say that none of us are qualified to do this. Will thought that facing up to not having this ability and setting a lower standard would probably enhance protection, but we would not know by how much. Richard thought that this was not a new situation, that this lack of complete knowledge and setting standards on one or two animal studies was normal. The point was to try to find a no effect level. Here we have many studies, a very toxic material, and difficulty predicting sensitization. Richard thought that even with this ambiguity we have a fair number of data points in the low exposure ranges. Will said that we can't really know what to do with it. What that means is that in

some sense it will be an arbitrary decision, and its ok to face that, and say that only an arbitrary decision can be made. Carl pointed out that the original standard (taxi) was arbitrary, and that the current state of information is much better, but the point is where should the limit be set? Carl said that we had a proposal at 0.1 on the floor. Craig Steinmaus said he thought it was reasonable. Richard said that the 0.1 took us further away from Kreiss's level of 0.3 where actual berylliosis cases were observed, and was consistent with Lieben's community exposure estimate. Richard also noted that Johnson found a median levels of about 0.1 to 0.7 between 1981 and 1997 at the Cardiff plant with no clinical CBD. Carl asked if there were any objections to the proposed limit 0.1 ug/m3. There were no objections. Bruce asked if the basis was those three studies(Kreiss, Liebens, and Johnson). Richard said the recommendation was consistent with all the studies listed on his summary, and the Johnson study.

Marc said that when you look at setting a number like 0.1, that means, for industry, that we need to meet 0.01 on average and that will push the limits of detection. Richard didn't agree that IH's shoot for 10% of the PEL. Marc said that the statistics require a significantly lower average. Mike said he didn't see a significant difference between 0.1 ug/m3 and 0.2 ug/m3(the DOE effective limit, and ACGIH proposed limit). Marc agreed that this was not a significant difference. Carl asked the members if they were still in agreement with a 0.1 ug/m3 recommendation. There was no objection.
Meeting adjourned.

7-11-02

Airborne Contaminants Advisory Committee

Draft Minutes

September 13, 2002 meeting

Attending:
Mike Cooper, Carl Foreman, Richard Cohen, Patricia Quinlan, Deborah Gold, Bruce Wallace, Will Forest, Steve Smith, Karen Jenkins, Patrick Owens, Barbara Schroeder, Sandra Morrow, Steve Terry

Bruce Wallace called the meeting to order at 10:15. All present introduced themselves. Richard Cohen, chair for this meeting, began with a review of the minutes from the June 17 meeting. Will Forest had emailed a corrected copy of the draft minutes with grammar and spelling changes, none substantial, and the committee members agreed to include those changes. Richard said that the exposure level cited as 0.1 ug/m3 on the fourth line from the bottom of page 6 and the fourth line from the top on page 7 should read 0.01 ug/m3. The minutes were approved with these changes.

Richard began a review of the action item open issues list dated 7-17-02. The first item was quantitative risk assessments and the summary information for them. Will Forest said that he had found some additional information including a risk assessment on dinitrotoluene by the US EPA, and had an updated summary sheet. Bruce agreed to copy and distribute this information. Richard asked if there was anything outstanding on item one? Item one is complete. Richard had copies of the studies mentioned on items two and three, so they are complete. Item four was open, as Tim Roberts was not able to attend the meeting. Item five was still open, as Will had ordered but not yet received the paper. Item 6 is complete. Bruce explained that he had sent a letter to the Amy Hegy, the lady that had made the original request to the Standards Board regarding glutaraldehyde. She had not responded, but he had been successful in contacting the group she represented. That group, Workers Against Senseless Toxic Exposure, had notified others and Karen Jenkins was present based on this.

Mike Cooper requested that a new item be added to the list regarding formalizing the carcinogen and non-carcinogen exposure limit processes. Patricia Quinlan noted that these were described in the May 5 minutes and the four attachments. Mike thought that they should be further formalized, and asked if there were copies of the attachments. Patricia agreed to send Mike a copy.

Richard said that that left three items on the list open. Patricia noted that there were still the three issues on the second page. Bruce said that the first and third issues, inhalable dust sampling and sensitization, would probably be discussed today as flour dust was on the agenda. Richard noted that the TLV limit for ozone incorporated a heavy, medium, and light work specification, and that this had no precedent in Permissible

Exposure limits. This work specification will be discussed when the limit for ozone is scheduled for discussion.

Mike said that he had a question about planning for discussion of substances where there had been interest shown by outside interests in particular substances, for instance asphalt fume. He wanted to know about planning and notification and said he had direct contacts from the asphalt group. Steve Smith said that this planning was on today's agenda as item 5. Bruce said that interested parities were put on the email distribution for minutes, agenda, and other general communication. He described other specific steps he had taken to notify those who had shown an interest in a specific topic. Steve said that there was also a Division web page that listed advisory committee meetings. Patricia suggested that if the members were aware of people who had particular interests, this should be followed up with Bruce so that they could be notified.

Richard asked if those nonmembers present wanted to add anything to the brief introductions earlier. Karen Jenkins explained that she had been an x-ray tech and had been exposed to glutaraldehyde in photo development. She said that there were several groups interested in this WASTE(Workers Against Senseless Toxic Exposure) and SNAFTA (New Zealand). She said that she had brought some information from the UK to share. Patrick Owens said that he was an IH and worked for Shell Oil at the Martinez refinery.

Glutaraldehyde:

Carl Forman described the use of glutaraldehyde at UC Davis. He said that they were switching to another sterilization process that uses para-acetic acid. He described the range of exposures that they had measured at UC Davis as 0.025 to about 0.075 ppm. These levels were measured in high use clinics and gastroenterology as TWA measurements. Carl referred to a study published in J Occ Med. 10/1989 that was based on their data. He said that the cases where there were excessive exposures and had had a problem were situations where people got in a hurry and deviated from standard protocols for handling the material. He said that when the levels got to near 1.0 ppm that you couldn't stand to be in the room. Mike asked Carl if any of the measurements were short-term measurements. Carl said that there were, especially when the levels got up to 0.1 ppm.

Richard stated for the current level for Cal/OSHA is 0.2 ppm ceiling, and that the ACGIH had lowered the TLV to 0.05 ppm ceiling. Mike asked what the limit of detection was, and Carl responded that it was approximately 0.025 ppm. Karen Jenkins asked if the samples were just done on the nurses where the scopes were soaked, or also on the x-ray people. Carl said that the samples were mainly taken in the GI lab, but not X-rays as they had gone to a closed system. Make asked what the concentration was for sterilization. Carl said that it was mixed down from a 50% solution to about a 3% level. Carl said that the percentage had increased in the last few years based on changes made by the infection control people. Carl said that the only time that there was a problem was in situations where people deviated normal practices and protocols.

Richard referred to an OEHHA chronic toxicity paper that did not determine a NOEL. They did show a LOEL of 26 ppb and a REL of 0.02 up to 0.035 ppb.

Carl said that there had been no complaints when levels were below 0.2 and he did not think that lowering the limit to 0.05 would be meaningful. Richard asked what the ACGIH basis was for the 0.05 ppm. Bruce said that the level was based on the relative potency with formaldehyde in studies of changes in nasal pathology in animals, reference 20 in the ACGIH documentation. The study found that glutaraldehyde was about 10 times more potent than formaldehyde. Carl said that he did not see sufficient evidence to support going as low as 0.05. Bruce referred to a recent recommendation by the British HSE at 0.05 ppm.

Richard asked if the PEL was the only issue that we should consider here, i.e. should we limit the discussion to just the ceiling or should it be expanded to the 8 hr TWA. Mike thought that we should return to the general process and try to establish a NOEL. Richard said that he did not feel comfortable going forward without a summary of all the dose response related studies, i.e. the "data points". There was a discussion of the OEHHA risk assessment document. Mike said that we need a summary sheet of the relevant studies. Patricia thought that Will Forest might help develop one. Will agreed to help. Patricia agreed that this should be done. Richard asked Karen if she wanted to add anything. Karen said that see had brought several documents that see would like to share with the committee. Richard said that those which could relate given

levels exposure to effects are most helpful, and the most important. (Copies of Karen's papers were made for the review.) Bruce noted that the date for the next meeting had been tentatively set for 11/1/02. Glutaraldehyde will be taken up again at the next meeting.

Flour dust:

Patricia distributed a three page summary for flour dust. She summarized that there was no current PEL other than the PNOC limit and the ACGIH TLV was set at 0.5 mg/m3 as an inhalable dust limit. Patricia said that in addition to ground grains, alpha amylase is added. It is an enzyme from aspergillus. This additive is also naturally occurring, but they apparently add more. There is only one animal study referenced in the documentation, ref. 63. The test concentration was 27 mg/m3; and the particle size range was 0.1 to 10 micron. All test animals showed an immune system response. No NOAEL or LOAEL was extablished.

There were approximately 25 human studies referenced in the ACGIH document. Sample techniques varied from study to study (respirable, total, or inhalable) and the range of exposures was 0.1 to 47 mg/m3. Patricia also included a quantitative risk assessment in the summary that was published after the ACGIH document. Patricia described several of the studies in the summary, including the Houba study. The Houba study was the largest study, and was used for the quantitative risk assessment described earlier. The PAS 6 inhalable dust sampler was used for measurement in this study.

The risk assessment was published in the Annals of Occupational Hygiene and used non-parametric models. They found increasing effect with increasing exposure. A classic epidemiological analysis showed a NOAEL at 0.5 to 1mg/m3 as inhalable dust. Another analysis did not indicate a NOAEL but did indicate a LOAEL of 0.5 mg/m3. Patricia thought that this would support a limit at 0.5 mg/m3, but that this would also raise the issue of the type of sampling method used for the limit, inhalable versus total dust measurement. Richard pointed out that particle size distributions would have a very significant effect when comparing the various methods. Bruce said that while this might be a problem in general, it might not be in this case, because the study used to set the limit used the same method as the limit itself. There was a discussion about possible variation between different types of flours, wheat, barley etc. There didn't seem to be a way to distinguish between these. Patricia pointed out that many of the studies showed a variety of adverse effects at levels below the PNOC limits and that this was ample justification for a reduced limit. Richard agreed and said that while it might not be possible to get to a no effect level with an allergen, the levels proposed would clearly have a positive impact on the problem of asthma in bakers. Mike asked several questions about the studies in the summary with low exposure value measurements. Patricia said that these were only exposure surveys and did not look for adverse effects. She said that the best study showing the exposure effect relation seemed to be the Houba study and its associated risk assessment. The discussion returned to sampling methods. Richard said that he found it hard accept that inhalable results were greater than total dust measurements. Patricia said that this was the result of the design of the samplers, and didn't relate to the names used. Patricia said that she had looked at several comparisons of total and inhalable sampling, and that the difference had been that inhalable was about twice total. Richard said that he supported using the same measurement method for the limit as was used in the studies used to set the limit. Richard asked if there was a proposal on the table? Mike thought that the reduction from PNOC levels to the TLV level was justified and would reduce the likelihood of sensitizations seen at the higher levels. Mike suggested that the scope of the limit might be expanded to cover a range of organic dusts. There was a discussion of this and it was pointed out that the studies were on flour dust in baking and milling operations. Patricia said that some of the studies included other grains than wheat, i.e., rye, barley, corn. Patricia proposed that the committee recommend the 0.5 mg/m3 limit for flour dust with a footnote that specifies the inhalable sampling method. The other members present supported this recommendation. Will Forest said that there seemed to be effects at the level proposed and there didn't seem to be an indication of a NOEL. Richard said that this happened last time with beryllium, you could not establish a NOEL. Bruce said that this is the case with carcinogens, the risk does not vanish. Bruce also said that in the case of the Houba risk assessment, different methods produced the same value for the LOEL and NOEL, according to what was said earlier. Richard asked if the recommendation should be lowered. Mike thought that there was too much uncertainty to support a reduction from the recommendation above (0.5). Richard asked given this was the committee ready to recommend 0.5 mg/m3. All present supported this recommendation.

Schedule meetings and plan agenda:
A meeting was scheduled for Dec 13 to follow the Nov. 1 meeting.

There was a discussion about how the committee was progressing through the list of substances that form the general agenda. Mike asked if there was a schedule for completion. Bruce said that there was no schedule, only a goal to complete the list (currently "list 10"). Bruce said that the committee was progressing at a significantly lower rate than that of the last round, but that the process of evaluating substances had changed and that change involved much more independent research. This seems to have slowed things down. Bruce estimated that it might take until the end of next year to finish. Bruce brought up several important substances ahead, asphalt fume, and methyl bromide. There was a discussion about scheduling benzene; the recommendation was to take it up last. Richard asked if the recommendations could be divided into two proposals to go to the Board, allowing what has been done so far to go forward. Bruce said that this was possible but that he would need to check with Division management before committing to do this. Steve Smith agreed, but said that the first package should include the glutaraldehyde recommendation if possible, as the Board had shown specific interest in this substance.

Substances for the next meeting, Nov. 1:
Glutaraldehyde
DNT
Methyl cyanoacrylate
Vinylidene chloride
n-hexane, skin
additional substance by Patricia/Craig

Dec 13:
methyl n-butyl ketone
1-hexene
vinyl bromide
additional substance by Patricia/Craig

Mike volunteered to take the lead on Asphalt. Barbara Schroeder asked where materials relevant to asphalt fume should be sent. Bruce said that he should receive them for distribution, and gave Barbara his card. Asphalt is planned for first meeting of 2003, Jan. Feb.

Meeting adjourned.

10-3-02

Airborne Contaminants Advisory Committee

Draft Minutes

November 1, 2002 meeting

Attending:
Mike Cooper, Richard Cohen, Patricia Quinlan, Bob Nakamura Bruce Wallace, Will Forest, Karen Jenkins, Patrick Owens, Robert Ku, Sandra Morrow, Mike Wilson, Nick Kalanges, Earl Arp, Craig Steinmaus, Patrick Beatty, Tim Roberts

Bruce Wallace called the meeting to order at 10:15. All present introduced themselves. Bruce said that Richard Cohen and Mike Cooper would attend but were delayed for about 30 minutes, and that Carl Foreman would not be able to attend due to illness.

Bruce asked if there were any corrections or comments on the draft minutes for the September 13 meeting. There were no corrections and the minutes were accepted as written.

Bruce Wallace asked if there were any changes to the order of items in the agenda. Bruce noted that Carl Foreman would not be leading the discussion on glutaraldehyde, but that he thought that he and Will Forest could lead the discussion as they had done the literature search and had prepared summaries. Bruce suggested delaying the fifth and ninth items until Tim Roberts arrived. Bob Ku agreed to discuss vinylidene chloride and also vinylidene flouride after glutaraldehyde, followed by methyl cyanoacyrlate and epichorohydrin.

Glutaraldehyde:
Will Forest began with glutaraldehyde. He noted that there was a lot of evidence that exposure to glutaraldehyde can cause asthma and thought that this was the most important health endpoint for setting an airborne exposure limit. While he thought that the relation between exposure and asthma had been established, the levels at which this occurred could not be quantified. He noted that many cases of asthma have been documented at levels below the current PEL, and others seem to have occurred at levels near the current TLV. He said that, as with other sensitizers, a reliable dose response relation could not be established. He thought that the current PEL was not protective for asthma, but did not have a recommendation for another value. Will said that his review included several low dose studies that showed the sensitization, and others which did not. Given these studies, he could not see a way to quantify the effect to the exposure.

Bob Ku asked what the ACGIH basis was for changing the TLV from 2.0 to 0.5? Bruce responded that the ACGIH rationale was based on a study involving the relative potency of glutaraldehyde and formaldehyde on rodents, and then setting a limit based on that and the formaldehyde limit.

Bruce passed out a summary sheet that had also been distributed in the last email. He said that the limit estimates from the animal studies in the top table were quite variable and did not seem estimate a consistent value. The animal studies included one by Zissu that was not included in the ACGIH bibliography. The lower table in the summary summarizes that human studies, Bruce noted that the last study was not referenced by ACGIH and said that he considered it the most important of those listed. He passed out copies of the study, Di Stefano/1999.
Bruce summarized the studies listed in the second table of the summary sheet. Bruce said that he found the last study Di Stefano the most interesting of these. This involved a series of confirmation tests on 24 healthcare workers in Birmingham England. All but three of these workers showed some indication of occupational asthma. The short term exposure measurements for these workers ranged from 0.2 ppm to 0.014 ppm. The median exposure value was 0.035 ppm and the mean was 0.051 ppm. Bruce referred to table 1 on page 1108 of the study that shows the exposure data. Bruce said that all the data collected was below our current PEL and that the majority of those studied were confirmed with asthma. Bruce suggested that this would justify a recommendation of 0.05 ppm limit. Craig Steinmaus said that, if he was understanding this correctly, that this shows evidence of sensitization at 0.035 ppm. Bruce agreed. Will reiterated his comments regarding the difficulty of quantifying the dose response relation with sensitizers such as this, and Bruce concurred with this opinion. Bruce thought that the concept of a NOEL with these sensitizers is a very tenuous one due to interpersonal variability, the possibility of "spike" exposures inducing the effect etc. Craig suggested that the sensitizers needed a different approach than searching for a NOEL or applying safety factors to a LOEL. Will said that the data needed to quantify exposure risk isn't collected, as is the case for many carcinogens, through carcinogen registries. Bruce commented that the British SHIELD asthma surveillance program found this group of workers. Will said that the problem was the lack of denominator data to do quantitative risk assessment. Craig thought that the exposure limit might be set based on other endpoints to avoid this difficulty. Will said that the other endpoint was irritant effect, but thought that asthma was really the endpoint of concern. There was a discussion about feasible methods for setting this limit and it was noted that it would not be possible to set a limit that would protect the subgroup of those already sensitized. Will thought that the goal should be to set a level to protect those not yet sensitized. Patricia thought that it seemed clear that the limit should be reduced to at least 0.05 and that the study seemed to indicate effects below that level as the median exposure, 0.035, in the Di Steffano study. Bob Ku said that most of the data seemed to be grouped at the lower end of the range in this study, and proposed that the lowest value in the range be considered as a limit. That would be about 0.015 ppm. Richard thought that this could be supported. Craig and Patricia concurred. Tim Roberts arrived late in the discussion, abstained based on that.

Vinylidene chloride and Vinylidene flouride:
Bob passed out two summary sheets one for each compound. Bob said that conforming to the ACGIH change in the TLV would require no change to the California PEL for vinylidene chloride. The change that the ACGIH made was to delete the STEL based on insufficient data for support. Bob said that after looking at the information he agreed with this conclusion. Bob said that this substance had been discussed before, but that there was a question about how the current California limit was adopted. The current limit was adopted shortly after the 1989 Federal update to the PELs based on the rationale in the preamble to that rule. Bob recommended that no change be made to the PEL. There were no objections to this recommendation.

Bob began with vinylidene flouride by noting that ACGIH had adopted a TLV of 500 ppm and that California did not currently have a PEL for this substance. Bob said that the ACGIH document reported that there were no human studies available. The rationale for the TLV was based on the relative potency concept that is similar to that used by the ACGIH for glutaraldehyde. They recognized that vinylidene flouride was metabolized at a rate 100 times slower than vinylidene chloride and vinyl chloride. They used this and the ACGIH limit for vinylidene chloride, 5 ppm, to arrive at the 500 ppm TLV for vinylidene flouride. The ACGIH document also referred to the rate of pre-neoplastic changes to the livers of rats as being about 1/100 of that observed with vinyl chloride. Bob said that his problem is that the current PEL limit for vinylidene chloride is 1 ppm and not 5 ppm. This would mean that using the same logic as the ACGIH would result in a recommended limit for vinylidene flouride of 100 ppm. Bob said that that was his recommendation to the committee. Bob said that both vinyl chloride and vinylidene chloride currently have the same PEL in California, 1 ppm. Then if you use the two biological indicators, the results of the study by Stockle (1979) showing relative potency for liver damage in rats, and the metabolism study Filser (1979), a 100 ppm limit for vinylidene flouride is indicated.

Craig asked what the result would be if the limit were extrapolated directly from the Stockle study. There was a discussion about the appropriate uncertainty factors that would be used in this case. Richard asked if there was evidence of genotoxicity. Will said that ACGIH had classified it A4 and that it was shown non-mutagenic in a salmonilla assay, and had a marginal response in mice. Richard thought that extrapolations of the three animal studies showing effects would show a range of limits between about 13 to 250 ppm. Bob said that the Stockle study could not directly compare the effects of vinyl chloride and vinylidene flouride because at ten weeks there were no enzyme deficient foci with vinylidene flouride, the test was extended to 14 weeks to see the effect.

Mike Cooper thought that Bob's rationale and recommendation at 100 ppm seemed the best choice given the limited data available. Will Forest said that he thought that it was reasonably consistent with the other studies listed in Bob's summary. Richard and Patricia agreed that this should be the recommendation using the Stockle and Filser studies as the basis. Bruce asked if there were any objections to the recommendation. Tim said that he did not see enough reason to deviate from the ACGIH value and took a neutral position (abstain) regarding the recommendation. There were no other comments or objections.

Methyl cyano acrylate:
Richard began by saying that his associate Sandra Morrow had done the research on this compound for him. Sandra began by describing the use of the compound as an adhesive, super glue and krazy glue are examples. Both the methyl and ethyl esters are used. The adhesive products were introduced in 1958. Sandra said that most of the limits summarized on the first page were based on the landmark article by McGee, 1968, listed on the second page. There are two descenting bodies, the ACGIH at 0.2 ppm based on the Lenzi 1974 paper, and the UK at 0.5 ppm based on Goodman 2000 paper. Sandra described the animal studies noting that there were no chronic exposure studies or carcinogenicity studies but that it had been shown to be cytotoxic and mutagenic. The McGee paper describes effects from the odor threshold at 1 ppm through pronounced visual symptoms at 60 ppm. The Lenzi paper is in Italian, but seems to indicate a no effect level at 0.4 ppm in a simulated work environment, and the exposure limit was set at half this value. Richard and Sandra wanted the paper translated particularly a paragraph near the end, Bruce agreed to try to get the translation. Sandra summarized the remaining studies and said that the Lenzi article would be the basis for recommending a lower limit at 0.2 PPM. Richard said that a recommendation would need to wait until the conclusions of the Lenzi paper could be verified.

Lunch Break

Planning for future meetings:

Dec. 13 meeting,
Location: San Francisco 455 Golden Gate, 10th Fl
Chairperson: Patricia Quinlan
Substances: Methyl cyano acrylate, Methyl n-butyl ketone, 1-Hexene, Vinyl bromide, Vinyl flouride, Hexachlorobenzene

Feb. 14 meeting,
Location: Oakland, 1515 Clay, 13th fl
Chairperson: Tim Roberts
Substances: Asphalt fume, Nickel, a substance from Tim's list

The following meeting,
Substances: Methyl vinyl ketone, Ozone

There was a review of the Action Items and Open Issues list.
Item four is closed as Tim was unable to find the letter and did not think it was important given his review of the Stayner (1993) paper. Item seven remains open. Regarding the Open Issues list, there was a lengthy discussion about the role of a sensitizer designation for substances in Section 5155. Bob Ku pointed out that if the sensitizer designation were placed on a substance there might be some confusion as to whether the limit set for the substance would or would not protect against sensitization. Bob said that some limits were set for sensitizers based on other endpoints meaning that one could not assume that the limit would protect from sensitization. Patricia pointed out that unlike the TLVs the PELs have regulatory effect, and she could not see how the designation would have a regulatory effect. Bruce agreed that this would not seem to have a regulatory effect and that the sensitizer designation should be part of the hazard communication program and contained in the MSDS. The consensus was that the sensitizer designation not be added to the exposure limits in Section 5155, open issue number three is closed.

Dinitro toluene:
Tim said that there had been an earlier discussion of this substance, and a tentative recommendation to make no change to the PEL. There was some interest in reviewing the Stayner, 1993, study of cancer mortality. This paper was distributed. Tim reviewed the study and did not find the study very powerful. Tim did not see a reason to make a change to the PEL. The numbers were quite small with 6 cases vs. 4 expected and there was no dose response indication. There was a discussion of the results of this study. Craig thought it unlikely that confounders generated the results. Will said the OEHHA risk estimate at the current limit was 1.7/1000. Bob said that he thought that the changes either up or down that had been suggested were small enough that he could support making no change at all. He said that variability in different methods of risk assessments would easily be larger than the size of the changes discussed. There was no consensus to support a recommending change to the PEL.

n-Hexane:
Tim said that Carl had been the lead on n-hexane and that the main issue had been whether to add a skin notation to the current PEL to control absorption through intact skin. Carl had reviewed the ACGIH rationale for the skin notation and had agreed with it. Tim said that Mike Wilson was present and wanted to make a presentation to the committee regarding his research and the adequacy of the current limit to control peripheral neuropathy. Mike introduced himself and passed out a paper summarizing his presentation. His research involved exposure assessment of automotive workers who had used n-hexane products and had developed peripheral neuropathy. Mike had made simulated exposure measurements for one worker who had developed neuropathy using an aerosol automobile parts cleaning product containing n-hexane. He used the product with the same frequency and duration as was reported by the mechanic. The results of the simulation was that the 8 hr TWA exposure measured by the simulation was approximately one sixth of the current PEL for n-hexane. Mike said that he was surprised that the levels turned out to be as low as they were given the heavy use of the product and that they were used indoors without local exhaust systems. The mechanics had also reported headaches and light-headedness. Mike also reviewed several studies regarding n-hexane exposure, including several that was not reported in the ACGIH document. One study in particular, Senagi-1980, was used by several other agencies, ATSDR, US EPA and OEHHA, in there risk assessments, and seemed to indicate that the current PEL and TLV would not be sufficiently low to prevent neuropathy. Mike described a risk assessment that he had done by fitting a curve to the dose response data of three studies: Sanagi-1980, Mutti-1982, and Chang-1993. This risk assessment indicated that approximately 12.6% of workers exposed at the current PEL might be expected to develop neuropathy. Mike had an estimate that there were approximately 65600 of 164000 auto technicians that used n-hexane products, and an estimate that 918 to 5380 of these might be expected to show symptoms at levels below the PEL. The model estimates that 12357 (130 per 1000) would be effected at the current PEL.

Epichlorohydrin:

Craig Steinmaus began by distributing a summary of research on epichlorohydrin. Craig described its use in manufacture of epoxy and phenoxy resins. Toxic effects: 2A IARC carcinogen, reproductive effects in animals, and respiratory irritant. Craig noted that the subchronic animal studies listed on the second page seemed to indicate a NOEL at around 5 ppm. Craig said that this was the basis that the ACGIH used for the 0.5 ppm TLV. Craig described risk assessments done by the EPA and OEHHA. Both were based on a study by Quast-1979 and appeared to be the same study referenced on page two by Sanodanoto. Craig said that these risk assessments incorporated an RGDR factor to correct ventilation effects between rats and humans, and he was not sure what the rationale was for this factor. It had a significant effect, a factor of ten, on the estimate. Will asked why the focus on the non-cancer data? Craig said because the numbers were lower; the lowest number was the non-cancer EPA worker value. Craig added he couldn't find the OEEHA cancer risk assessments. Bruce noted there was a pretty big disparity with the cancer risk assessment on the fourth page. Patricia thought that there was a way to resolve this, the recommendation could be 0.01 ppm if the RGDR is ignored. Tim said he wanted to be sure its achievable, generally. He and Bruce will check LLNL and OSHA on feasibility of measurement. Pat asked if there was workplace data. Craig said one showed 1.0 ppm, another 0.1 ppm. Bob Ku asked where the 0.1 came from. It was the EPA worker without RDGR. Patricia noted the study says that .026 was measured, and that may be the detection limit. Craig said he could probably see if safety factors can be discounted, then it would go to .03. Bob Ku asked if the endpoint was reproductive or something else? Bob thought repro and irritation don't require the subchronic to chronic conversion adjustment, can get that factor out which would increase this by a factor of 10. That makes the proposal 0.1 ppm. Will said there is confusion about the uncertainty factors. EPA treated the subchronic to chronic differently. Would it be helpful to ask OEEHA why the number for CA differs from the EPA? Craig said they use different studies, EPA used inhalation. He was not sure why OEEHA used GI study. When Richard does the non-carcinogen calculation, doesn't he apply a factor of 10? Looking at that, there would be a factor of 1000. Bruce said that was for LD50 studies. Will asked what would bring the group to a proposal? Bob Ku suggested using factors of 10 for the reproductive effects and animal conversion to get 0.05ppm. The other members agreed with this approach and made this the recommendation.
Meeting adjourned.

11-12-02

Airborne Contaminants Advisory Committee

Draft Minutes

December 13, 2002 meeting

Attending:
Mike Cooper, Richard Cohen, Patricia Quinlan, Bob Nakamura, Bruce Wallace, Will Forest, Robert Ku, Tim Roberts, Elizabeth Treanor, Bob Barish, Dwain Blum, William Callahan, Brandon Milar

Bruce Wallace called the meeting to order at 10:20. Bruce noted that Carl Forman would not be able to attend and that Tim Roberts would attend but might arrive late. All present introduced themselves. Patricia Quinlan began as chair for this meeting by reviewing the agenda. It was suggested that an item "5a" be added to discuss a skin notation for n-Hexane as the minutes of the last meeting were not clear as to the recommendation for a skin notation. Patricia asked if there were any comments or corrections for the Nov 1 minutes. There were no corrections to these minutes.

Methyl Cyanoacrylate:
Richard Cohen referred to a partial translation of the Lenzi paper and the summary sheet for Methyl cyanoacrylate distributed at the last meeting. Richard said that the ACGIH position seems to be based on the Lenzi paper as it has the lowest exposure with irritant symptoms of any of the studies listed. The Lenzi paper shows irritant effects at 0.44 ppm or about 2 mg/m3 and recommends an exposure limit of 1 mg/m3 (0.2 ppm). Richard said that this would support a recommendation at 0.2 ppm, but that it is only based on a single study. Bruce noted that the McGee article in the summary seems to show effects around 2 ppm, so it is not inconsistent with the Lenzi paper. Richard agreed. Mike Cooper asked if there was an issue with detection at this level. Richard said that Paustenbach had made measurements as low as 0.003 ppm in his

study of manufacturing facilities. Bruce asked if there was sensitization, at least dermal, seen with this substance, if so this isn't a simple irritant. Richard said that it had been observed. Patricia said that a recommendation had already be made back in May for Ethyl cyanoacrylate at 0.2 ppm. Richard said that the Ethyl TLV had been set by the ACGIH on the basis of its similar response to Methyl cyanoacrylate and was based on the Methyl studies, particularly the Lenzi paper. Richard proposed recommending 0.2 ppm and deleting the STEL. There was no disagreement with this recommendation.

Methyl n-butyl ketone:

Mike Cooper began by distributing a summary sheet and several pages from the 1978 NIOSH criteria document for ketones. Mike reviewed some of the animal studies and noted that the main concern was neural damage with the metabolite 2,5 hexanadione thought responsible for this effect. Mike said that the most important human study was the 1973 study cited by NIOSH of a printed fabric plant in Ohio. In this study 89% of workers in the production facility showed symptoms of neuropathy, with exposures estimated by measurements at various locations at between 1 and 156 ppm. There was a similar plant that used MEK and this served as a control for this plant. The ACGIH noted that there were confounding factors in the Ohio plant, such as worker cleaning their hands with MBK. Mike described a 1978 study that confirmed the 2,5 hexanedione in the serium of humans exposed for 4 hours at 100 ppm and 7.5 hours at 50 ppm. There was a discussion of the similarity of the metabolism of this compound with that of n-hexane. Mike noted that this compound had been compared to n-hexane and the pulmonary absorption was significantly higher for the MBK. He also said that the 1978 exposure study had included a skin absorption experiment that had confirmed significant absorption through intact skin. Mike said that he thought that the addition of the 10 ppm STEL and skin notation was justified, but he thought that the 5 ppm TWA should also be reconsidered. Mike thought that a reduction to 1 ppm based on irritation observed at 3 ppm and the higher rate of absorption should be considered. Richard said that the reproductive effects seen in rats at 1000 ppm could also be cited as a basis for a lower recommendation if safety factors were used, 10x for animal to human, 100 for observed reproductive effects. Richard also noted that this was the lower end of the range of concentrations measured at the Ohio plant. There was no disagreement with this approach or recommendation, 1 ppm TWA and 10 ppm STEL.

n-Hexane review:

Patricia returned to the discussion of n-Hexane and noted that the minutes had not indicated whether there was concurrence with a skin notation recommendation. Tim Roberts said that his review had supported the addition of a skin notation. There was general agreement with this recommendation. Patricia asked if a change to the current exposure limit should be considered in addition to the skin notation or perhaps an action item. Tim said that Mike Wilson's presentation was intended to point out problems below the current PEL but would not necessarily be used to set a particular value. Patricia thought that the decision would be whether to try to consider it in this round of changes or recommend that it be considered in the future. The recommendation was to make n-Hexane an action item to be considered at the end of the current review.

Vinyl bromide, and Vinyl fluoride:

Bob Ku began by distributing three handouts. Bob also referred to a paper distributed earlier by Storm and Rozman on methods for establishing limits for Vinyl Halides. Bob said that the current PEL is 5 ppm and the new TLV is 0.5 ppm. Bob summarized the rationale for the ACGIH limit. Cancer was the endpoint of concern, it is structurally similar to Vinyl chloride, its metabolite is also similar (2-bromoethylene oxide), it causes angiosarcoma in animals as does Vinyl chloride, it is genotoxic in short term screening tests with or without metabolic activation. It appears more potent than Vinyl chloride in genotoxic assays and it also appears to produce more liver angiosarcomas in long term animal tests. The ACGIH limit for Vinyl chloride is 1 ppm and the limit for Vinyl bromide was set at 0.5 ppm due to its apparent higher potency.

Bob described a graph distributed earlier as a representation of the three rat studies for Vinyl bromide, Vinyl fluoride, and Vinyl chloride. The graphical results also indicate the increased potency of the bromide and fluoride compound over the Vinyl chloride. The derivation of a USEPA IRIS RfC (0.003mg/m3) for Vinyl bromide was also summarized. This was based on a non-cancer liver endpoint in the same study that had observed angiosarcomas in rats at 7% in the low dose group.

Bob returned to the Storm and Rozman paper. He said that this paper used the Vinyl halides to demonstrate several different quantitative risk assessment approaches, "threshold" and "non threshold". He said that based on table 4 of this paper and assuming and acceptable risk of 10^{-3}, that he had adjusted the exposure levels listed in this table and found the adjusted limits to range from 0.08 to 0.12 ppm for no threshold

models, and 0.03 to 0.4 ppm for non threshold models for Vinyl bromide. There was a discussion about the adjustments used to produce these ranges. Will Forest asked if adjustments had been made to the "no threshold" levels but had not been made to the "threshold" levels. Bob said that this was true. Will said that he thought both should be adjusted. Bob disagreed, he said with the "threshold"/safety factor approach the risk is not estimated, a presumed safe level is the result. Bob made the point that in this particular case the results happened to come out the same for both models at the 10^{-3} risk level. Bob said that based on this he would recommend a limit of 0.1 ppm for Vinyl bromide, primarily based on the "threshold" (BMD+factors) approach and secondarily on the results of the "no threshold" models at 10^{-3}. Richard said that he supported Bob's recommendation and that the EPA IRIS model for non-cancer liver endpoints used many factors that he would not use in setting limits. With those factors removed he thought that a limit based on the non-cancer liver endpoints would be near the 0.1 ppm limit proposed.

Lunch break

Planning for the February 14 meeting in Oakland:
At the last meeting Asphalt fume and Nickel were placed on the agenda for the February meeting. Patricia said that nickel item should include both nickel compounds and nickel subsulfide.

Elizabeth Treanor asked if the Oakland room had a speakerphone or similar facility. She said that one of the potential participants, Larry Cooper, had a teaching assignment that conflicted with the meeting and wanted see if he could participate via phone. Bruce said that he would check on the equipment situation in Oakland and get back to Elizabeth.

Bruce said that there had been basically three groups that had shown interest thus far in the asphalt topic, the roofers, the pavers, and the refiners. Bruce said that he had suggested in earlier conversations with representatives of these groups that they make 15-20 minute presentations at the meeting, with emphasis on health effects of exposure and information on dose-response, avoiding other topics such as control programs and outreach etc. There was some concern that the presentations would drift off into areas that would not be of interest to the committee members or relevant to setting exposure limits. Bruce said that this would need to be handled, if necessary, by the chairman (Tim Roberts). Mike Cooper suggested that the presentations might be centered on the answers to two questions: What dose response data do you have? What would you recommend as a limit and why? Bruce said that there had been requests earlier from representatives of these groups asking if they could answer specific questions, and that he had said that the questions should be forwarded through him. Elizabeth said that the roofers group would like to have the researchers that did the studies present to answer questions, but she didn't know whom to invite given the large number of studies. Richard said that he wouldn't know which were of most interest until later. Mike Cooper suggested that unpublished data might be available, and that the groups might be able to provide that. Bruce said that specific questions should be routed through him and he would forward them and cc the members and interested parties.

Patricia asked if we could plan a meeting date for the meeting after Feb. 14 and tentative substances for that meeting.

Date: April 11
Chairman: Richard Cohen
Substances: Coal dust, BHT, Methyl vinyl ketone, Styrene

Mike Cooper asked if the proposal based on the recommendations thus far would be coming back to the committee for review. Bruce said that this was not typically done, that once the Divison submits its proposal to the Standards Board it is a public document, and after notice it is clearly available to all, but it is currently a work in progress and may or may not come back to the committee.

Patricia asked if there was any thing on the action item list that needed to be discussed. Bruce said that he had looked in to the sampling and analytical methods for epichlorohydrin based on the new recommended limit (0.05 ppm, Action Item #8), and had found that the current NIOSH method would not work at this level. A new method would need to be developed. Mike said that this should be noted in the proposal. Bruce said that he would include this in the drafts.

Returning to Vinyl bromide and Vinyl fluoride:

Bob began by saying that the information on Vinyl fluoride was similar to Vinyl bromide but generally there was less information on Vinyl fluoride. Bob said that currently there is no PEL for Vinyl fluoride and the ACGIH has set the TLV at 1 ppm. The ACGIH rationale states that cancer is the endpoint of concern and there is a comparison with the TLV for vinyl bromide that finds that the compound is less potent than Vinyl bromide and there fore the 1 ppm limit based on the 0.5 ppm limit for VB. Bob said that it is metabolized in the same way as VB and VC. There is some evidence of genotoxcicity and it causes liver angiosarcomas in animals. In cell culture studies it seems to be metabolically activated more slowly than VB. Bob said that the ACGIH had used the units milimolar amount per unit volume (molecules/volume) for the comparison and not mass per unit volume. Bob said that there was a difference in the animal studies that was not accounted for in the ACGIH rationale. In mice the most frequent effect for VF was broncioalveolar adenoma and that this was apparently not seen with VC or VB. Bob said he did not know what to make of this. Bob continued that the Storm and Rozman paper also had used several models to set exposure limits and these can be seen in table 5. Bob adjusted the "no threshold" results to 10^{-3}, and found the concentrations to range from 0.1 to 0.37 ppm. The threshold models showed 0.1 to 1.2 ppm as the acceptable concentrations. Bob said that based on this and using the same reasoning as with VB that he would recommend a limit of 0.2 ppm Vinyl fluoride. Richard said that he supported both recommendations, 0.1 for VB and 0.2 for VF. Patricia poled the members and there were no objections to these as a recommendation.

1-Hexene:
Tim Roberts began by describing the uses of 1-Hexene and noting that the information on this compound is sparse. The TLV for 1-Hexene new and there is no PEL. There was a discussion about the recent change to the TLV to 50 ppm. This apparently was the result of a reanalysis of a thirteen week subchronic inhalation study in rats. Based on this the NOAEL in rats was estimated at 1000 ppm. The TLV was based on a 20-fold reduction from this value at 50 ppm due to the limited number of studies and species. Richard said that he would support a recommendation at 50 ppm. There was a discussion and it was concluded that given the limited information available, that this was a good recommendation. There were no objections to recommending a limit of 50 ppm. Will Forest offered to do another search and see if there was additional information available on the compound, and report his findings at the next meeting. Patricia said that the issue might be reconsidered if Will found something important.

Hexachloro benzene:
Patricia began by distributing two handouts on Hexachloro benzene. The first was her summary of information on the compound the second was a similar document from OEHHA. Patricia described the uses and properties of the substance and reviewed the animal data and noted that there were no inhalation studies, only feeding studies. She said that the primary effects observed were liver and neurological. Several of the studies demonstrated excesses of hepatic tumors in different species. Patricia described a study of 348 cases of acquired toxic porphyria cutanea tarda by accidental ingestion of grain contaminated with HCB in Turkey and two other studies measuring air concentrations in a manufacturing plant and blood concentrations of workers in a plant making chlorinated solvents. Patricia said that the ACGIH had used several studies to derive the TLV. The Roseman study of rhesus monkeys, showing a NOEL of 0.033 mg/kg/day and adjusting this to and estimated NOEL for a man of 0.00033 mg/kg/day. This was estimated to correspond to a 2.31 ug/m3 HCB TWA. They compared this to the Currier study of blood levels with no observed adverse effects and estimated that the dose in this study corresponded to a 2.9 ug/m3 TWA exposure. The TLV at 2 ug/m3 was set on this basis. Patricia said that this level should be recommended as the PEL.

Mike Cooper noted that the OEHHA risk estimate would make the limit higher if the 10^{-3} risk level is used. Patricia said that the current level is too high based on both the ACGIH and OEHHA analysis. Bob Ku asked if the committee found the 100-fold reduction from the monkey NOEL acceptable. Richard said that there were more than an animal to human extrapolation involved, because it was a feeding study the absorption and pharmicokenetics are additional uncertainties. Richard said that he could support the 2ug/m3 recommendation. Patricia said that the ACGIH level was also based on the NOEL (non-cancer endpoint) in the blood level study. Mike noted that the follow-ups on the accidental ingestions didn't indicate excesses of cancer. Will said that a studies such as these are notorious for not having sufficient power do demonstrate this effect. Bob Ku thought that, absent specific information, the HCB was probably more bio-available via the inhalation route compared to ingestion, and that this would argue for the lower limit of 2 ug/m3. Patricia poled the members and there was no objection to 2.0 ug/m3 as the recommendation.

Meeting adjourned.

1-10-03

Airborne Contaminants Advisory Committee

Draft Minutes

February 14, 2003 meeting

Attending:
Mike Cooper, Richard Cohen, Patricia Quinlan, Craig Steinmaus, Bruce Wallace, Will Forest, Robert Ku, Tim Roberts, Carl Foreman, Don Elisburg, Charles Axten, Barbara Schroeder, Peter Grass, Gary Blackburn, Gary Fore, Earl Arp, Jay Bosley, William Callahan, Steven Tucker, Elizabeth Treanor, Anthony Kriech, Jim StMartin, John Gamble, Ed Starbuck, James Melius, Russell Snyder, Bob Krul, Daniel Garcia, Carlos Offermann, Daniel Smith, Art Sampson, Doug Ziegler, Ronald Johnson, Jeff Scott, Patrick Owens, Bill Fayerweather

Tim Roberts called the meeting to order at 10:15. The committee members introduced themselves followed by the others attending. Tim reviewed the agenda and asked if there was anyone in the audience that was planning to make a presentation on the second substance for today, Nickel. There was no response. Tim asked if there were any comments or corrections for the draft minutes for the Dec 13 meeting. Bob Ku said that he didn't have any substantive changes but that he had seen some typos. He said that he would forward them. Tim asked if the minutes would be accepted given correction of the typos. There was no objection to accepting the minutes on this basis.

Tim introduced the first presenter on asphalt, Jim St Martin. Jim introduced himself and said that he was the president of the Asphalt Pavement Association. He said that he was here today with representatives of several national labor organizations as well as several local labor organizations. Jim expressed his gratitude for being allowed to make a presentation to the committee and expand on the written submissions to the committee. He stated that his organization was committed to assure the highest level of safety and health for workers. He introduced several experts that would make presentations, Dr. Jim Melius, followed by Bob Krul, Dr Bill Fayerweather, Dr. John Gamble, and Peter Grass. Jim also said that Dr. Gary Blackburn, Tony Kriech and Dr. Charles Axten would be available to answer questions in areas of specialization noted as well as Dr. Lawrence Kupper, by telephone, on the analysis of research by Dr Tor Norseth.

Dr. Jim Melius said that he was with the Laborers International Union but was here today on behalf of the California Asphalt Pavement Alliance. He described a partnership that he had been involved with for the last six years concerning asphalt. This involved engineering controls, as well as research into health effects. Partners included NIOSH and OSHA. Jim said that paving and roofing processes were different, but there was an overlap and that he would try to deal mainly with paving issues. He said that the major problem with the research so far is that a dose response relationship has not been established, that there is not a basis for lowering the current 5 mg limit. He said that NIOSH had been looking into asphalt exposure since the early 70s and that they had been working with them to among other things establish a research agenda and combine available data to look for dose response. He said that NIOSH had done a health hazard review in 2000 and had not been able to make a case for changing their REL. Jim referred to the current IARC European study that is partially complete and that significant positive findings have not resulted. The alliance has looked into the feasibility of conducting an epi study of asphalt pavers in the US. Bob Herrick? of Harvard is doing an exposure assessment study as part of this. Jim said that the studies cited by the ACGIH do not support the TLV recommendation adopted, and recommended no change to the current PEL. They were open to a change if new information were to come to light that would support one. Bob Ku noted that the NIOSH REL was 5 mg/m3 as a 15 min STEL, and asked if the group supported the limit on that basis. Jim said that the 15 minute REL might not be a very practical way to evaluate exposure. Asphalt is a

complex mixture and there are real questions as to what is the correct parameter for measurement. For irritation a short measurement is indicated.

Jim introduced Bob Krul to begin the roofing presentation. Bob described his background, introduced the remaining panel members, and said that these presentations were intended to assist the committee in its review of the current limit for asphalt fume. He said that he thought that after the review he hoped that the committee would share the view that a change to the current limit was not justified by currently available information.

John Gamble began by reviewing the IARC study. IARC began reviewing the existing epidemiological studies in 1994 and concluded that a new study was needed. In 1995 they planed a cohort mortality study with a nested case control study. The cohort results have been published, and planning for the case control study is in process. Coal tar is a problem with planning the study and it occurs in recycled paving. Craig Steinmaus asked what the approximate relative risks might be with coal tar exposure. John thought it might be about 2 to 3. He thought that in high exposures such as coke ovens that it wouldn't get above 10. IARC was also concerned about incomplete work histories and smoking. There was a discussion about the smoking data in the Dutch group in the IARC cohort. Bruce Wallace said that it seemed that the Danish group in the IARC study had a large effect on the study outcome, and asked if there was there any information on smoking for that group. John said that he didn't believe there was any data from Denmark, that the information would need to come from the case control study. Craig said that it looked like smoking would be the biggest issue because the high relative risk of LC makes it powerful confounder. Craig referred to the Dutch study and the rates of current smoking, and noted that there were only five smokers in the second to highest category and one in the highest category. Craig said that there were several methods that could be used to estimate the maximum level of confounding that might occur, and asked if this had been done. John said that there was a problem that smoking information was not available for earlier exposures where both coal tar and smoking were likely higher. Craig noted that increased smoking might not be a problem for confounding, it would only be a problem if it was higher than the control group. Tony Kriech noted that coal tar is a continuing problem with studying asphalt in Europe do to the recycling of old pavement. He had been involved in two studies where old pavement was sampled in Denmark. The pavement was analyzed and related to when it was placed in an effort to gauge exposure. Gary Blackburn noted that coal tars show potency differences of 500 to 1000 in genotox assays. Bruce said that he thought there were rodent studies showing a difference of about 10 between asphalt and coal tar. Gary said that there were studies showing this, but that potency also strongly depends on the temperatures used to generate the fume.

Bill Fayerweather began a presentation on a morbidity study at Owens Corning plants. The study was able to control the possible confounders. The exposures were well characterized, and no relation was found between increasing asphalt fume exposure and the health outcomes assessed. Craig Steinmaus and noted the exposures were well below the current limit. Bob Ku also said that the health surveillance was from 1993 after the earlier high levels had been reduced. Bill said that these were average exposures with large variability and that the xray results would be an indication of cumulative effect including early exposure.

Peter Grass of the Asphalt Institute characterized asphalt as a complex mixture of substances with no two asphalts being the same. He said that despite these differences, no qualitative differences in chemical composition related to health effects have been found and that the same was true for asphalt fume. He said that no adverse health effects have been demonstrated as the result of exposure to asphalt fume as it is found in the workplace.

Dr Larry Kupper was connected to the meeting via speaker phone. The members of the committee introduced themselves to Dr. Kupper. Craig Steinmaus asked Dr Kupper why the Jonckheere-Terpstra test was selected to analyze the data in the Norseth study. Dr Kupper said that this test is designed to pick up monotonically increasing trends. It does not impose a quantitative scale on the data, the frequency of reported symptoms. Other analyses were done that did involve assigning quantitative values to the data and the results were consistent across the two other methods used. Craig said that the initial analysis had 50 workers and asked if the other workers were included in the second analysis. Dr. Kupper said that the second analysis used data from 79 workers. There was a discussion about other analysis done using other symptom scores and this larger sample size and unadjusted for covariates, the results looked similar to table 5. Bob Ku noted that the exposures were averaged over several days and asked if daily data were available and how variable the daily data was. Dr. Kupper said that he thought it was quite variable, but the analysis

was only done with the data available, i.e. the data averaged over several days. Bob referred to statements made on page 4 of the reanalysis that indicated that significant Spearman correlations with the responses "nausea" and "sore throat/coughing" and the exposure "asphalt fume". Dr. Kupper said that the symptoms nausea and sore throat/coughing seems to show up over a lot of different exposures. He thought that this is cause for concern. These seemed to show up when working indoors and when amine was used. He didn't think that the Norseth study was definitive enough to be used to set a limit.

Bruce Wallace said that the analysis included a binary variable, indoors and outdoors, and that this would seem to be related to the exposure variable. Dr. Kupper asked Bruce if he thought it was related to exposure or outcome. Bruce he thought it would be related to both, intuitively. Dr Kupper said that this variable, indoor outdoor, was clearly a confounder. Bruce said that it didn't make sense, how could you get the independence between indoor/outdoor variable and exposure? Craig said that it was in the causal pathway so its not a confounder. Dr Kupper said that its a counfounder and if you put it in regression analyses, it makes a difference, the effect of an exposure is effected by whether you control for this variable. By definition its a confounder. Craig reiterated that the variable should not be in the causal pathway. Bruce said that there was no independence there. Dr. Kupper agreed that they were not independent.

Richard Cohen asked given the current limit what an industrial hygienist should measure to best indicate the level of exposure; we have seen several different types of measurements in these studies. Several commented that many compounds and volatiles had been measured in the research, no specific recommendation was made. Dr. Melius said that the components of the fume that are the most important are not rally known, and that there did not seem to be a practical alternative to the traditional methods, benzene soluble and total particulate. The European method includes both the particulate and volatile fraction. There have been comparisons between the US method and European method and there is reasonable correlation.

Richard Cohen asked if the amine additives were used in the US and what they were. John Gamble said that they were often di-amines from fatty acids. They are used in the US, but use varies from state to state, some use lime.

Bruce Wallace asked how the excesses of brain and bladder cancer seen in addition to the lung cancer excesses in Danish studies could be explained. John Gamble said that these were the Hansen studies and that all causes of mortality were high in these studies. The subsequent IARC study did not confirm this. He suggested several other possibilities, but said he couldn't point to a cause. Tony Kriech said that there had been samples of Danish pavement sampled and that coal tar was found to be in use as late as 1970 based on these samples and records of when the pavement was placed. The top mastic layer did not contain the coal tar, but the underlying layer did. Both layers were palaced by the same workers. Jim Melius said that the mastic layer was done at much higher temperatures.

Lunch break.

Planning for next meetings,

Next meeting: April 11
Chair: Rich Cohen,
Location: San Francisco,
Substances: Coal dust, BHT, Methyl vinyl ketone, Styrene, and possibly Nickel

Following meeting: June 6
Location: Oakland
Substances: Ozone, Methyl bromide, Allyl glicidyl ether, Cyclonite.

Richard Cohen distributed a summary outline. Richard thanked those who were attending for their contribution to the review of asphalt. He said that the item D) on the summary is incorrect based on the discussion before lunch. Craig Steinmaus referred to the Chase study and said that it indicated increased symptoms below the current PEL. Craig asked what was wrong with that study. Richard Cohen said that the study was complicated by other concurrent exposures, cellosolve, aldehyde, and that it wasn't clear that the asphalt measurements used the benzene soluble fraction. Bruce Wallace said that they said they were

measuring asphalt fume and comparing results to the TLV, so it seems that they were using the soluble fraction, because otherwise they could not make a valid comparison. There was a discussion of the range of substances measured. Richard said that he was having trouble seeing a dose response relation in these studies.

There was a discussion of the mutaginicity studies. Bob Ku said that the epidemiological studies should be given more weight, as it is almost impossible to set a limit based on a mutaginicity study.

The discussion returned to irritant effects. Craig Steinmaus said that he thought that the Norseth study was the most important of those for this effect. He said that the symptom sum data (raw data, including all the workers in group1) that he had heard today has lost the dose response that was apparent before in Table V.

Mike Cooper said that the recommendation from Richard and his review was to leave the current limit unchanged. Tim Roberts asked if there were any comments on this recommendation. Bob Ku wanted to raise the issue of the NIOSH REL as a 15 minute ceiling vs the 8 hr TWA at 5 mg/m3. Bob said that he did not see where the 5 mg/m3 came from. There was some speculation that the limit might be related to PNOC levels for routine dust. Jim Melius said that he thought that recently NIOSH had been retreating from the 15 minute basis for the limit, not for health reasons, but for feasibility of measurement reasons. John Gamble said that he didn't see how it was possible to make a measurement at that level in such a short time. Tony Kriech said that there was a problem limit of detection and that as air flows across the filter the deposited fume particles can re-volatilize loosing sample.

Tim Roberts polled the members to see the level of support for recommending no change to the current limit. There was no objection to this as the committee recommendation.

Nickel:
Craig distributed a two page summary for Nickel, soluble compounds, insoluble compounds, and Nickel subsulfide. Craig noted that the TLVs were expressed as "inhalable" fractions and that the studies were done using "total dust". This leaves the question, how do you do the conversion. They cited a paper on this comparing the two measurements (P.J Tsai, 1996). Craig said that the ratio of total to inhalable seemed to be about 2 to 3. The ACGIH had first derived a TLV based on the total dust studies and then applied a factor to convert them to inhalable limits. The ACGIH seemed to base their recommendations on the NTP studies of mice and rats. These are summarized on row 5 of the first page. Craig was not sure how the ACGIH derived the standard for the metal. Craig said that he had looked for other recommendations/risk assessments. Those are summarized on the rows below 5 on page 1. The EPA risk assessments were based on refinery dust, but this is a combined exposure including subsulfide. This is a problem when trying to set limits for the other classes of compounds. Craig adjusted the EPA assessment to occupational exposures at 10-3 risk. The ARB assessments were also based on a mixed exposure cohort, subsulfide and oxide. There was an international review (Doll), which concluded that there was not evidence for metal being carcinogenic, and estimates of concentrations for the other classes. Craig said he could not find a carcinogenic assessment for nickel, the summary is for pulmonary effects in animals. The OEEHA values are very low compared to other estimates, they use large safety factors, 300, in the case of insoluble and subsulfide.

Craig said that he started with subsulfide, considering the EPA and ARB assessments would indicate a limit of 0.01. The LOEL in the OEEHA assessment would give a similar value if corrected with a factor of 10 instead of 300. For the inhalable fraction this would mean about 0.02 mg/m3. Richard questioned the need for this conversion. Bob said that it seemed that a non cancer endpoint was driving the limit, unusual. Richard said that he had not heard of any indication that lung fibrosis was a problem with nickel exposures, at least not at low doses, he said that he was more concerned with the cancer endpoint. Richard said that he favored the approach of using the existing assessments for the cancer endpoints and the 0.01 recommendation. Craig said that the recommendation was for the subsulfide. Craig said that increases in relative risk were seen at about the same level for oxide exposures as with subsulfide. This would tend to support a similar limit for insoluble compounds, 0.01 to 0.02. For the soluble compounds the effect is less clear, animal data is negative, and the human data indicates that it is more potent than subsulfide. His recommendation was 0.01 for the soluble. Richard repeated his recommendation that the limit be on the total dust basis unless there is a reason to go with inhalable. Bob noted that the EPA risk assessments assumed a 70 year lifetime. Was this a factor in the occupational estimate? Craig said that he had not

thought about that; the recommendations should be increased by 2 to 0.02. Craig said that he needed more time to work on a recommendation for the metal.

Meeting adjourned.

3/10/03

Airborne Contaminants Advisory Committee

Draft Minutes

April 11, 2003 meeting

Attending:
Mike Cooper, Richard Cohen, Patricia Quinlan, Craig Steinmaus, Bruce Wallace, Will Forest, Robert Ku, Tim Roberts, Carl Foreman, Julianne Broyles, Dan Leacox.

Richard Cohen called the meeting to order at 10:15. The committee members introduced themselves, followed by the others attending. Richard asked if there were any comments on the agenda. Patricia said that they were not planning to discuss Coal dust, Item IV on the agenda. Craig was going to continue with the Nickel discussion and hopefully finish it today instead of starting on Coal dust. Richard asked if there were any comments or corrections for the draft minutes of the Feb. 14 meeting. Craig referred to page 2, third paragraph, and sentence 17. He thought that the reference at the end of the sentence should be changed from "the control group" to "the exposed group". Others thought that the comma in this sentence should be replaced with a semicolon. Craig asked that the "and" after his name in the second sentence of page three be deleted. Craig referred to page 5, paragraph under Nickel, second to last sentence, and asked that the part of the sentence after the comma be deleted and replaced with the word "metal". Craig referred to page 6, sentence beginning with "For the soluble"; the word "is" should be replaced with "may be". Tim said that he had seen some typos and gave Bruce his marked up copy. Richard asked if the minutes were accepted given these corrections. The minutes were accepted on that basis.

Richard said that he had a document describing the limit development process that he had agreed to prepare and would distribute at the lunch break.

Nickel:
Craig distributed a summary page and described the recommendations for nickel compounds that had been discussed at the last meeting. The recommendations were for soluble, insoluble, and subsulfide. They were primarily based on the three carcinogen risk assessments discussed at the last meeting. Craig said that he had gotten similar values using non-cancer endpoints. He could not find any good data to support a limit for nickel metal based on the carcinogen endpoint. Craig said that IARC had placed metallic nickel in group 2b, with sufficient evidence for animals. The animal data, while positive, is not based on inhalation exposures. He had found that the human studies tended to have concurrent exposures to other nickel compounds, mixed exposures, and that studies with only nickel metal exposure were not available. Craig thought that the only way to set a limit for the metal would be to use non-cancer endpoints. Craig said that he had listed four studies with the lowest LOELs on his summary. He said that he could not find a NOEL at lower levels than the LOELs listed. The LOELs were about 0.1 mg/m3. Three of the published studies seemed to be based on the same experiment; the doses and number of animals were the same. Craig said that the recommendations at the last meeting for the other compounds were 0.02 mg/m3. Will Forest said that the information on nickel metal did not seem as clear as that for the other compounds, and asked if there was a basis for setting a limit for the metal that was different from the other compounds. Craig said that he agreed that there wasn't good data to support a different limit. Craig recommended that the limit for metal be the same as the limits recommended for the other compounds. The animal data showing LOELs at about 0.1 mg/m3 support a reduction from the current limit. Richard agreed that this was a reasonable approach and said that it would be difficult to translate the effects noted in the animal studies to disease humans. Will Forest said that if all recommendations for nickel compounds and the metal (excluding nickel carbonyl) had the same recommended limit, then the limit should be expressed as a single limit with the exception of nickel carbonyl. Craig and Richard agreed with this recommendation. Craig said that the animal non-cancer data

and the IARC classification(sufficient evidence in animals) both support the change. Richard polled the other members. Tim asked if there were any organo-nickel compounds. None of the members could think of any. The proposal to have a single limit excluding carbonyl for nickel and nickel compounds was accepted without objection.

BHT:
Bob Ku began by distributing a summary sheet on BHT. The ACGIH had a TLV of 10 mg/m3 since 1976. It was reduced to 2 mg/m3 apparently based on pulmonary irritation. This seemed to be based on animal testing and not on results with humans. Bob said that he had reviewed other sources for references to sensory irritation. He said he found some that said there was irritation eyes, nose and throat (from MediText) but could not find references to studies that had observed human irritation. Bob said that after looking at the ACGIH document and reviewing the studies referenced, he recommended leaving the limit at 10 mg/m3 (PNOC limit) and not lowering it to 2 mg/m3. Bob went on to describe the ACGIH document and his ideas of how the ACGIH had come to adopt the change to 2 mg/m3. This, according to Bob, seemed to be based on fractions of RD50 levels and the estimate that the RD50 in the mouse was 32.7 mg/m3. Bob said that in this case the mice were exposed to the vapor phase at this level by heating the BHT. This level of vapor would not be possible in normal exposures because of the low vapor pressure of BHT. Exposure in the workplace would predominantly be to particulate BHT and not the vapor. Bob went on to summarize the systemic toxicity information he had found (for other effects, not irritation). Bob said that it had been studied as an "antioxidant" cancer-preventing agent in clinical studies, and also in animal studies for causing cancer. The information is mixed, and Bob noted that ACGIH relied on the IARC classification for BHT, group 3. Bob reviewed the information on repro/developmental toxicity that he had found and concluded that this would not be a basis for changing the current limit. He said that a possible compelling reason for a change is summarized on the second page. That is the WHO Acceptable Daily Intake that was set on a NOEL of 250 mg/kg/day in the mouse and a safety factor of 500, to give an ADI of 0.5mg/kg/day. This might convert to an 8-hr inhalation exposure of 3.5 mg/m3. Bob noted that the ADI limit is intended for the general population including the very young and old and otherwise compromised groups, and it is a seven day a week limit. Bob reiterated that he had not seen a basis in this review for a reduction from 10mg/m3. Patricia said that the current limit for BHT is not an explicit limit but the same as the PNOC limit at 10 mg. If there were a reduction to 2 mg/m3 a new sampling and analytical method would need to be developed, the current gravimetric method would not work because the other components of the dust would need to be removed from the sample weight. Patricia said that she could support a recommendation of no action, as there was no current PEL to change. There was no objection to this as the recommendation.

There was a short discussion of the SARS problem. Julianne Broyles asked if she could get advice on what employers should do with employees that were thought to be infected. Richard Cohen volunteered to talk with her about this at lunch and invited those interested to participate.

Planning for the next meetings:

Next meeting: June 6
Location: Oakland
Substances: Ozone, Methyl Bromide, Allyl glicidyl ether,
Cyclonite, Coal dust (from April 11)

Following meeting: Sept. 12
Location: San Francisco
Substances: Bis(2-dimethylaminoethyl)ether, Styrene (carried over from April 11)

n-Hexane:
There was a return to the topic of n-Hexane; there was a question of whether a skin notation had been recommended for this compound. Patricia referred to the 11-1-02 minutes and said that the subject of a skin notation had been briefly discussed prior to Mike Wilson's presentation. Carl had recommended adding the skin notation. Tim said that he had also recommended this change. Patricia proposed that the committee recommend a skin notation for n-Hexane. There were no objections to this as the committee recommendation for n-Hexane.

Methyl Vinyl Ketone:

Richard distributed a one page summary on methyl vinyl ketone as well as a one-page summary on exposure limit development. Richard said the TLV for this substance is a new one at 0.2 ppm C, with a skin notation. There is no current PEL for the substance. Richard said that it did appear that this substance is readily absorbed through the skin and it has a strong irritant potential. Richard summarized the inhalation data in animals. One of these studies was in Russian and not available. Another was in French and Richard was having difficulty interpreting it. In general there is not a lot of published information on this compound. Richard said that the ACGIH limit was derived from the RD50 value of 5.28 ppm in the Schaper study and taking 3% of that value. Richard said that this exposure limit was consistent with the results of the Morgan study. Richard said that he was concerned that the levels for LC50 in two studies were consistent and quite low relative to the TLV. Bob Ku said that there have been studies that had compared LD50 values to EPA reference dose levels, rfd. The studies tried to estimate the factor that would be necessary to apply to the LD50 to reach the reference dose level. The factor to accommodate 90% of substances studied is much higher than 1000; it is about 100000. Richard said that based on his review, he would recommend 0.1 ppm ceiling and a skin notation. Craig said that we might ignore the LC50 information, given that we don't have the Russian study, and with the Morgan LC level is described as >4. That would leave the Morgan study (2000) of nasal and WBC effects in rats and mice at 0.5 ppm. The Morgan study is more recent than the ACGIH document. Richard described the effects seen as increases in white blood cell counts and hyperplasia/metaplasia in the nasal epithelium (might be a precursor to cancer). Mike Cooper said that there seemed to be general agreement with the skin designation, but the levels well below .2 ppm would be a significant change from the TLV. Richard said that currently there is no standard so the adoption will be a new limit and not changing the current limit. Richard noted that the TLV is a ceiling limit. Bruce said that this would be more protective than the equivalent eight hour limit. Tim mentioned that if we were considering a lower limit as a ceiling limit, that measurement methods would be a concern because long term integrated samples could not be done, short term measurements are much more difficult at low levels. Richard proposed a 0.05 ppm ceiling limit based on the lowest effect levels in the Morgan study (2000) of 0.5 ppm and a safety factor of 10 for animal to human uncertainty and that the 0.5ppm was a lowest observed effect level.

Styrene:

Tim began by passing out a two page summary sheet on Styrene. Richard asked Dan Leacox if he wanted to present anything to the committee. Dan said that he was there to observe and determine what the committee needed from the SIRC (Styrene Information Research Center). He said that he should not be considered a Styrene expert. Tim began the summary by describing the current PEL 50 ppm, STEL 100 ppm, and Ceiling 500 ppm. The current TLV is 20 ppm and 40 ppm STEL with no ceiling. Tim described the acute health hazards ranging from irritation to death depending on concentration. Chronic hazards included neurological effects including neuropathy. Carl Foreman continued by adding that Styrene is a suspect carcinogen with an IARC designation of 2b. The clinical endpoints reported were color vision loss, hearing loss, and peripheral neuropathy/nerve conduction decrement. There was a discussion of two different methods of assessing color vision. Tim referred to the TLV recommendation section of the ACGIH document that said quoting the document: "Taken together, the Gobba et al.,(191,192) Eguchi et al.,(193) and Campagna et al.(194) data linking acquired dyschromatopsias with occupational styrene exposure at workplace air concentrations greater than or equal to 50 ppm TWA and the study results of styrene-induced changes in cochleovestibular function(184,189) mirror in the transient, but clear decrements in peripheral and CNS function.(7,176-181) ". Richard asked Carl if he had looked at the chronic toxicity summaries from OEHHA. He didn't have it with him. Patricia had the chronic summary with her and said that OEHHA had proposed 0.2 ppm as the inhalation reference exposure level. She said that the endpoint was neuropsychological. Richard commented that there was a big difference between this level and the levels being considered for the occupational limit. Craig said that after looking at the OEHHA summary briefly, that it seemed to be a well written document. Craig said that in his experience that they had often applied very large safety factors, but they did not seem to do that in this case. Richard said that the 0.2 ppm was a 24 hour level that would need to be adjusted by a factor of four compare with occupational exposures. That would be about 1 ppm. There was a discussion about the Federal OSHA Current limit and the 50 ppm limit in the 1989 rulemaking that was reversed. Dan Leacox said that the industry was primarily adopting 50 ppm as the limit. Bruce asked Dan Leacox how the industry was reacting or dealing with the reduction in the TLV to 20 ppm. He said that he was not sure, but that they did not fully agree with it. Richard asked Carl and Tim if they had found any more recent studies of styrene than those in the ACGIH document. Carl indicated that he had not found any. Dan said that the SIRC had offered to send a representative out to answer questions that the committee members might have. Craig said that if the 15 ppm LOAEL described in the OEHHA summary (based on the 1984 Mutti study) is accepted, then a ten fold reduction to about 1.5 ppm would be

indicated (based on 15 ppm being an effect level). Richard agreed with this analysis. Craig said that this was dependent on the validity of the conversion of urine measures to airborne exposures used by the study. Bruce suggested that the people from SIRC might want to weigh in on this idea. Richard agreed and added that given the differences in the limits discussed that their information might clarify the situation. Craig noted that the Mutti study was an occupational study and that the public health limit did not need to be converted to an occupational limit, that the study could be used directly. There was a request to get the two Mutti studies referenced in the OEHHA summary (both were published in 1984, only one is listed in the ACGIH bibliography). Will said that he could find these studies and forward them. Richard thought that the continuation of the styrene discussion should be scheduled for the Sept 12 meeting. That would allow review of the studies mentioned today and allow the SIRC to participate. The members agreed to postpone further discussion of styrene until the Sept meeting.

Meeting adjourned.

4/24/03

Airborne Contaminants Advisory Committee

Draft Minutes

June 6, 2003 meeting

Attending:
Mike Cooper, Richard Cohen, Patricia Quinlan, Craig Steinmaus, Bruce Wallace, Will Forest, Robert Ku, Carl Foreman, Dan Leacox, Andrew Salmon, Allan Smith, William Ngai, Bruce Hoang, Anne Katten, Elizabeth Yelland, Steve Smith, Harvard Fong, Tom Duafala, Vincent Piccirillo, Michael DiBartolemeis.

Mike Cooper called the meeting to order at 10:15. The committee members introduced themselves, followed by the others attending. Mike began with a discussion of the minutes for the April 11 meeting. Patricia said that the fourth line down on page 2 should read "disease in humans". Bob Ku said that the units were incorrect on page 2 the sixth line from the bottom. Richard Cohen said that the limit that was agreed to was not explicitly stated at the end of the first paragraph on page 2. Bruce agreed to add a sentence indicating that a single limit at 0.02 mg/m3 was the committee recommendation. Mike suggested that the descriptions of the substances to be discussed at today's meeting and the substances planed for Sept 12 should be changed to reflect the current agenda. Bruce agreed to make this change. Mike wanted a sentence added to the first paragraph of page 4 that stated that the 0.05 ppm ceiling limit proposed by Richard was the committee recommendation. The other members present agreed that this was the case. Bruce said that Dan Leacox representing SIRC had asked that the next discussion of the limit for styrene be delayed beyond the Sept 12 meeting, but that this could be discussed after lunch under the agenda item "Schedule future meetings".

Mike moved on to the discussion of today's agenda. Richard suggested that methyl bromide be moved up to the first item as most of those present were interested in that substance. Craig Steinmaus said that he was prepared to begin the discussion of methyl bromide as first on the agenda. Mike said that ozone would be the second item on the agenda.

Methyl bromide:
Craig distributed a three page summary of the research on methyl bromide. He began with the first page summarizing the animal studies for methyl bromide. Craig said that the first study listed, Reuzel, seemed to be most important and had been used in several risk assessments that he had from OEHHA and DPR. The nasal irritation LOEL at 3 ppm was the basis for these risk assessments. The study showed effects at the lowest levels, 3 ppm, compared to the other studies. Other studies had shown effects at slightly higher levels; Craig referred to Honma, saying that dose dependent reductions in brain norepinephrine had been observed at 10 ppm. Craig also referred to two other studies that seemed to show effects at near these levels, the NTP mouse study and the Schaefer study of dogs. The Shaefer study showed effects at low

concentrations but not at higher concentrations, i.e., did not show good dose response. Craig noted that one of the studies that had looked for cancer had been positive. That study, Danse, had seen cancer of the forestomach at the high dose.

Going to the second page of the summary, Craig said that multiple studies had shown positive results for genotoxcicity. Several human studies are listed; most of these have poor exposure information. Craig described the Anger study (1986) as positive for neurological effects, but the exposures were across a wide range, and there were age and education differences between the exposed group and the controls. TWA exposures in this study were estimated at less than 5 ppm.

Criag said that IARC had listed methyl bromide as group 3. Two more recent studies have been published in 2003. The first, Mills, showed an OR of 1.59 for prostate cancer in farm workers (not statistically significant). The second, Alavanja, showed an excess in pesticide applicators, OR 3.47 (significant).

Craig reviewed the basis for the recommendations from ACGIH, NIOSH, OEHHA (2000), USEPA (1992), and DPR. All except NIOSH used the Reuzel 1991 study as the basis their analysis.

Bob Ku asked if any human studies had been published that were negative for cancer. Craig said he did not know if there had been, but a PubMed search did not find anything. Craig said that it seemed that the Reuzel study, LOEL at 3ppm, was the best available study to use as a basis for setting the exposure limit. Craig said that what was needed was the appropriate factors to adjust this to a worker limit. Bob Ku said that he found it unusual that the duration of the study was 29 mo, this is longer than a typical 2 yr. cancer study. Bob said that didn't have the study, but that the IRIS data base described interim sacrifices at 55 and 105 weeks, and that the effects were not seen at this time for the lower doses. Bob thought that, given no effects seen at 2 yrs, the study might be overly representative of a workers exposure. Craig said that the comparison was between exposed and unexposed animals, and that the time extension was not long compared to 2 yrs. Andrew Salmon said that the number of animals in the interim sacrifices were small and would not have the statistical power that the final sacrifice had.

Mike said that the others attending might have some ideas on these issues. Andrew said that the approach suggested on page 3 of Craig's summary was consistent with the OEHHA approach, as far as exposure times and interaspecies adjustments, but what seemed to be missing was the RGDR (Regional Gas Deposition Ratio), an adjustment for the area in the respiratory tract that the effect is observed between humans and the lab animals. Vincent Piccirillo noted that the nose of the rat is quite deferent than that of a human. The rat uses olfaction as a primary means of feeding and has much more relative surface area used for this. Vincent said that the findings in the Reuzel study were not noted until late in the study and were very slight. There was a peer review of the pathology seen in this study and the reviewer's opinion was that the 3 ppm results showed no effect. Vincent said that there had been studies that indicate that after an initial exposure and some damage to the nasal epithelium, there is regeneration of the epithelium even with continued exposure. The studies had shown that olfaction had not been effected by the damage to the epithelium. Vincent said that these factors brought into question the applicability of this study to human exposure. Mike asked if the peer review of the pathology had been published. Vincent thought that the EPA had published it. Craig noted that the risk assessments he had referred to had all noted the problems described by Vincent and still used the 3 ppm as a LOEL for the assessment. Andrew said that the endpoint that was being considered was not really irritation, it was the histological change to the nasal epithelium. These were accompanied by acute necrosis at high doses. Allan Smith noted that while the effects were described as slight, the proportion of animals showing the effect was large. This could not be described as a marginal effect, given the number of animals demonstrating the effect. Vincent described a "white paper" that discussed the issues noted above and the applicability of the study to human exposure. Vince offered to submit the paper to the committee. Craig said that he would like to review this paper prior to making a final recommendation. Criag said that the Reuzel study was not the only study showing effects, other studies noted earlier had shown adverse effects at levels near 10 or 20 ppm. The combined effect of multiple studies showing adverse effects should be considered in setting the limit.

Anne Katten said that if the damage to nasal epithelium results in damage to the workers ability to smell, then that is a significant problem. Michael DiBartolemeis said that the DPR seasonal limit used two studies of dogs as its basis. The Schaefer study had already been mentioned, but the earlier study by Newton had not. The Newton study (1994) was the original basis for the target air concentrations for seasonal exposures.

The results of that study were that there was a dose response for neurotoxicity. This resulted in the lowest dose tested being designated as a LOEL, 5 ppm, and an estimated NOEL of 0.5 ppm. The end point here is different than in the rat studies, neurotoxicity. It is a very relevant endpoint. Michael said that there is a requirement under FIFRA for a developmental neurotoxcicity study and that has not been done, and this creates a data gap. The National Academy of Science reviewed the DPR risk assessment and pointed to problems in the Newton study, and the Schaefer study responded to some of those problems. The current DPR risk assessment uses 5 ppm as the NOEL rather than the 0.5 ppm estimated from the earlier study.

There was a discussion about current exposures in agriculture. Several application techniques have been prohibited by DPR because they could not be mitigated to reduce exposures to an acceptable level. The current 200 ppb DPR limit translates to 5 ppm for 1 hr. Bob Ku asked what current exposure levels were in agriculture. Exposure data generated from 1992 to 1996 showed that levels were below 0.6 ppm 8 hr TWA. Exposures for house fumigators had a mean of 0.8 ppm. Area samples for house fumigation ranged from 1 to 12 ppm.

Vincent Piccirillo said that there was some disagreement about the NOEL level in the two dog studies. The data has been interpreted to indicate NOEL levels as high as 20 ppm. Craig said that with the controversy surrounding the dog studies, he would like to read the commentary on the Reuzel study, and make a decision as to whether it should be used as the basis for standard setting, and return to the controversy with the dog studies only if the Reuzel study is rejected. Craig said that the Newton and Schaefer studies were industry reports and asked if they were available. Tom Duafala said that he would attempt to provide the two studies for the committee. Allan Smith thought that standard setting should be based on published studies. Craig agreed but said that reviewing the unpublished information should be done out of fairness.

Anne Katten said that there was some concern about polymorphism and glutithyon conjugation in the area of neurotoxcicity. There is some information(Halyer?) that there may be a genetic predisposition to the neurotoxcicity of methyl bromide. Anne thought that the intraspecies uncertainty factor of 10 might not be adequate. Vincent Piccirillo said that he disagreed with that conclusion, and referred to another document that demonstrated the opposite.

Mike Cooper asked Craig how we should proceed. Craig thought that the white paper should be reviewed and that the topic be tabled pending the review of the white paper and dog studies. Tom Duafala said that he would try to get these documents and forward them to Bruce Wallace. Craig said that most of what had been said today was discussed in the literature and that the things that he hadn't seen were the white paper, and dog studies. Richard asked if the issue of reproductive toxicity had been dealt with. Craig said that he would like to see the American Biogenetics study. Andrew said that this study had the same confidentiality issue as the dog studies. A summary of reproductive toxicology from the medical toxicology unit of DPR is published. Mike suggested that the discussion be tabled pending the review this information and scheduled for the Sept 12 meeting.

Lunch break

Scheduling future meetings:

A letter was received from the Styrene Research Information Center that requested a delay in the discussion of styrene until it had completed a literature review. This review was not scheduled to be complete until after the Sept 12 meeting. Mike asked if the committee would agree to delay this discussion. There was agreement to delay the discussion to the November 14 meeting.

Sept 12 meeting:
Location: Oakland; Chair: Craig S.
Substances: Methyl bromide, Allyl glicidyl ether, Coal dust and Quartz, Cyclonite

November 14 meeting:
Location: San Francisco; Chair: Patricia Q.
Substances: Styrene, Refractory ceramics (Rich), 1,4 Dioxane (Bob), Glyoxol

Will Forest said that HESIS had been working on a new substance, 1 bromo propane. It has been introduced as a substitute for ozone depleters. There is no exposure limit for this compound. Will said that

they would supply a summary of research on the substance and papers if the committee would consider a limit. There was agreement that the committee would consider a limit for this compound if the information were supplied.

Ozone:

Mike Cooper began by distributing a three page summary and described the current limits and exposure guidelines. Mike described the animal studies and noted that above concentrations of 0.3 ppm the concentration seemed to have a greater effect than the exposure duration. Mike referred to page two of the summary and noted that small decrements in FVC were observed in studies at exposures above 0.1 ppm with moderate exercise and a duration of 6.6 hrs. Chronic effects were not observed in the studies at levels below those producing acute effects. Mike thought that the specification of light, moderate, or heavy work as is specified in the TLV would be difficult to include in the Cal/OSHA PEL. While it might be acceptable in a guideline, it would be difficult to distinguish these levels for enforcement purposes. Mike recommended that three work level approach not be recommended by the committee, and leaving the current levels unchanged or possibly changing the current 0.1 ppm limit to a STEL. Bob Ku said that he had seen a study, Gong 1986, which was listed in the acute toxicity summary by OEHHA that was not included in Mike's summary. Bob said that the OEHHA summary of this study said that exercising adults exposed to 0.12 ppm for one hour showed a decrement of 5.6% in FEV(1). Richard said that this was a very borderline/marginal effect. Bob said that he agreed with Mike that the differences between the three levels specified by the ACGIH were minimal. Patricia said that the specification of light medium heavy work levels would not be practical, as they did not have objective measures to distinguish them. Both Allan and Richard said that they were concerned that was little research looking for long term effects from ozone exposure. Patricia said that most long term air pollution studies included other substances in addition to ozone. There was a discussion of the outdoor air levels of ozone in polluted air and the difficulty of measuring occupational exposures given the ozone levels in smoggy areas of the state. Patrica suggested that the current limit not be changed. Mike said that Folinsbee, 1988 and Horstman, 1990 could be used to support a ceiling limit at 0.1 ppm and that this had been the TLV limit prior to the change 1997. Richard said that the Abbey study described in the ACGIH document also supports this change. The consensus of the members supported a recommendation at 0.1 ppm as a ceiling on this basis.

bis(2-Dimethylaminoethyl)ether (DMAEE)

Bob Ku distributed a summary sheet on this compound. There is no current PEL. Bob said that the were no human studies available for the compound, but that there have been reports of ocular and irritation effects in humans. The ACGIH TLV is based on a 14 week inhalation study of rats showing signs of eye and respiratory tract irritation at 0.23 ppm, with periodic swelling at 0.23 ppm (Losco 1996). The TLV also included a skin notation based on severe effects on the skin and eyes of rabbits and kidney effects in rabbits with dermal application. The substance has been associated with transient glaucopsia (blue-grey vision) as has Triethylamine. Bob said that he would not have set the limit values at quite the same levels that the ACGIH had, but given the sparse data on the substance, there weren't strong reasons for different values. Bob recommended that the limit be set at the same level as that of the TLV including a skin designation. There was a discussion of appropriate uncertainty factors when the endpoint is irritation. Bob said that the traditional interspecies and LOEL to NOEL factors were developed for food additives and this was on the basis of systemic effects. Bob said that he was unaware of any research that looked at interspecies variation for direct acting agents. Allan said that the term irritant has been used to describe an effect that is short term and in some ways to demote its importance. He was concerned that the ocular effects might not fit this description. Bob said the effects were described as reversible and that the problem he had was that the information was insufficient to use a safety factor approach reasonably. Richard and Craig said that they agreed with Bob's assessment. The other members agreed to make the recommendation 0.05 ppm with a skin notation. Allan suggested that the guidelines (the original guidelines from Richard) be changed to state that for mild reversible effects (reversible in an hour) that interspecies uncertainty be reduced to 1. Bob said that not aware of any guidance on how to set a STEL that might be included in the guidelines.

Cyclonite:

Carl distributed a one page summary, described the uses of cyclonite and that the intermediates used in manufacturing cyclonite are absorbed through the skin. Bob Ku said that he had taken the 1.5 mg/kg NOEL reported for rats (ACGIH document ref # 24) and used the following conversion X 70 kg (human) /10 (animal to human) /3 (human to human) /10 m3 (10 m3 respiration). This gave a limit of 0.35 mg/m3 that is very close to the TLV of 0.5 mg/m3. There was a discussion about the studies that were looking for cancer as an

endpoint. Bob said that it was not clear that the studies listed (ACGIH #23,24,25) were negative for hepatic carcinomas and adenomas. There was agreement that this substance should be tabled and that a search for a risk assessment be made and ACGIH refs #23,24,25 be reviewed. Will said that he could get the studies and would look for a risk assessment. This substance will be discussed in Sept.

Meeting adjourned.

6/19/03

Airborne Contaminants Advisory Committee

Draft Minutes

September 12, 2003 meeting

Attending:
Mike Cooper, Richard Cohen, Patricia Quinlan, Craig Steinmaus, Bruce Wallace, Will Forest, Robert Ku, Andrew Salmon, William Ngai, Bruce Hoang, Anne Katten, Elizabeth Yelland, Tom Duafala, Vincent Piccirillo, Michael DiBartolemeis, Sandy Galganski, Arthur Lawyer, Julia Quint, Bob Nakamura, Anne Katten

All present introduced themselves.

Craig began with review of the agenda. Patricia said that the cyclonite and quartz agenda items would be impacted because Carl and Tim were not here. Bob Ku said that it might be possible discuss cyclonite because Will had done some research on cancer studies and it had been discussed at the last meeting. Bruce suggested that this could be discussed later in the meeting.

Craig began the review of the minutes for the last meeting. Bruce said that the reference on the last page to ACGIH ref. 24 should be a reference to number 23. The minutes refer to a rat study and 23 is a rat study, 24 is a mouse study. Craig said that page 3, last paragraph, glutathion is mispelled. There were no other changes.

Methyl bromide:
Craig said that the next item was the continued discussion of methyl bromide. He said that at the last meeting we were looking at the Reuzel study showing effects at 3 ppm. There were some comments that said that rats were more susceptible to methyl bromide effects. The effects were only seen in the olfactory epithelium, and that the rat has a greater percent of olfactory epithelium than humans. Another argument was different airflow dynamics rats vs. humans that could produce greater exposure. Craig said that he had volunteered to read a white paper by the methyl bromide industry. Craig said that there were several arguments made in that paper. The differences in rat and human noses are described. The paper says that the effects in Reuzel were reversible, and that they were very slight. The degeneration and hyperplasia noted in Reuzel are normal processes. Craig said that he had looked into most of the references given in the white paper. He agreed that there were differences in the olfactory epithelium between the two species. He said that he could not find anything that would lead him to believe that there would be substantial differences in toxicity on this basis. He didn't see any evidence of that. Based on that, he thought that effects seen in the Reuzel study should be used as the LOEL for our risk assessment. Mike Cooper asked if the effects were seen in other studies. Craig said that similar effects were seen in several other studies, but at higher doses. Craig said that as it was left last time he had wanted to review the white paper and the arguments for

not using the 3 ppm as a LOEL. He said he had done this and described the effects as: hyperplasia of the basal cells, focal thinning of the olfactory epithelium, and occasional cyst like glandular structures in the sub mucosa. Craig said that he thought that the 3 ppm should be used as the LOEL and that left decisions as to what factors to apply to derive a standard. Patricia said that the summary handout from last meeting had two methods for doing this. Craig said that he would tend to go with method #2. With the rationale that he was using there was no conversion from LOEL to NOEL since the effects are slight and use an interspecies safety factor of 3. The other approach that other agencies use is to include the RGDR of 0.23. With that and not including an interspecies factor you get 0.7 ppm and that rounds to 1. Craig said that his recommendation was 1 ppm. Patricia said that this was the same value as ACGIH.

Andrew Salmon said that the RGDR was considered a pharmicokenetic adjustment, but that this was only one part of the interspecies uncertainty. It does not replace all uncertainty and possible differential response between species in US EPA or Cal EPA assessments. Richard Cohen said that if you considered the other studies listed in the summary many had significantly higher LOELs and in some cases NOELs. These should also be considered. Anne Katten said that she was concerned with the safety factor of 3. She said that the rats don't have glutathion transferase, and that other studies with other endpoints have shown the rat to be less to methyl bromide than other species. Craig said that he had not seen that data. Anne said that the OEHHA acute document discussed that. Andrew said that the OEHHA document did not say that they did not have the enzyme at all, but only that it was not found in the eurithrosites. Andrew said that the mechanisms were not sufficiently understood to make a case for the significance of the observation. This was the basis for OEHHA sticking with the default uncertainty factors.

Craig asked Andrew if the default uncertainty factors of 3 and 10 were even more arbitrary than the RGDR. In other words why 3 and why 10 and not other values, are these scientifically based. Andrew said that the uncertainty factors used have a justification in terms of the range of variation expected across all chemicals. Dr. Alexaev has published and made presentations showing the range of variation between NOELs and LOELs and additional work on interspecies variation for a range of different compounds. The indication of this is that the conventional safety factors that are used are not too wide of the mark. Bruce asked a question about the relation of NOELs to LOELs. He said that it seemed odd to try to standardize a distinction between these two things because he thought that in principle the values were immediately adjacent to each other. Andrew said that the difference was based more on the design of the experiment and dosing rather than the science of the dose response curve.

Richard said that the other studies that are summarized put us in the same range and the lower ones are within an order of magnitude of Craig's recommendation of 1 ppm. Mike asked if we should accept Craig's recommendation. Anne said that she understood that normally an intra species factor was not used based on the assumption of healthy adult populations, etc. She said that with glutathion transferase that there is polymorphism in the population that effects sensitivity. This made her very uncomfortable without an itra species factor. Vince P. said that there was a great deal of debate as to whether the populations that have the polymorphism are more or less sensitive. Vince said that the data is limited and that makes it difficult to make a decision on sensitivity. Richard Cohen said that if you look at the other studies they use many species, including unfortunately some human data. Richard said he favored looking at all the studies for consistency in addition to the rat study. Andrew said that the OEHHA approach included consideration of other studies in other species but that the guideline they used requires that the most sensitive response in the most sensitive species be used. They could not deviate from the guideline unless the mechanism of action is well understood and the effect could be discounted in humans. Vince said that in some of the other studies that systemic effects are seen at higher levels, and that the effect here was localized in the nose and did not involve other organs or systems. Bob Ku said that when considering the various sources of uncertainty, inter/intra species, LOEL to NOEL adjustments, etc. that it was his experience that they were not considered independently. When you think you are using a large factor in one place it effects decisions on other areas. Bob thought that you couldn't isolate every step in the process. Bob brought up the interim sacrifices at the one year and two year points in the Reuzel study. Bob referred to his notes from the last meeting. He had looked at the lifetime of the rat vs. the time they were exposed. The total exposure time was 17 % of the lifetime of the rat. The interim sacrifices were 7.3 % and 14.4 % of lifetime. The working exposure based on 40 yrs/40 hrs/week that works out to 4.7% of the life of the worker. This is another perspective on exposure, were the exposures to the rats might be greater than anything expected for workers on this basis. He said that he understood that the interim sacrifices had less power to detect effects due to fewer animals involved, but that the exposure time had exceeded that expected for workers on a percentage of life basis. Andrew said that his organization's mandate required that the guidelines be

developed and followed. He said that he didn't support the idea of mixing and relating the factors for different types of uncertainty. Bruce said that this agencies mandate did not require a specific approach to setting exposure limits. The mandate was written in very broad terms as setting limits that protected from material impairment. Andrew said that with the experiments with laboratory animals it was always necessary to extend the time or increase the doses beyond what might be normal for the target population to keep the experiment at a manageable size.

Craig asked the members if anyone wanted to use a different approach than using the LOEL of 3 ppm and using a safety factor of 3. Patricia said that some of the cancer studies caused concern and that she thought that the approach that went to .2 ppm might be preferable. Craig said that the problem with those studies was that the exposures were very mixed. Craig had spoken to Paul Mills about this and he had agreed that this was a problem. Will Forest mentioned the dog studies effects at 5 ppm. Craig said that it was difficult to interpret these results as they didn't show dose response. Bob said that he thought that the NOEL might be somewhere between 3 and 40 but that we probably couldn't get more precise than that. He said that the 3 ppm with a factor of 3 was reasonable. Will asked Craig how he had chosen between the two methods in the summary. Craig said that his choice was based on the effects being described as slight. There was a discussion about the reversibility of the effects seen. Craig and Andrew both said that this would not be a consideration in developing the limits. Michael DiBartolemeis said that it was his understanding that there was no exclusion for pregnant women in the methyl bromide standard and that developmental neurotoxicity studies had not been done. OEHHA has been supporting a lower subchronic limit because of this data gap. Craig said that there was a reproductive study that found effects at 30 ppm. Michael said that the concern was with developmental neurotoxicity. Craig said that we have talked about many potentially important uncertainties, but does that cause any of the members to change their minds about the factors to use? Patricia said that she would like to see an additional factor added based on some of these concerns possible reproductive cancer effects to produce a recommendation of 0.1 ppm. Craig said that even if you did this with the 30 ppm reproductive effects you would still come back to 1 ppm with an additional factor. Where cancer was the endpoint we had not used a safety factor approach but had tried to estimate the risk level. Craig said that it looked like there were two proposals at this point 0.1 and 1. Patricia said that she thought there should be a lower recommendation, but said that it looked like the other members were supporting the recommendation at 1. Craig asked Bob what he thought. Bob said that he was comfortable with 1 as the recommendation. He thought if we waited for answers to some of these questions then the standard might stay where it is now, 5 ppm, and that would not be good. Craig polled the other members and all supported the 1 ppm as the recommendation.

There was a short discussion about Will Forest taking a new job in Santa Cruiz. Members expressed appreciation for the help he has given to the committee over the years. Julia Quint said that HESIS will continue to support this committee, provide technical assistance, and attend the meetings.

Cyclonite:
Patricia said that Carl had distributed a one page description at the last meeting. It described its use but didn't show the summary of studies. Bob had made some comments described in the minutes that showed that you could derive a limit near the TLV using ACGIH reference 23. There was a discussion about whether cancer should be the endpoint and recommendation to look for risk assessments. Will found references to three old studies that were not available on line. Craig asked if we had any idea what the doses were in those studies. There was a discussion of one of the three studies, the mouse study, ACGIH ref 25. This study had shown cancers at the high three doses. There was agreement that this study should be reviewed before making a recommendation.

Lunch break

Allyl glycidyl ether:
Bob Ku distributed a two page summary for this compound. Bob said that the information was mainly from the ACGIH, he had looked at other sources and there wasn't much available. The current PEL is at 5 ppm and the ACGIH is recommending 1 ppm. The ACGIH limit is based on respiratory tract irritation, potential sensitization and other nonspecific irritant effects. Bob said that there was a Dutch limit at 0.1 ppm, he found an abstract for their documentation but it did not describe how the Dutch limit was derived. Bob reviewed the acute and subchronic data on the summary, describing it as sparse. Bob referred to the RD 50 study by Gagnaire, saying that type of study had been used to establish exposure limits for sensory irritants and describing work in this area done at the University of Pittsburgh. Bob said that this was often done by taking

0.03 of the RD 50, which resulted in 0.2 ppm in this case. This is shown at the bottom of page two. Bob said that this is not far from the 1 ppm recommendation. Bob said that there were other non irritant systemic effects seen in the acute and subchronic data, decreases in body weight, increases in kidney weight, corneal opacities. These at are higher concentrations, above 30 ppm. Bob said that an NTP study had shown some evidence for carcinogenicity. Rich asked Bob if there hadn't been an ACGIH limit at 1 would his recommendation be 0.2. Bob said probably, but he would be hard pressed to come up with any number in that case. Bruce said that the levels used in the NTP study were near the RD 50 values and might be used. Will Forest said that the NTP study should be available on line. Richard proposed that the recommendation be tentatively set at 0.2 on the basis of the RD 50 and that the NTP report might change that recommendation. Several other members supported this approach. Bob said that he had thought about using the NTP data, and speculated that if 10 % of the animals were effected at 10 ppm, then to get to 10-3 there would need to be about two orders magnitude reduction to about 0.1 ppm. Bob reviewed his notes and said that they found 3/46, 6.5%, of the male mice with adenomas. The proposal was to recommend 0.2 ppm pending review of the NTP report.

Scheduling future meetings:

November 14 meeting:
Location: San Francisco; Chair: Patricia Q.
Substances: Styrene, Refractory ceramics (Rich), 1,4 Dioxane (Bob), Glyoxol (Craig), and possibly finish Cyclonite, and Allyl glycidyl ether.

Bruce said that the Styrene was delayed pending additional information from SIRC. This was due in mid October. There was a discussion as to who would lead on this compound. Bruce said he would check with Carl and Tim to see if they could lead at the next meeting. Based on that, if its not on the agenda for the next meeting it will need to planned for next year.

January 9 meeting:
Location: San Francisco; Chair: ?
Substances: Crotonaldehyde (Bob), 1 bromo propane (Julia), Quartz (Patty)

There was a discussion about Benzene. Patricia said that this would be a problem because it is not really a 5155 substance given the vertical standard. Dealing with the broad issues with this would be outside the scope of this committee. Patricia proposed that this not be done by the committee and possibly referred to another committee. There was no opposition to this proposal.

Coal dust:
Patricia distributed six page summary of data on coal dust. Patricia said that she had included information from a 1995 criteria document. She said that the emphasis was on the coal dust and not on the silica component of coal dust. Current PEL is 2 mg/m3 respirable and the ACGIH is recommending 0.9 mg/m3 respirable bituminous and 0.4 mg/m3 respirable anthracite. Health effects are CWP, PMF, Silicosis, and COPD. The ACGIH had primarily used the worker studies to derive the TLV, these are summarized starting on page two of the handout. Patricia reviewed references 23 and 24 at the bottom of page two. Those show estimates of CWP and PMF at the current limit(2mg/m3 resp) for various grades of coal based on 40 yr exposure. Patricia said there was no NOEL determined in these studies, that the risk assessments are based on the rates directly observed in the studies. Patricia described an anomaly in the 1988 study of lung function at the bottom of page 3. The non smoking non dust exposed workers had worse lung performance than non smoking dust exposed. Richard said that looking at these studies that it appeared that Category I CWP was occurring at about 1 to 3 % at 1 mg/m3. Patricia said that this seemed to be the case and the estimates were that 1 in 5 would go on to develop PMF. There were no estimates for a NOEL. There was a discussion of the various methods and ranking used to characterize the coal in these studies. Patricia said the high rank anthracite coal was about 1 % of US coal. Craig said that if you look at the first Hurley study you could estimate a 1 % chance of getting PMF at about 1 mg/m3 with high rank coal and 40 yr exposure. Craig said that the other studies could be included with a meta analysis, but the risk looks like about 1% at 1 mg/m3. When we look cancer we look at risks like 0.1 %, and PMF is a very bad outcome, so the 1 % risk should be reduced. A factor of ten would do this. Patricia said that she agreed that there was still a large percentage of people that would develop this disease. Patricia said that the estimates varied greatly with the rank of the coal, the average carbon of US coal is 83%. The last page of the summary shows (based on ref

23) predicted prevalence of PMF at 1 mg/m3, 83 % carbon, 40 yrs, 58 yrs old; of 1.7 %. Richard said that he would have trouble supporting 1 mg/m3 given these risk estimates.
Patricia said that it appeared that something need to be done as the current limit clearly had even higher risks of these outcomes. Where should we go? Craig said we don't have data down to 0.1 mg, so we are assuming a linear extrapolation, and that is generally the most conservative assumption. Bob said that this could be tested if we could see the dose response data at levels higher than 1 mg to see what the curve looked like in the other direction. Richard proposed 0.1 mg/m3 as his recommendation based on the assumption of a 10 fold reduction from the risk at 1 mg/m3 (a straight line assumption) and acknowledgement that this wouldn't not be a no effect level. Craig agreed with this recommendation. Craig asked if was any other opinions, and there were none.

Meeting adjourned.

9/30/03

Airborne Contaminants Advisory Committee

Draft Minutes

November 14, 2003 meeting

Attending:
Mike Cooper, Richard Cohen, Patricia Quinlan, Craig Steinmaus, Bruce Wallace, Robert Ku, Michael DiBartolemeis, Sandy Galganski, Julia Quint, Bob Nakamura, George Cruzan, Jack Snyder, Tim Roberts, Steve Smith, Gene Livingston, Flora Ratpah, Johm Schweitzer, Gregory Good, Daryn Dodge, Jim Collins, Susan Ripple, Dan leacox

All present introduced themselves.

Patricia Quinlan (Chair for this meeting) asked if there were any changes needed for the agenda for this meeting. There were none.

Patricia moved to item III of the agenda, review of the minutes for the Sept. 12 minutes.
Mike Cooper brought up the proposal of publishing a paper on the methodologies used by the committee that had been discussed at the last meeting. Mike asked if Bruce Wallace had reviewed this proposal with DOSH management. Bruce said that his recollection of the discussion was that he had said that there was no objection to the committee publishing such a paper, but that the Division would not use this to establish it's policy, or bind future committees. Richard Cohen noted that he recalled Bruce's response. Patricia said that the publication could be from the advisory group and not an official DOSH document. Mike said that he wanted an affirmation that it would be an independent project. Patricia suggested that it should not be officially in the minutes. Bruce said that DOSH has not asked the committee to do this project.

Patricia said that there were some errors in the minutes. Page 2 line 13, should read "studies with other endpoints have shown the rat to be less sensitive to methyl bromide than other ". Misspellings on page 2 second paragraph, glutathione and erythrocites. Page 2 third paragraph line 6, should read "implication of this"; fourth paragraph line 7, should read "intra species factor". Page 3 line 12, should read "where the exposures"; page 3 second paragraph line 6, should read "dog studies showed effects". Page 4, second paragraph, line 1 should read "Santa Cruz".

Styrene:
(Editors note, there was a preliminary discussion of Styrene in April 03, a package of information from the SIRC was distributed to the committee prior to this meeting.)
Patricia asked if the SIRC was ready to start their presentation. George Cruzan began by describing SIRC's most recent literature review. He said that exposures have historically been grouped into three categories by industry. Monomer production with low exposure, synthetic rubber production with relatively low exposure,

and open and closed molding with exposures about 20 ppm for closed and currently about 50 ppm for open. In the past open molding had exposures in the range of 100 ppm. Richard Cohen asked George where he had gotten these exposure estimates. George said that there was a review paper in 1994, Critical Reviews in Toxicology. IARC included exposure information in their reviews in 1994 and 2002. George said that Styrene had been studied extensively in the past starting in the 60s through the current time. The studies cover a wide range of exposures from >200 to around 10 ppm. The studies look at a variety of endpoints. There are conflicting results among these studies. The three areas that SIRC would like to discuss are color discrimination, hearing, and behavioral. George introduced Gregory Good to discuss color discrimination.

Gregory said that he had been asked by SIRC to do a literature review of color vision studies, and evaluate the consequences of this loss to individuals. He passed around a color panel set for the Lanthony desaturated 15 test, and described it as a difficult test with very subtle differences between the color caps. He also passed around the Farnsworth test. It is used for occupational color evaluations and has larger changes between adjacent colors. Patricia said that she had been in a group in doing several studies years ago using the Lanthony panel and that a special light was used to illuminate the panel. She asked if that was still the case. It is. Gregory said that two sets of caps had been reversed to show the group what an error corresponding to a Color Confusion Index of 1.23. Gregory said that this error was typical of the means for the CCI in many of the studies. Bruce Wallace asked if this was the means for controls or exposed groups? Gregory said that, depending on the study, the normals (controls) had been, 1.10, 1.15, and 1.22. Gregory described the age effect of color vision, decrements starting at about age 45 and steeper drops starting at about age 55. He described the mean CCIs for the "high exposure" groups for six studies with high exposures near 50 ppm. The means ranged between 1.13 and 1.33. He described a study done for US Customs to establish color vision ranges for inspectors, normals had a mean of 1.04, mild abnormals <1.8 with few complaints about color vision, moderates with 2.2 to 2.4, and severe defectives at > 2.4. Gregory said that the means from the high exposure styrene groups are in the range where there are few noticeable problems due to color vision for an individual. Gregory said that one of the problems with the studies he reviewed was that the control groups were selected by their history for lack of congenital color vision problems. The problem is that many people with slight color deficits will not know that they have this problem without testing. (Editors comment, this sort of misclassification would tend to bias results toward the null, making a significant association seen even stronger than it appears) He said that when exposures were over 50 ppm then the mild color deficits were apparent but with lower levels the results were fuzzy and its difficult to set a threshold. There was a discussion about the use of urine metabolites as a gauge of exposure in some of the papers. Bob Ku asked if there had been a study where the color vision test had been performed several times in succession. Gregory said that Lanthony had done repeated tests and had seen a learning effect where scores improved with successive tests over a short period. He was unaware of studies of the reliability of the test over periods of about at week. There was a discussion about the 1996 Campagna study that found a threshold for effect at 4 ppm for color vision deficits (range of exposure 2-103ppm, mean CCI 1.15). Bruce Wallace asked Gregory why he found this result surprising. He said that all prior studies had not found a level near 4 ppm as a no effect level. The Goba 1991 study found no difference between the medium exposure group and the controls. That group had a median CCI of 1.07 and the controls had a median CCI of 1.11. Bruce said that in the Campagna 96 study they combined data from two similar studies such that the number of test subjects was >200. The other two earlier studies had 75 and 69 test subjects. It would seem that the Campagna study had much more power to detect the effect. Gregory said that the mean CCI in this study is 1.15 for the whole group and this is a very normal value and typically below the levels for control groups. Gregory said that the studies with exposures below 50 do not show consistent results. Tim Roberts asked if the CCIs in this range would have any effect on work performance. Gregory said that not knowing exactly what the work was, he could not be sure, but it was unlikely that CCIs in this range would have a significant effect. Julia Quint asked if these small decrements would continue with further exposure. Gregory said that he didn't know if they would. Bob Ku asked a question about the mechanism for congenital color vision problems. Was it a shift in wavelength of the color receptors? Gregory said that it was thought that the transmission of blue cone signals across the retina surface was decreased by styrene exposure. Patricia asked if there were any patterns in the types of errors made on the color vision test that might correlate with neuropsychological test results. Gregory said that he was not aware of any comparisons between these tests. Tim Roberts distributed a recent review article by Gobba (2003). He said that he had found it interesting. George Cruzan commented that this was a review article and that it did not have new data. There was a reference to the conclusion drawn in the last paragraph on page 695 of this paper. Tim referred to another suggestion in the paper that styrene seemed to have a synergistic effect on age related color vision loss. Gregory said that he had seen the statements to this effect, but had not seen any data or analysis in the papers to support this suggestion.

George Cruzan began the second presentation referring to the second page of his handout on ototoxicity. George described the animal studies on that page. He described NOAELS as ranging from 500 to 650 ppm for 4 to 13 week studies. He said that noise was a major confounder for human studies. Most studies did not control for noise exposure. George described the Muijser study, 1988, this study had three groups, controls, low exposure, and high exposure groups. There was no significant difference between the control group and exposed groups. There was a significant difference between the low exposure and high exposure group at 8 khz. The authors concluded that this suggested a hearing effect at high frequencies. Sass-Kortsak 1995, no styrene effect. Calabrese 1996, no styrene hearing effect, small study, balance effects noted. Morioka 1999, tested high frequency threshold, compared to 75 th percentile of controls to exposed. The less than four year exposed group did better than controls, > 5 year exposure did worse.

Tim Roberts referred to a recent study in Poland, Sliwinska-Kowalska 2003, and asked George if he had seen it. He said he had. The paper was distributed. Exposures in this study averaged 11.7 ppm. The study showed significant odds ratio for hearing loss. Richard said that it did not appear that the effect of noise had been adequatly controlled.
George said that the European counterpart orginazation of SIRC had the same view.

George began with neurobehavioral effects. He said that studies had looked at a large number of endpoints. For studies that found an effect at a particular level you can find other studies at that level or higher where the effect is not seen. The studies for these effects have conflicting results. George said the most reported effect is slowing of reaction time. The first study, 1972, showed an effect at 130 ppm and no effect at 115. Cherry, 1980, effect at > 92 ppm. Mackay, 1986, no effect 44 ppm. Mutti, 1984, eight endpoints. They saw statistically significant slowing of reaction times at 75 ppm, slowing at 50 ppm but not significant, and results similar to controls at 25. They divided the subjects into four groups based on next morning urine metabolites (Saturday morning). Controls were matched by education, age, vocabulary, and sex. Dr Cherry questioned the technique for matching by vocabulary. The paper only reports only differences from control. George said that there were several questions about the study, the validity of the control group, the exposed group appears the same as a 1983 study with different controls and the exposed group was compared as a whole, it is clear that the 1984 control group was tested at a different time than the exposed workers, and general concern for matching for all the parameters. Alcohol is a confounding factor in this study; they eliminated subjects at 80 ml per day. They asked them not to consume on the last two days (before Saturday). Two problems caused by alcohol, direct effects and exposure estimate bias via urine metabolites. Richard said that to allow this level would allow regular drinkers in the study and that in its self could cause problems with the study. Some one mentioned that the controls could also include people in this category. Richard said that the effect would be to increase the uncertainty of the results.

George said that OEHHA had done a benchmark dose analysis using this study. George said that given the study you can't do a traditional benchmark dose analysis, because reporting is based on differences (more than 2) from controls. Jim Collins disagreed with this.

George described a recent paper by Ska, 2003, looking at 50 volunteers, given 2 ppm (as control level), 25 ppm with four 50 ppm excursions, 50 ppm constant exposure, and 50 ppm with four excursions to 100 ppm. Exposures were for 8 hours, with two weeks between exposures. No effects on reaction times were observed. Single exposure study, subjects at rest when exposed. George summarized by saying that there was no gold standard study that could be used to establish the NOAEL or used for bench mark dose analysis. There are conflicting results and limitations in the studies. Jim Collins asked if SIRC was sponsoring any current studies in this area. SIRC is not currently but is considering the sponsoring a study in the future. Jim Collins referred to a recent report by Broadkin (?) that indicates abnormal liver enzymes appearing in the blood of people exposed > 25 ppm. George said that he had not seen this report, but there were studies done in the 60's and 70's looking for liver enzyme problems at higher levels with no reports of enzyme problems.

Tim Roberts referred to a Health Effects Institute case cohort study a significant increase in ischemic heart disease, 2003. George said that this was in styrene-butadiene rubber where exposures are low, other cohort studies in the US and Europe with much higher exposure levels have not seen excess ischemic heart disease. The data for the cohort in the 2003 paper has not been updated since 1991. SIRC has contracted with the U of Alabama to update this cohort, a draft update is due soon.

Bob Ku asked what the clinical significance of the reduced reaction time might be. George said that he didn't know how to estimate this but that with alcohol use some impairment is allowed before the level becomes illegal for driving. There was some discussion about the possible long term effects and on reaction times.

Mike Cooper asked if SIRC had a recommendation regarding the exposure limit, the PEL. George said that they could not see a reason to lower it from where it is.

There was another discussion of the Polish noise study. Richard said that he thought that the "Styrene only" group with noise exposure of 80.3 db might have been effected by that level of noise.

There was a discussion of cancer results in mice. George said that it was thought that this was due to the particular metabolism in the lung of mice. Lung cancers have not been seen in rats. Human data is mostly negative.

Lunch break

Craig Steinmaus attended after lunch and introduced himself.

Styrene discussion continued:
Richard said that the cancer endpoint had not been reviewed thus far and asked if the OEHHA chronic assessment considered this end point. It did not. Richard asked if there had been epidemiological studies of worker cohorts. George said that there was a 15,000 member cohort that has had an average follow up of 19 yrs that is negative. There is a study in Europe that involves eight different cohorts. Average follow up of 13 yrs, it is negative for within country differences. There is a positive trend with average exposure for lymph/haemoatic cancers. Craig asked if there were any animal studies. George stated that there were some positive studies in mice, and all studies in rats were negative. Craig said that he would like to look at the positive mouse studies. Craig said that he would also like to see the results of the EPA risk assessment software with the mouse study data. George said that he could supply these studies. Bob Ku said that simply using the model would not help without an idea about the underlying mechanism/threshold effect. George said he could send a summary of the studies. Bruce asked George to forward this summary via him to Craig.

Richard asked if it was worth looking into reproductive endpoint. George said that there were two reviews by Nigel Brown. He said the review did not note specific effects other than maternal toxicity. George said that these reviews could be included with the summary of cancer studies.

Craig asked Jim Collins what bench mark dose model had been used in the OEHHA risk assessment. Jim said that he was not sure and would need to go back and look to find which was used. Gene Livingston asked if it would be helpful if they would summarize what had been discussed this morning and forward it to the committee (via Bruce). Craig (and others) thought that was a good idea. Bruce gave Craig the Polish noise and HEI eschemic heart disease studies that were distributed this morning. Bob said that he thought the no or low effect level was somewhere in the range 20 to 50. He said that given the traditional approach given that would be to apply factors of 3 or 10 to those levels. That would bring you down to low numbers. Craig said that those levels might approach the OEHHA chronic limits if they were converted to worker levels(40 hr exposures vs 24/7). Richard agreed. Bob said this is the standard approach, but hard question is, is that biologically relevant. George said that the EPA and OEHHA had drawn different conclusions about the NOEL and LOEL levels from the Mutti study. The EPA had concluded that the NOEL was 25 and OEHHA had concluded that the LOEL for the study was 15. George referred to the control group problem he had described earlier.

Mike Cooper asked what rationale had been used by the ACGIH for the 20 ppm TLV. George said that it was not clearly stated, the NOELs are listed in the document as 50 or higher. Bruce asked if the 1997 ACGIH document considered the 1996 Campagna study and its 4 ppm intercept. George said he didn't know. Bruce said that other studies seemed to show effects below 50, the Polish noise study, HEI etc. Bruce said these studies might be subject to confounding effects, but that did not mean that it could be concluded that they were confounded. George said that a tenet of science is that effects are reproducable, and that for all these studies showing effect there are others not showing effect. Bruce said that studies with low statistical power to show effects that are negative should not be used to undermine other studies with sufficient statistical power and which show an effect. He said that was the point that he was trying to make

earlier with Compagna, a study with over 200 subjects showing the effect, and two other studies with 69 and 75 subjects not showing the effect. The Compagna study would seem to have more power to detect effects. Richard said that there seemed to be a number of data points below 50. Richard said that we were missing a summary of studies in tabular form, the type we usually do. George said that he had a table that summarized the studies in tabular form and could forward it. Richard suggested that we forward it to Tim. Bruce said he could work with Tim to review the table and distribute it.

Planning future meetings:
Jan 9, 2003
San Francisco
Chair: Bob Ku
Substances: Crotanaldehyde, 1 Bromopropane, Quartz, Glyoxol, Dioxane

March 12, 2003
San Francisco
Substances: Styrene,

There was a short discussion of allyl glycidyl ether. There had been a tentative recommendation of 0.2 ppm at the last meeting. Bob said that he had looked into the NTP studies, and they did not indicate the need for a different recommendation. This discussion completed the review of allyl glycidyl ether.

Bruce asked Craig if he could read the Polish noise study and see if he agreed with Richard's assessment of the study. Craig said that he would do that.

There was a short discussion about the public hearing on Dec 18 for the first set of recommendations.

Refractory ceramic fibers:
Richard distributed a two-page summary of the studies of refractory ceramics. The said that the animal studies are summarized under numeral #1. The effects appear to be similar to those of asbestos. They are interstitial fibrosis, pleural plaques, lung cancer and mesotheleoma. These effects are seen in animals and some of them in humans. Richard said the ACGIH logic was that since the effects are similar to asbestos but it seems less potent, and the asbestos limit is 0.1f/cc, the limit should be 0.2f/cc. Richard said the only human study thus far, Lemasters 2003, was not positive for lung cancer or mesothelioma, there was an increase observed in urinary cancers. There was a risk assessment by Moolgavkar that estimated 4/100000 at 1f/cc. Bruce said that this appeared to be quite a low risk given the exposure level (approx. x 10 the asbestos limit). Richard went on to describe the human studies on page 2 of fibrosis and pleural changes. He said that the most significant, in his view, were the Lockey studies. Bob Ku asked a question about the units of exposure in the fibrosis studies. Richard clarified that the units were fiber-months, not fibers per month per cc. It is a cumulative exposure measure, the usual unit in asbestos is fiber-years. Richard said that this these studies taken together would support a recommendation at 0.1 or 0.2 f/cc. Richard said that this was consistent with the cancer risk estimate at about 1/1000 at 0.2. (Editors note, the adjustment to the Moolgavkar estimate is incorrect at the bottom of page two. The adjustment shows the risk going up as the concentration goes down.). Mike Cooper asked if Richard thought that the lung function decrease in the Lockey 1998 study was significant. Richard thought it was. Craig said that the Moolgavkar paper seemed to use the least conservative estimate of exposure, this might cause the risk estimate to be low. Craig said that he considered several models and selected the one he used because it had pharmico-kenetic data to support it. Bob said Moolgavkar had developed his own model and asked if he had used the MKV model for this risk assessment. Craig said that he had. Craig said that the results of the fibrosis studies could represent a LOEL, or the results could have been confounded by other exposures. Bruce asked what the exposure time was for the workers in the Lockey 1998 study. Richard said that they had been in their jobs more than 7 yrs. Craig said that he supported the lower value 0.1 f/cc. There was a discussion about the exposures in the Lockey study, and it was estimated that if the workers were exposed for >7 yrs. Then the exposures must have been near 0.7 f/cc, or less for longer exposure durations. Richard asked if there were other opinions on the recommendation. Patricia said that she supported Craig's recommendation. Bob asked if the asbestos limit were 0.1 f/cc, then the recommendation would be saying that these fibers have the same potency as asbestos. Is this the case? Richard said that the original studies for asbestos involved very high exposure levels and the results of studies for RFC are showing effects at lower levels. Mike said that he could see that three of the studies indicate that the level should be below 0.2 f/cc. Richard reviewed the ACGIH rationale, that was that while the product is relatively new, lung changes have been observed and

the persistence of these fibers appears greater than other synthetic vitreous fibers. The potency of the RCFs was thought intermediate between those fibers and asbestos. Bob said that he thought that the 0.1 recommendation was reasonable. There was general agreement to recommend a 0.1 f/cc limit.

Meeting adjourned

12/9/03

Airborne Contaminants Advisory Committee

Draft Minutes

January 9, 2004 meeting

Attending:
Mike Cooper, Richard Cohen, Patricia Quinlan, Craig Steinmaus, Bruce Wallace, Robert Ku, Julia Quint, Bob Nakamura, Bob Barish, Steve Smith, Jim Collins, Len Welsh, Tom Mitchell, David Gonzalez

Len Welsh gave a briefing to the committee about the changes to Section 5155 that had been proposed by the Board last November. Len said that prior to the notice for the change, the Division had been contacted by groups associated with glutaraldehyde that had not been involved in during the committee's consideration of these changes. Those groups had been concerned about the business impact of the recommended change. The current committee primarily looks at the scientific basis for setting limits, and is not well equipped to assess the business impacts of these changes. Len said that the Division had agreed to hold an advisory meeting to consider the impacts of the proposed change for glutaraldehyde. There is also an Executive Order from the governor (S-2-03) that requires a more extensive review of business impacts for all ongoing rulemaking proposals. The Executive Order will require a change in our process that will implement the review of impacts. This is particularly true where limits are proposed below existing TLVs. The review of impacts will depend on information that will need to come from industry. The Division has decided to separate all the substances in the proposal with limits below the TLV and have an additional advisory process to reconsider their impacts and the scientific basis. Len said that there had been an explicit request to reconsider the proposed limit for MMA and that Board member Bob Harrison had asked that sensitizer or carcinogen designations be considered.

Steve Smith said that DOSH has an ongoing obligation to take advice from the advisory committee and then look more at impacts and identify affected groups as part of this.

Mike Cooper said that he wanted to publish the methodology that the committee had developed used. This would be helpful to understand the recommendations.

Richard Cohen said that he had an initial draft that was being transcribed, but that it was not ready to go.

Bob Ku (Chair for the meeting) moved on to the first item of the agenda.

All present introduced themselves.

Bob said that he had seen several typos in the minutes for the November 14 meeting. He gave Bruce a copy with markups rather than discuss them. Bob asked if there were any other changes that needed to be made to the minutes. There were no other changes suggested.

Agenda item IV, Glyoxol:
Craig Steinmaus distributed a handout on glyoxol. Craig said that there weren't many studies for this compound. Craig summarized the sources he used for the review and described its uses. The TLV is a new one at 0.1 mg/m3. Craig referred to the subchronic oral study summary on the handout and noted that the LOELs/NOELs seen are in the range of 100 mg/kg. The other studies are summarized in the table below. There are positive studies for genotoxicity and mutagenicity and only one inhalation study. This inhalation study was used to set the TLV. The two higher doses in this study produced squamous metaplasia of the epithelium of the larynx in the test animals. The lowest dose was a no effect level. Craig noted that the numbers of animals in this study was small, 10 at each dose. Craig referred to a table at the bottom of the first page showing some other aldehydes and metaplasia in rats exposed to formaldehyde.

Craig referred to the second page of the handout. It shows three possible approaches for deriving a limit. Craig said that given the single inhalation study and the other information regarding genotoxcicty and that it promotes tumors, he could not see a justification for the ACGIH limit. That limit is only a factor of four below the NOEL value in the study. Rich Cohen agreed that the ACGIH limit did not have enough margin from the subchronic study. There was a discussion of the three methods on the second page and Mike Cooper asked if there was support for the middle approach that would recommend 0.01 mg/m3. Bob asked if anyone disagreed with this recommendation. There was no disagreement.

Item V, 1 Bromopropane:
Julia Quint distributed the summary section of the NTP report on 1 Bromopropane (NIH No. 04-4479). 1 Bromopropane is a "new" chemical that has been developed as a replacement solvent for other ozone depleters. It is intended to replace methyl chloroform and other chlorinated solvents. It is anticipated that this substance will be used widely. Production in the US is about 1.5 million pounds and more than that is imported. It is an analog of DBCP, and has shown reproductive/developmental and neuro toxicity. The NTP report deals with reproductive and developmental effects and sets a NOEL for rats at 100 ppm. HESIS recommends a limit between 1 and 3.3 ppm. Craig asked Julia how these two values were derived. Julia said that the 3.3 ppm is from the NTP NOEL adjusted with uncertainty factors and exposure time corrections. The 1 ppm is from the OEHHA toxicity data review and its reference exposure level, 220 ppb, adjusted for occupational exposures. Julia said that their recommendation also includes a skin notation. Heins Alar? at NIOSH has done some modeling of skin absorption and there is a general consensus that there is significant absorption. Julia distributed a report by Beck and Caravati on nurotoxicity observed in workers spraying glue containing 70% 1 BP. The report concluded that these exposures were associated with lower extremity neurotoxicity and elevated plasma bromide levels (median air concentrations were 130 ppm 1 BP). Craig asked Julia if she had a copy of the Honma 2003 study. Julia said she did not have it with her. Craig said that the description of the study hints that there may be effects at 10 ppm. There was a discussion about USEPA SNAP program limit of 25 ppm for industrial settings and 1 ppm for the general population (this is described in Julia's "1-Bromopropane" handout). Julia said that a bench mark dose approach was used. Jim Collins said that this approach uses information to establish a dose response curve and then usually finding the 5% incidence point. Taking the lower bound of this point is the benchmark dose. Then uncertainty factors are applied. This approach avoids trying to establish LOEL to NOEL. Richard said that he supported the recommendation at 1 ppm based on the OEHHA data review. Bob Ku said that he also supported the recommendation on the same basis after confirming that this was based on the OEHHA REL derivation from the Ichihara 2000 study. The other members agreed with this recommendation. The skin notation will depend on the availability of data to support the conclusion that absorption is a significant route.

Lunch Break

Planning future meetings:
March 12, 2004
San Francisco
Chairman: Mike Cooper
Substances: Methyl methacrylate (request from Len Welsh), Styrene, Cyclonite, 1,4 Dioxane

There was a discussion about cyclonite for the March meeting. Will Forest had responded to an earlier request to search for a cancer risk assessment and had given a link to an EPA IRIS document on cyclonite. He was unable to get copies of the rodent studies ACGIH refs 23,24,25. Craig had expressed an interest in seeing the mouse study, ref 25, at an earlier meeting.

There was another discussion about the February 10 meeting to discuss the glutaraldehyde proposal. Bob asked if anyone was interested in attending from the committee. Mike Cooper said that he would be interested. Bob said that he thought that the role might be to explain the basis for the committee's recommendation. Patricia said that she might also be able to attend.

1,4 Dioxane:
Bob Ku referred to his handout that had been distributed in November. He said that the limit would be substantially different depending on whether the cancer endpoint is used or not. Bob described the TLV at 20 ppm as a slight reduction from the current PEL at 25 ppm. Bob said that the stated rationale by the ACGIH was control of liver/kidney toxicity and to harmonize with other agencies. Bob said that this was odd as many other agencies are at the 25 level. Bob said that the substance has low accute toxicity as shown on the summary. The inhalation studies have tended to use high levels and short durations, the Torkelson study is an exception, 111 ppm for two years. Julia asked if there had been any range finding studies. Bob said, referring to page two, that Torkelson had done some studies at lower levels and also seen no effect. Bob said that the Kociba oral studies had also been done in 1974 and those could have been used for range finding. Bob said that he had done a conversion shown in the footnote on page one to convert the 111 ppm to an oral dose. That came out to 75 mg/kg/day. The Torkelson dose falls approximately at the middle dose of the Kociba studies. Bob said that liver and nasal tumors had been observed at the high dose in the Kociba study. These were also seen in mice in the NCI study. Bob said that tests for genotoxicity have been negative, and some have commented on the mechanism of action suggesting that the toxicity occurred when metabolism was saturated.

Bob said that OEHHA had derived both accute and chronic RELs (non cancer). These had used different studies, and different adjustments (uncertainty factors). The two derivations resulted in the same REL, 0.8 ppm. Bob described the cancer limits, NIOSH (1977) had set a limit of 1 ppm for 30 minutes, based on cancer potential and measurement sensitivity. Bob said that OEHHA and USEPA had done cancer potency estimates. Bob had converted these to air concentrations at a 10-3 risk level at the bottom of page three of the summary. These came out to 0.1 and 0.247 ppm respectively. Bob said that Prop 65 had also estimated cancer risk and the conversion of there estimate was on page four, that came out 0.117 ppm at 10-3 risk. Bob said that the major issue was that there were agencies that had estimated cancer risk, but ACGIH had not used that approach. Bob thought that the biological question was, does it cause cancer at the levels we are considering. Mike asked what designation IARC had for dioxane. The ACGIH document did not state the IARC designation. Bob thought that another question was whether it was carcinogenic by the inhalation route. Craig said that in the absence of mechanistic data he thought that we would need to assume that it is. He said that we had five studies in three different animals. Bob said that there was mechanistic data, but that this data might not satisfy everyone. Craig said the converted cancer estimates were for 24 hour exposures, work exposures would be 7/5, 52/48,24/8, and 80/40. This would be a factor of about 8. So that would increase the cancer estimates to about 0.8 ppm. Craig said that the IRIS estimate would be higher, and asked if there was a reason to use it over OEHHA. Craig asked if there was agreement to use these cancer estimates. Bob said that he did not favor that approach. Rich asked Bob why he didn't favor that approach. Bob said that he felt that the saturation kinetics argument should be given some weight, and he fell into that "camp". Bob said that there were four or five articles on this saturation kinetics but there would always be some uncertainty as to how this would apply to humans. If the studies are done in humans it is done in cell culture and how this translates is still uncertain. Craig said that he wanted to see these kinetics studies. Bob described one metabolism study by Anderson. That study notes that, based on these quantitative estimates, human populations continuously exposed to 740 to 3700 ppb. would be unlikely to experience increased frequencies of tumors. Bob said that his recommendation is based on the Torkelson study and the adjustments shown on page four, at 10 ppm. Rich said that he didn't see a big difference between this value and the TLV. That makes the decision about whether to use the cancer estimates more important given the large difference between the TLV and the 0.8 ppm cancer estimate. It was decided to table the discussion pending a review of the kinetics papers and put it on the agenda for March 12.

There was a short planning discussion about Styrene. Craig said that he had prepared a presentation and had collected the studies described in the minutes for the last meeting. Rich said that George Cruzan had said that he would provide a summary of studies and suggested that Bruce send an email as a reminder.

Quartz:

Craig distributed a two page handout on silica. He described a derivation of an exposure limit based on silicosis and a bench mark concentration technique (BMC01) by OEHHA with the occupational to public health conversions removed. Those gave results 8.8, 15.9 and 15 ug/m3. These three results were based on occupational studies by Hnizdo, Steenland, and Hughes. Craig also described a limit derived by Allan Smith (March 2003) also on the silicosis endpoint and using the same studies. This one used the NOAEL approach and gave slightly lower values due to the uncertainty factors used. Craig referred to four other risk assessments on the second page of the hand out. He noted that the last one was based on a large pooled cohort and used lung cancer as the endpoint. Jim Collins said that IARC had it in Group 1. Patricia said the if you looked at all the assessments they average about 10 ug/m3. Bob Ku said that Allan Smith's assessment used an uncertainty factor of 10 for intraspecies. He said that if the study population was large then there and there was some knowledge of variability, then this factor would not need to be as large. Jim Collins said that was the basis for OEHHA choosing 3 instead of 10 for this factor. There were seventeen thousand people in the cohorts in the studies they considered, and that some of the people who got silicosis at the low doses represented sensitive groups. On the other hand there weren't significant numbers of women involved. This was part of the reason OEHHA chose a factor of 3. Bob asked if there was a proposal. Patricia said that 10 ug/m3 seemed reasonable. Bob asked if there was any discussion of this proposal. There was general support and no opposition to this as the recommendation.

Crotonaldehyde:

Bob began by saying that there was less data for this compound so there should be less controversy. Bob distributed a three page summary. Bob described the current use and that the current PEL was 2 ppm with no skin designation. The TLV is 0.3 ppm ceiling with a skin designation. The ACGIH rationale was that it is equipotent to formaldehyde and the TLV for formaldehyde is 0.3 ceiling. This is supported by Sim and Pattle, and Steinhagen and Barrow. The skin designation is based on dermal LD50 values under Accute Tox Data. The inhalation studies show effects at all concentrations used, and the RD50 values combined with the Shaper (1993) approach to predicting an acceptable limit gives 0.1 ppm. There is one drinking water study of rats, while liver cancers were observed, there was no dose response. Bob described a gavage study by Wolfe. There were effects on the stomach and nasal cavity of rats and mice at levels above 5 mg/kg/day. It is generally positive in genotoxicity screening tests. The mechanism is not well documented but thought to be saturation of glutathione dependent metabolism leading to DNA protein crosslinking similar to formaldehyde. Human volunteer studies show irritation and lacrimation at 4 ppm for 30 minutes exposure. Bob described an IH survey conducted by NIOSH (not noted in the ACGIH document); this found levels up to 1 ppm in a plant where irritation was reported. Bob said that he supported the 0.3 ppm ceiling limit with skin designation based on the ACGIH documentation and his review. Craig asked Bob if he had tried to determine what the equivalent inhalation doses would be for the oral studies. Bob said that he had estimated the mg/kg levels for the drinking water studies based on the assumption of 20ml/day drinking. This is in italics on the second page. Bob said that you couldn't really compare these studies to the inhalation studies because the effects (endpoints) are different. Craig and Patricia said they supported Bob's recommendation. There was no disagreement with this as the recommendation.

Meeting adjourned

1/23/04

Permissible Exposure Limit Advisory Meeting

Draft Minutes

March 30, 2004

Steve Smith called the meeting to order. Steve asked that when introductions were made that the substance that the person was interested in be indicated. Steve said that he had received submissions on various

substances, and that these would be available to those interested that didn't already have them. The submissions were on the following substances: acetone, beryllium, 2-butoxyethanol, methyl methacrylate, molybdenum, and proplyene oxide. Steve described the advisory process that was used in California prior to proposing changes to our standards. The nine substances that are on today's agenda were taken from the current proposal at the Standards Board and brought to this meeting to solicit additional information. The purposeof this meeting is to review and seek additional information on the earlier committees recommendations and, importantly, to seek information on impacts of the proposed changes and technical issues such as sampling and analysis information. Another question is what impacts a change to the TLV would generate. We plan to consider this information and use it to develop a new proposal that will probably be noticed later this year.

All present introduced themselves. Dan Leacox and Gene Livingston representing the Methacrylate Producers Association, substance methyl methacrylate. Greg Gorder with Technology Sciences Group. George Fulton with Lawrence Livermore National Laboratory, substance beryllium. Jim Johnson with Lawrence Livermore National Laboratory, substance beryllium. Mark Kolanz with Brush Wellman, substance beryllium. Deanna Harkins with US Army, substance beryllium. Harvard Fong with Department of Pesticide Regulation, substance propylene oxide. Susan Ripple with Dow Chemical Co, substances propylene oxide, 2- butoxyethanol, epichorohydrin, and methyl methacrylate. Judith Freyman with ORC, substance acetone. Jim Salowski with DOE, substance beryllium. Jonathan Frisch with PG+E, user of many substances on the agenda. Elizabeth Treanor with Phylmar Regulatory Roundtable, substances acetone and beryllium. John Bankston with Sonoco representing the Am. Chemistry Council, substance acetone. David Mckinley with ISP Algenates, substance propylene oxide. Gary Van Riper representing International Molybdenum Association, substance molybdenum. Scott Budde with San Jose Delta Associates, substance beryllium. Edward Flaherty with San Jose Delta, substance beryllium. Kathleen DiZio with IBM. Richard Corley with Pacific Northwest National Laboratory/American Chemistry Council, substance 2-butoxyethanol. Tom Mitchell with the Cal/OSHA Standards Board.

Steve Smith distributed several documents and presentations that had been received earlier. Steve continued with a review of the agenda. Steve emphasized that the main issues of interest were the review of the previous recommendation and its scientific justification, the sampling limitations technical feasibility issues, and the potential economic impacts.

Acetone:

John Bankston began a presentation on acetone. An outline of the presentation is attached here:

OCCUPATIONAL EXPOSURE LEVELS For ACETONE

John Bankston
Chair, ACC Acetone Panel
March 30, 2004
Panel Perspective

■Sensory irritation is the right endpoint.

■ACGIH TLV of 500 ppm and STEL of 750 ppm are sufficient to protect against sensory irritation.
Critical Review Article by Arts et al. [*Critical Reviews in Toxicology. 32(1):43-66 (2002)*]

▪Good overview of the literature.
▪Key portion of the article – Controlled Studies on Acetone-Exposed Workers by Dalton and co-workers at Monell Chemical Senses Center.
▪Helps make sense of the confusing array of studies in the published literature, including studies of workers who indicate little or no irritation at relatively high levels, and studies of naïve subjects, who sometimes report irritation at relatively low levels.

Dalton et al. Studies - Overview

▪Perception of odor can influence subjective reports of "irritation."
▪Cognitive bias – whether a person is given negative or positive information about the chemical – can influence subjective reports of irritation.
▪Experienced workers find acetone less irritating than previously unexposed controls, so-called naïve subjects.
▪Previously unexposed naïve subjects report little or no irritation at levels as high as 800 ppm if they are first given positive (favorable) information about acetone.

First Dalton Study

▪Acetone-exposed workers and naïve (previously unexposed) controls.
▪Both groups were exposed to 800 ppm for 20 minutes.
▪Workers rated odor as weak to moderate; controls rated it as strong to very strong.
▪Workers rated irritation as "barely detectable to weak"; controls rated it as strong.

Second Dalton Study

▪Naïve volunteers were given positive, negative or neutral information about acetone.
▪Exposed to 800 ppm acetone for 20 minutes, and also to a known non-irritant (phenylethyl alcohol, or PEA).
▪Subjects given positive (favorable) information rated odor as weaker (compared to other groups) and irritation as "barely detectable to weak."
▪Some subjects reported irritation when exposed to PEA, which has an odor but is non-irritating.
▪Perceived irritation of acetone correlated with perceived odor intensity and perceived irritation from the non-irritant control odorant PEA.

Dalton et al. Studies - Conclusion

▪Strong support for the current ACGIH TLV and STEL.
▪Workers and naïve subjects who were given a favorable bias rated the sensory irritation from exposure to 800 ppm as "barely detectable to weak."
▪ACGIH:
  ▪**"These two studies point up the importance of using caution in employing naïve individuals in tests assessing the irritancy of chemicals from occupational situations . . ."**
  ▪**"Thus, the possibility of a perceptual (cognitive) bias in the reporting of eye, nasal or throat irritation may be a major confounding factor in a number of older studies . . ."**

Other Studies Described in

Arts et al. 2002

- Other studies described in the critical review by Arts et al. used objective techniques to assess threshold for irritation (eye and nose).
- Show that when odor is completely separated from irritation, such as by the lateralization technique, sensory irritation is detectable by subjects only when acetone concentrations reach the thousands (10,000 and above).

Letter from Nichols,

President of ACTWU

- "During certain operations (Press stripping and start-up operations), our experience shows that excursions can go well above 1000 ppm without significant irritation."
- Exposures in these operations can be controlled through comfortable, loose-fitting respirators; there was no concern that jobs might be lost.
- Workers know when they are experiencing irritation.
- Union also invited ACGIH to visit a plant, reflecting their confidence in their views. See letter from Eric Frumin, Director of Occupational Safety and Health for ACTWU.

Letter from Dr. Michael Stark,

Rhone-Poulenc AG

- Exposures well above 1000 ppm during the changing of filter presses.
- "Our workers are asked to wear breathing protections during the removal of the plates (masks and active breathing apparatuses are provided), but which is mostly refused."
- Supports conclusion that workers do not experience significant irritation even at levels above 1000 ppm.

International Standards

- UK (1991) adopted STEL of 1500 ppm.
- German MAK Commission (1994) adopted 8-hour TWA of 500 ppm and STEL of 2500 ppm.
- European Scientific Expert Group (1995) adopted 8-hour TWA of 500 ppm; STEL was determined to be unnecessary.

Older, Less Reliable Studies

- Several studies upon first glance might appear to support a limit below 500 ppm.
- Many were described and considered in the ACGIH documentation, which determined that 500/750 ppm TWA/STEL would be protective.
- Many also were addressed in the technical support documents for the international standards cited above, and again no TWA was set below 500 ppm, and STEL values ranged from 1500 to 2500 ppm to not necessary.

Nelson et al. (1943)

- Study is 60 years old.
- Used only naïve subjects.
- Some of the subjects were university students who were working on the study.
- Exposures were for only 3-5 minutes.
- No opportunity for adaptation.
- No method to address impact of odor or cognitive bias, esp. important obviously with naïve subjects.
- Exposure levels are uncertain – levels were calculated rather than measured (based on amount of acetone placed on a hot surface).

Nelson et al. (1943) Cont.

■**Authors advised at the end of their paper that it should not be used as the basis for setting occupational limits.**
■**Contradicted by the modern controlled studies by Dalton et al.**
■**Precisely the type of study ACGIH expressed caution about.**

Conclusion

■Sensory irritation is the right endpoint.

■ACGIH TLV of 500 ppm and STEL of 750 ppm are sufficient to protect against sensory irritation.

■Studies by Dalton et al. provide strong support for ACGIH TLV and STEL.

John began by stating that the ACC's position was that sensory irritation was the correct endpoint for standard setting and that the ACGIH TLV and STEL are adequate to protect against that irritation. He referred to the review article by Arts et al as a good overview of the studies for acetone. John described the cognitive biases that are present when odor is present, as described in the Dalton et al studies. He said that naive subjects that were given favorable information about acetone rated irritation from exposure at 800 ppm as "barely detectable to weak". John said that the ACGIH had stated cautions about the use of naive test subjects. Sensory irritation is detected using lateralization technique when concentrations reaches levels in the thousands of ppm. He described the international standards noted above. John said that the Nelson et al study had many of the problems noted above and was not considered as robust as more recent studies. It used naive subjects and did not make direct measurements of exposure concentrations. This study has been contradicted by more recent studies. John restated the position that the current TLV and STEL are adequate for protection against irritation.

Steve Smith asked if there were any comments about sampling or other feasibility issues. Bruce Wallace said that he had reviewed the Nelson study earlier and had a similar opinion that it did appear dated compared to current study designs. John Frisht said that acetone was widely used in his company and that at a change would at least require a reevaluation of those places where it is used. He thought that the impact of a change to the TLV would be substantially less. Judith Freyman said that she wanted to also make the point that going to levels below the TLV would cause many problems for employers. Steve Smith said that there seemed agreement with those present that the TLV levels were most appropriate for the exposure limit.

Beryllium:

Deanna Harkins began a presentation on the US Army's beryllium surveillance program.
An outline of the presentation is attached here:

Department of the Army

Beryllium Surveillance and Medical Monitoring Policy: To Be or not to BeLPT?

Deanna K. Harkins MD MPH
USACHPPM

Department of the Army

Beryllium Surveillance and Medical Monitoring Policy

15 August 2002

Department of the Army

Be Surveillance and Medical Monitoring Policy

- Policy reflects current regulatory requirements, subject to change

Department of the Army

Be Surveillance and Medical Monitoring Policy

Policy

- Occupational exposure limits
  - Current OSHA PEL is 2.0 ug/m^3
  - TLV of 0.2 ug/m^3 adopted if published as final by ACGIH
  - For interim, 0.2ug/m3 is prudent action action level

Department of the Army

Be Surveillance and Medical Monitoring Policy

- Occupational exposure limits (con't)
  - Engineering controls, work practices, and training must be instituted
  - Appropriate personal protective equipment (PPE) must be used where elimination not possible

Department of the Army

Be Surveillance and Medical Monitoring Policy

Policy

- Periodic medical surveillance
  - Exposure history & physical
  - Focus on pulmonary system
  - Complaints and abnormalities related to pulmonary system evaluated based on medical judgment

Department of the Army

Be Surveillance and Medical Monitoring Policy

- Periodic medical surveillance (con't)
  - Asymptomatic workers: BeLPT not required

nor recommended
- Symptomatic workers with exposure: BeLPT (two + results required for sensitization)
- Biopsy is Army standard for diagnosis of CBD
- Symptomatic sensitized workers should be evaluated by a pulmonologist

Department of the Army

Be Surveillance and Medical Monitoring Policy

References:
10 CFR, Part 850, 8 Dec 99, Chronic Beryllium Disease Prevention Program
OSHA Hazard Information Bulletin, 2 Sep 99, Preventing Adverse Health Effects from Exposure to Beryllium on the Job
DODI 6055.5-M

Department of the Army

Be Surveillance and Medical Monitoring Policy

References (con't)
Duebner DC, Goodman M, and Ianuzzi J. "Variability, predictive value, and uses of the beryllium blood lymphocyte proliferation test (BLPT): Preliminary analysis of the ongoing workforce survey. Applied Occupational and Environmental Hygiene, Vol 16(5) 2001

Department of the Army

Be Surveillance and Medical Monitoring Policy

References (con't)
Kolanz, Marc. Introduction to Beryllium: Uses, regulatory history, and Disease. Applied Occupational and Environmental Hygiene, Vol 16(5) 2001
Memorandum, Subject: Work Place Exposure to Beryllium, AMCSG-I, 7 May 2002

To Be or not to BeLPT?

Potentially Exposed Population

- **Products**: Aircraft mechanical components, x-ray windows, non-sparking tools, dental prosthetic devices, trace contaminants in welding consumables, machinable parts containing beryllium
- **Operations**: welding, machining, helicopter maintenance, hazardous waste and ordnance disposal, dental prosthetics

To Be or not to BeLPT?

Purpose

- **Screening**: Early detection of preclinical disease in persons *without* signs and symptoms of target condition
- **Diagnostic Testing**: Evaluation of patients *with* signs and symptoms of target condition
- **Surveillance**: Follow-up screening in persons diagnosed *with* and treated for target condition

To Be or not to BeLPT?

Screening Must be Shown to be Effective

- WHO Criteria for Appropriateness of Screening

–**Evidence-based medicine = Effort to link clinical and public health practices to the** quality **of supporting** evidence**, to examine that evidence** systematically**, and to judge its quality with** standards **for critical appraisal (Woolf and George 2000)**

To Be or not to BeLPT?

Screening Must be Shown to be Effective

- WHO Criteria for Appropriateness of Screening
  - **Burden of suffering**
  - **Accuracy and reliability of test**
  - **Effectiveness of early detection**
  - **Acceptable harms**
  - **Tradeoff between benefits and harms**

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria #1 Burden of Suffering
  - **Army air monitoring results show most results are below the current Army Action Level = 0.2 ug/m^3**
  - **To date, the Army has not detected any cases of CBD**

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria #1 Burden of Suffering
  - **Diagnostic criteria for CBD – Prior to 1989**
    - Significant exposure to beryllium
    - Presence of beryllium in lung tissue, nodes, urine
    - Lower respiratory tract disease/clinical course
    - Radiologic interstitial disease consistent with fibronodular process
    - Restrictive or obstructive ventilatory defects or diminished CO diffusing capacity
    - Noncaseating granulomas on lung or node biopsy

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria #1 Burden of Suffering
  - **Diagnostic criteria for CBD – After 1989**
    - Exposure
    - Hypersensitivity
    - Granulomatous disease or mononuclear cellular disease

What is missing?

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- CBD has shifted from a disease to a **precondition** for a disease
  - **Clinical significance?**
    - Granulomas & mononuclear infiltrates can remain latent

–**Progression to clinical disease inevitable?**

- Probability measures suffer from meager data/small numbers
- Natural history remains to be defined in well-designed longitudinal study

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria #2 Accuracy and Reliability of Test

–**Blood BeLPT lacks good sensitivity, specificity, and PPV**

- Sensitivity = $\frac{TP}{TP + FN}$ = $\frac{\text{True Positives}}{\text{All those with the disease}}$
- Specificity = $\frac{TN}{TN + FP}$ = $\frac{\text{True Negatives}}{\text{All those without the disease}}$
- PPV = $\frac{TP}{TP + FP}$ = $\frac{\text{True Positives}}{\text{All those who tested positive}}$

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria #2 Accuracy and Reliability of Test

–**Disparate criteria for what constitutes a positive result**

–**No consistent application of reference standard**

- Asymptomatics with normal BeLPT do not undergo bronchoscopy/biopsy → ? TN and ? FN
- Denominator is not 'All w/ or w/o disease' but subset identified through screening test itself

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria #2 Accuracy and Reliability of Test
  - **Unblinded studies**
  - **Selection bias not addressed: few studies characterize non-participants → inflate prevalence of CBD**
  - **PPV likely to be low unless worker has has reasonably high probability of having the disease**

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria #2 Accuracy and Reliability of Test
  - **PPV applies to** *intermediate outcome* **→ overestimates PPV for true clinical disease**
  - **Nonstandardized laboratory methods → inter- and intra- laboratory disagreement (split and repeat)**

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria # 3 Effectiveness of Early Detection
  - **Benefits of primary prevention unclear given already low levels of exposure, substitutions**
  - **Benefits of secondary prevention doubtful: No controlled studies documenting efficacy of corticosteroid therapy, esp. for precondition CBD**
  - **No prospective controlled studies show early removal from exposure improves outcomes; mute issue for former workers (litigation)**

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria # 4 Acceptable Harms
  - **Physical harms of test and f/u testing, retesting**
  - **Psychological harms: Labeling, worry, absenteeism, discrimination in job eligibility**
  - **Physical risks from treatment: Steroid therapy**
  - **Harms of the screening process affect large numbers due to low PPV**

To Be or not to BeLPT?

WHO Criteria for Appropriateness of Screening

- Criteria # 5 Tradeoff - Benefit vs. Harm
  - **Likelihood and magnitude: How many will benefit and to what degree?**
    - Paucity of evidence to define how many and magnitude*
    - Very existence of benefit equivocal
  - **Minimize harm: High prevalence of CBD expected that minimizes FP per case of CBD?**
  - **Maximize benefit: Large portion of current workers who would benefit from removal? Tx?**

To Be or not to BeLPT?

•**Conclusions**:

—**Restrict BeLPT testing to** exposed **workers with** clinical presentation **consistent with CBD**

—**Two + results required for sensitization**

—**Medical judgment**

—**Biopsy is Army standard for diagnosis of CBD**

Deanna described several uses of beryllium in the Army, including non sparking tools. She said that Be is an essential strategic material. The Army is currently using 0.2 ug/m3 as its action level. The Army medical surveillance program is symptom based; it does not use BeLPT. Deanna said that the BeLPT test did not meet the Army's criteria for a surveillance procedure. Denna said that other organizations had changed the criteria for diagnosing CBD to exclude symptoms. Sub clinical CBD. She asked if this subclinical disease met the meaning of material impairment in LC 144.6. She said that the granulomas could remain dormant through life, and had other causes. The progression rates to clinical disease vary from 30 to 80%. Bruce Wallace said, regarding these rates, that with cancer as an outcome and in the context of OSHA regulation, rates greater than 1/1000 were considered unacceptable. Mark Kolanz clarified that the 30 to 80% was based on pre 1989 studies and that was progression from early symptoms and not from the "pre clinical" CBD. Deanna noted that other factors can complicate diagnosis and that cigarette smoke contains Be.

Mark Kolanz began a presentation.

Comments of Brush Wellman Inc.
to the California OSHA,
Division of Occupational Safety and Health,
Permissible Exposure Limit Advisory Committee
March 30, 2004
Sacramento, California

Marc Kolanz, CIH
Vice President
Environmental Health and Safety
Brush Wellman Inc.
17876 St. Clair Avenue
Cleveland, Ohio

Cal-OSHA Beryllium PEL Review Process

The beryllium PEL, as currently proposed, is contrary to the Occupational Safety and Health Standards Board mission to *"promote, adopt, and maintain reasonable and enforceable standards that will ensure a safe and healthful workplace for California workers."*

Cal-OSHA Beryllium PEL Review Process

The Airborne Contaminants Advisory committee review of the beryllium PEL:

- Used sensitization and/or subclinical CBD study data as health outcomes (Yoshida, Kreiss). The committee's approach is contrary to California Labor Code section 144.6 which defines a health outcome as a material impairment of health or functional capacity. Only studies identifying clinical CBD meet this definition.

- Inappropriately used median air sample data in making its PEL recommendation (Kreiss, Cullen). Current ACGIH exposure assessment protocols identify exceedances of the PEL as an important factor when evaluating worker health risk.

Cal-OSHA Beryllium PEL Review Process

The Airborne Contaminants Advisory committee review of the beryllium PEL:

- Used studies containing erroneous air sample data (Eisenbud)

- Utilized studies containing only general area sampling data which is known to underestimate personal exposures (Yoshida, Cotes)

- Resulted in an admittedly arbitrary PEL recommendation for beryllium as noted in its June 17, 2002 minutes

Economic Analysis of the Proposed Beryllium PEL

- The Initial Statement of Reasons position that the cost to comply with a new beryllium PEL is estimated to be insignificant to none is not supported by a cost analysis as is required under Labor Code Section 147.1.

- Consistent achievement of the current beryllium PEL has not been found to be technologically or economically feasible for all beryllium manufacturing operations.

- Adoption of a Cal-OSHA PEL for beryllium ahead of adopting a federal OSHA could place California industry at a competitive disadvantage.

Recent Relevant Scientific Information

- Cardiff beryllium study concludes that compliance with the current 2 µg/m3 limit effectively prevented clinical CBD (Johnson 2001)[1].

- Most recent beryllium cancer study finds no statistically significant cancer risk for beryllium (Levy 2002)[2].

- ACGIH Biological Exposures Indices committee found clinical CBD as the appropriate end-point for setting an occupational exposure limit for beryllium (ACGIH 2002)[3].

Recent Relevant Scientific Information

- In vitro blood testing surveillance studies identify that the presence of beryllium sensitization in an individual can be a transient event. (Deubner 2001)[4].

- In vitro blood testing surveillance studies identify a positive test in 1-2% of the general population. (Kolanz 2001)[5].

- Beryllium exposure studies typically exceed the current OSHA PEL greater than 5% of the time. (Kolanz 2001)[6].

References

- Johnson J., et al. Beryllium Exposure Control Program at the Cardiff Atomic Weapons Establishment in the United Kingdom. Appl Occup Environ Hyg 16(5): 619-630 (2001).
- Levy P., Roth H., Hwang P., Powers T. Beryllium and Lung Cancer: A Reanalysis of a NIOSH Cohort Mortality Study. Inhalation Toxicology 14:1003-1015 (2002).
- American Conference of Governmental Industrial Hygienists. Biological Exposure Index Feasibility Assessment for Beryllium and Inorganic Compounds (2002).
- Deubner D., Goodman M, Iannuzzi J. Variability, Predictive Value, and Uses of the Beryllium Blood Lymphocyte Proliferation Test (BLPT): Preliminary Analysis of the Ongoing Workforce Survey. Appl Occup Environ Hyg 16(5): 521-526 (2001).
- Kolanz, M. Introduction to Beryllium: Uses, Regulatory History, and Disease. Appl Occup Environ Hyg 16(5) 559-567 (2001).

- Kolanz, M., Madl, A., Kelsh, M., Kent, M., Kalmes, R., Paustenbach, D. A Comparison and Critique of Historical and Current Exposure Assessment Methods for Beryllium: Implications for Evaluating Risk of Chronic Beryllium Disease. Appl Occup Environ Hyg 16(5): 593-614. (2001).

Mark said that the proposed limit was contrary to the Boards stated mission adopt reasonable and enforceable standards. Mark said that the proposal was not reasonable because that the scientific basis used to formulate the proposal was flawed in that it was admittedly arbitrary. The proposed standard will create an economic hardship and will be difficult to enforce. Mark said that the approach used for cadmium might be used because there is one limit to be achieved with engineering controls and another for respiratory protection. Mark objected to the committees use of sensitization or subclinical CBD as a health outcome and said that this was not consistent with the description of material impairment in LC 144.6. Mark said that they felt that only studies identifying clinical CBD would meet this definition. The committee's use of median air sampling data in making it's recommendation was inappropriate. Median data is misleading in characterizing risk. In the studies relied upon, the current PEL was exceeded 8 and 10% of the time. Another study used by the committee had erroneous air sampling data, the Eisenbud study. In 1998 Eisenbud identified an error in calculations in the earlier study. The values in the earlier study should have been 2.5 times higher. He calculated in the later paper a 40 hour exposure limit of 0.84 ug/m3. Other studies used area sampling, which underestimates personal exposure. Some of these area samples were over the current limit of 2 ug/m3.

Mark disagreed with the cost impact estimate in the Initial Statement of Reasons. He said that he believed that LC 147.1 required that a cost analysis be done. He did not think that this had been done. Brush Wellman did supply some cost analysis in the Federal OSHA RFI. Between 1957 and 1998 Brush Wellman has spent approximately 330 million dollars on beryllium heath and safety. Consistently achieving the current PEL is not always achievable. There are some operations that cannot be controlled with engineering controls and require respiratory and other PPE. Brush Wellman in Ohio has been cited by Federal OSHA several times. In each case it was shown that it was not possible to improve on the engineering controls Brush Wellman had place at the time, and the citations were withdrawn. We believe that the adoption of the proposed limit will put California at a competitive disadvantage with the rest of the US. Mark said that the existing TLV and PEL are the same at 2 ug/m3. There is a proposed change to the TLV that would reduce it to 0.2 ug/m3 and they are waiting for further studies before adopting it. A problem with the proposed TLV is that it is expressed as a total "inhalable" dust limit. This is a problem because the inhalable sampler captures more dust than a "total" dust sampler. Mark said most studies are pointing to small particles as an important factor and it doesn't make sense to have a method that gathers more large particles. Mark said that the Cardiff study was not given enough consideration. Jim Johnson is here today and the author of that study. Mark said that the review of the study emphasized median values and subclinical disease. Mark mentioned the Kreiss study and said that subjects with only positive lung tests no granuloma were included as having subclinical disease. Bruce asked if there had been updated study of the Kreiss cohort. Mark said that there had, it was in 99 or 2000 by NIOSH. Mark said that the BeLPT test result was not a health effect. The results have been seen to reverse for some positive individuals over a period of a few years. There is great variability in test results within and between labs. Unexposed individuals seem to show a 1 to 2% positive rate for the BeLPT. Mark asked for a reconsideration of the proposed limit.

Lunch break

Jim Johnson began a presentation on his study of the Cardiff facility in the UK. Jim described the facility and industrial hygiene program (1961-1997). Jim said that respirators were used for some operations but that could not be accounted for in the study. The medical surveillance program included chest x-rays and monthly spirometery. All employees with exposures over 1.5 ug/m3 were referred for additional evaluation. Cardiff tried to use the BeLPT test but stopped due to reliability concerns. The personal monitoring data for 194 employees showed a range of exposure, depending on production level, of 0.1 to 0.4 ug/m3. Bruce Wallace asked if these were mean values. Ans: yes. Jim said that the industrial hygiene information and

medical evaluation of this facility was very extensive. A limitation was that there was no sensitization survey and lack of details on the respirator program. The facility also had no exposures to oxides, only metal. Correlation was not found between static sampling and personal sampling. The facility had a captive state of the art laboratory and results were available quickly allowing fast response to exposure levels. Even with all the controls, the 2 ug/m3 limit could not be met all of the time.

Jim began a second presentation, a historic review of exposures at DOE facilities. Jim said that before the mid 1980s beryllium was "below the radar" at DOE facilities. Most measurements before that time were static and not personal air samples. This was the same technique that was used for radioactive samples. Samplers were not placed near machines because it slowed things down. Surface contamination was used to evaluate programs. Respirators were available but not required. The initial beryllium chronic disease case at Rocky Flats (DOE nuclear weapons facility) case was in 1984. That was the sentinel event, it is currently the biggest occupational disease topic in the department's history, greater than radiation. There were significant exposures above 2 ug/m3, mainly because they were not detected. Rocky flats used the metal Oak Ridge (Y-12) used the oxide. Livermore and Y12 had implemented strict programs for Be. At Livermore in the early 60's Ross Kuzian was in the health program. He decided to make a factor of 10 reduction from the 2 ug limit. That was the target for control at Livermore and intended to assure that the 2 ug limit was not exceeded. The controls at Rocky Flats were almost non existent, as was the documentation.

James Slawski described the DOE 10 CFR 850 program to estimate costs for reduction to 0.2 ug/m3 for all facilities. Some of these facilities would need to be rebuilt at a very high cost, as they are not state of the art. He could not give details regarding these facilities. The "action level" of 0.2 ug/m3 was adopted in 10 CFR 850 in late 1999.

Bruce Wallace asked if the exposures at the Cardiff facility were generally low relative to the 2 ug/m3 standard. Jim said that the levels were generally below 2 ug, but background levels were measured by area samplers at .3 to .02 ug. That means that the plants might be above the DOE action level of 0.2 ug/m3. This is the level that DOE is trying to reach.

Jim Johnson described his experience with several private companies where he had been a consultant on their Be programs. They had used 2ug as the limit and extensive engineering controls. The biggest problem was with compliance with use of PPE, respirators and outer clothes.

Scott Budde described his company (San Jose Delta)as a parts fabricator that makes parts from Be oxide that they get from Brush Wellman. They are a small company with less than 50 employees. He said that they don't have the resources to determine what it would cost or what would need to be done to comply with a lower limit. Scott said, in response to a question, that the current air levels were less than 2 ug. He said that they did both zone samples and personal samples. Some maintenance tasks required respirators. There was some discussion about the engineering controls used. He said there were a variety of products produced. The rooms were under negative pressure, and when jobs could be done in them, glove boxes were used. Steve Smith asked if they had a medical surveillance program. Scott said that they used National Jewish. They brought new employees into a non beryllium facility until baselines were done on lung function and BeLPT (the last five years). They have not had any sensitizations during the life of the program.

Jim said that this was similar to the case with the Cardiff facility. They designed the facility as if they were working with plutonium. Glove boxes, and double HEPA filters. Jim thought that to achieve levels below 0.2 ug, close capture ventilation would not work, that glove box type systems would needed.

2-Butoxyethanol:

Richard Corley began a presentation on 2-butoxyethanol. The outline of the presentation is below:

American Chemistry Council Ethylene and Propylene Glycol Ethers Panel

Comments on Proposed PEL for 2-Butoxyethanol

Richard A. Corley, Ph.D.
Center for Biological Monitoring & Modeling
902 Battelle Blvd.
P.O. Box 999, MS P7-59
Richland, WA 99352
ph (509)376-8462
e-mail: rick.corley@pnl.gov

Existing PEL's for 2-Butoxyethanol

California	25 ppm
ACGIH	20 ppm
European Union	20 ppm
Numerous European Nations	20 or 25 ppm
NIOSH REL	5 ppm*

*1990 value based upon hemolysis; level recommended prior to research on species differences in susceptibility

(http://egep.org/occexp.htm)

Agree with DOSH that Hemolysis is not of concern to humans

- Hemolysis is due to the metabolite, butoxyacetic acid (BAA)
- Numerous *in vitro* studies show significant species differences in sensitivity to BAA (e.g. Carpenter, Ghaneyem, Mehendale, Udden)
- Humans are at least 150 times LESS sensitive than rodents
- There are no known sensitive subpopulations

? Old ? Sick ? Young ? Inherited blood disorders

Agree with DOSH that Hemolysis is not of concern to humans (continued)

- Hemolysis has not been observed in humans—even attempted suicides
  - **Gualtieri et al., published late 2002**
  - **Several earlier references**
- Haufroid study flawed
  - **Hematocrit methodology**
  - **Exposed group had greater alcohol consumption than controls**
- PEL calculated on hemolysis could be as high as 125 ppm, which causes sensory irritation

California's Reported Basis for Proposed PEL

- Carpenter (1956) studies
  - **Eye and nose irritation in three (2 M, 1 F) human volunteer exposures at 195 ppm for two 4-hr periods**
  - **Eye and nose irritation in 3 volunteers exposed at 113 ppm for 4 hr**

Other Relevant Data on Human Irritation

- Prior to CA DOSH Evaluation
  - **Johanson (1986)—No irritation in 7 male volunteers exposed to 20 ppm for 2 hr while exercising on a bicycle ergonometer (50 W)**

◆After CA DOSH Evaluation

●Two U.K. HSE Studies (Jones 2003a and b)—no irritation in four volunteers (2 M, 2 F) exposed to 50 ppm for nine 2-hr periods for both inhalation and skin-only exposures

●U.K. HSE recommends small uncertainty factors when principal effect is sensory irritation

◆Based upon human data, PEL's of 20 or 25 ppm will be protective of workers for irritation

Other Relevant Animal Data

◆Rodents typically more sensitive than humans to nasal irritants due to differences in anatomy which affect airflows through the nose

◆Chronic inhalation studies conducted in rats (125 ppm) and mice (250 ppm) for 6 hr/day, 5 days/week for 2 yr—no evidence of nasal irritation

ACGIH's Rationale for a 20 ppm TLV

"A TLV-TWA of 20 ppm is recommended to minimize the potential irritant effects from exposure to 2-butoxyethanol."

"…, the revision on the TLV-TWA to 20 ppm was instituted for the purpose of achieving harmonization with other international, occupational health exposure standards."

Economic Impact

◆2-Butoxyethanol is widely used in California

◆The 2001 EPA Toxic Release Inventory includes 121 companies in California that emit glycol ethers

◆Many of these are small firms

◆Each company would have to deal with a new, lower PEL

●Adoption of a value lower than ACGIH, the industry norm, could result in additional costs without any commensurate work health benefit

Conclusion

◆DOSH should either maintain the current California PEL of 25 ppm (which is protective) or reduce it to 20 ppm to be consistent with ACGIH and other guidelines

◆This would protect workers from sensory irritation (or any other effect) without causing economic dislocations

Richard said that the NIOSH REL of 5 ppm was based on hemolysis. This concern has not been found to be warranted. Richard reviewed the studies listed in the outline. Several recent studies have not shown irritation at about 50 ppm in humans. Chronic exposure studies of rats and mice at 125-250 ppm have not shown effects on nasal tissue. Richard said that the ACGIH had made their change to be consistent with the MAC limit. This change was not based conclusions from new studies. Richard said that either 25 or 20 ppm would protect workers and recommended those values.

Molybdenum:

Gary Van Riper began a presentation on molybdenum. Gary was representing the International Molybdenum Association. Soluble molybdenum compounds had been at 5 mg/m3 for many years. The NTP did a study in the mid 90s. That was the first study that showed indications of the trioxide being a carcinogen. The Moly Association believes that the level should not be changed and it should be at the 0.5 level. That level will be fully protective. The NTP study was a two year study of rats and mice. The results were consistent with exposure to a direct acting irritant. The trioxide has a ph of 2.1. The Moly Association had three experts review the NTP study. Lung tumors were seen in the mice, but those tumors occur spontaneously at high rates. Bruce said that he had heard this was the case with liver tumors in these mice, but not lung tumors. Gary said that it is true for lung cancers. Gary had attended the review of this study in Washington and the consensus of the group was that the results did not indicate that the trioxide was a carcinogen. The respirable fraction for sublimed oxide is 0.15% and zero for chemically formed oxide. The NTP ground the dust to very fine particles. This made all the trioxide available to the lung. This makes the

exposure 665 times greater than that a worker would experience. This is a big safety factor. A positive dose response was not seen. Bruce said that there were other effects noted in the Chan study besides tumors. Bruce said that those other outcomes could establish a LOEL of 10 mg/m3 on those other outcomes. Gary said that he didn't know about those effects in the study.

The Droste paper, done in Europe, did a survey of 400-455 people with cancer in a hospital. They were questions about job history. The study was seriously flawed. There was no dose response determined and there was concurrent exposure to other carcinogens. Based on this the ACGIH changed the designation from A3 to A2. They did not change the TLV of 0.5 mg/m3. Gary said that the work force is very stable in the moly plants and there has not been any epidemiological indication of cancer problems with these workers. There was personal sampling done in one of the chemical plants and the levels were in the range of 0.2 to 0.3 mg. Going to a level below that would require a change in equipment.

Gary described the uses of Mo, steel alloys, catalysts, additives to greases and plastic, pigment. Not normally used as pure metal.

Bruce said that he remembered that the Chan study had several tables to display its results, and one of them dealt with non carcinogen effects. He thought that this was the basis for the current proposal. Gary said that two factors of ten were used to set the limit. Bruce said that using the safety factor approach indicates that the endpoint was not cancer. Gary said that the fact that the material was micronized (converted to 100% respirable) before exposure to the animals should be considered. Steve Smith asked if the Moly Association would support the TLV level of 0.5 mg/m3. Gary said that it did.

Methyl methacrylate:

Steve Smith began with methyl methacrylate by noting that the prior committee had discussed the limit at two meetings and had made a recommendation of 20 ppm vs. the TLV of 50 ppm. Steve said that it had also been reconsidered by that committee at a meeting earlier this month (March 12). The recommendation had been left as it was from that meeting. Bruce Wallace said that the committee had found on the key study, the Marez study, that the health outcome results were persuasive and solid. They said that the only thing that could be left would be questions about the exposure background of those health outcomes that had been raised. They found the letter from Dr Haguenoer not impressive or not persuasive. Subsequent to that meeting the MPA has forwarded some data from the two plants in France where Marez did his research. The committee said that if it could be demonstrated that the Marez exposure data under reported the actual exposures then they might find that persuasive.

Bruce asked Gene Livingston if that was a fair description. Gene said that he would describe it differently but not in total terms. Gene said that he represented the Methyl Producers Association (MPA). He said that they recommend a limit at 50 ppm and also consider setting a STEL. The MPA had submitted substantial additional information to the committee. Gene said that the focus of the committee discussion on March 12 was the Marez (French) study. Gene said that the difference from Bruce's description was that the exposure levels in the Marez study were well below the experience anywhere else. These were well below the other studies and the studies that had been forwarded from the MPA that were recommended for setting the limit. Gene said that part of the problem (with Marez) is that it is impossible to determine the process or location where the measurements were made and the timing of those measurements. At the same time we had data that indicated other plants a few years later had significantly higher levels of exposure. What the ACAC said was that if you could demonstrate that the processes were the same at the two French plants as with the UK plants and the German plant, then that would cause them to discount the Marez study. We have provided (after March 12) a description of the process and a comparison. Gene explained why in the late 80's when Marez did his study, the processes were the same in the UK, German, and French plants. All the plants used the process developed by ICI and licensed to other producers. Gene described that process and differences from more recent processes. During the time of the Marez study was there was little control of exposure. When the Marez paper was published, later in 1993, the plants went back and checked their

clinical data to check for the problems Marez described. Those were mild airway obstruction and chronic cough. It called into question the Marez data. At the same time was a data call for exposure data from plants (for the EU risk assessment for existing chemicals). The processes were changing to reduce exposure also at this time. Even then (~1993) the TWA levels were between 50 and 100 ppm. These were basically the numbers that were coming out at that time.

Bruce Wallace said he had looked at the MPA exposure data submissions. One was obviously UK data, probably the Darwen plant. They have a median value for exposures of 11 ppm for pre 1993 personal TWA samples. Bruce said he found that surprising given the descriptions of exposures in the 50 to 100 range during that time period. How can you contend that the exposures must have been over 50 when the data you provide shows the median at 11 ppm? Dan Leacox said that there was a spectrum of activities/ tasks, and the background level TWA was 5 ppm. You can get a very different result in one part of the plant vs. others. Bruce said that these were shift average exposures significantly below 25 ppm. Dan said one of the reasons that the European bodies dismissed the Marez study was that they couldn't confirm where the measurements were taken. Low exposures at some locations are not indicative exposures causing health effects. Bruce said that that might be possible, but we heard (on March 12) that Marez made his health assessment of the workers first during his study and then later made his exposure measurements. It would seem extremely odd since he had only 40 test subjects when he excluded workers with prior histories that might influence lung function, that he would then go back to measure the exposure of workers other that those 40. He wouldn't have done something that silly, not going back to the same workers that had the lung function tests. He did manage to get his PhD.

Gene Livingston said that the letter from Marez's faculty advisor recommending that the study not be used to set the exposure limit is a strong indictment in Europe. There was other data given by Dr. Pemberton questioning the measurements and under reporting exposures given the use of badges (rather than pumps). Gene said that it had been demonstrated that, while the processes were the same in the different plants, you would get different measurements depending on where you were in the plant. The Marez measurements make no sense in terms of the high exposure processes in the other plants. The evidence indicates that the kinds of problems that Marez saw are caused by peak exposures and there was no recording of peak exposures only TWAs. That is the reason we recommend considering a STEL. The ACAC members said you can control the peaks by controlling the average concentrations. He said that that gives you a false indication of what a PEL ought to be. The peak at a short part of a shift can cause the irritation and we recommend a STEL at 100. This would minimize the kinds of exposures that would cause the problems that Marez saw. Bruce said that this is a speculation and it is a repeated speculation. Gene said that he agreed, but to understand this data in the context of the other studies requires that kind of conclusion. Plants today are using best available technologies are still getting exposures in the high 20s. There will be problems achieving the 20 limit with small plants, hopefully they can make it with 50. Dan said that there are other small users that are not these cast acrylic plants.

Susan Ripple said that Dow had just acquired another company. They have a large state of the art facility in Houston Tx. Most of the exposure levels in the drumming process are above 50. The background levels in these operations were around 10.

Bruce said he had several comments on the submissions from the Methacrylate Producers Assn.
Bruce distributed a handout attached here:

pat Docu

Bruce said that there was specific data sent to us that was taken from the plants where Marez did his study. Those measurements were made in 1993. The main issue seems to be what the exposures were of the workers Marez studied. The submission describes, on the first page, that this data was submitted to the European Union as part of the data collection exercise for Existing Chemical Risk Assessment of MMA. The mean TWA concentration of this data is 42.3 ppm. Bruce said that the cover sheet for the EU risk assessment is on the fifth page and a summary of exposure measurements is on the second to last page. You can see in the middle of Table 4.1 a summary of cast sheet production. There are five different means listed and five different ranges with those data sets. The time frame, 1993, is ideal for the data from the French plants to be included. Yet when you convert the means over to parts per million there is no 42.3 ppm in this table. Also the highest short term concentration (15 min) is listed in the right column at 183 ppm. Turning to the last page is a plot of the means of 8 hr TWAs from the EU risk assessment, with numbers 1 through 5. Marez's means are directly below. The Atofina mean is outside the range of all of them. The Atofina mean is not represented in the table.. The data that was given to us and supposedly to the EU risk assessment in Dortmund has a highest 15 minute value of 764.9 ppm. The maximum 15 minute value in the EU risk assessment is 183 ppm. This difference is a huge problem. To have an attribute on the data that it was given to the EU risk assessment and then to have it not reflected in the final report given the five means and ranges, would cause me to question whether it was ever given to them. There is no evidence of it in the table.

Apart from the Atofina data there was German and English data given to us. Bruce said that he had mentioned earlier the median of the pre 1993 UK data. The median and mean aren't the same for these data but shouldn't be too far apart. The median was 11 ppm for cast sheet production at the UK plant (pre 1993). The median values of exposure in the German plant ranged from 30 to 40 ppm. These plants were described as cookie cutter versions of each other and would have similar exposures. How could you assume that you could make comparisons from plant to plant and country to country given these differences?

Dan Leacox said that the row marked cast production in Table 4.1 was one step in production. He said this was putting together the cast. Dan went on to describe putting the sheets of glass together and holding them with clips. Dan referred to the production steps below cast production, cast filling and syrup production. He said that these were the high exposure activities. Bruce said that those medians were even lower at 11.7 and 10.2 ppm in the 1993 time frame. Dan said that in the early 90's the control technologies were being implemented. Dan said he thought that the suggestion earlier that the data (Atofina) had not been submitted to the EU was based on a misunderstanding. Dan thought that Bruce had confused the Marez data with the data taken later at the same plants. Bruce said that the submission says that the data was from 1993 and that this data was reported to the EU as part of the data collection exercise. It should have gone to the folks in Dortmund. That is the data we are talking about. There is no indication of this data in the EU risk assessment. Dan said that they might need to go back to Mark Pemberton to clarify this.

Steve Smith said that we should move on and that Gene and Dan could respond later after reviewing Bruce's comments. Gene said they could do that. Steve asked if there was acrylic sheet production in California. Gene said that there wasn't any sheet production and that this is where the real exposures were.

Propylene oxide:

Susan Ripple began a presentation on monitoring for propylene oxide. She described two validated methods. The lowest level for the NIOSH method is 0.9 ppm. Consultation with NIOSH indicates that the method can't be made to go lower. The OSHA method lowest level is 0.35 ppm. This is based on a 5 liter air sample. The Dow method has a lower limit of 0.1 ppm. This would work for the proposed limit. It collects 42 liters. NIOSH is collecting 4.8 liters. The samples must be shipped refrigerated and stored in a freezer.

Susan said that she was going to make the presentation for the ACC (American Chemistry Council). The presentation is attached here:

oat Docu

Susan summarized the current exposure limits. The ACC panel agrees that nasal effects are appropriate for setting limit. The committee did not consider more recent studies. That information was supplied to Cal/OSHA. The ACGIH used 30 ppm (as a NOEL in animals) and arrived at 2 ppm as the TLV. Susan concluded that available science does not support the proposed PEL at 1 ppm. 2 ppm is highly protective of workers. California should adopt 2 ppm as the PEL.

David MCKinley began a presentation on propylene oxide. The presentation is attached here:

oat Docu

David said he is an engineer with ISP in San Diego. ISP makes food products from kelp. Described his plant in San Diego. Boats are used to harvest the kelp. Alginic acid fiber is extracted from the kelp and propylene oxide is used to make propylene glycol algenate. Other algenates are also made. The products are used in a variety of food products shown on the slide. David described the competition for this plant. The plant has been running for many years and has been able to meet that competition in part due to the propylene oxide process. The propylene oxide is very important. The plant has a Process Safety Management program for PO, a reactor purge scrubber, a catalytic oxidizer for the dryer. IH data shows most exposures in a range of 2 to 10 ppm. David said that ISP accepts the ACGIH TLV as a corporate policy. Its goal is to reach that limit regardless of the PEL. They also have a goal to protect the workers without using respirators. Our workers agree with this goal. They don't like using the respirators with the heavy work involved. David said that reaching 2 ppm is an achievable goal with modification of the current process. David said that reaching 1 ppm would require a new process, not based on batch reactors. This would not be possible with existing competition. The only possible solution would be to put everyone in respirators. ISP would like to see the limit set at 2 ppm even though this will require additional control projects in the plant. David said that they believe control at 2 ppm is achievable. A 1 ppm limit would be a big problem for the plant.

Eipchlorohydrin:

Susan had some comments on monitoring for epichlorohydrin. There is one monitoring method. The method has a detection limit of 0.01 ppm based on 24 liters. The proposed limit is only five times the detection limit. Dow has a method that uses 48 liters it also has a detection limit of 0.01 ppm. Refrigerated shipping and frozen storage is required.

Steve Smith said in conclusion that minutes would be made for this meeting. The information from this meeting and the other committee will likely be used to make a new proposal. That will go forward to another public hearing process. All those who have participated in this process will be included. It is possible that in reviewing what we have there will be a need to seek additional information, but the hope is that we can move forward with a new proposal. There seemed to be a consensus of those here today that the TLV was an acceptable level to go forward with for the substances considered. Steve said that we would continue to welcome additional information, particularly on impacts and the other types of information on today's agenda.

Meeting adjourned

4-29-04

Glutaraldehyde Advisory Meeting

Draft Minutes

February 10, 2004

Attending:
Mike Cooper, Patricia Quinlan, Bruce Wallace, Julia Quint, Steve Smith, Len Welsh, Tom Mitchell, Denise Senior, Barbara Morrow, Tom Tremble, Erica Stewart, Tom Marsh, Kris Quigley, Robert Harrison, Patrice Sutten, Karen Jenkins, Roger Richter, Deepak Plaha, Joe Ascenzi, Barbara Smisko, Judi Freyman, Teresa Pichay, Greg Gordor, Pamela Dalton, David Tobia, Rich Shumway, Julia Klees, Janice Prudhomme, Artie Lawyer, Susan Tarlo, Dan Leacox, Stephen Derman, Susan Ripple, John Mehring, Kathy Krol, Deborah Gordon, John Balmes

Len Welsh made some introductory remarks. He said that meetings like this were a great help in developing rulemaking changes. He summarized the history of the proposed change to the limits for glutaraldehyde and more than 20 other substances. Many of those changes were to the same value as the ACGIH TLV, but others were not. Glutaraldehyde is one of substances with proposed limits lower than the TLV. The Governor has requested a regulatory review of business impacts of changes. This means that substances with changes below the TLV will need to be reviewed more thoroughly and emphasize business impact. The information need to assess the impacts will need to come from meetings like this and the employers or others that have the information.

Introductions were made by all present. Deborah Gordon was on a conference call phone.

Steve Smith described the earlier advisory committee that had reviewed information and made a recommendation in late 2002. This meeting is intended to supplement the information from that earlier process. He said that many documents have been submitted before the meeting. A bibliography is available and we can provide copies of the documents. There are several presentations that will be made today and discussions can follow them. We are very interested in information that relates to business impacts, measurement issues, the form of the limit Ceiling and STEL limits, and a sensitizer notation.

Bruce Wallace summarized the proposed change and the three studies that were cited in the Initial Statement of Reasons. These studies are relied on to substantiate and provide a basis for the change. The DiStefano and Gannon studies where health effects were assessed and workplace air levels were measured, and the Vyas study with a large amount of exposure information.

Pam Spencer began the first presentation. The slides for the presentation are attached here:

bat Docu

Pam described the weight of evidence method of evaluating evidence for regulatory decisions. This information is used for hazard assessment. The Information is also used to estimate dose response and then risk at a given exposure.

Pam went on to describe the animal data that was available relevant to glutaraldehyde. Genotoxicity and carcinogenicity assays: cell cultures are positive as a mutagen, results in mammalian cells are difficult to interpret. When gluraraldehyde is tested in the whole animal all the results are negative for cancer. These studies are considered more relevant than the invitro studies. Pam said that irritation studies are positive with concentrations above 1%. Repeated dose studies show that it is an irritant by inhalation. 13 week studies confirm the irritant effect. Other target organ effects were not seen, ie liver or kidney. Dermal sensitization is confirmed at greater than 0.5%. Reproductive studies

are negative. Developmental studies are also negative. Based on this irritation and skin sensitization are clearly effects that need to be controlled.

Julia said that one of the findings in the rodent assays had not been mentioned, nasal metaplasia. Pam said that this is a common finding in rodents with irritants. Julia said that the ACGIH had used the relative potency with formaldehyde for this effect to establish the TLV. Glutaraldehyde was estimated to be x10 more potent than formaldehyde.

Arthur Lawyer introduced Susan Tarlo from the University of Toronto. Susan discussed the human studies and health effects in a presentation attached here:

bat Docur

Susan said that the respiratory human effects could be separated into irritant effects and hypersensitivity effects. These can involve the nose and eyes as well as the lung. Exposure factors and host factors are important in developing these conditions.
Short or long exposures can cause sensitization followed by effects at much lower exposure levels. Little is known about the exposure conditions that cause sensitization. It is suspected that higher levels exposure, peaks, are more important than chronic levels of exposure but this has not been established. Susan said that with bakers asthma and latex, exposure to higher mean exposure levels are correlated with higher rates of sensitization. For most substances it is not known whether peaks, 15 minute excursions, or long term averages are most important. The other responses, irritant responses are much more clearly dose-exposure related. There can be accute or chronic responses. With very high exposures asthma can be induced by irritants, "reactive airways dysfunction syndrome". This can persist for weeks to years. Sensitization to the agent may or may not occur due to this type of exposure. Another characteristic of irritant exposures is that those already having asthma produce greater response to the irritation than those without asthma. The chronic effects of exposure to irritants needs to be assessed using epidemiology. Chronic obstructive lung disease is one of these endpoints. Susan said that in the Vyas study the only association found for glutaraldehyde was chronic bronchitis.

Susan described ten human studies that she had reviewed. Latex is a possible confounder as most of these studies are in health care settings. Several studies did not measure exposure peaks or accidental spill concentrations. The importance of these is not known. The Vyas study attempted to look at peak exposures and found that spills were fairly common, occurring 1-2 times a year in a high proportion of workers. Susan said that the cross sectional studies did not have control groups and that a healthy worker effect might underestimate the effect in a population (survivor bias). Susan also said that selection bias could be present given the possibility that hospitals/workers with problems might not want to participate in the study. Both these factors might cause underestimation. Using questionnaires while a sensitive technique, is not very specific. Bioassays have not been very successful with glutaraldeyde. Serial peak flow readings are often used, but unless the readings are recorded electronically, there can be problems with this data. Challenge tests have been considered the gold standard for diagnosis. Only a few of the studies have used challenges. In general all the tests can produce false positives and negatives, so a combination of the tests has the most diagnostic value. Bruce Wallace asked if antibody assays were used with isocyanate exposure. Susan said that the tests were difficult and not generally available. Poor correlation with sensitization had been seen with these tests for isocyanates.

Susan went on to describe individual studies. Some are cross sectional; others are case series studies. The second and third studies, DiStefano and Gannon, confirmed asthma using peak flow methods and challenge tests. The Vyas study looked at a large group of current and former workers. Vyas found that the FEV1 levels were lower for former workers compared to current workers, there was no control group. This might be expected with a "healthy worker" effect. Eye nose and chest symptoms were more common in former workers, but the only significant association for a clinical outcome and glutaraldehyde exposure was chronic bronchitis. Susan described the range of exposures measured in the Vyas study. There was a discussion about spills. The Vyas had measured spills with results about 100 ppb. Pam Spencer said that other spills had been measured as high as 600 ppb.

Susan summarized by saying that gultataldehyde can act as a sensitizer with a presumed immune response. Based on other respiratory sensitizers, the greater the concentration, the greater the fraction of people that become sensitized. Once sensitized, very low levels will generate a response. Irritant effects are more clearly concentration dependent. Very high levels can induce asthma independent of sensitization. There was a question about high molecular weight

allergens. Susan said that for flour or animal dander skin tests could be done more reliably. This had allowed the correlation between exposure levels and fraction developing reactions. This is still about 5%, with those who are allergic to other things more likely to be sensitized. With glutaraldehyde the role of background allergy and other host factors has not been very well described. There was a discussion of the DiStefano study. Bruce Wallace said that almost all cases that were challenge tested had not shown positive results on skin tests for other allergens, while the majority of all the cases had. He thought that this was curious. Susan said that reactions to other agents had not been shown to be a risk factor for low molecular weight agents. It hadn't been shown to be a protective factor either.

John Balmes, UCSF/UCB, joined the meeting by speaker phone. John said that he was aware that Susan Talro was involved in a medical surveillance program in Ontario for occupational exposure to isocyanates. He said that he agreed that there was not a lot known about the levels of exposure that were responsible for induction of asthma due to isocyanates or glutaraldehyde and we also don't understand the imunilogical mechanisms. Given that we may be just waiting for people to present with asthma. John asked what Susan thought about the usefulness of the medical surveillance program? Susan said that she agreed that medical surveillance is useful, and that the best outcomes occurred by early detection followed by removal. In Ontario isocyanates have been the most common cause of occupational asthma. A surveillance program was set up. The program requires workplace monitoring, medical surveillance with pre-employment screening, and lower levels. An evaluation of the program has been done. There was an initial increase in cases, and then the annual incidence went down to below historical levels. The cases were also less severe than previously. Exactly what part of the program caused this improvement has not been determined. Susan said that if lower levels are included in the program then there must be some sort of enforcement mechanism.

John asked given the low levels in the DiStefano and Gannon studies used as challenges and that the proposed limit is near those levels. Also given that we don't know what the thresholds are to produce sensitization, what are your thoughts on limit values? Susan said that with the levels, the lower the better, the lowest that would be reasonable considering other factors. There was a discussion about the low level exposure to irritants leading to asthma and reference was made to Susan Tarlo and Gary List's study of radiation technologists. Susan said that the technologists were compared to a control group of physiotherapists. The technologists had a significantly higher rate of adult onset asthma compared to the control group. The male technologists showed an odds ratio of about 7. There was another question to Susan and John about the value of the limit. John responded that he thought that he favored a limit near the proposed value with the hope that this would prevent new cases.

Pam Spencer displayed a slide that showed that healthcare only accounted for 15% of glutaraldehyde, and that 75% was used in FIFRA water treatment another 10% is non biocide use. Pam noted that all of the health complaints come from healthcare and not from other uses. Richard Sumway said that his company made tissue heart valves and used glutaraldehyde in the process. Patricia Quinlan asked what exposures had been measured in this process. Richard said that all operations were compliant with 0.2 ppm but that there was a lot of variation some values above and below 0.05. Mike Cooper asked what the experience was with respiratory problems. Richard said that in the last 5 yrs about 400 individuals had worked in the process, about 4,000,000 work hours. During that time they had six potential cases.

Lunch break

The next presentation was by Pamela Dalton. The slides are attached here:

bat Docu

Pamela said that her presentation dealt with symptoms of irritation of eyes and nose. Pamela described the limitations of many of the studies that had been discussed earlier. She said that one limitation was that you could not control exposure for some of these studies but the researcher could only study the levels that occurred with the actual operation studied. Another problem is individual variability in response to irritant effects. Differences in response to odor are seen when different types of information about the substance is provided. Irritation is seen at much highter levels than levels where odor is detected. Pamela said that her data demonstrated that women increased their sensitivity to odors from repeated (intermittent) exposure compared to men. This apparently demonstrates that men do not learn much from repeated exposure. Pamela described a personality trait called "negative affectivity" and said that this was a general

trait to consider things detected as adverse. Subjective responses to isopropyl alcohol correlated with this trait even with no changes in objective irritation measures were noted.

Pamela described an experiment where odor and irritation thresholds for glutaraldehyde were measured. This study (B. Cain, 2003) used young female volunteers and involved concentrations near 1 ppb for odor detection and near 500 ppb for irritation. The volunteers had no history of prior exposure to glutaraldehyde. The threshold for odor detection was 0.27 ppb, for ocular irritation, 394 ppb, and for nasal localization, 427 ppb. Susan said that these results were for exposures of just the eyes or nose alone. The effects might be different if there was concurrent exposure to the whole body. The length of exposure might also be a factor as these were brief exposures. The study also looked at irritation from longer exposures, 15 min, at concentrations up to 100 ppb. No irritation was noted from these exposures.

Bruce Wallace said that he could see risks associated with this experiment. He said that we have heard that little was known about the levels of glutaraldehyde that induce sensitization. The levels in this experiment used to determine irritation threshold were near 500 ppb. We have also heard that the levels measured in 1 and 5 liter spills in England were about 100 ppb. In this situation we have volunteers exposed to levels about five times the levels measured in these spills.

Pamela said that these were very short exposures and that there would be follow up on these individuals for some time. This would help ascertain that they did not experience any health symptoms. Bruce said that you would not necessarily know unless there was subsequent exposure.

Pamela Spencer said that the Cain study was initiated and sponsored by Union Carbide and BASF. It was based on a position of those two companies that glutaraldehyde is not a respiratory sensitizer. The position holds that glutaraldehyde is mediating the asthmatic reactions that are being reported from irritant induced mechanism. Federal OSHA had seen the study protocol and had made comments during its development.

Steve Smith noted that the next agenda item would involve current exposure information and measurement asked if there were any more presentations on sensitization. Deborah Gordon made a presentation via the speaker phone. The slides are attached here:

bat Docur

Deborah described the purposes of the Sen notation. It can be used when induction threshold may not be known. Deborah described several notations used by other organizations and some of the criteria used to assign them.

Bob Harrison asked what basis the ACGIH used to assign the Sen notation. Deborah said that the Sen may or may not indicate that a threshold for induction had been identified. You would need to look at the documentation to see if a threshold for sensitization (induction) had been identified. Julia Quint noted that in some cases as with the isocyanates, that structrual similarity was used to set a limit when direct data is not available. That limits are set by analogy. Susan Ripple said that the organizations she worked with did not attempt to set exposure limits that would protect those already sensitized.

Steve Smith said that there were some present that wanted to discuss current exposure levels and feasibility of control. Steve asked if there were others that had information they wanted to provide on these issues. Deborah Gordon said that she had some information about exposures in xray processing. The slides are attached here:

bat Docu

Deborah described the development process. The glutaraldehyde is used in the first step, development. Some of the concentrates used to make working solutions have high percentages of glutaraldehyde, up to 40%. Worst case simulations were done for the

processor operations and mixing. The air levels were non detect. Detection limit for mixing was about 20 ppb. Hospital studies were done. Results on slides. Deborah concluded that current exposures are below the proposed OEL. Karen Jenkins asked what the temperature of the processing solutions was during the simulations. Deborah said they were about 90 degrees.

Mike Cooper asked if there have been any health problems with exposure in the hospital studies or at Kodak itself. Deborah said that they had not seen them. There was a question about the relevance of these studies given the low levels and lack of evidence of responses.

Continuing with exposure information, Steve Derman began a presentation. The outline of the slides for the presentation are here:

Utilization of a Modified Glutaraldehyde Analytical Method -

Results & Ramifications

Stephen Derman
MediSHARE Environmental Health & Safety Services

American Industrial Hygiene Conference & Exposition • June 2002

Glutaraldehyde's Health Hazards

- Nasal, eye, upper respiratory irritant
- Conjunctivitis & eye irritation
- Skin sensitization
- Dermatitis
- Allergic contact dermatitis
- Nausea
- Headaches

Applications

- As a cold sterilant

Products Included*

- Cidex (2.4%)
- Cidex Plus (~3.4%)
- Metricide (~2.4%)
- Omnicide (~2.4%)

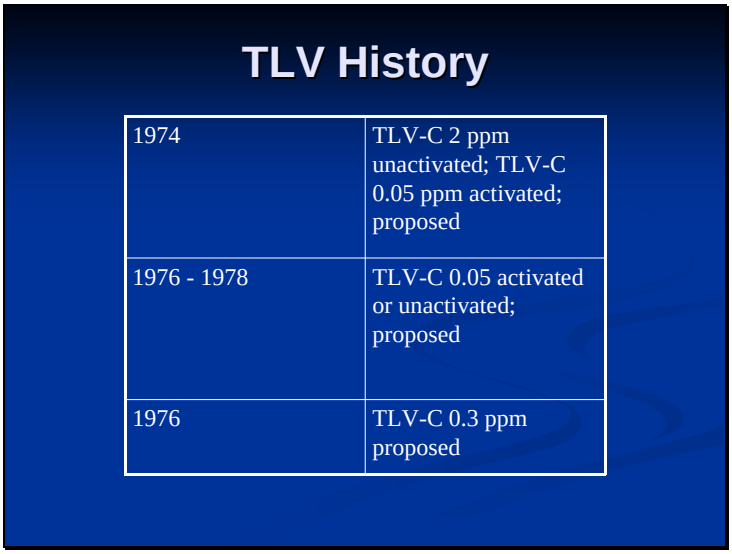
- ***Mention of these products does not necessarily imply either endorsement or lack or thereof of these products. They are examples of products that contain glutaraldehyde**

The Issue

- TLV = 0.05 ppm *Ceiling*
- OSHA PEL = ø
- OSHA "Transitional PEL" = 0.2 ppm *Ceiling*
- CAL-OSHA PEL = 0.2 ppm *Ceiling*

- Virtually all work processes involving glutaraldehyde are 1 to 2 minutes long

TLV History



TLV-C History

TLV-C History

1977	0.2 ppm proposed
1979 - “present”	TLV-C 0.2 ppm
1995	0.05 ppm proposed
1997 - present	0.05 ppm
1998	Sensitizer proposed
1999	Sensitizer, A4

Analytical Methods

- OSHA 64 Analytical Method:
  - **15 Liters @ 1 liter/minute**
- NIOSH 2532 Analytical Method:
  - **0.05 to 0.5 L/minute**
  - **Minimum Volume: 1 L @ 0.2 ppm**
    - i.e. 4 minute sample, 0.5 L/min. @ 0.05 ppm

Level of Detection of Analytical Methods

Level of Detection of Analytical Methods

NIOSH	0.3 µg per sample
OSHA	0.268 µg per sample

Work Processes Associated with Glutaraldehyde

- Cold Sterilization
- Pouring fresh solution into holding containers
- Disposing of expired solution

The Challenge

- Identify an effective sampling and analytical method that can:
  - **Truly and accurately identify exposures**
  - **In a brief time period**
  - **That represents one's exposure(s)**

The Solution

- Develop a more sensitive analytical method

0.05 µg per sample

- Compared to 0.3 µg per sample

Sampling Process

- Fourteen health care organizations
- Based upon work processes
  - **Disinfecting equipment**
  - **Removing & rinsing equipment**
  - **Disposing of solution**
  - **Preparing new solution**

Areas Affected

- Cardiology/EKG
- Central Processing
- Diagnostic Imaging - Radiology
- Endoscopy
- Ear Nose & Throat
- Family Practice
- Medical Offices

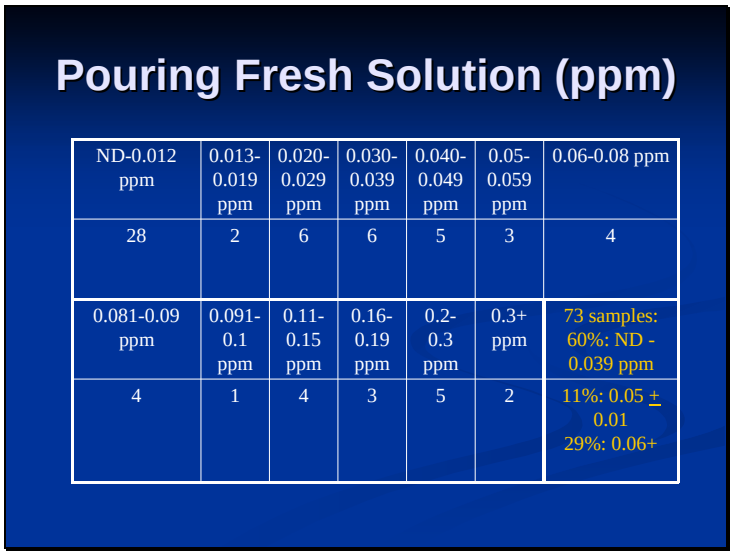
Areas Affected

- OB/GYN
- Respiratory Services
- Surgery
- Ultrasound
- Urology

Findings (ppm)

Column1	ND-0.012	0.013-0.019	0.020-0.029	0.03-0.039	0.040-0.049	0.05-0.1	0.11-0.2	0.21-0.29	0.3+
Ambient Air	15		1						
Cleaning/Disinfection Equipment	4	2	1	1	1			1	
Disposing of Solution	21		6	2	5	2		1	
Removing Equipment	13	3	1	1		2	1		1
Rinsing Vessels	1					1			
Neutralizing Solution	3								
Other Processes	9								

Pouring Fresh Solution (ppm)



Summary

■The usefulness of this modified sampling and analytical technique was demonstrated in evaluating TLV exposures

■Thanks to DataChem Laboratories in assisting in researching and adopting this method

Steve Derman

Medishare Environmental Health & Safety Services
3180 De La Cruz Blvd., Suite 100
Santa Clara, CA 95054
(408) 330-7508, ext. 214
S_derman@attbi.com

Steve said that his presentation primarily dealt with the healthcare industry. He gave some background on glutaraldehyde and use in healthcare. He said that he had been working on the problem that, while the new TLV was a ceiling, the available methods were 15 minute integrations. He had contacted the OSHA SLC lab and the NIOSH contract lab Datachem and the result was a method that could measure at the TLV with sample time of 1 minute. Steve summarized his findings on slides 16 and 17. Steve also distributed a diagram showing the frequency of exposures (185 samples) at various levels based on the method described above:

bat Docu

Steve said that pouring solutions generated the highest levels in his investigations, those are shown on slide 17. There was a question about the sampling. Steve said that he had used between 1 and 3 minute sample times for these measurements. The sample time was task oriented. There was a comment that more than half of the measurements were below the proposed limit. Arthur Lawyer asked if these levels were taken in small offices or in Hospitals. Steve said that they were from a variety of locations and types of facilities.

Bruce Wallace said that he had some information about a new measurement method called "solid phase micro extraction". The data sheet is here:

bat Docu

This method appears to allow measurements of 0.0015 ppm with a two minute sample time.

Erica Stewart began a presentation on exposures and controls at Kaizer Perminente. Outline of her Slides are here:

Proposed Glutaraldehyde Ceiling Limit

Reduction by Cal/OSHA

Standards Board Advisory Committee

February 10, 2004

Healthcare Glutaraldehyde Uses

- As Cidex cold sterilizing and disinfecting solution for endoscopes & other delicate instruments that may be damaged by steam, heat or hypochlorite solutions.
- As a component of X-ray film processing chemicals
- Histology & Pathology Fixative ingredient

Glutaraldehyde Use Areas

- Gastroenterology (GI)
- Operating Room or Ambulatory Surgery
- Respiratory Therapy
- Urology/Cystoscopy
- Head & Neck Surgery
- Sterile Processing
- Obstetrics/Gynecology
- Ultrasound/Radiology
- Family Practice
- Histology/Pathology

Sampling Methodologies - Why Important?

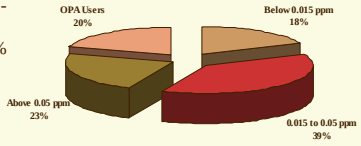
- OSHA 64 - Using 37mm 2,4 dinitrophenylhydrazine impregnated filter cassettes. Sampling rate of 1 liter/min. for 15 minutes. Minimum detectable concentration = 0.0163 ppm using approved methodology.
- NIOSH 2532 - Silica Gel sorbent tube impregnated with 2,4 dinitrophenylhydrazine. Sampling rate of 200 cc/min. for 15 minutes. The accuracy of this methodology is not determined but analysis down to 0.01 ppm is available by some laboratories.
- All ACGIH referenced studies involved sampling periods of 15 minutes or greater though referenced as PEAK exposures.

KP Exposure Ranges

- Peak exposures from 60 areas monitored from 1998-2003
- Before switch to OPA, 22% were less than 0.015 ppm, 40% were between 0.015 and 0.05 ppm and 38% were equal to or greater than 0.05 ppm.
- Kaiser focuses on areas with exposures above 50% of exposure limit or if reports of signs/symptoms of exposure.

KP Exposure Ranges

- Peak exposures from 60 areas monitored from 1998-2003
- Before switch to OPA, 22% were less than 0.015 ppm, 40% were between 0.015 and 0.05 ppm and 38% were equal to or greater than 0.05 ppm.
- Kaiser focuses on areas with exposures above 50% of exposure limit or if reports of signs/symptoms of exposure.

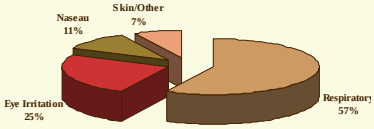


KP Worker's Comp Cases

429 total exposures from 1/2001 to 10/2003
414 incidents from splashes/spills to skin or eyes.
44 indemnity cases, others were medical only.

KP Worker's Comp Cases

- 29 total exposures from 1/2001 to 10/2003
- 14 incidents from splashes/spills to skin or eyes.
- 4 indemnity cases, others were medical only.



Pros & Cons - Switch to Cidex OPA

4Pros

–Low vapor pressure so minimal inhalation risk (100 times lower exposure than Cidex).
–Switch can be accomplished relatively quickly compared to engineering controls.
–OPA has no regulatory or recommended exposure limits so no associated monitoring.
–Reduces disinfection time to 12 min. manual and 5 min. automated processing from 20 min. for Cidex.
–Allows at least 50% more disinfection cycles before solution failure.

4Cons

–Unknown possibility of employees developing chemical sensitivity/asthma similar to glutaraldehyde
–Requires same engineering controls as Cidex to be safe.
–Requires treatment as a hazardous waste which may require treatment tank
–Some local POTWs may not allow sewerage
–Cost is 4 times as much as Cidex. ~$1,200,000/yr. for Kaiser

Pros & Cons - Engineering Control and Remodel Changes

4Pros

–Will control exposures from any chemicals used in a department, now and in the future.

4Cons

–Completion may not be possible in immediate future (within 1 year) due to 300-400 user areas.
–May not protect highly sensitive individuals
–Requires budgeting and planning
–Requires ongoing system maintenance
–Remodels/increased exhaust ventilation may not work in existing locations (example Woodland Hills).
–Some recently remodeled departments cannot achieve 0.05 ppm.
Energy intensive (heating areas with high exhaust ventilation).

Erica said that the major use of glutaraldehyde was for high level disinfecting. They have used several sampling strategies, and both the OSHA 64 and NIOSH 2532 methods. There are over 600 measurements from 1998 to 2003. Kaizer had switched to OPA in those areas where it was difficult to reduce levels. Before the switch to OPA about 22% of levels were less than 0.015 ppm. These measurements are not the typical levels that exist at Kaizer because selection of monitoring location is driven by problem reports. Kaizer uses Nalsco and has increased the sample rates in some cases to 2 lpm and shortened the sampling time based on advice from the OSHA SLC lab (Warren Hendriks). Erica summarized KP's workers comp experience. She said that following back the workers comp information to particular exposures was difficult. Were 29 cases that seemed to be related to disinfectants, including 14 incidents of splashes or spills. 57% of the cases involved respiratory issues.

Erica described Kaizer's approach to implementing engineering controls. They try to use these for all uses of sterilants, but this is limited in the case of older facilities. In some cases recirculating systems (PCI medical) are used for low volume use of sterilants. Erica said that the ventilation upgrades to convert facilities for GI in hospitals can run about 400k$. The minimum is about 100k$. Erica said that reducing the limit would increase the use of alternatives such as OPA. Erica said that one problem with this approach was cross sensitization between different aldehydes. Remodeling is a more permanent solution, but Kaiser has 30 hospitals with about 10 user areas per hospital as well as other facilities.

Erica said that many of the architects are not really as familiar with high static pressure exhaust systems as with HVAC systems. With information gained in buildouts, room templates are updated so that standardized designs can share these benefits. These templates very depending on utilization.

There was a discussion about problem reporting and John Mehring said that the employee is often viewed as the source of the problem without looking into the work environment and engineering controls. Susan Ripple asked if the labor organizations had taken steps to promote safe work practices and said that there is an expectation that the employees follow safe work practices. Pamela Spencer added that even if the levels are lowered to the levels proposed that without safe work practices the problems will not be solved. Denise Senior and Karen Jenkins said that they had done all the

things that they had been told about. John Mehring said that these arguments that focus on work practices are the same arguments that he has heard in the context of unsafe medical devices. He said that it took a regulation to correct this problem at its source. He thought that this was another case of putting the onus on the worker.

Erica Stewart said that she was not clear as to what the change intends to protect. Is it intended to protect workers that are already sensitized? Steve Smith said that the goal is to prevent sensitization from occurring and not to prevent reactions in sensitized workers. Bruce Wallace said that the Initial Statement of Reasons clearly stated that the change was to protect against sensitization. Steve said that this had been discussed at length today but that the issues of feasibility still needed further discussion. These will need to be discussed in a meeting to follow this one. Steve asked that the information to be presented be submitted well before the meeting so that it could be distributed.

Meeting adjourned

Glutaraldehyde Advisory Meeting

Draft Minutes

May 4, 2004

Attending:
Mike Cooper, Julia Quint, Steve Smith, Tom Mitchell, Denise Senior, Tom Tremble, Erica Stewart, Tom Marsh, Robert Harrison, Patrice Sutten, Karen Jenkins, Roger Richter, Deepak Plaha, Joe Ascenzi, Barbara Smisko, Judith Freyman, Teresa Pichay, Greg Gordor, Rich Shumway, Julia Klees, Janice Prudhomme, Artie Lawyer, Dan Leacox, Stephen Derman, Susan Ripple, John Mehring, Kathy Krol, Bruce Wallace, Dan Cardin, Tom Robinson, Barry Foose, David Tobia, Dennis Shoji, John Crawford, David Estrada, Mitch Cohen, Gene Livingston, Purua Grover, Pam Spencer, Tom Mitchell

Steve Smith made introductory remarks. He described the meeting on February 10 and the agenda items carried forward. The main issues for today are current uses, current practices, and effects of proposed changes to the exposure limit for glutaraldehyde. Other issues are skin exposure, the sensitization notation, and measurement methods.

Steve asked if there were comments on the draft minutes of the February 10 minutes. Artie Lawyer said that he had some comments that he could make, but to save time he would forward them by the end of the week.

All present introduced themselves.

Steve Smith summarized the previous meeting noting that it appeared possible to meet a 0.05 ppm limit. There was a concern that 0.015 could be met. Some of those present on Feb 10 supported the 0.015 limit. Steve described other issues such as other types of exposure such as skin contact and the need to warn of risks through hazard communication and a possible sensitizer notation.

Gene Livingston said that the industry groups he represented recommended a limit of 0.05 ppm as a ceiling with a sensitizer notation. He also said that it would take some time to come into compliance and suggested a two year implementation of the change. Gene said that the reasons for this recommendation could be briefly summarized by Pam Spencer. Steve said that he would prefer that we move on to the items remaining on the agenda and return to the scientific rationale at the end of the meeting.

Susan Ripple began a presentation on monitoring feasibility. Susan noted that there were two validated active monitoring methods, NIOSH silica jell tube, and OSHA 64 using treated filters. She presented a slide that showed that four labs that had a detection limit one tenth of 0.015 ppm for a 15 minute sample at 2 lpm using OSHA 64. None of the passive methods or direct reading methods meet the requirements for 15 minute sampling. Susan said that the method described at the last meeting (Solid Phase Micro Extraction) could work at these levels for a short term measurement, but that it was very expensive and required a high level of expertise. It requires analysis within 24 hrs. Susan said that these methods assumed that a 15 minute sample would be acceptable for evaluating a ceiling exposure. There are serious concerns these 15 minute samples not capturing the peak exposures associated with spills and other short term activities. Susan said that if you could not characterize the actual exposures in 1, 2, 3 and 5 minute samples then you could not put in the right controls whether they are administrative or engineering. The OSHA and NIOSH methods also had interferences from some alcohols. Using the badge samplers would cost about 50 $ but

these are not validated for term short samples. The OSHA 64 method has a total cost of about 250$ per sample including labor and a report. Reducing the sample time below 15 minutes broadens the variability up to 54% in some instances. This requires more samples and increases costs. About six more samples for one job task. Erica Stewart said that Kaiser estimates sampling at about 75 $ per sample. Susan said that there was great variability between workers doing the same task. The range could be from non detect to 100 ppb.

Bruce Wallace asked assuming that the limit is expressed as a Short Term Excursion Limit, would the OSHA 64 method be adequate for a 15 ppb limit in those terms. Susan said it would. Steve Durman said that the peaks would not be detected by those measurements. Bruce said that the research that is the basis for setting the limits used these "15 minute" measurements. Our body of knowledge does not include an understanding of what these peaks are. Erica Stewart said that Kaiser had taken some shorter term measurements, 5 minutes.

John Mehring said that he didn't understand why all the labs could not meet the requirements for minimum detection levels. Susan thought that the differences in instrumentation might explain the differences. John thought that monitoring was not done very frequently.

Teresa Pichay thought that the feasibility of measuring thousands of dental offices was a major concern. John Mehring asked how frequently they monitored now. Teresa said that they currently monitored for formaldehyde using passive badges. She said that her association had not gotten any questions about glutaraldehyde monitoring and that they were planning to do some monitoring to see what the exposures are.

Dan Cardin began a presentation on canister monitoring technique. This method uses a small stainless coated canister and GC/MS analysis. The method is at least ten times more sensitive than OSHA 64 for glutaraldehyde. OSHA has a method based on these canisters PV 2120. The method can be used to sample for multiple compounds in a single analysis. The analysis is direct and does not involve measuring a derivative as in OSHA 64. The method does not use solvents for desorption and the associated dilution of the analyte. The sample time can be long or short with the method. The canisters can be reused after cleaning hundreds of times. Analysis requires heating the canister causing the glutaraldehyde attached to the walls into the gas phase. Erica Stewart asked if the method had the same interferences as the OSHA. Dan said that wasn't a problem, the MS could resolve the glutaraldehyde from the alcohols.

Richard Shumway asked about problems with variability with standards used to calibrate the analysis. He said that there were problems with these solutions decreasing over time. Susan Ripple asked how the degradation products of glutaraldehyde were accounted for with this method that heats the canisters. Dan said that they had not seen any degradation and if it were the present it would be seen as a tail on the peak coming off the column. The reason that this system works without degradation of reactive compounds is the inert silica liner in the canister. Formaldehyde is also reactive, but it is stable in this system.

The samples can be done with critical orifices or pulsing valves to control sampling times. Replicate measurements have shown have shown a theoretical detection limit of 0.34 ppb. The dynamic range of measurement can be extended by injecting varying volumes to cover from parts per billion to parts per million without changing the field collection procedure. The personal sampler uses a 1/32 i.d. silonite coated tube inside a teflon tube to take the sample.

There was a question about the cost of these measurements. There was an estimate from Tom Robinson of 120 $ for the sampler and analysis.

Lunch break

Teresa Pichay wanted to clarify her earlier comments by saying that the costs of sampling was not a major issue, but the other costs of compliance might be a major issueand were unknown at this time.

Steve Smith asked if there were any more comments regarding sampling/analysis. He said that we would need to follow up with NIOSH to see if they had or would develop a method based on these canisters for glutaraldehyde at the lower levels proposed.

Steve moved on to the next agenda items, controls and feasibility.

Tom Tremble representing Advanced Medical technology Association began a presentation. Tom described the uses of glutaradehyde in healthcare including the use in tissue heart valves. There is concern that the lower levels might

necessitate changes to the process of making the valves. This could cause a FDA review that might delay or jeopardize the safety of these devices. California is home to a large number of medical device manufacturers. The costs of meeting 0.015 ppm limit could overwhelm some of the small companies. This reduction would have an adverse effect on start up companies as well. Tom also said that lowering the PEL might not have its intended effect if compliance was not also considered.

Richard Shumway made a presentation on tissue heart valve manufacturing. Richard described the three purposes of glutaradlehyde in manufacturing tissue heart valves, sterilization, cross linking, and rejection prevention. The valves have a stent that surrounds them with natural tissue leaflets. There are about 300000 procedures done world wide each year. Glutaraldehyde is critical to the manufacturing of these valves. Edwards has a new facility(1997). There are about 400 employees working each day with glutaraldehyde. There is low turnover in these employees. Over the last five years there have been six suspect respiratory cases. Richard presented data on the four areas sampled recently with OSHA method 64. Prior to that the company had used passive badges. The ranges were .01-.1, .003-.06, .01-.04, and .003-.02 ppm. The respective means were .05, .03, .02, and .01 ppm. Five of the cases were in the second area and the last in the third. These measurements were personal samples. In the past there was reluctance to use active sampling in the clean room. Bruce asked which of the four areas had the largest number of employees. Dennis Shoji said that the second area (department) was the largest. Bruce Wallace said that he couldn't see a local exhaust system in the pictures shown earlier of the manufacturing area. Dennis said that each station had one, a slot system. Dennis said that they were redesigning the work stations to use a new down flow system to reach the .05 level. Dennis said that dermal problems had been more of a problem in the past than respiratory problems. Richard went on say that a reduction from .05 to .015 would take a change to the concentration of glutaraldehyde in the process. This would require a FDA requalification. This would be devastating and might motivate moving manufacturing out of California.

Erica Stewart began a presentation by responding to an earlier question by John Mehring that Kaiser did not have a specific value for an exposure limit. The goal is to reduce exposures to the lowest feasible level and to be in compliance with regulatory limits. Exposures are categorized into five types, below detection, within 25% of limit, 50 % of limit, 75 % of limit, and at the limit. These categories indicate the level of response that made. Erica said that Kaiser had concerns in the following areas, sampling methodology whether the limit is a ceiling or STEL, the timelines for compliance with .05 or .015, doubts about the level at which sensitization occurs. Erica said that another problem was interference with sampling by alcohols, these are used extensively in endoscopy. Erica said that permitting for accute care facilities through OSHPD takes about two years. Non-accute care facilities also takes a significant amount of time. Currently Kaiser is involved with many projects for seismic upgrading.

Erica said that even if the change was with capital equipment (not a facilities change) like ductless hoods, it would still take a year to put them in place. The time would be, identifying the area, sizing the unit, purchase, installation, and training. Substitution might be used, Cidex OPA, but this also would take some time. Cidex OPA has the problems: it makes a hazardous waste, hazardous waste training is required, recent concerns in the allergy immunology area regarding OPA. Advanced Sterilization Products has recently made some warnings about successive use in some procedures.

Erica said that there was no consensus and continuing debate about the level at which sensitization occurs. We (Kaiser) are unable to say what level we think is safe. We intuitively believe that lower levels are more protective. If spills are important in producing sensitization, then 15 minute exposure limits won't get at those shorter type tasks that may be related to sensitization.

Erica presented a cost breakdown for manual and automatic endoscope reprocessing (AER) areas. Erica said that some maintenance tasks like changing filters generated exposures above 0.015 even with their latest design layout for AER facilities and may not be able to meet .05. Upgrade costs for a single bay scope washer are estimated at 200k$. For manual areas, at a limit of .05, the total estimate for costs is 12 million if local exhaust is required. If GUS stations (recirculating hoods) are used the total is 60k$. The worst case estimate for the 0.015 level involving local exhaust upgrades is 55 million. The lowest estimate for 0.015 is 276k$. There is a strategic plan to centralize processing. There is resistance to this from users, time delays and equipment damage. The current data won't allow a conclusion as to whether these changes will meet 0.015. Historical data shows 15 % of measurements above .05, 69% above 0.015. This data is not representative of typical exposures because the sampling is preferentially done in areas with complaints.

Erica described several problems with conversion to OPA. There have been cases of anaphylaxis associated with OPA use. It is a hazardous waste. It is 3 to 4 times as expensive as glutaraldehyde.

With either limit, 0.05 or 0.015, monitoring to ensure compliance is estimated to be more than 500k $. The total cost estimate (Kaiser) for the 0.05 level is 24 million. The total cost estimate for the 0.015 level is 67 million.

Bruce Wallace asked how frequently the filters were changes on the AERs? Erica said about every 6 months. Bruce said that this was a maintenance and not a normal use activity that could use PPE instead of local exhaust.

Bob Harrison asked if there were plans to monitor around the GUS stations. Erica said that they wanted to do that just at the end of the useful life of the filter, at six months.

Roger Richter noted that there could be a situation where upgrades were put into place and then seismic upgrades would cause them to be redone. Erica said that the planning for new hospitals would incorporate these features.

Steve Smith summarized the presentations thus far. There are serious concerns about the feasibility of meeting a 0.015 level. These range from some think that it couldn't be met at all to those estimating costs and time to possibly reach this level. At .05 there were still concerns and costs described, but feasibility didn't seem to be in doubt.

Steve said he would like to open the topic of the type of limit, ceiling vs STEL. Steve said that the STEL is the more achievable measurement but it may or may not characterize or control the peak exposures. Susan Ripple said that Dow did not consider a STEL an appropriate limit. With short tasks, say one minute; the 15 minute average will significantly underestimate actual peak exposures. These could be in the range that causes irritation. Pamela Spencer said, based on Pamela Dalton's presentation at the last meeting, that we have quantitative data about levels that cause irritation. Irritation can trigger asthmatic like symptoms. We know that we can use this to set levels that at least control irritant effects that could induce asthma. This is where a ceiling is important. Steve asked if there was any support for a STEL limit. There was no support for changing from a ceiling limit to a STEL. Steve said that the current limit is a ceiling limit and current methods use a 15 minute average. This requires characterizing actual peak exposure with this method (indirectly). Pamela Dalton said that if a .05 level is chosen then it would be necessary to maintain levels below that. This will give you a larger margin of safety for any type of sensitization reactions that you are protecting against. When you look at the levels for irritation and compare to the ACGIH level you have an eight to ten fold safety factor. The data for sensitization is less certain, and with the data seen today we are not seeing a lot of sensitization at levels below 0.05. With other industrial applications with glutaraldehyde, occupational asthma has not arisen as an issue. There is antidotal evidence that 0.05 is protective against induction. Steve Smith said that it appears that this group feels that a ceiling level is most appropriate.

Steve asked if there was an interest in putting a Sensitizer notation on glutaraldehyde. There was a discussion about the general issue of identifying sensitizers. There were concerns expressed about identifying some sensitizers and leaving others not designated. Susan Ripple said that the ACGIH list is a comprehensive list of sensitizers. Steve asked if the sensitizer notation glutaraldehyde should wait until a comprehensive set of changes were made. Several present said that it would depend on the timing of the change. Steve said that it appeared that there was support for a sensitizer notation for glutaraldehyde. The broad issue of all substances will need to be considered by another group.

Steve moved on the last agenda item. We have a recommendation of 0.05 as a ceiling from the industry representatives. The current proposal is 0.015 C. This level was recommended by the original committee and by the labor representatives today. We have heard about the difficulty and cost of reaching this level and questions about sampling at this level. We have heard about new measurement methods seem to work at any level discussed but those will need additional validation. It seems that industry cannot live with the 0.015 level on an economic feasibility basis. Steve asked if it would be possible for labor to make the concession to support a 0.05 level.

John Mehring said that California had been in a position of leading with changes before rather than just following what others have done. In the case of requiring safety devices on medical equipment California led the nation, meeting these requirements was described as impossible at the time.

Pamela Spencer described the need for additional elements beyond just setting an exposure limit. They need hazard information, appropriate control measures and work practices, protective equipment.

Julia Quint said that it was important to distinguish between irritant induced asthma and sensitization induced asthma. There aren't large amounts of data on the levels that produce sensitization for these types of toxic materials. There is

also the complication that people move out of these jobs and there isn't much exposure data. Julia said that because of this HESIS is advocating medical monitoring that can link early symptoms with exposure information.

Pamala Spencer said that she supported medical monitoring, but that the people in the studies cited were already sensitized and had responded to very low concentrations. Julia said that was correct, but that the researchers had also gone back to look at the exposures in the workplaces where they had come from and recreated exposure situations and measured the exposures.

Bruce Wallace said that the committee had used the workplace exposure data from the DiStefano study directly to make its recommendations. There were no factors applied to go from human LOEL to NOEL. The recommendation was set at the bottom of the range of short term exposures measured in those workplaces.

John Mehring said that he thought that what might be needed is a comprehensive standard for glutaraldehyde. John said that he might have more confidence in a .05 level if there were other protections in the standard. Steve Smith said that the model for other compounds was to require medical monitoring at a level below the limit, the action level, which was typically set at half the limit. Steve asked if there was support for this idea. Steve said that there was a current requirement in Section 5155 for medical monitoring that could be applied on a case by case basis.

David Tobia didn't think that expecting employers to have a medical surveillance program at about 0.025 was very realistic. Almost everyone would be in the program given the data we have seen.

Gene Livingston said that several people had left the meeting and that they would need to consider these types of requirements and respond later. Dan Leacox asked how this group would develop these requirements. Steve Smith said that draft requirements could be written by the DHS representatives, or very general requirements could be developed that left the details of the program to the physician. This might also be considered as part of the larger issue of sensitizers in general. Steve suggested that a proposal could be drafted that included the limit at .05, medical monitoring, a sensitizer notation, and a phase in period, and this draft distributed to this group. Steve asked that suggested language be sent to him by the end of the month. He would try to send a proposal to the whole group by the end of June and schedule another meeting after that.

Meeting adjourned

5-21-04

MEETING RECORD

Cal/OSHA
Glutaraldehyde Advisory Meeting

Thursday October 14, 2004
1515 Clay Street
Oakland, CA

Attendees

Karen Jenkins, injured worker
Denise Senior, SEIU Local 250
Barry Foose, Kaiser Permanente
Joe Ascenzi, Advanced Sterilization Products
Kathy Krol, Center for Endoscopy
Rich Shumway, Edwards Lifescience
John Mehring, SEIU
Dan Leacox, Livingston & Mattesich
Stephen Derman, MediShare

Erica Stewart, Kaiser Permanente
Mitch Cohen, Kaiser Permanente
Deepak Plaha, Medtronic
Tom Tremble, Advanced Medical Device Association
Dennis Shoji, Edwards Lifesciences
Cheryl Christenson, Edwards Lifesciences
Janice Prudhomme, California Department of Health Services
Judi Freyman, ORC Worldwide
Liz Brott, Kaiser Permanente
Paul Brownson, Dow Chemical
Pam Spencer, Dow Chemical
Greg Gorden, Technology Sciences Group
Artie Lawyer, Technology Sciences Group
Roger Richter, California Healthcare Association
Julia Klees, BASF
Susan Ripple, DOW Chemical

Steve Smith, DOSH, meeting chair
Bob Barish, DOSH
Tom Mithchell, Cal/OSHA Standards Board

MINUTES

The meeting was opened by Steve Smith, Supervising Industrial Hygienist, DOSH. Steve gave a brief update on progress since the last meeting in May with respect to developing language for a footnote to supplement whatever PEL was agreed to. Steve noted his understanding that industry representatives felt that a PEL of 0.05 ppm ceiling limit was reachable, but not without some concerns that might be addressed by a delayed implementation after adoption. Steve said that the meeting today would include discussion of supplemental protections such as medical monitoring, in light of the fact that the Division's PEL committee had recommended a PEL of 0.015 ppm ceiling.

Dan Leacox noted absence from the minutes of the May meeting of a comment made by Mike Cooper that differences of the magnitude of 0.015 and 0.05 were not usually considered by the Air Contaminants Advisory Committee that he had participated in.

Steve Smith briefly reviewed the history and status of the current round of PEL amendments.

Tom Tremble said that his recollection was that there was agreement at the last meeting in May for a PEL of 0.05 as a Ceiling Limit. Steve Derman agreed with Tom Tremble's recollection. Artie Lawyer agreed with Tom and Steve and said that today's meeting was intended to address supplemental elements that would compensate for the compromise from the 0.015 ppm level proposed by the Air Contaminants Advisory Committee based on health effects only. John Mehring said that SEIU would like to see the Ceiling Limit be 0.015 ppm, but in the interest of consensus SEIU could accept 0.05 ppm ceiling if it was coupled with a footnote to address communication issues associated with safe use. Steve Smith said that a possible medical monitoring element for glutaraldehyde might look like that from the federal OSHA formaldehyde standard which focuses on asthma. Artie Lawyer suggested that what was generally agreed was that a statement would be made about medical monitoring but that it would not be a new requirement. Artie Lawyer also said that recognizing the sensitizing effects of glutaraldehyde, a footnote should be included in Table AC-1 of section 5155 to address employee training and education. He suggested that this could be an interim measure until the Sensitizer Advisory Meeting (SAM) being organized by the Division developed a more comprehensive approach.

Steve Smith noted that many glutaraldehyde users already had medical monitoring programs in place and that what was proposed was not a new medical monitoring requirement but rather direction for existing programs. John Mehring said that the basis of SEIU's support for the footnote on training and education and acceptance of lowering the Ceiling Limit

to 0.05 ppm rather than 0.015 ppm was that the SAM would would be looking at medical monitoring requirements for sensitizers. Artie Lawyer and Mitch Cohen agreed that medical monitoring should be part of the SAM discussion.

Judi Freyman wanted to know if the SAM was a follow-on to the present meeting on glutaraldehyde, or independent, and in either case, had a charge for it been developed. Janice Prudhomme asked if the SAM would address only 5155 substances or even substances that are not chemicals. Julia Klees wanted to know what the definition of sensitization was for the purpose of the SAM. Steve noted that there are some substances in 5155 such as wood dust that are not chemicals. He noted that his vision was to limit the SAM's initial charge to substances in section 5155 and that the question of a definition of "sensitization" would be a subject of discussion at that meeting.

Returning to discussion of the education and training footnote, Steve noted that it was intended to be temporary until the SAM developed a more comprehensive approach. Artie Lawyer said that he believed that the proposed footnote passed out by Steve did accurately reflect the results of the two sub-group meetings that had taken place. He thought that Steve's addition of references to specific Title 8 sections was helpful.

The draft proposal for both the PEL and footnote that was passed out at the meeting read as follows:

§5155. Airborne Contaminants.

---

* * * *

TABLE AC-1
PERMISSIBLE EXPOSURE LIMITS FOR CHEMICAL CONTAMINANTS

Chemical Abstracts Registry Number [a]	*Skin*[b]	*Name*[c]	*PEL* [d]		*STEL* [o]		
			ppm[e]	*mg/M*3[f]	*Ceiling*[g]	*ppm*[e]	*mg/M*3[f]
		* * * *					
111308		Glutaraldehyde	~~0.2~~ **0.05**	~~0.82~~ **0.2**	C		

Footnotes:

* * * *

s) Glutaraldehyde can cause occupational asthma and skin sensitization responses such as contact dermatitis. Potential symptoms include shortness of breath, chest tightness, wheeze, cough, skin rash, hives, and irritation of the nose, throat, skin or eye. Hazard communication training required by sections 5191 or 5194 shall address these health hazards and symptoms along with the measures taken by the employer to evaluate and control exposures such as medical evaluations, exposure monitoring, ventilation systems, work practices, and personal protective equipment. The communication system required by section 3203 shall encourage employees to report possible symptoms and questions about the evaluation and control measures.

Paul Brownson suggested modifying the second sentence of the footnote to state that *"Exposure related symptoms may include…."* This was done. In sentence 3 Artie Lawyer suggested the phrase "*which can include*" rather than "*such as*." This change was made. Judi Freyman suggested that sentence 4 should include reference to "*sources of information and contacts for information on evaluation and control measures*." This suggestion led to an extended discussion. The footnote wording agreed to by those in attendance was:

s) Glutaraldehyde can cause occupational asthma and skin sensitization responses such as contact dermatitis. Exposure related symptoms may include one or more of the following: shortness of breath, chest tightness, wheeze, cough, skin rash, hives, and irritation of the nose, throat, skin or eye. Hazard communication training required by sections 5191 or 5194 shall address these health hazards and symptoms

along with the measures taken by the employer to evaluate and control exposures that can include medical evaluations, exposure monitoring, ventilation systems, work practices, and personal protective equipment. The communication system required by section 3203 shall inform employees where to report possible health symptoms and where to ask questions, report concerns, and receive information about the employer's evaluation and control measures.

Steve Derman asked if this footnote would apply only to glutaraldehyde. Steve Smith replied that it was a temporary measure specific to glutaraldehyde and that the planned SAM would take up the possibility of a more generally applicable statement. Steve Derman expressed concern that the footnote could be viewed as suggesting that other substances might be excluded from the requirements stated. Steve Smith acknowledged this as a possible concern. Steve Derman suggested that this issue should be reviewed by the Division's Legal Unit to address this concern. Steve Smith acknowledged that internally there may be a concern with this potential issue. Artie Lawyer said that applying the footnote developed for glutaraldehyde to other substances in section 5155 would be likely to result in opposition from other sources, for example those interested in isocyanates.

After lunch, Steve Smith opened the discussion of requests for an extended effective date for an amended Ceiling Limit. Steve said that the effective dates of standards and amendments are shown in the "History" notes found at the end of each Title 8 standard. Steve said that usually, and unless requested otherwise, Title 8 standards take effect 30 days after their filing with the Secretary of State in Sacramento.

Artie Lawyer proposed a footnote indicating an implementation timeframe for an amended Ceiling Limit to 0.05 ppm of 30 days or when "technically feasible" but not longer than 2 years He noted that while a 30-day period might be feasible for some employers and operations, some operations would require extensive modifications to achieve the proposed Ceiling Limit.

Tom Tremble asked about the timeframe for promulgation of a revised Ceiling Limit. Steve Smith said that with the usual timeframes of the rulemaking process the earliest an amended standard would be likely to be adopted would be summer 2005.

Roger Richter said that with their special requirements for design review, hospitals cannot modify ventilation systems in under two years.

Steve Smith noted that a revised Ceiling Limit would not have to be initially achieved by engineering controls. He noted that Title 8 section 5141provides that control by means of respirators is acceptable during the time necessary to install or implement feasible engineering controls. Barry Foose of Kaiser said that respirators could be problematic, especially if employees and their unions objected to their use. Deepak Plaha noted that his company continues to make modifications to their processes in order to achieve the Ceiling Limit of 0.05 ppm or less, but the use of respiratory protection in some job tasks is not an option, i.e. microscope work. Therefore, the use of respiratory protection on an interim basis would not be feasible and a 2-year implementation period would be necessary to incorporate adequate engineering controls . Mitch Cohen said that Kaiser would not be able to control all exposures to a Ceiling Limit of 0.05 ppm until 2007. Erica Stewart said that substituting ortho-phthalaldehyde (OPA) was not a good solution as it was at least a skin sensitizer. Tom Tremble said that engineering controls, not respirators, were the way that exposures should be controlled. Judi Freyman said that if a Ceiling Limit of 0.05 ppm was adopted it would be important to provide time for affected employers to come into compliance.

Dennis Shoji suggested that a requirement for a "compliance plan" coupled with the 2-year timeframe for compliance could address concerns over the longer than usual time allowed to achieve the new PEL. Steve Smith noted that Division compliance personnel already have a requirement to assess feasibility before issuing a citation. He also noted that employers with particular difficulty achieving compliance in the time allowed could pursue a temporary variance. Artie Lawyer asked how long that process can take. Steve said that it can happen quickly as it does not go through the formal process with the Standards Board required for permanent variances. John Mehring suggested that the question of the effective date was more appropriately addressed by the Standards Board. Steve Smith said that in most cases regulatory proposals made to the Standards Board don't address the effective date. Steve said that it is an item on the Form 400 submitted along with the rulemaking package to the Office of Administrative Law, and that justification was required if a timeframe other than 30 days is requested. Artie Lawyer suggested amending the Ceiling Limit and providing a variable effective date. Judi Freyman said that if the effective date was not addressed in the proposal but only left up to the Standards Board then employers would oppose the reduction of the Ceiling Limit to 0.05 ppm.

Mitch Cohen supported the idea of requiring a "compliance plan" as an alternative to a 30-day compliance requirement.

Steve Smith suggested a possible approach for allowing the time requested for compliance while also generating immediate workplace improvement: retention for 2 years of the existing Ceiling Limit of 0.2 ppm with adoption of a PEL-TWA of 0.05 ppm which would convert to a Ceiling Limit at the end of the 2 years. There was general agreement from employer and manufacturing representatives that this approach would be acceptable and employee and union participants at the meeting did not express objection.

Steve Smith stated he would send draft language and these minutes to the members for one last review before developing the proposed rulemaking package. When the proposal is sent to the Standards Board for public hearing the members will be included in the mailing list for that process. Mr. Smith thanked the members for their attendance and working to develop a consensus proposal.

END – No attachments