Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
January 14, 2015 Public Meeting
Docket Number: EPA–HQ–ORD–2014–0882
HSRB Website: http://www.epa.gov/osa/hsrb

Committee Members: (See EPA HSRB Members List—Attachment A)

Date and Time:	Wednesday, January 14, 2015, 10:00 a.m. – 3:20 p.m. EST (See *Federal Register* Notice—Attachment B)	
Location:	Via Teleconference and Webinar	
Purpose:	The EPA HSRB provides advice, information and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Rebecca T. Parkin, Ph.D., M.P.H.
	Vice Chair:	Jewell H. Halanych, M.D., M.Sc.
	Board Members:	Gary L. Chadwick, Pharm.D., M.P.H., C.I.P. Liza Dawson, Ph.D. George C.J. Fernandez, Ph.D. Kyle L. Galbraith, Ph.D. Edward Gbur, Jr., Ph.D. Elizabeth Heitman, Ph.D.* John C. Kissel, Ph.D. William J. Popendorf, Ph.D., M.P.H. Kenneth Ramos, M.D., Ph.D., Pharm.B.† Suzanne M. Rivera, Ph.D., M.S.W. Jun Zhu, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the Meeting Agenda (see Attachment C), unless noted otherwise.	

Wednesday, January 14, 2015

Commencement of Public Meeting and Review of Administrative Procedures

Before the meeting was called to order, there was a brief discussion and explanation of how to use the Adobe® Connect webinar system to accomplish the objectives of the meeting. Dr. Toby Schonfeld (Designated Federal Officer [DFO], HSRB [or Board], Office of the Science Advisor [OSA], EPA [or Agency]) convened the meeting at 10:00 a.m. and welcomed Board members, EPA colleagues and members of the public. She expressed appreciation on behalf of

* Indicates the Board member attended the morning sessions only
† Indicates the Board member attended the afternoon sessions only

the Agency for the time and diligent work of the Board members in preparing for meeting deliberations. She also thanked the EPA staff for their efforts in preparing for the meeting.

Dr. Schonfeld noted that she will be acting as DFO and, as DFO under the Federal Advisory Committee Act (FACA), she serves as liaison between the HSRB and EPA and is responsible for ensuring that all FACA requirements are met regarding the operations of the HSRB. Also in her role as DFO, she must work with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied. HSRB members were briefed on federal conflict of interest laws and have completed a standard government financial disclosure report, which has been reviewed to ensure that all ethics requirements are met. Dr. Schonfeld noted that all the agenda times are approximate, and the group will strive to have adequate time for Agency presentations, public comments and the Board's thorough deliberations. She also announced that Thomas Burke is the new EPA Deputy Assistant Administrator for the Office of Research and Development.

Dr. Schonfeld then turned the meeting over to HSRB Chair, Dr. Rebecca Parkin. Dr. Parkin notified members that copies of all meeting materials will be available at http://www.regulations.gov under docket number EPA–HQ–ORD–2014–0882, and supporting documents are available on the HSRB website at http://www.epa.gov/osa/hsrb. The hand icon on Abode Connect will be used for Board voting and to ask questions.

Dr. Schonfeld noted that, in accordance with FACA, meeting minutes, including a description of the matters discussed and conclusions reached by the Board, will be prepared and must be certified by the meeting Chair within 90 days. The approved minutes will be available at http://www.regulations.gov and on the HSRB website at http://www.epa.gov/osa/hsrb. The HSRB also will prepare a final report in response to questions posed by the Agency, which will include the Board's review and analysis of materials presented. The final report will be available at http://www.regulations.gov and on the HSRB website at http://www.epa.gov/osa/hsrb. Dr. Schonfeld then turned the meeting back over to Dr. Parkin.

Introduction of Board Members

Dr. Parkin welcomed the Board members and asked them to introduce themselves with names, affiliations and expertise. The Board members completed their introductions.

Welcoming Remarks

EPA Human Subjects Research Review Official (HSRRO) and acting DFO Dr. Schonfeld (OSA, EPA) provided opening remarks. She reiterated the importance of the Board's work and asked for patience as any technical challenges are addressed during the virtual meeting. Dr. Parkin thanked Dr. Schonfeld for her comments.

Session 1: Review and Approval of the HSRB Final Report of the November 5, 2014 Meeting

Background

Dr. Parkin introduced Session 1 and asked everyone to lower their hands in Adobe Connect to begin the review and approval of the HSRB Final Report of the November 5, 2014 meeting.

Public Comments

Dr. Schonfeld announced that there were no public comments entered into the record.

Board Discussion of the Draft Final Report

Dr. Parkin called for any comments, edits, and corrections regarding the draft HSRB Final Report of the November 5th meeting. Dr. John Kissel explained that he and Dr. William Popendorf discussed that the methodology in the final report is not conservative and biomonitoring is not included. Dr. Kissel elaborated that EPA protocols can underestimate dose and, if the biomonitoring step is excluded, there is no guarantee that the dose is not underestimated. The methodology and exclusion of biomonitoring should be considered by EPA when evaluating this study.[‡] Dr. Parkin responded that Dr. Kissel's suggestions were included in Section 2.

Dr. Kissel also explained that the Agency derives the Margin of Exposure (MOE) by estimating exposure and comparing the exposure to the index. He noted some of the calculations used a dermal absorption factor of 100% while other compounds used an absorption factor considerably less than 100%. For most compounds the assumed dermal absorption factor does not significantly impact the analysis, but, for compounds such as tefluthrin, an assumed absorption of 100% will result in the compound being under the MOE. Dr. Kissel suggested that tefluthrin no longer be considered if 100% absorption is assumed. Dr. Parkin asked Dr. Kissel to review from line 293 to determine if his suggestions are reflected.

Dr. Popendorf generally agreed with Dr. Kissel's points. He explained that the chemicals and compounds that do not use an absorption factor use a dermal toxicity value. The three compounds that used a dermal absorption factor used oral toxicity and used the dermal absorption to adjust the oral toxicity to determine what the dermal toxicity might be. Dr. Popendorf agreed with Dr. Kissel's suggestion to point out that the information used to derive EPA's dermal adjustments was not documented and took scientific issue with the recommendation to use 100% adsorption, since 100% absorption is rare. He suggested that, on a policy basis, the Board specify how the Agency should proceed regarding the use of absorption factors.

Dr. Popendorf had sent a revised paragraph to Dr. Kissel that either deleted the recommendation to use a dermal absorption of 100% or described the implications of that absorption result in the need to exclude one of the compounds. Dr. Parkin brought members'

[‡] Collier, R. H. (2014, July 25). *Determination of Dermal and Inhalation Exposures to Workers During Open Pour Loading of Granules, AHETF Study No. AHE170.* Agricultural Handler Exposure Task Force, LLC.

attention to lines 301-303 in the draft on page 9 and read the line. She noted that Dr. Popendorf suggested that the second half of that line be deleted and asked for other members' opinions. Members did not have any comments. Dr. Parkin agreed with the suggestion to remove the 100% absorption assumption based on the Board's past recommendations that are traditionally not specific. Dr. Parkin called for a vote to remove the directive that 100% absorption be assumed and replace it with alternative language. The majority of members agreed. Dr. Parkin suggested replacing line 302-303 with:

> "When availabilities less than 100% cannot be adequately justified, citation of relevant studies that the agency relies on must be included."

Dr. Kissel disagreed, explaining that if an assumption is made, it must be based on a study and a justification should be included regarding how the particular study is similar to the conditions that the Agency is interested in. Dr. Popendorf agreed with Dr. Kissel's push for increased Agency transparency and suggested replacing the rest of the paragraph that begins on line 301 with:

> "The Agency should review the loading conditions used to develop the dermal absorption factor for these four surrogates for their relevance to the field conditions to be tested within this protocol to assure that the MOEs are indeed adequate."

Dr. Kissel responded to that suggestion, explaining that this language still leaves the dermal absorption to EPA. His main issue is that the Board is not requiring transparency regarding the information on which EPA bases its decision. Dr. Parkin suggested adding "The Agency should review and document" to Dr. Popendorf's replacement.

Dr. Parkin called for a vote to replace the paragraph beginning with "if availability is less than 100%" on line 301 with:

"The Agency should review and document the loading conditions used to develop the dermal absorption factor for these four surrogates for their relevance to the field conditions to be tested within this protocol to assure that the MOEs are indeed adequate."

Members approved the change.

Dr. Parkin asked for additional questions or comments and, hearing none, she took a vote on the Board's approval for the HSRB November 5 Final Report. Members approved the Final Report with the above replacement beginning on line 301.

Session 2: A published report: Ezratty, Veronique et al. (2014) Repeated Nitrogen Dioxide Exposures and Eosinophilic airway Inflammation in Asthmatics: A Randomized Crossover Study. *Environmental Health Perspectives*. Volume 122, Number 8, August 2014. (MRID 49519201)

Background

Dr. Parkin introduced Session 2 and noted that Dr. Maddalena, who was to lead the Board's Scientific Assessment, was not on the phone. The EPA asked that the review of the study not be delayed. Dr. Parkin asked other members of the Board to provide their science

review and invited LT Jonathan Leshin (Office of Pesticide Programs [OPP], EPA) to make his presentation describing EPA's science review.

EPA Science Assessment

LT Leshin explained that the study was conducted at Hospital Bichat in Paris, France and the purpose was to determine the health effects of nitrogen dioxide exposure, specifically addressing lung inflammation in asthmatics. Study subjects included five females and 14 males, all of whom were nonsmokers with normal spirometry, suffered from asthma, and were without symptoms of respiratory infection within 6 weeks of the study. The study was a double-blind crossover study and each subject was his or her own control. Control measurements were taken 10-30 days before the study began. Each participant was exposed to three series of three exposures, i.e. clean air, 200 ppb of nitrogen dioxide, and 600 ppb of nitrogen dioxide; during each series only the chamber engineer knew when each exposure was administered. Day 1 involved an exposure for 30 minutes, a sputum measurement taken six hours after exposure, and then another hour observing the subject. Day 2 involved two 30-minute exposures with a one-hour break between exposures, followed by 6 hours before sputum measurement and another hour under observation. Day 3 involved no exposure, one sputum measurement and the one-hour observation period. Each exposure series was separated by 2 weeks to act as a washout and all participants were observed for one hour after sputum measurements were taken. In the measurement chamber, nitrogen dioxide exposure was measured continuously using chemiluminescence to provide a rough estimate of the actual exposure. Spirometry was measured before the study and sputum induction was used to determine the total inflammatory cell count, differential cell count, and eosinophil cationic protein levels. Subjects were also asked for a subjective measurement of how they felt.

LT Leshin described the study results. No changes in spirometry were observed and no subjects reported symptoms during or after exposures. There was a significant increase in the percentage of eosinophils in the sputum at the 600 ppb level on Day 2. No changes in eosinophil level in the sputum were observed at 0 and 200 ppb exposures or on Day 1. There was a significant change in the number of eosinophils on Day 2 at 600 ppb and at 200 and 600 ppb on Day 3. An increasing trend in the absolute number of eosinophils was observed at 200 ppb; Day 2 was non-significant but Day 3 was significantly increased above baseline. No changes in the number of macrophages or neutrophils were observed. There was a significant increase in eosinophil cationic protein levels at 600 ppb.

LT Leshin relayed the study conclusions: (1) Nitrogen dioxide increases eosinophil airway response which is indicative of general airway inflammation. (2) Nitrogen dioxide exposure increased eosinophil cationic protein levels which indicated that eosinophils are not only recruited but activated by nitrogen dioxide exposure. LT Leshin concluded his presentation by noting that, based on the information from this study, the Agency proposed that the no observed adverse effect level (NOAEL) be 200 ppb and the lowest observed adverse effect level (LOAEL) be 600 ppb for nitrogen dioxide.

Board Questions of Clarifications—Science

Dr. Parkin invited Board members to ask questions for clarification. Dr. Parkin asked if the Agency reached out to authors to address the issue that no raw data was available. LT Leshin responded that the EPA did reach out but the author could not share the raw data.

Hearing no additional questions of clarification, Dr. Parkin asked Ms. Sherman to present EPA's ethics review.

EPA Ethics Assessment

Ms. Sherman informed the Board members that under EPA guidelines, the Ezratty et al. (2014) report is considered an intentional exposure toxicity study and, therefore, is required to undergo review by the HSRB.

Ms. Sherman explained her methodology for performing her ethics review. She obtained the information for EPA's ethics review from Dr. Veronique Ezratty including copies of the ethics approval letter, consent forms, and study protocol in French. Ms. Sherman was able to complete a rough translation through collaboration with colleagues and Google Translate and those documents were provided for the HSRB members for review.

Ms. Sherman outlined the ethical considerations for the study. Five females and 14 males ages 20-29 years were selected for the study. With regards to informed consent, Ms. Sherman explained that female participants were required to sign a consent form that stated they were using effective birth control and were not pregnant. The consent form clearly explained that there were no benefits to subjects, the study procedures, risks and discomforts associated with participation, and subjects were free to withdraw at any time. The fact sheet clearly explained what nitrogen dioxide is, common sources and exposures, the subjects were free to withdraw at any time, comparable levels of study exposure experienced in daily activities, identified possible side effects including irritation of the nose and throat, nasal congestion, runny nose, breathing difficulties or cough, and perception of unusual smell. The fact sheet clearly specified that the sputum tests may cause coughing and subject identity was protected.

Risk of study was minimized based on a list of inclusion and exclusion factors and the selection of the dose level with the objective to minimize adverse health effects. There was close monitoring of subjects during and after the study was completed and medical oversight and assistance from nursing staff.

With regards to respect for subjects, subjects were paid 2,000 euros for participation which was increased from the initial amount of 1,500 euros. This information was found in protocol amendment 2008. Ms. Sherman deemed this amount reasonable based on the 12 visits and level of participation. The study protocol was reviewed and approved by the Bichat Hospital Ethics Committee who applied the Declaration of Helsinki standards and the French law pertaining to subjects who are unable to provide consent for themselves.

Ms. Sherman described the ethical standards applied for the conduct of the study, which EPA must consider when determining reliance on a completed study that was conducted prior to implementation of the 2006 Human Studies Rule. EPA regulations governing the Agency's reliance on research contain two standards. Standard 40 CFR Section 26.1703 prohibits EPA reliance on data involving intentional exposure of pregnant or nursing women or of children, and Section 26.1704 prohibits EPA reliance on data if there is clear and convincing evidence that the conduct of the research was fundamentally unethical or was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

Ms. Sherman stated that the conclusion of her review was that the requirements of CFR Section 26.1703 were met by the study because the subjects were over age 18 and the females were confirmed to not be pregnant or nursing. Regarding CFR Section 26.1704, there was no clear and convincing evidence that the conduct of the research was fundamentally unethical, and there was no clear and convincing evidence that the conduct of the research was deficient relative to prevailing ethical standards. There was no evidence of any intent to harm the subjects or that informed consent was lacking. The study underwent an independent ethics review and approval, pregnant women were excluded, and subjects were monitored before and after the procedures in accordance with the ethical standards at the time. Ms. Sherman presented EPA's conclusion that if the study is deemed scientifically valid and relevant, there are no barriers to EPA's reliance on the study.

Board Question of Clarification— Ethics

Dr. Parkin called for questions of clarification regarding EPA's ethics assessment. Dr. Heitman explained that the compensation for subjects was originally 2,000 euros and the ethics reviewers approved to reduce the amount to 1,500 euros. Dr. Dawson noted that the payment was increased from 1,200 to 1,500 euros as noted on page 38 of the background materials and suggested that the compensation was ethical given any of the amounts discussed above.

Dr. Parkin asked for additional questions for clarification, and hearing none, asked Dr. Schonfeld for public comments.

Public Comments

Dr. Schonfeld announced that there were no public comments entered into the record before the meeting and noted that there is one public comment from the member of the public offered during the meeting. Dr. Schonfeld invited Mr. Will Ollison to comment. Mr. Ollison asked whether the subjects' identification of strange odors could allow them to infer their level of exposure, which would compromise blinding. LT Leshin responded that, in theory, this is true, but no subjects reported smelling a strange odor.

Charge Questions

Before beginning the Board's discussion, Dr. Parkin asked Ms. Sherman to read the charge questions into the record. Ms. Sherman read the following charge questions:

Charge to the Board—Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study adequate for quantitative use in support of an inhalation risk assessment for the use of nitrogen dioxide as a medical equipment sterilant?

Charge to the Board—Ethics:

- Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?

Board Science Assessment

Dr. Parkin informed the group that she did not have any comments from Dr. Madallena to share. Dr. Parkin asked the Board for any questions or comments on the science of the study.

Dr. Popendorf commented that the Ezratty et al. (2014) paper is one of the cleanest he has assessed in some time. Dr. Parkin agreed.

Board Statistical Assessment

Dr. Parkin asked Dr. Fernandez to give his presentation describing the Board's statistical review of the Ezratty et al. (2014) paper.

Dr. Fernandez explained that based on the study design, the statistical approach utilized should be a mixed model procedure in order to accurately analyze the data. Dr. Fernandez noted that the researchers used a generalized linear model (specifically, the GLM procedure in SAS version 9.4), which is not an appropriate model for analyzing repeated measures. Dr. Fernandez explained that, as a result, the treatment mean standard errors, confidence intervals, and p-values may be incorrect. He warned that the study results and conclusions may not be reliable and urged EPA to obtain the raw data and re-run the appropriate statistical analysis.

Dr. Gbur agreed that GLM is not an appropriate statistical approach and using it could have serious implications, echoing Dr. Fernandez's sentiment. He pointed out that someone other than the statistician may have written the statistical analysis section and urged EPA to contact the statistician named on the paper to confirm which method was used. Dr. Zhu commented that the two statistical methods are often confused for one another and agreed it would be worth checking with the statistician. Ms. Sherman remarked that the issue may stem from an incorrect translation of the text. Ms. Sherman confirmed that EPA will attempt to contact the authors and asked Dr. Fernandez and Dr. Gbur to email her the specific questions that EPA should pose to the study authors. Dr. Parkin asked that Dr. Fernandez and Dr. Gbur copy her and Dr. Schonfeld on their emails to Ms. Sherman.

LT Leshin inquired whether changes in measures of confidence resulting from the use of a different model would impact the overall study results and conclusion, given that the responses among the 600 ppb group were drastically different than that of the control group. Dr. Gbur responded that the GLM model cannot manage the correlation structure between the repeated measures and that this is an issue. LT Leshin asked for clarification on whether the issue is that GLM does or does not correlate the measures. Dr. Gbur explained that the default assumption in GLM is that, no matter how far apart in time two measures are taken, they are correlated the same. He added that if the model does not account for the correlation structure among repeated measures, the impacts on confidence measures can be substantial.

Dr. Dawson commented that the paper was published in a well-respected journal and that it is surprising that their statistical reviewer(s) did not identify this issue, as well.

There were no additional questions or comments.

Board Ethics Assessment

Dr. Parkin asked Dr. Heitman to give her presentation describing the Board's ethics review of the Ezratty et al. (2014) paper.

Dr. Heitman stated that she agreed with Ms. Sherman's ethics assessment and, based on the information available, the Ezratty et al. (2014) publication does meet the requirements of 40 CFR part 26 subpart Q. She continued on by noting that the study was approved by the ethics committees of two hospitals, all participants signed thorough informed consent forms, and met all applicable French ethics requirements. Dr. Heitman also pointed out that in an original document, the study was entitled, "Repeated Exposure to Weak Doses of Nitrogen Dioxide," which underscores the minimal risk posed by study participation. Dr. Heitman also mentioned that she was unable to determine the amount that participants were compensated.

Dr. Parkin asked for any questions or comments and there were none.

Response to Charge Questions

Is this study scientifically sound, providing reliable data?

Dr. Halanych proposed the following response to the above charge question: "The scientific methods are adequate from a scientific standpoint, but the statistical methods need further review."

Dr. Dawson voiced her opinion that the science is sound until the statistical methods have been verified. Dr. Dawson recommended the following response: "The scientific methods are sound pending verification that the statistical methods are sound." Several members agreed and Dr. Parkin asked Dr. Dawson to repeat her proposal. Dr. Dawson proposed the response read: "The results in this study are scientifically sound pending verification of the statistical methods."

Dr. Popendorf asked whether the Board will have the opportunity to review the paper after the statistical methods are determined or whether the Agency will be reconsidering the soundness of the science. Dr. Fernandez again voiced his concern that the results and conclusions may be erroneous if the reported methods were, in fact, the statistical methods used. Dr. Halanych proposed the following response to draw attention to the importance of the specific statistical methods: "If the statistical analysis cited was the methodology used, we find that parts of the results may not be scientifically sound. If, in fact, this was a translation error and they used the appropriate statistical method, then we find the study to be scientifically sound and approved."

LT Leshin asked whether the modifications to the model listed in the methods section impacts the current discussion. Dr. Fernandez replied that there is still a potential issue with the correlation structure of the statistical model.

Dr. Parkin asked Dr. Halanych to repeat her proposed response to charge question one into the record. Dr. Halanych proposed the following response: "If the statistical analysis cited was, in fact, the methodology used, we find that parts of the results may not be scientifically sound. If they, in fact, used a model and analysis procedure that corresponds to the statistical description of a double-blind crossover design, we find the study to be scientifically sound."

Dr. Parkin asked for any responses or modifications and there were none. The Board passed the response to the first charge question with unanimous approval.

If so, is this study adequate for qualitative use in support of an acute dietary risk assessment for fluoride?

Dr. Parkin noted that it is difficult to answer this charge question without knowing the answer to the first charge question. LT Leshin suggested that the study be considered in support of a weight-of-evidence analysis. Dr. Parkin proposed dropping the "if so" phrase to simplify the Board's response to the new charge question: "Is this study adequate for use in support of a weight-of-evidence analysis?" There were no objections and the above was approved as the new charge question.

LT Leshin proposed the following response to the modified charge question: "This study is adequate for use in support of a weight-of-evidence analysis pending resolution of the statistical issue noted above."

Dr. Parkin asked for any responses or modifications and there were none. The Board passed the response to the second charge question with unanimous approval.

Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?

Dr. Heitman proposed the following response to the above charge question: "The published report by Ezratty et al. (2014) meets the requirements of 40 CFR part 26 subpart Q."

Dr. Parkin asked for any other responses or modifications and there were none. The Board passed the response to the third charge question with unanimous approval.

Dr. Parkin concluded Session 2 and dismissed the participants for lunch at 11:45 AM EST. Dr. Parkin asked the Board members to reassemble at 12:55 PM to troubleshoot technical issues before the start of Session 3 at 1 PM.

Session 3: A published report: Spak, C.J. et al. (1989) Tissue Response of Gastric Mucosa after Ingestion of Fluoride. Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden. *British Medical Journal*. 298:1686-7. (MRID 49489101)

Background

Dr. Parkin called Session 3 to order and introduced the topic before inviting Dr. D'Agostino (OPP, EPA) to give his presentation describing EPA's science review of the Spak et al. (1989) paper.

EPA Science Assessment

Dr. D'Agostino explained that the study was conducted at Huddinge University Hospital in Sweden, and the purpose was to determine the response of the gastric mucosa to a single dose of fluoride. Study subjects included eight females and four males ranging in age from 22-45 years of age. All subjects were considered healthy volunteers and fasted overnight prior to the endoscopies. Subjects were exposed to 1000 mg F/L of sodium fluoride solution which dissociates into fluoride ions inside of the body allowing toxic responses to fluoride to be measured. Endoscopies were performed and videotaped before and after exposure and again two hours after dosing which is consistent with the pharmacokinetics of fluoride; i.e., its rapid absorption and when we would expect to see an acute response in the gastric mucosa. The control endoscopy was performed two weeks before exposure and subjects served as their own controls.

The body and antrum of the stomach were evaluated macro- and microscopically. The macroscopic evaluations were done live and later another gastroenterologist graded the findings on the videotapes. Macroscopic grading was done using a modified Lanza scale (0-4) based on petechiae and gastric mucosal erosions. Microscopic evaluations relied on two biopsy specimens taken from each area, the body and antrum of the stomach. These four samples were graded on a 0-3 scale based on damage to the surface epithelium, gastric pits and inflammatory responses. Wilson's signed rank test was used to compare the gastroenterologists' findings.

Dr. D'Agostino described the study results. He noted that there was no difference between the live and recorded endoscopy measurements. Fluoride exposure increased macroscopic lesions in the stomach. Only one person had a lesion (grade 1) in the control condition, while all twelve subjects had lesions (grade 4) after exposure. Antrum macroscopic lesions were less extensive than the stomach. Lesions ranged from one to four and were observed in six subjects. Microscopic lesions were similar to macroscopic lesions in the stomach. Antrum microscopic lesions ranged from one to two and were observed in 10 of the 12 subjects, similar to the stomach lesions. Four subjects reported nausea as a side effect.

Dr. D'Agostino relayed the study conclusions. (1) One ingestion of fluoride at 1000 mg F/L resulted in adverse effects on the gastric mucosa. (2) The lowest observed adverse effect level (LOAEL) of the study was identified as 1000 mg F/L, the only dose tested.

Board Questions of Clarification—Science

Dr. Parkin asked for questions of clarification. Dr. Halanych noted that 1,000 mg F/L was the concentration and subjects were actually exposed to 20 mg F/L. Dr. D'Agostino confirmed that 20 mg of fluoride was in a 1,000 mg of solution and exposure to 20 mg F/L was correct.

Dr. Chadwick asked how the LOAEL can be determined if only one dose was tested. Dr. D'Agostino clarified that the EPA set the LOAEL based on the results of the study and EPA review.

Hearing no additional questions of clarification, Dr. Parkin asked Ms. Sherman to present EPA's ethics review.

EPA Ethics Assessment

Ms. Sherman informed the Board members that the Spak study is considered a toxicity study and was conducted in the 1980s, preceding the EPA human studies rule implemented in 2006. Standard 40 CFR Section 26.1607 requires HSRB review for pre-rule intentional exposure toxicity studies upon which EPA intends to rely. She mentioned that there was very little information regarding the ethics of the study despite her efforts. She reviewed records and contacted grants providers of the study including: the Swedish Medical Council, the National Institute of Dental Research, and the United States Public Health Services. Her ethics review was based on the information provided in the published paper.

Ms. Sherman outlined the ethical considerations for the study. Regarding subject selection, 12 subjects, eight females and four males ages 22-45 years, were selected for the study. There was no information that suggested that the female subjects were pregnant or nursing. No information was available regarding how subjects were recruited but all subjects were referred to as volunteers in the study article. Risks were minimized by using a dose level considered safe at the time. This was based on previous studies that used higher doses and the use of a higher dose for children's dental purposes. There was no information regarding the explanation to subjects of the risk associated with exposure or procedures.

There was no subject compensation information available with regard to respect for subjects. Ms. Sherman noted that subjects' privacy was protected, as indicated through the absence of subject identity in the study article. There was no information indicating if the study procedures went under an ethics review.

Ms. Sherman described the ethical standards applied for the conduct of the study, which EPA must consider when determining reliance on a completed study that was conducted prior to implementation of the 2006 Human Studies Rule. EPA regulations governing the Agency's reliance on research contain two standards. Standard 40 CFR Section 26.1703 prohibits EPA reliance on data involving intentional exposure of pregnant or nursing women or of children, and Section 26.1704 prohibits EPA reliance on data if there is clear and convincing evidence that the conduct of the research was fundamentally unethical or was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

Ms. Sherman stated the conclusion of her review that the requirements of CFR Section 26.1703 were met by the study because the subjects were over age 18 and there was no indication that female subjects were pregnant or nursing. Regarding CFR Section 26.1704, there was no clear and convincing evidence that the conduct of the research was fundamentally unethical, and there was no clear and convincing evidence that the conduct of the research was deficient relative to prevailing ethical standards. There was no evidence of any intent to harm the subjects. There was no evidence that the conduct of the study was deficient in a way that impaired subjects' informed consent or placed them at an increased risk. Ms. Sherman presented EPA's conclusion that, if the study is deemed scientifically valid and relevant, there are no barriers to EPA's relying on the study.

Board Questions of Clarification—Ethics

Dr. Parkin asked for questions of clarification. Dr. Rivera asked for clarification on the standard of no evidence of unethical conduct rather than evidence of ethical study conduct. Ms. Sherman responded that the studies that predate the 2006 EPA rule are held to the standard of

clear and convincing evidence that the study was unethical and noted that this standard is lower than the standard applied to more recent studies. Dr. Dawson explained the alternative to accepting the data provided in this study is to conduct a new study that would expose more people and impose additional costs. She suggested that if the alternative is considered then it would be more ethical to accept the study rather than conduct a new one.

Dr. Gbur asked if there are similar studies conducted on this particular topic that are more recent and Dr. D'Agostino responded that the EPA does not have other studies to rely on regarding this topic.

Dr. Chadwick noted that Sweden subscribes to the Declaration of Helsinki standards and would presume that the study would have been done in compliance with the second revision of those standards. He added that the Karolinska Institute is one of the leading research programs and opinioned that the study was conducted using ethical procedures.

Public Comments

Dr. Schonfeld called for public comments, and none were offered

Charge Questions

Before beginning the Board's discussion, Dr. Parkin asked Ms. Sherman to read the charge questions into the record. Ms. Sherman read the following charge questions:

Charge to the Board—Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study adequate for quantitative use in support of an acute dietary risk assessment for fluoride?

Charge to the Board—Ethics:

- Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?

Board Science Assessment

Dr. Parkin asked Dr. Ramos to give his presentation describing the Board's scientific review of the Spak et al. (1989) paper.

Dr. Ramos remarked that the study was straightforward and well laid out with a limited scope. The experimental design was reasonable and well-conceived. Two endoscopies were performed, the first was completed to establish subject baseline and the second was completed two weeks later one hour after exposure to a 53 mMol dose of sodium fluoride. The pathological macroscopic and microscopic evaluations and biopsies were consistent with conventional clinical procedures and scales for mucosa evaluation used were clearly defined in the manuscript.

Dr. Ramos did not observe major issues with the study procedures but noted the limited scope. Only a single dose in a single point of time was examined. He expressed his concern that the decision for examination two hours after exposure was not justified and there was no specification as to if the second pathological examination was blinded. The scale utilized for macroscopic and microscopic evaluations could have been expanded; however, based on the date

the study was conducted, this scale was conventional at the time. The study referenced and attempted to establish correlates with aspirin and other well-known gastric irritants in the commentary reference but did not utilize a toxic control and never addressed the issue that these tissues could adapt, as is the case for aspirin. Despite those concerns, Dr. Ramos did not identify any major scientific problems with the study and the design of this study justifies the conclusions that were put forward.

Dr. Parkin expressed appreciation to Dr. Ramos for his scientific review of the study and asked for questions from the Board.

Dr. Popendorf brought the Board's attention to the third paragraph in the comment section that will be relevant to the next study for HSRB review. There were no additional comments on the science assessment of the study.

Board Statistical Assessment

Dr. Parkin asked Dr. Gbur to give his presentation describing the Board's statistical review of the Spak et al. (1989) paper.

Dr. Gbur provided his science review. He remarked that the Wilcoxon ranked test was used for all analyses in the study. The Wilcoxon ranked test does not depend on a normal distribution but relies on the underlying assumptions that the difference between the control and data are continuous measurements and are symmetric around the center of the distribution, which was zero for this study. He noted that these assumptions are consistent with the study.

Dr. Gbur expressed concern that the scales of the microscopic evaluation were an ordered categorical scale, indicating that the difference between zero and one is not the same as the difference between two and three. This would prevent the ability to treat each ranking in the scale as a number. This caused question for the appropriateness of the Wilcoxon ranked test and calls into question the validity of the microscopic results. The macroscopic scale included counts and can be treated as numbers. Dr. Gbur raised his concern regarding quoting p-values from the study. Despite these concerns, he suggested that this is a scenario where a formal statistical analysis is not needed to draw conclusions from the data. An effect can be observed when one examines the macroscopic and microscopic data for the stomach and the microscopic data for the antrum.

Dr. Gbur's main concern related to the macroscopic evaluation of the antrum. In five of the twelve subjects no antrum lesions were observed in either the control or after exposure and one subject showed a decrease in symptoms after exposure. Dr. Gbur continued that significant affect was less clear with macroscopic antrum lesions to the extent of the other three measurements. Aside from those issues, Dr. Gbur stated that the study data supported the conclusions and analysis was statistically sound.

Dr. Parkin thanked Dr. Gbur for his analysis as asked the Board if they had any questions or comments. Seeing none on the science assessment, Dr. Parkin then turned to the ethics review.

Board Ethics Assessment

Dr. Parkin asked Dr. Halanych to give her presentation describing the Board's ethics review of the Spak et al. (1989) paper.

Dr. Halanych reiterated that very little information was available regarding the ethical conduct of the study. She noted the potential societal value of the study as the amount of fluoride exposure in this study was less than the amount children swallowed during fluoride treatments at the dentist at the time, and therefore posed little risk to the participants. Dr. Heitman reviewed that there was no information available regarding subject pregnancy or nursing status and the subject recruitment methods. There was no ethical review, informed consent, or participant compensation information available. Dr. Heitman thanked Ms. Sherman for the information that Sweden had ethic review committees in 1978 and when the study was conducted in 1989, there should have been an ethical review documented.

EPA standard 40 CFR 26.1703 was met by the study because the subjects were over age 18. However, Ms. Sherman could not state that the study did not intentionally expose pregnant or nursing women. Regarding CFR Section 26.1704, there was no convincing evidence that the conduct of the research posed significant known risk because the fluoride doses were not considered high at the time of the study but the conduct was deficient relative to the ethical standards prevailing at the time in Sweden, specifically lacking the ethics review and informed consent. The informed consent should have explained that there were no benefits and the risks, specifically the exposure ulcerations and the endoscopy procedure. However, there was no convincing evidence that the study was conducted in a way that placed participants at increased harm or impaired their informed consent. Considering the alternative of exposing additional participants to high doses of fluoride in a new study and despite the omission of information in the article, Dr. Halanych recommended that the EPA can rely on this data.

Dr. Parkin asked for other comments on ethics, and seeing none, transitioned to addressing the charge questions.

Response to Charge Questions

Is this study scientifically sound, providing reliable data?

Dr. Ramos proposed the following response to the above charge question: "The data is scientifically sound providing reliable data."

Dr. Parkin asked for any responses or modifications and there were none The Board passed the response to the first charge question with unanimous approval.

If so, is this study adequate for point of departure use in support of an acute dietary risk assessment for fluoride?

Prior to Dr. Gbur's proposed response the Board deliberated several issues, including the use and definition of the term quantitative, concerns regarding weight-of-evidence, analyses of the data, and the validity of the p-values in the study. Dr. Elizabeth Mendez with the EPA's Office of Pesticide Program explained that the study provided some of the most scientifically sound and reliable information regarding the establishment of EPA's point of departure for the acute dietary risk assessment for fluoride. She proposed that the charge question be rephrased to replace "quantitative" with "point of departure."

Dr. Parkin proposed the following response to the revised charge question: "The study is adequate for point of departure use in support of an acute dietary risk assessment for fluoride."

All members approved the revised question and response to the second charge question.

Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?

Prior to the proposed response to the third charge question, members of the Board discussed several issues, including removing "convincing" from the response, the implementation of Sweden standards that would have required an ethical review when the study was published, and the level of commonality regarding including study ethics reviews with the published article. Dr. Schonfeld reminded the Board that the standard states that the EPA may not rely on research initiated before April 7, 2006 if there is clear and convincing evidence that the conduct of research was fundamentally unethical. The standard did not call for evidence that the study was fundamentally ethical.

Dr. Halanych proposed the following response to the third charge question: "Considering the time the study was conducted and based on the information provided that no children or obviously pregnant or nursing women were included, we did not find convincing evidence that the study was conducted in a way that placed the participants at an increased harm or impaired their informed consent, this study meets the ethical standards of 40 CFR part 26 subpart Q."

All Board members approved the revised response to the third charge question.

Session 4: A published report: Hansson, T. and Roos, B. (1987). The Effect of Fluoride and Calcium on Spinal Bone Mineral Content: A Controlled, Prospective (3 years) study. Sahlgren's Hospital, University of Gothenberg, Sweden. *Calcified Tissue International*. 40:315-317. (MRID 49489102)

Background

Dr. Parkin called Session 4 to order and introduced the topic before inviting Dr. D'Agostino (OPP, EPA) to give his presentation describing EPA's science review of the Hansson and Roos (1987) paper.

EPA Science Assessment

Dr. D'Agostino explained that the purpose of the study was to determine if lower doses of fluoride than those used in previous studies can increase bone mineral content (BMC) without unwanted side effects. Study subjects included 100 postmenopausal women (average age 66) with one to three vertebral compression fractures within the thoracic or lumbar spine (women were excluded if they had a fracture in the third lumbar vertebra (L3)). There were four treatment groups of 25 women: the first received 30mg sodium fluoride and 1g calcium per day (Group A), the second received 10mg sodium fluoride and 1g calcium per day (B), the third received 1g calcium per day (C), and the fourth received 1 starch capsule (placebo) per day (D). The sodium fluoride capsule was given in the morning and the capsule containing calcium was given in the evening. Daily treatment continued for three years. BMC of the L3 was measured by dual photon absorptiometry at the study outset and after 1, 1.5, 2, and 3 years. Dr. D'Agostino noted the

limited information reported regarding the timing, frequency, and severity of participants' adverse reactions; the methods for collecting adverse reaction data were not described. Although the publication lacked details of the BMC statistical analyses, the authors reported p-values. The Health Effects Division (HED) performed the Fisher's Exact-test to analyze adverse effects.

Dr. D'Agostino described the study results of the effect of sodium fluoride on BMC, but pointed out that beneficial effects are not considered by EPA when setting no observed adverse effect levels (NOAELs) or lowest observed adverse effect levels (LOAELS). BMC was statistically increased at Years 2 and 3 of the study. The HED analysis revealed adverse gastrointestinal effects at 30mg sodium fluoride and 1g calcium, but not in the 10mg sodium fluoride and 1g calcium, 1g calcium alone, or the placebo groups. Nausea and gastritis were reported by 4 women in Group A, while a fifth woman experienced peptic ulcers at Month 10 of the study and dropped out.

Dr. D'Agostino highlighted several issues with the study, namely that there was no information on timing and severity of adverse reactions, that the study population was not representative of the national population, and that there was no information provided regarding participants' adherence to the study protocol. Additionally, he indicated that there may be potential confounders which were not accounted for. He noted that despite these concerns, the study can support the acute risk assessment qualitatively (i.e., assessing whether gastric irritation may follow fluoride exposure, but not for determining NOAELs or LOAELs).

Board Questions of Clarification—Science

Dr. Parkin asked for any questions of clarification from the Board.

Dr. Popendorf inquired where the data from Groups B, C, and D came from and whether further information was provided regarding the difference between "mild gastrointestinal symptoms" and "mildly adverse effects." Dr. D'Agostino responded that no other information was provided regarding the difference between the two previous terms. He followed by explaining that the numerators for Groups B, C, and D were inferred from the statement in the study summary that no serious side effects were registered in these groups.

Dr. Gbur asked if HED got the information from the results section. Dr. D'Agostino replied that HED performed the adverse effect analysis and the numerators were inferred from the paper's summary.

Dr. Fernandez questioned whether a significant increase in adverse effects are also biologically significant. Dr. D'Agostino explained that EPA is collecting data to determine whether fluoride can cause gastrointestinal distress, which is generally reported as nausea and/or gastritis. He said, for this reason, EPA believes these are biologically significant responses.

There were no additional questions of clarification. Dr. Parkin asked Ms. Sherman to present EPA's Ethics review.

EPA Ethics Assessment

Ms. Sherman explained that this study was conducted prior to the promulgation of the 2006 Human Studies Rule, but that 40 CFR §26.1607 requires HSRB to review pre-rule intentional exposure toxicity studies upon which EPA intends to rely.

Ms. Sherman detailed her attempts to obtain additional information regarding the study's ethical conduct and/or review from the hospital at which the study was conducted, the Swedish Medical Research Council, and the regional ethical review board, but did not receive any replies.

From the information available in the publication, Ms. Sherman determined that the study subjects were adults who were not pregnant or nursing. No information was available regarding how the study subjects were recruited, whether risks were explained to the study subjects and what actions were taken to minimize risks, whether participants were informed of their ability to withdraw at any time, whether subjects provided informed consent, whether subjects were compensated, or whether the study protocol underwent an independent ethics review. Alternatively, Ms. Sherman noted that the administered dose was considered safe at the time and participants were not identified in the publication. Based on the ethical standards outlined in 40 CFR §26.1703 and 40 CFR §26.1704 that prohibit EPA's reliance on data from studies that involve the intentional exposure of children and/or pregnant or nursing women or contain clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards of the time, Ms. Sherman established that EPA is permitted to rely on the data in Hansson and Roos (1987).

Board Questions of Clarification—Ethics

Dr. Parkin asked for any questions of clarification from the Board. The Board posed no questions or comments to Ms. Sherman regarding EPA's Ethics Review.

Public Comments

Dr. Parkin called for public comments and none were offered.

Charge Questions

Ms. Sherman read the following charge questions for the record:

Charge to the Board—Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study adequate for qualitative use in support of an acute dietary risk assessment for fluoride?

Charge to the Board—Ethics:

- Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?

Board Science Assessment

Dr. Parkin asked Dr. Popendorf to give his presentation describing the Board's science review of the Hansson and Roos (1987) paper.

Dr. Popendorf explained that the study presented simple, scientifically sound data, but lacked information that led to uncertainties that may render it inadequate for use in a qualitative risk assessment for fluoride. Dr. Popendorf noted his agreement with EPA's science review and noted four uncertainties in addition to those named by the Agency. He first pointed out the lack of information regarding recruitment and compliance tracking, which could influence the observation of adverse effects among study subjects. Dr. Popendorf also noted that there was no information on investigator or subject blinding. Dr. Popendorf remarked that Figure 1 contained no data points, so the variance in BMC over time could not be determined. The final uncertainty Dr. Popendorf raised was the ambiguous information on adverse effects at sodium fluoride doses less than 30mg.

Dr. Parkin asked the Board for any questions or comments on Dr. Popendorf's presentation. Dr. Rivera commented that it appears the study was not blinded, as the control group received one placebo capsule daily, while other groups received one capsule twice daily.

Board Statistical Assessment

Dr. Parkin asked Dr. Zhu to give her presentation describing the Board's statistical review of the Hansson and Roos (1987) paper.

Dr. Zhu noted that the publication included very few details regarding the investigator's statistical approach, echoing the previous speakers' concerns about remaining uncertainties. Dr. Zhu explained that although the study appears to utilize repeated measures, the statistical analysis was not reflective of this design. Dr. Zhu also commented that it appears a number of participants dropped out of the study, but the authors did not include such details in the paper.

Dr. Parkin asked the Board for any questions or comments on Dr. Zhu's presentation. Dr. Gbur asked about the meaning of a note associated with Table 1, but the group could not determine its relevance.

Dr. Parkin inquired whether the denominator used in the adverse reaction calculations should have accounted for participant drop-out. Dr. Zhu replied that she believes the denominators should not include drop-outs. Dr. Gbur voiced his opinion that incomplete data do not belong in the analysis, but noted that he is unsure whether including drop-outs would have an impact on the overall results. Dr. Parkin pointed out that these details may not be important in the context of EPA's intended use for the study. Several Board members voiced their desire for further information on participant drop-out.

Dr. Parkin asked for any additional questions or comments on the statistical approach and there were none.

Board Ethics Assessment

Dr. Parkin asked Dr. Rivera to give her presentation describing the Board's ethics review of the Hansson and Roos (1987) paper.

Dr. Rivera's presentation generally reflected EPA's ethics review. Dr. Rivera noted that children and pregnant or nursing women were not involved in this study. She also acknowledged

that the study authors did not address a number of issues, including whether the study was approved and/or overseen by a board, whether participants were informed of their risk, and whether investigators and study subjects were blinded to their treatment group. Dr. Rivera voiced her concern that although the publication does not provide evidence that the rights of the study subjects were abused, there is no evidence to prove that they were respected.

Dr. Parkin asked the Board for any questions or comments on Dr. Rivera's presentation. Dr. Galbraith asked when calcium supplementation became a widely accepted clinical treatment for osteoporosis. Dr. Galbraith noted that if calcium supplementation was known to be beneficial at the time of the study, the inclusion of the placebo group (Group D) may not have generated new knowledge and may be an ethical concern. Dr. Halanych responded that daily calcium supplementation is not recommended for all women and is only recommended in the instance that diet does not provide the recommended amount.

Dr. Dawson also commented that doses administered in this study were lower than those in previous studies, but conceded that determining potential ethical issues would require researching standards of practice at the time. She noted that the charge to the Board is to consider whether there is evidence of egregious ethical issues and that the prior question, while appreciated, may not be relevant to the current discussion.

There were no additional questions or comments.

Response to Charge Questions

Is this study scientifically sound, providing reliable data?

Dr. Popendorf proposed the following response to the above charge question: "While the lack of numerous details in the article leads to uncertainty noted by both the Agency and the Board, the study appears to be scientifically sound and provide reliable data."

Dr. Parkin asked for any responses or modifications and there were none. The Board approved the response to the first charge question.

If so, is this study adequate for qualitative use in support of an acute dietary risk assessment for fluoride?

Dr. Popendorf requested clarification from EPA regarding the meaning of "qualitative" in the above charge question before offering a proposed response. Dr. D'Agostino explained that EPA intends to use this publication to support other studies that have observed gastrointestinal effects after fluoride exposure, rather than use it quantitatively to establish a point of departure.

Dr. Parkin asked for further questions or comments and there were none.

Dr. Popendorf proposed the following response to the above charge question: "Because the authors report that some mildly adverse effects may have occurred below 30mg sodium fluoride/day and adverse effects may have occurred below that dose that were not reported by study subjects, this study cannot be used to support the establishment of a NOAEL or LOAEL,

but it may be used as part of a weight-of-evidence analysis on the acute dietary risk assessment for fluoride."

Dr. Parkin asked for any responses or modifications and there were none. The Board passed the response to the second charge question with majority approval.

Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?

Dr. Rivera proposed the following response to the above charge question: "The Board was not provided enough information to make a judgment about whether the research was conducted in a manner that was significantly deficient relative to the ethical standards prevailing at the time."

Dr. Dawson agreed that there is not enough information to fully assess the ethics of the study, but urged the Board to consider whether the lack of information was worth prohibiting EPA from using the data. Dr. Rivera questioned how much harm would be done by prohibiting EPA from relying on the data. Dr. Dawson pressed that the issue is whether or not there were serious human subjects violations. Dr. Chadwick noted that EPA has set a low standard for studies published before the regulation was in place and wondered if the charge question could be amended to reflect its value in a weight-of-evidence assessment. Dr. Parkin reminded the Board that their charge is to assess whether the study meets the regulations.

Dr. Rivera suggested using the language, "The Board was not shown evidence to suggest the conduct of the study was fundamentally unethical" as a compromise for the Board's response to the charge question. Ms. Sherman pointed to the fact that, unlike the Spak et al. (1989) study, the Board could affirm that no children or pregnant or nursing women participated in the Hansson and Roos (1987) study and urged a modification to the charge question. Dr. Halanych proposed the following response to the above charge question: "Considering the time the study was conducted and based on the information provided, we found no children or obviously pregnant or nursing women were included and we did not find convincing evidence that the study was conducted in a way that placed participants at increased harm or impaired their informed consent. This study meets the ethical requirements of 40 CFR part 26 subpart Q."

Dr. Parkin asked Dr. Rivera if this language was appropriate. Dr. Rivera noted that it is a good compromise and that if the group approves the language, she will abstain.

Dr. Gbur questioned the relevance of CFR §26.1703 in this context, given that the population is postmenopausal women. Ms. Sherman agreed that children and pregnant or nursing women were not involved and proposed removing "obviously" from the response. Dr. Gbur asked whether the standard must be addressed if it is not applicable. Dr. Parkin responded that the record must show that children and pregnant or nursing women were not involved.

Dr. Parkin asked for any other responses or modifications and there were none.

Dr. Halanych proposed the following response to the above charge question: "Considering the time the study was conducted and based on the information provided, there were no children or pregnant or nursing women were included and we did not find convincing evidence that the study was conducted in a way that placed participants at increased harm or impaired their informed consent. Therefore, this study meets the ethical requirements of 40 CFR

part 26 subpart Q."

The Board passed the above response to the third charge question with majority approval.

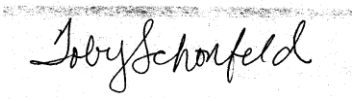
Closing Remarks

Dr. Parkin thanked the Board for the incredible meeting and expressed appreciation to all of the members for their time, effort, preparation and focus. She noted that the draft deadlines will be posted on the SharePoint calendar. She turned the meeting over to Dr. Schonfeld.

Dr. Schonfeld informed the group that Ms. Sherman will give an update on the next in-person meeting. Ms. Sherman noted that April meeting will cover topics including a report from the Agricultural Handlers Task Force and a new protocol for a new series of insect repellants.

Dr. Schonfeld announced she had no further business for the Board and adjourned the meeting at 3:20 p.m.

Respectfully submitted:



Toby Schonfeld
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:

Rebecca T. Parkin, Ph.D., M.P.H.
Chair
Human Studies Review Board
United States Environmental Protection Agency

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by Board members during the course of deliberations within the meeting. Such ideas, suggestions and deliberations do not necessarily reflect definitive consensus advice from the Board members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final report prepared and transmitted to the EPA Science Advisor following the public meeting.

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

Rebecca Parkin, Ph.D., M.P.H.
Professorial Lecturer, Environmental and Occupational Health and
Epidemiology and Biostatistics
Milken Institute School of Public Health
The George Washington University
Washington, DC

Vice Chair

Jewell H. Halanych, M.D., M.Sc.
Assistant Professor
Internal Medicine Residency Program
University of Alabama at Birmingham
Montgomery, AL

Members

Gary L. Chadwick, Pharm.D., M.P.H., C.I.P.
Senior Consultant
HRP Consulting Group, Inc.
Training and Consulting in Human Research Protections
Fairport, NY

Liza Dawson, Ph.D.
Research Ethics Team Leader
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

George C. J. Fernandez, Ph.D.
Statistical Training Specialist
SAS Institute, Statistical Training and Technical Services
Sparks, NV

Kyle L. Galbraith, Ph.D.
Human Subjects Protection
Carle Foundation Hospital
Urbana, IL

Members (continued)

Edward Gbur, Jr., Ph.D.
Professor
Agricultural Statistics Laboratory
University of Arkansas
Fayetteville, AR

Elizabeth Heitman, Ph.D.
Associate Professor of Medical Ethics
Center for Biomedical Bioethics and Society
Vanderbilt University Medical Center
Nashville, TN

John C. Kissel, Ph.D.
Department of Environmental and Occupational Health Sciences
School of Public Health
University of Washington
Seattle, WA

Randy Maddalena, Ph.D.
Physical Research Scientist
Indoor Environment
Lawrence Berkeley National Laboratory
Berkeley, CA

William J. Popendorf, Ph.D., MPH
Professor Emeritus
Department of Biology
Utah State University
Logan, UT

Kenneth Ramos, M.D., Ph.D., Pharm.B.
Associate Vice President
Precision Health Sciences
Professor of Medicine
Arizona Health Sciences Center
Tucson, AZ

Suzanne M. Rivera, Ph.D., M.S.W
Vice President for Research and Technology Management
Case Western Reserve University
Cleveland, OH

Jun Zhu, Ph.D.
Professor of Statistics and of Entomology
Department of Statistics
University of Wisconsin – Madison
Madison, WI

Attachment B

FEDERAL REGISTER NOTICE ANNOUNCING MEETING

[*Federal Register* Volume 79, Number 250 (Wednesday, December 31, 2014)]
[Notices]
[Pages 78860–78863]
From the *Federal Register* Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2014–0882]

==========

ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–ORD–2014–0882; FRL–9920–92– ORD]]

Human Studies Review Board; Notification of a Public Meeting

AGENCY: U.S. Environmental Protection Agency.

ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA) Office of the Science Advisor announces a public meeting of the Human Studies Review Board to advise the Agency on the ethical and scientific reviews of EPA research with human subjects

DATES: This public meeting will be held on January 14, 2015, from approximately 10:00 a.m. to approximately 5:00 p.m. Eastern Time. Comments may be submitted on or before noon (Eastern Time) on Wednesday, January 7, 2015.

ADDRESSES: The meeting will be conducted entirely on the Internet using Adobe Connect. Registration is required to attend this meeting. Please visit the HSRB Web site: *http://www.epa.gov/ hsrb to register*.
Comments: Submit your written comments, identified by Docket ID No. EPA–HQ–ORD–2014–0882, by one of the following methods.
Internet: http://www.regulations.gov: Follow the online instructions for submitting comments.
Email: ord.docket@epa.gov.
Mail: The EPA Docket Center EPA/DC, ORD Docket, Mail code: 28221T, 1200 Pennsylvania Avenue NW., Washington, DC 20460.
Hand Delivery: The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA WJC West, at 1301 Constitution Avenue NW., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding federal holidays. Please call (202) 566–1744 or email the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site http://www.epa.gov/epahome/dockets.htm.

Instructions: The Agency's policy is that all comments received will be included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information or other information the disclosure of which is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or email. The http://www.regulations.gov Web site is an "anonymous access" system, which means the EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an email comment directly to the EPA without going through http://www.regulations.gov, your email address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, the EPA recommends that you include your name and other contact information in the body of your comment and with any electronic storage media you submit. If the EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, the EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to receive further information should contact Jim Downing at telephone number (202) 564–2468; fax: (202) 564–2070; email address: downing.jim@epa.gov; mailing address Environmental Protection Agency, Office of the Science Advisor, Mail code 8105R, 1200 Pennsylvania Avenue NW., Washington, DC 20460. General information concerning the EPA HSRB can be found on the EPA Web site at http://www.epa.gov/hsrb.

SUPPLEMENTARY INFORMATION:

Meeting access: Access to this Internet meeting is open to all at the information provided above.

Procedures for providing public input: Interested members of the public may submit relevant written or oral comments for the HSRB to consider during the advisory process. Additional information concerning submission of relevant written or oral comments is provided in Section I, "Public Meeting" under subsection D. "How May I Participate in this Meeting?" of this notice.

I. Public Meeting

A. Does this action apply to me?

This action is directed to the public in general. This Notice may, however, be of particular interest to persons who conduct or assess human studies, especially studies on substances regulated by the EPA, or to persons who are, or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act or the Federal Insecticide, Fungicide, and Rodenticide Act. This notice might also be of special interest to participants of studies involving human subjects, or representatives of study participants or experts on community engagement. The Agency has not attempted to describe all the specific entities that may have interest in human subjects research. If you have any questions regarding this notice, consult Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.**

[[Page 78862]]

B. How can I access electronic copies of this document and other related information?

In addition to using regulations.gov, you may access this Federal Register document electronically through the EPA Internet under the ''**Federal Register**'' listings at http://www.epa.gov/fedrgstr/.

Docket: All documents in the docket are listed in the http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in http://www.regulations.gov or in hard copy at the ORD Docket, EPA/DC, in the Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA WJC West, at 1301 Constitution Avenue NW., Washington, DC 20460. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding federal holidays. Please call (202) 566–1744 or email the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm). The Agency's position paper(s), charge/questions to the HSRB, and the meeting agenda will be available by the early January 2015. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and other related documents that are electronically, from the regulations.gov Web site and the EPA HSRB Web site at http://www.epa.gov/hsrb/. For questions on document availability, or if you do not have access to the Internet, consult Jim Downing listed under **FOR FURTHER INFORMATION.**

C. What should I consider as I prepare my comments for EPA?

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data that you used to support your views.
4. Provide specific examples to illustrate your concerns and suggest alternatives.
5. To ensure proper receipt by the EPA, be sure to identify the Docket ID number assigned to this action in the subject line on the first page of your response. You may also provide the name, date and **Federal Register** citation.

D. How may I participate in this meeting?

You may participate in this meeting by following the instructions in this section. To ensure proper receipt by the EPA, it is imperative that you identify Docket ID No. EPA–HQ–ORD–2014–0882 in the subject line on the first page of your request.

1. *Oral comments*. Requests to present oral comments will be accepted up to noon Eastern Time on Wednesday, January 7, 2015. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments during the call. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via email) to Jim Downing, under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern Time, Wednesday, January 7, 2015, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB Designated Federal Official to review the meeting agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation and the organization (if any) the individual will represent. Oral comments before the HSRB are generally limited to five minutes per individual or organization. Please note that this

includes all individuals appearing either as part of, or on behalf of, an organization. While it is our intent to hear a full range of oral comments focused on the science and ethics issues under discussion, it is not our intent to permit organizations to expand the time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, further public comments may be possible.

2. *Written comments*. Submit your written comments prior to the meeting. For the Board to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments on or before noon (Eastern Time) on Wednesday, January 7, 2015. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the HSRB members may not have adequate time to consider those comments prior to their discussion during the meeting. You should submit your comments using the instructions in Section I., under subsection C., ''What Should I Consider as I Prepare My Comments for the EPA?'' In addition, the agency also requests that persons submitting comments directly to the docket also provide a copy of their comments to Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.** There is no limit on the length of written comments for consideration by the HSRB.

E. Background

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act 5 U.S.C. App. 2 § 9. The HSRB provides advice, information, and recommendations to the EPA on issues related to scientific and ethical aspects of human subjects research. The major objectives of the HSRB are to provide advice and recommendations on: (1) Research proposals and protocols; (2) reports of completed research with human subjects; and (3) how to strengthen EPA's programs for protection of human subjects of research. The HSRB reports to the EPA Administrator through the Agency's Science Advisor.

1. *Topics for discussion*. At its meeting on Wednesday, January 14, 2015, EPA's Human Studies Review Board will consider scientific and ethical issues surrounding these topics:

a. A published report: Repeated Nitrogen Dioxide Exposures and Eosinophilic Airway Inflammation in Asthmatics: A Randomized Crossover Study

b. A published report: Tissue response of gastric mucosa after ingestion of fluoride

c. A published report: The effect of Fluoride and Calcium on Spinal Bone Mineral Content: A Controlled Prospective (three year) Study

2. Meeting minutes and reports. Minutes of the meeting, summarizing the matters discussed and recommendations, if any, made by the advisory committee regarding such matters, will be released within 90 calendar days of the meeting. Such minutes will be available at http://www.epa.gov/osa/hsrb and http://www.regulations.gov. In addition, information regarding the Board's final meeting report will be found at http://www.epa.gov/osa/hsrb or from the person listed under **FOR FURTHER INFORMATION CONTACT.**

[[Page 78863]]

Dated: December 16, 2014.

Robert Kavlock,

Interim Agency Science Advisor.

[FR Doc. 2014–30408 Filed 12–30–14; 8:45 am]

BILLING CODE: 6560-50-P

Attachment C

US ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
January 14, 2015 PUBLIC MEETING AGENDA

Internet Virtual Meeting
The meeting will be conducted at the following website:
https://epa.connectsolutions.com/hsrb

Wednesday, January 14, 2015

HSRB WEB SITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA–HQ–ORD–2014–0882

9:50 AM **HSRB members login online**

10:00 AM* **Convene Public Meeting –** Jim Downing, Designated Federal Officer, EPA Human Studies Review Board, Office of the Science Advisor
Virtual Meeting operations –Rebecca Parkin, Ph.D., MPH, HSRB Chair
Introduction of Board Members –Rebecca Parkin, Ph.D., MPH, HSRB Chair
Opening Remarks – Toby Schonfeld, Ph.D., Human Subjects Research Review Official, EPA

Session 1: **Review and Approval of the HSRB Final Report of the November 5, 2014 Meeting**

10:15 AM **Public Comments**
10:20 AM **Board Discussion of Draft Final Report**

Session 2: **A published report: Ezratty, Veronique et al. (2014) Repeated Nitrogen Dioxide Exposures and Eosinophilic airway Inflammation in Asthmatics: A Randomized Crossover Study. *Environmental Health Perspectives.* Volume 122, Number 8, August 2014. (MRID 49519201)**

10:40 AM **EPA Science Review Highlights –** LT Jonathan Leshin, Ph.D. (Antimicrobial Division, OPP, EPA)
10:50 AM **Board Questions of Clarification** – Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA staff
11:05 AM **EPA Ethics Review Highlights -** Ms. Kelly Sherman (OPP, EPA)
11:15 AM **Board Questions of Clarification** – Rebecca Parkin, Ph.D., MPH (HSRB Chair), and EPA staff
11:30 AM **Public Comments**
11:35 AM **Board Discussion**

Charge to the Board - Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study adequate for quantitative use in support of an inhalation risk assessment for the use of nitrogen dioxide as a medical equipment sterilant?

Discussants: Randy Maddalena, Ph.D. (George Fernandez, statistics)

Charge to the Board - Ethics:

- Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?

Discussant: Liz Heitman, Ph.D.

12:45 PM Lunch

1:30 PM Reconvene – roll call

Session 3: A published report: Spak, C.J. et al. (1989) Tissue Response of Gastric Mucosa after Ingestion of Fluoride. Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden. *British Medical Journal. 298:1686-7.* (MRID 49489101)

1:35 PM **EPA Science Review Highlights –** Jaime D'Agostino, Ph.D., (Health Effects Division, OPP, EPA)
1:45 PM **Board Questions of Clarification** – Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA staff
2:00 PM **EPA Ethics Review Highlights** - Ms. Kelly Sherman (OPP, EPA)
2:10 PM **Board Questions of Clarification** – Rebecca Parkin, Ph.D., MPH (HSRB Chair), and EPA staff
2:25 PM **Public Comments**
2:35 PM **Board Discussion**

Charge to the Board - Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study adequate for quantitative use in support of an acute dietary risk assessment for fluoride?

Discussants: Ken Ramos, M.D., Ph.D. (Ed Gbur, Ph.D., statistics)

Charge to the Board - Ethics:

- Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?

Discussant: Jewel Halanych, M.D., M. Sc.

Session 4: **A published report: Hansson, T. and Roos, B. (1987). The Effect of Fluoride and Calcium on Spinal Bone Mineral Content: A Controlled, Prospective (3 years) study. Sahlgren's Hospital, University of Gothenberg, Sweden. *Calcified Tissue International.* 40:315-317. (MRID 49489102)**

3:25 PM **EPA Science Review Highlights –** Jaime D'Agostino, Ph.D., (Health Effects Division, OPP, EPA)
3:30 PM **Board Questions of Clarification** – Rebecca Parkin, Ph.D., MPH (HSRB Chair), EPA staff
3:45 PM **EPA Ethics Review Highlights** - Ms. Kelly Sherman (OPP, EPA)
3:55 PM **Board Questions of Clarification** – Rebecca Parkin, Ph.D., MPH (HSRB Chair), and EPA staff
4:10 PM **Public Comments**
4:15 PM **Board Discussion**

Charge to the Board - Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study adequate for qualitative use in support of an acute dietary risk assessment for fluoride?

Discussants: Will Popendorf, Ph. D. (Jun Zhu, Ph.D., statistics)

Charge to the Board - Ethics:

- Does the study meet the applicable requirements of 40 CFR part 26 subpart Q?

Discussant: Suzanne Rivera, Ph.D., M.S.W.

5:00 PM* **Adjourn**