Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
June 11, 2014 Public Meeting
Docket Number: EPA–HQ–ORD–2014–0411
HSRB Website: http://www.epa.gov/osa/hsrb

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

Date and Time: Wednesday, June 11, 2014, 10:30 a.m. – 4:00 p.m.
(See *Federal Register* Notice—Attachment B)

Location: EPA, One Potomac Yard (South Building)
2777 S. Crystal Drive, Arlington, VA 22202

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.
Board Members:	Liza Dawson, Ph.D.
	George C.J. Fernandez, Ph.D.
	Kyle L. Galbraith, Ph.D.
	Edward Gbur, Jr., Ph.D.
	Sidney Green, Jr., Ph.D., Fellow, ATS
	Elizabeth Heitman, Ph.D.
	John C. Kissel, Ph.D.
	Randy Maddalena, Ph.D.
	William J. Popendorf, Ph.D.
	Kenneth Ramos, M.D., Ph.D., Pharm.B.
	Leonard Ritter, Ph.D., ATS
	Linda J. Young, 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, June 11, 2014

Commencement of Public Meeting and Review of Administrative Procedures

Mr. Jim Downing (Designated Federal Officer [DFO], HSRB [or Board], Office of the Science Advisor [OSA], EPA [or Agency]) convened the meeting at 10:40 a.m. and welcomed Board members, EPA colleagues and members of the public. He expressed appreciation on behalf of the Agency for the time and diligent work of the Board members in preparing for meeting deliberations. He also thanked the EPA staff for their efforts in preparing for the meeting.

Mr. Downing noted that in his role as DFO under the Federal Advisory Committee Act (FACA), he serves as liaison between the HSRB and EPA, and is responsible for ensuring that all FACA requirements are met. Also in his role as DFO, he 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 they have completed a standard government financial disclosure report. In consultation with the Deputy Ethics Officer for OSA and the Office of General Counsel (OGC), Mr. Downing reviewed the reports to ensure that all requirements are met.

Mr. Downing informed Board members that several interesting and challenging topics are on the agenda for the meeting. He noted that agenda times are approximate, and the group will strive to have adequate time for Agency presentations, public comments and the Board's thorough deliberations. He noted that six HSRB members would be participating remotely; the partial virtual format might present some technological challenges. All speakers, including Board members and members of the public, should use their microphone and identify themselves before speaking, as the meeting is being recorded and broadcast on the Internet. Copies of all meeting materials will be available at http://www.regulations.gov under docket number EPA–HQ–ORD–2014–0411, and supporting documents are available on the HSRB website at http://www.epa.gov/osa/hsrb. Following the presentations, time has been scheduled for the Board to direct questions of clarification to EPA staff and the sponsors of the studies discussed. This time is to be used for points of clarification rather than Board discussion. There will be a public comment period, and remarks must be limited to 5 minutes. Mr. Downing noted that one anonymous public comment had been received, which read "My wife and I oppose any Rules or Regulations proposed by the HSRB." Given that the HSRB does not propose rules, Mr. Downing concluded that the comment was not germane to the meeting's discussion.

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. Mr. Downing then turned the meeting over to the HSRB Chair, Dr. Rebecca Parkin.

Introduction and Identification of Board Members

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

Opening Remarks

Mr. Jack Housenger (Director, Office of Pesticide Programs [OPP], Office of Chemical Safety and Pollution Prevention [OCSPP], EPA) introduced the Agency's new Human Subjects Research Review Official (HSRRO), Dr. Toby Schonfeld (OSA, EPA). He invited Dr. Schonfeld to provide opening remarks.

Dr. Schonfeld stated that she was delighted to be at the meeting. She described her background in philosophy and bioethics, and added that she has served as Vice Chair for an Institutional Review Board (IRB)—an experience that helped to wed her interest in science and medicine with her experience in bioethics. As the HSRRO, Dr. Schonfeld has both narrow and broad roles. Her narrow responsibility is to review research by EPA scientists or EPA-funded scientists. Through its additional HSRB review beyond the traditional IRB process, EPA is very thorough in evaluating human subjects research. Dr. Schonfeld noted that she is fortunate to participate in the process. In a broader role, Dr. Schonfeld directs the Agency's human subjects ethics program, of which HSRB is a part. She is interested in providing education and training for Agency scientists performing research and those doing the peer review. Dr. Schonfeld emphasized that all staff need to know about human subjects research. It is not always easy to figure out what constitutes research, and what is a human subject. Dr. Schonfeld commented that she was looking forward to implementing training programs at EPA Headquarters, as well as in program and regional offices, and perhaps extending the training to the public.

Dr. Schonfeld was impressed with the caliber of the HSRB members and their diverse perspectives. She expressed excitement for the new avenues through which the Agency and the HSRB can work together beyond the reviews. By engaging in collaboration opportunities in the future, Dr. Schonfeld stated that she is looking forward to partnering with each of the Board members.

Dr. Parkin thanked Dr. Schonfeld for her comments and expressed delight at her appointment and contributions of expertise. Dr. Parkin then invited Mr. Housenger to provide welcoming remarks.

Welcoming Remarks

Mr. Housenger welcomed Dr. Schonfeld to her first HSRB meeting. Mr. Housenger noted that he was part of the first HSRB meeting in 2006; he is familiar with all of the work that occurs in preparation for the meetings. In 2006, EPA was working on completing 10,000 tolerances for pesticide residues on food to determine safety. Mr. Housenger explained that the additional challenge of HSRB review for the effort did not prevent completion of the task. At first, it was difficult to determine what research needed to be reviewed by the HSRB. However, over the years, review has resulted in higher quality data sets, a better understanding of the science behind the exposure data, improved intentional dosing studies and better EPA decisions. Mr. Housenger asserted that the Board's important work has improved many Agency decisions.

Mr. Housenger expressed his appreciation to the OSA staff, who ensure that the meeting is well planned and proceeds smoothly. He also thanked Lt. (Dr.) Jonathan Leshin (OPP, EPA) and Ms. Kelly Sherman (OPP, EPA) for their presentations during the meeting. He also acknowledged the Board members for their time in reviewing the background materials, attending the meeting and completing their deliberations and report.

Mr. Housenger introduced the three studies from the public literature that EPA intends to use in human health risk assessments. The use of these data from the public literature demonstrates EPA's commitment to integrate all types of data from all sources to make decisions based on the best available data.

Session 1: A published report by Paul *et al.* (1988) of an intentional exposure human study measuring the effects of small increases of dietary iodine on thyroid function

Background

Dr. Parkin introduced Session 1, in which the Board reviewed a 1988 intentional exposure study publication.

Ms. Sherman explained why the Board was asked to review the three studies selected by EPA. Unlike the typical research proposed by third parties that the Board reviews, the three studies in the public literature were identified by EPA scientists as a robust basis for the Agency's upcoming regulatory decisions on iodine products. In the near future, the iodine products to be evaluated include disinfectants for hard surfaces in food-handling establishments and livestock venues, as well as pending applications for new products, such as fibers in textiles and carpets that contain cuprous iodide. In that context, EPA scientists searched for relevant studies to use for a human health risk assessment (HHRA). A 2000 National Academy of Sciences (NAS) report addressed the nutritional aspects of iodine to set recommended daily allowances and tolerable upper limits. Although the NAS numbers might appear to be obvious choices for an EPA HHRA, the particular requirements of the Agency's human studies regulations would have entailed reviewing, through the HSRB, all of the nearly 100 human studies referenced in the NAS report. Because of these regulatory requirements, the Agency was compelled to select key studies that seemed best for the risk assessment. Dr. Leshin selected the key studies, which include two from 1988 and one from 1995, for use in future risk assessments. The HSRB review is atypical because there is a lack of information and no raw data to analyze. EPA contacted one investigator for each study to ask about the ethics. Ms. Sherman turned over the discussion to Dr. Leshin for EPA's science review.

EPA Science Assessment

Dr. Leshin presented EPA's science review regarding the 1988 Paul *et al.* study. He explained that EPA's quantitative risk assessment pertains to the risks of iodine exposure via the oral route and requires the establishment of a point of departure for iodine exposure. Many studies address the safety of human iodine exposure via the oral route. EPA's proposal is to use the three studies—Paul *et al.* (1988), Gardner *et al.* (1988) and LeMar *et al.* (1995)—in a weight-of-evidence approach to quantitatively determine the toxicity and no observed adverse effect level (NOAEL) for iodine exposure. The studies do not include raw data and are a subset of those used in the NAS report.

The NAS report examined approximately 100 papers to produce its recommendations on iodine, including a recommended daily amount and a tolerable upper intake level for adult men and women. The NAS used Paul *et al.* and Gardner *et al.* as the standard for establishing a tolerable upper intake level and the LeMar *et al.* study to show a safety range after high-dose exposure. The question for the Board is whether the studies are scientifically valid and ethically acceptable for use in EPA risk assessments for systemic iodine toxicity.

The Paul *et al.* study was conducted at the University of Massachusetts Medical School expressly to determine a tolerable upper intake level for iodine consumption. It involved nine males and 23 females (none pregnant), ages 23 to 56, who were considered euthyroid (having no history of thyroid disease or use of medications known to affect thyroid function or previous

reactions to iodine) and with no antithyroid antibodies detected. An additional five age-matched males were not given iodine supplements and used as controls.

The test substance was sodium iodide dissolved in water (250, 500 or 1,500 micrograms per milliliter [µg/ml] per day), and co-administered with 5 milligrams per milliliter (mg/ml) of ascorbic acid. The test substance was administered as two 0.5 ml solutions for 14 days. The men received 1,500 µg per day (µg/day) and women received either 250, 500 or 1,500 µg/day (total). Some women were studied at two dose levels at least 1 year apart. All subjects maintained their normal diets. Although some diets may have been higher in iodine than others, an average dietary intake of 300 µg of iodine per day was assumed.

All of the test subjects completed initial evaluations for the study, measuring the following. On day 0, baseline levels were measured for thyroxine (T_4), triiodothyronine (T_3) and thyroid-stimulating hormone (TSH), as well as resin T_3 uptake and free T_4 index (FT_4I). Stimulated TSH was measured after stimulation by thyrotropin-releasing hormone (TRH) every 15 minutes for 1 hour, and on day 15, the initial protocol was repeated. The endpoints included serum T_4, serum T_3, resin T_3 uptake, FT_4I, TSH and stimulated TSH.

Results showed no effects in any endpoint at the 250 and 500 µg dosing. There was a decrease in serum T_3 and serum T_4 and concomitant increase in TSH at the 1,500 µg dose. Results also showed a maximum increase in serum TSH after dosing with 1,500 µg of iodine. There was a relative increase in both the male and female subjects. In addition, results showed that at the 500 to 250 µg of iodine dose range there was no change in response to TRH. There also were no changes in weight, symptoms of thyroid dysfunction or other adverse effects reported. At the 1,500 µg/day dose, there were small, but statistically significant, decreases in T_3 and T_4. There also were compensatory increases in TSH and TRH-induced TSH. Although statistically significant, the changes were not considered biologically significant because the before and after values were within normal range and not seen as adverse.

Board Questions of Clarification—Science

Dr. Parkin invited Board members to ask questions for clarification. Dr. Liza Dawson stated that although Dr. Leshin had indicated that the study's purpose was to define an upper tolerable limit exposure, she did not glean that purpose when she read the study. The authors cited larger doses in which effects had been found, but they were interested in lower doses because of food dye exposures for which the researchers wanted to know if the dye or iodine was affecting the thyroid. Dr. Leshin responded that the authors cited that a person can safely ingest as much 80 µg of iodine a day. For "tolerable" levels, the researchers were examining subchronic, subacute, long-term exposure. The scenario with regard to dyes then was used to extrapolate to what is tolerable. The NAS used the study and applied additional safety factors.

Dr. Dawson noted that the Board is being asked to look at the study in its temporal context, which at that point was not to establish an upper tolerability level, although it could be used for that purpose. The ethical standard of the time should be applied in evaluating the study, not an ethical lens reflecting 2014 standards. Dr. Leshin responded that EPA is looking at the study in the context of how potential iodine loads affect the upper limit of ingestion. The study could be used to help a future regulator define where to draw a regulatory line, but the study itself did not do so.

Dr. Leonard Ritter commented that the Board members should remind themselves that the studies were not conducted for a regulatory purpose. The question the Board might be answering is slightly different. Nevertheless, the levels of exposure reported in the literature as safe were much higher than the levels being used today. Dr. Leshin commented on safety, noting that what is tolerable to a population is not necessarily the same for individuals. In Japan, the diet is rich in iodine, with individuals ingesting 80 µg to 100 µg of iodine per day, whereas EPA is looking at the 1.5 µg range. "Safe" is a broad and relative term. The LeMar *et al.* study intended to show that a regulatory limit can be set that is protective, but is still a long way from being unsafe.

Dr. Edward Gbur noticed a discrepancy in the number of subjects listed, which was 32 in some places and 36 in others. Dr. Leshin noted that some subjects had participated twice.

Dr. Linda J. Young asked what would be considered a bad outcome. For example, could it be any change in measured indicators, or a change of a certain magnitude? In addition, she asked if there was a change in any of the markers and if some were more important than others. Dr. Leshin responded that, generally, a change outside of the historical or normal range would be considered an adverse effect. There is a difference between the statistical significance of a change and the biological effect of that change.

Dr. Elizabeth Heitman observed that the study's report tended to use the concept of change within normal levels, as opposed to any change being adverse. The authors' idea of normal encompassed all of the changes within what today would be seen as the normal response. Dr. Leshin noted that the authors were not drawing a regulatory conclusion, but were perceiving effects resulting from a given dose of iodine—changes that the authors considered within a normal range. From a regulatory perspective, the question is whether EPA considers the changes to be adverse. Changes within the normal range in EPA studies may or may not be considered adverse. EPA's question is whether the study is scientifically valid and ethically conducted.

Dr. Sidney Green noted that the top page of the document reviewed had a title referencing a 90-day oral toxicity study. Dr. Leshin clarified that the reference is a standard classification code used in the Agency's computer system. The coding schema is irrelevant to the study. Dr. Green asked for clarification about the statement that the initial protocol was repeated on day 15. From his reading of the report, he did not glean any idea that after 15 days the initial protocol was repeated. Dr. Leshin clarified that the iodine dosing was performed for 14 days, and the tests conducted on day 0 were repeated on day 15.

Dr. Green noted that the authors indicated that some subjects were treated at two dose levels 1 year apart. He asked why that information was provided in the report, but with no rationale and no data with respect to the two women at the end of the 1-year period of observation. Dr. Leshin responded that he could not speak directly to the question, but his assumption was that the researchers had subjects willing to complete the study twice. Perhaps the researchers asked some individuals to come back to repeat the study with a different dosing, with specimens probably collected throughout the year. Dr. Gbur added that Dr. Green's discussion concerned the earlier question regarding 32 versus 36 participants in the study. Dr. Leshin responded that it was not explicitly stated, but implied, that four subjects completed the study twice.

Dr. Parkin commented that only men are referred to as controls. She asked if the controls were baselines rather than true controls, and whether Dr. Leshin had any additional information on the matter. Dr. Leshin responded that the data were comprised of within-subject self-controls. None of the data from the five age-matched controls is presented anywhere in the report. Figure 1 in the report refers to controls, day 0, and exposed, day 15.

Dr. Dawson asked about the choice of the three journal articles for Board review from among the broader selection referenced in the NAS report. Dr. Leshin affirmed that the two 1988 articles were chosen because they were identified by the NAS in defining a tolerable upper limit; the NAS experts believed that the two articles were the best representatives in developing a tolerable upper limit. The LeMar *et al.* article was chosen to examine the wide margin of safety for iodine.

Dr. Parkin, noting no further questions of clarification, asked Ms. Sherman to present her ethics review.

EPA Ethics Assessment

Ms. Sherman stated that EPA regulations require that older studies be presented to the HSRB for review. The rules apply to toxicity studies, not exposure studies. Essentially, the report contained no information about ethics, so the ethics review was based on information received from Dr. L. E. Braverman, the Principal Investigator (PI) of the study, during two conversations. The first was with Dr. Leshin in February 2014, and the second with Ms. Sherman occurred more recently. The information was limited by what Dr. Braverman could remember and pertained to such issues as whether the study was valuable. The study was deemed important because Americans were starting to ingest more iodine.

Among the 32 subjects selected (9 males and 23 females between the ages of 23 and 56), the females were tested for pregnancy; none was pregnant or nursing. Dr. Braverman could not recall anything about the population from which the subjects were obtained, but he asserted that they were healthy and had no history of thyroid disease or any conditions that would cause them to be more sensitive to iodine. The report contained no information about risk minimization. Dr. Braverman indicated that the researchers thought that the dosing regimen was so low that it was unlikely to cause adverse effects. Normal medical safety procedures were followed in drawing blood from the subjects, and they were told that they could withdraw at any point. It is unknown whether the subjects were told that they would receive a benefit to their health from participating in the study or if they received an explanation of the risk-benefits balance.

Dr. Braverman could not recall if there was any independent ethics oversight, and the report does not mention such oversight. However, he confirmed that the subjects completed written consent forms. The researchers explained the context of the study and possible results of iodine ingestion. The subjects were not paid for participating and, as far as EPA can tell, their privacy was protected. No subjects' names appear in the report. Although EPA's documentation rules require that when research is submitted to the Agency, the researchers bear the responsibility of pursuing any information gaps, that rule does not apply in this case because EPA decided on its own initiative to use the studies.

Ms. Sherman noted that she faced the task of determining what ethical standards applied at the time for the conduct of the study. The study took place before the implementation of

EPA's human subjects rules. A requirement under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), Section 12(a)(2)(p), stipulating that it is unlawful to conduct pesticide research on humans, was in effect at the time. However, that requirement did not apply directly because the study did not involve pesticides research and was conducted for a medical purpose. Because the study was partially funded by the National Institutes of Health (NIH), the 1974 regulations of the Department of Health, Education and Welfare applied to the study, including the requirement for IRB review and approval, as well as fully informed, written and voluntary consent. The 1983 Declaration of Helsinki, containing the same principles, also was informative in considering the ethical standards of the day.

EPA regulations governing the Agency's reliance on research contain two standards that apply in considering whether to rely on human exposure studies. The Code of Federal Regulations (CFR), Section 26.1703, prohibits EPA reliance on data involving intentional exposure of pregnant or nursing women or of children; 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 not 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. While EPA does not possess a full record, there is enough information indicating that the researchers were trying to protect subjects, who were volunteers and provided informed consent. EPA does not know if there was an independent ethics review, but there also is no evidence that an ethics review was not conducted. The subjects provided consent, were informed of risks and procedures, were permitted to withdraw, and were advised to seek medical attention if they felt ill during the study; those sensitive to iodine exposure were excluded. Ms. Sherman concluded that if the Paul *et al*. study is scientifically valid and relevant, there are no ethical barriers to EPA's use of the data in HHRA, according to the FIFRA or the CFR standards.

Board Questions of Clarification—Ethics

Dr. Kyle L. Galbraith noted that Ms. Sherman had stated there was nothing in the report concerning ethics. Although he understood that this was probably the standard at the time, it made the Board's work difficult. The Board's job is to determine if there is clear and convincing evidence of any unethical conduct. He asked Ms. Sherman if EPA had made any attempt to contact the University of Massachusetts Medical School or the Beth Israel Deaconess Medical Center IRBs to determine if an ethics review was conducted. Ms. Sherman responded that EPA had not contacted those institutions, but was able to converse with Dr. Braverman twice. Dr. Leshin added that Dr. Braverman had indicated that many records were likely lost or had disappeared with the passage of time. Dr. Galbraith noted that IRB records would be separate from those of the investigator and suggested that the institutional records be sought.

Dr. Heitman asked for the definition of "toxicity study" that was being applied in the discussion. The authors did not view their research as a toxicity study. Mr. William Jordan

(Deputy Director, OPP, OCSPP, EPA) responded that the use of the word "toxicity" in describing the types of research submitted for HSRB review is connected to concerns voiced in the congressional arena leading to regulation. The way that Members of Congress and staff view toxicity encompasses any kind of biological change used by EPA in deriving an endpoint for a regulatory risk assessment. Because controversy has tended to attach to reliance on research with human participants, EPA intended to interpret and apply the toxicity modifier broadly. That was the reason that EPA brought the study to the HSRB even though the effects observed were not biologically consequential. Dr. Heitman responded that toxicity is a classification term of art used by EPA, but not one that is recognized medically.

Dr. Jewell H. Halanych asked if EPA had obtained any information about how individuals were recruited when speaking with Dr. Braverman. Ms. Sherman responded that she had queried him about recruitment, but he responded that he had no memory on that matter. Dr. Leshin added that it was likely informal, such as a bulletin board flyer, and not a specific recruitment call.

Public Comments

Mr. Downing announced that there were no public comments entered into the record.

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 relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine?

Charge to the Board—Ethics:

- Does the study meet the applicable requirements of 40 CFR Part 26 Subpart Q?

Board Science Assessment

Dr. Parkin announced that the floor was open for discussion. Dr. Green stated that he viewed the study with a different perspective than the objective Dr. Leshin had described. Specifically, he evaluated the study in terms of whether it was scientifically sound, not in terms of whether it supported the establishment of a tolerable upper limit for iodine. In the report, the authors explicitly state that it would be difficult to establish a tolerable upper limit for iodine for a number of reasons. One reason was that the response to iodine is variable depending on the subject to whom it is administered. The authors cited Hashimoto's and Graves diseases, as well as others. Dr. Green believed that the authors concluded that the 14-day study could be used to establish a tolerable upper limit for iodine. He asked Dr. Leshin if his interpretation of the study was that it could be used in support of a tolerable upper limit for iodine. In response, Dr. Leshin stated that the study was part of the weight of evidence to be used in defining a tolerable upper limit.

Dr. Green asked about the importance of the mechanism or mode of action, and whether that played a role in EPA's establishment of tolerable upper limits for chemicals generally, and iodine specifically. Dr. Leshin responded that human studies represent the best possible case, because no animals react to iodine in terms of humans' hypothalamic-pituitary-thyroid axis. Humans and animals react differently to iodine consumption, and the effects are human-specific. Given the abundance of existing human studies, it would be difficult to justify substituting animal studies. In this case, given the special nature of iodine, the studies represent the best possible evidence for EPA to make a regulatory determination.

Dr. Randy Maddalena agreed with EPA's assessment. His review of the report indicated that it provided scientifically reliable data that could be used in support when setting EPA standards, as the study would be part of the weight-of-evidence approach.

Dr. George C. J. Fernandez commented that after reviewing the report, he had some doubts about the statistical validity of the results reported. The purpose of the study was to compare the baseline at 0 days and 15 days. The researchers used the paired T-test. Statistically, that approach is valid because using a paired T-test can remove confounding effects among the subjects, such as age. For that part of the study, the authors were correct. However, they reported only the mean and standard error of the two populations. They did not report the mean difference coming from the paired T-test, which is the key statistical information to be evaluated. Although the results were reported as a paired T-test, the data are uncertain. Because the report is unclear on the issue, it is difficult for the Board to draw a statistical conclusion. He strongly recommended that EPA try to obtain the data from the investigators if at all possible. Dr. Leshin agreed that in a perfect world, the Agency would have access to the data, but EPA only has access to the short report published in 1988. All that EPA has to go on is what is in the report and confidence in the researcher's calculations within the peer-reviewed publication.

Dr. Young commented that all three papers are deficient statistically. She would have analyzed the whole experiment, rather than performing a series of T-tests. From the scientific viewpoint, presenting the means plus and minus the standard errors, rather than difference, would be more informative. The Board will have to trust that the researchers performed the paired T-test correctly. The use of T-tests tends to provide significant results more often than is appropriate, which is protective of human health. Dr. Young noted that similar comments likely will be raised regarding the other papers. In reviewing the papers individually, some trends that are present might be missed. Dr. Young asserted that although the report was statistically flawed, the conclusions could be used reasonably.

Dr. William J. Popendorf largely agreed with Drs. Fernandez and Young. His question pertained to the fact that all of the samples were run in duplicate. It would be possible, depending on the reproducibility of the method, for the samples to be sufficiently different to reach different conclusions if the samples were run separately. Dr. Young stated that, in her experience, when duplicate samples are run, they are averaged, creating more stability and not affecting the significance of the difference between day 0 and day 14.

Dr. Gbur noted that the studies were taken from a 2000 NAS report, but even since 1995 the practice of statistics has evolved. He asked if, other than the NAS study and the two papers, there were other more recent papers that would make it easier to judge statistical validity. Dr. Leshin responded that there were not, to the best of his knowledge. Iodine toxicity is a settled

field in science, so little work is being done. Iodine research is focused on treating iodine deficiency.

Dr. Parkin called for a Board response to the first question. All agreed that the study is scientifically sound and provides reliable data. On the second question, all agreed that the study supports a quantitative assessment of exposure to iodine. The Board then moved to the ethics evaluation.

Board Ethics Assessment

Dr. Dawson largely agreed with the analysis that Ms. Sherman conducted on the ethical aspects of study and reiterated her key points. The minimal risk of the study lowers the ethical pressure to confirm procedural elements. In a study conducted so many years ago, the standards might have been more relaxed than today, but the subjects in the study were unlikely to have been harmed because it was, ultimately, a benign protocol. Regarding the nature of the indirect evidence about the study, NIH funded it in part, so an IRB review was required. The low risk of the study made it more acceptable to rely on the indirect evidence, the conclusions about informed consent and other issues. The larger philosophical question concerns the appropriate action if a study is not quite right but provides useful data.

Ms. Sherman stated that she appreciated all of the comments. She noted that EPA's rules have an exception allowing the use of unethical research if it would lead to a more stringent regulatory outcome and improve public health. Regarding 40 CFR Part 26, she was unsure if she should use that as evidence of IRB reviews, but decided to do so because the study was funded by NIH. Also, Dr. Braverman had indicated that the subjects were not compensated.

Dr. Heitman took a more conservative position. In 1985, there were stringent requirements for IRB review. She was unwilling to trust the memory of the PI regarding payments because the standard in 1985 was that subjects were paid. Ethical policies had to be decided institutionally to determine how much could be paid in compensation for needle sticks and as compensation, not for harm, but for the effort of participating. She suggested that it might only require calling the University of Massachusetts IRB since part of their responsibility is to respond to questions. She was uncomfortable with not trying to verify the IRB review. Arguably, it might have been a serious ethical deficiency if there was no IRB approval.

Dr. Heitman also stated that the language of toxic effects was not what the original investigators would have seen as applicable to their study. Caution is needed when talking about minimal tolerable changes in doses to ensure that reviewers are not reading into the study a greater statistical power for regulatory purposes than was ever intended.

Dr. Halanych, focusing on the compensation issue, expressed concern about vulnerable populations of students being used to please a PI. The lack of IRB protection also made her uncomfortable.

Ms. Sherman asked for guidance on what she should do if she contacts the University of Massachusetts IRB and finds no additional information. Dr. Heitman responded that in such a case, the Board would have to consider the issue. She agreed that it was a minimal risk study. Saying that there were no significant effects or harm, and that changes occurred within normal baseline and normal American diet and thyroid response, was descriptive. Dr. Young countered

that, given the scientific literature of that day, the study would not be considered at all qualitative or descriptive. It is definitely a quantitative study. The study passed peer review, and it was not uncommon to see this type of analysis in the literature 30 years ago. Moreover, the study's weaknesses would actually, if one believed the significance, tend to be protective of human health.

Dr. Popendorf agreed with the comments about the IRB review and certainly, for due diligence, the IRB should be contacted. The less information provided, the harder it is to reach the conclusion that there were not ethical issues. There is a good chance that research employees or students within the institution were used as subjects, given that several participants were contacted and sampled 1 year later.

Dr. Galbraith added that if the IRB has no records, it might be possible to obtain information from the study funders, NIH and the Center for Environmental Health and Human Toxicology. To his knowledge, there is no formal timeline for IRBs to maintain records, but each IRB is supposed to have a policy regarding record retention. Dr. Ritter responded that he was not sure IRBs would keep records from 30 years ago.

Dr. Dawson added that with regard to NIH, she doubted records have been kept. She had started to look and would be happy to follow up, but NIH has very strict requirements about what is kept and not, and there is a time limit on everything. Keeping records costs money. She offered three possibilities for the Board's consideration. First, a search for the records could result in a determination that the IRB records do or do not exist. If an IRB review is found, that would be excellent, but if no records are found, the Board would be back where it started. The most problematic case would be if records exist for IRB reviews at the time, but the Paul *et al.* study was not among them. The conclusion would be that the study was unethical and had no IRB review, so EPA cannot use it. That would raise the question of whether that would be the right interpretation of an ethical standard when the goal is to protect human subjects. In no way should IRB review be taken lightly. However, Dr. Dawson asked what the ethical bounds would be if the Board stated that EPA should not use the study for conclusions about iodine exposure. Maybe another human study would have to be performed to obtain the right data. If the Board is recommending pursuing the IRB review records, it should know why it is doing so and how to respond to the answer.

Mr. Jordan thanked Dr. Dawson for delineating a suggested path and added several thoughts. The Board's comments suggest ways that EPA can be more diligent in trying to locate records and information relating to the research. EPA will pursue that avenue and see what the Agency finds, possibly leading to no records. He noted that there was no indication of deficient ethical standards at the time.

Dr. Schonfeld raised concerns that the absence of evidence is being construed as evidence of absence. There is no positive evidence of abuse and no indication that subjects were not abused. Trying to obtain copies of documents to have positive evidence of some factors, such as evidence of an IRB review, however, might shift the balance.

Ms. Sherman asked if the Board could provide EPA with a final determination in the event that no records are found, and it is uncertain if the records were lost or an IRB review did not occur. That way, the Board would not have to discuss the matter again at its next meeting. Dr. Parkin asked Dr. Dawson if she was ready to propose a different question for the Board to

vote on. Dr. Dawson stated that the consensus seemed to be that if there is documentation of an IRB review, the Board would find the report acceptable; if there is no such evidence, but a sincere effort was made to find the records and there is no other evidence of unethical conduct, the Board also would approve the use of the data.

Dr. Halanych urged that for due diligence, EPA should try to find the records, but because it is a low-risk study, the data should not be discarded. Dr. Young suggested that there were three potential sources of IRB review and all should be checked. Dr. Parkin added that NIH is a potential fourth source.

Dr. Parkin called for a new vote on the issue. She paraphrased the statements to ensure that the correct question was on the table. The questions and votes were as follows:

1. The Board is requesting that EPA use due diligence among all sources that were mentioned to identify records of IRB review. If any records are found, the Board would find the study acceptable for use. All voted "aye."

2. If no documentation is found of IRB review but sincere efforts were made, the Board would find the study acceptable for use based on there being no evidence of unethical conduct of the study. All voted "aye."

3. If IRB records are found for the four institutions, but they do not have a record of this study being reviewed, the Board would not approve use of this study by EPA. The vote was split: the four "nay" votes were Drs. Maddalena, Dawson, Young and Green.

Mr. Jordan stated that the Board in its discussion recommended that EPA contact the four institutions regarding IRB records, but likely only one possesses records. It is uncertain which institution has the records. He was clear about the Board's thinking in the event, for example, that the University of Massachusetts has records but no record of this research being reviewed. He was unsure of the case if the University of Massachusetts lacks records but one of the other three institutions has them, although not of this study being reviewed.

Dr. Dawson responded that if the University of Massachusetts was the only institution that required IRB review at the time, and it lacked records, that would be a "no records" scenario. The critical issue is whether the University of Massachusetts reviewed the study, since it was the PI's institution, and if the grant was to the PI, it should have been reviewed. Dr. Heitman added that the Beth Israel Deaconess Medical Center or another institution could have held a review, any positive evidence from that source should provide dispositive reviews. Dr. Parkin noted general agreement.

Dr. Parkin announced a lunch break.

Session 2: A published report by Gardner *et al.* (1988) of an intentional exposure human study measuring the effects of low dose oral iodide supplementation on thyroid function

Background

Dr. Parkin conducted a roll call to determine the members present on the videoconference following the lunch break. She called Session 2 to order and introduced the topic before inviting Dr. Leshin to make his presentation describing EPA's science review.

EPA Science Assessment

Dr. Leshin explained that the study was conducted at the Department of Medicine, Medical College, Richmond, Virginia. The study objective was to determine a tolerable upper limit for iodine consumption. The subjects included 30 males, ages 22 to 40, euthyroid, with no history of thyroid disease, use of medications known to affect thyroid function, or previous reactions to iodine. There was no age-matched control; each person acted as his own control.

The test substance was sodium iodide dissolved in water (500, 1,500 or 4,500 µg/ml per day), co-administered with 1 mg/ml of ascorbic acid. This was administered as two 0.5-ml solutions twice daily. The study lasted 14 days. The subjects were randomly sorted into groups dosed with either 500, 1,500 or 4,500 µg/ml. The subjects maintained their normal diets. Some diets may have been higher in iodine than others, but the assumed average dietary intake of iodine was 200 µg/day.

All subjects had initial evaluations for the study. After an 8-hour fast, measurements were taken of their baseline levels of T_4, T_3, T_3-charcoal uptake, and TSH. Stimulated TSH was measured after stimulation by TRH every 15 minutes for 1 hour. On day 15, the protocol was repeated. The endpoints included serum T_4, serum T_3, T_3-charcoal uptake, TSH and stimulated TSH.

Dr. Leshin noted that there were no statistical changes in T_3 in either the 500 µg/ml or the 4,500 µg/ml dosing groups, but there was a statistically significant change in the 1,500 µg/ml dosing group. There was a compensatory increase in TSH at all dosing levels. At the 1,500 and 4,500 µg/day doses, there were decreases in serum and free T_4. There was no change in T_3-charcoal uptake or serum T_3 in any dosing group. At 500, 1,500 and 4,500 µg/day, there were increases in both basal TRH and induced TSH.

Board Questions of Clarification

Dr. Parkin asked for questions of clarification. Dr. Popendorf raised two questions. In the methods section of the report, the researchers only specify that measurements were conducted at a commercial laboratory. He asked if there was any other information about the specific methods used. Dr. Leshin responded that there was none reported in the report. Dr. Popendorf also noted that on pages 27–52 of EPA's review, the Agency indicates that the study is labeled qualitative and does not provide a lower endpoint than an existing study. He asked what existing study is being referenced, and Dr. Leshin clarified that it was the Paul *et al.* study.

Dr. Kenneth Ramos noted that in the summary slide on TSH values, Dr. Leshin stated that both the baseline as well as the TRH and stimulated TSH were stimulated doses, but he did

not think this was true for baseline values at 500 µg/day. Dr. Leshin agreed. In addition, the assumed baseline consumption of iodine in this study was 200 µg/day. In the Paul *et al.* study, it was 300 µg/day. Dr. Ramos noted references of 700 µg/day to 800 µg/day on page 287 of the report. Dr. Leshin replied that those are direct estimates taken by the Food and Drug Administration or U.S. Department of Agriculture market basket analyses. Assuming participants in the study consumed more iodine would make any values EPA uses for its assessment more protective.

Dr. Gbur asked for a definition of qualitative. Dr. Leshin responded that the definition derives from EPA's open literature guidance. A study is deemed qualitative if among its measures the study does not provide a lower endpoint than an existing study. It is a term of art.

EPA Ethics Assessment

Ms. Sherman stated that the study was similar to the Paul *et al.* study. Under EPA guidelines, it is considered a toxicity study and therefore required to undergo review by the HSRB. She omitted the discussion of the study's value to society because that point was established already.

The subjects were all male. Therefore, considerations related to pregnancy and nursing do not apply. Based on a conversation with Dr. D. F. Gardner (Medical College of Virginia), the subjects were medical students or employees of the Medical College of Virginia, including individuals whose names appeared on a list of interested research candidates maintained by the research center. The inclusion and exclusion criteria indicated that the subjects had to be healthy, euthyroid, not on any medications that would affect thyroid function and have no history of thyroid disease.

In terms of risks faced by the subjects, it was a low-risk study using small doses of iodine. Ms. Sherman did not know what the subjects were told in terms of risk, benefits or the risk-benefit balance. The study was reviewed and approved by the Virginia Commonwealth University IRB. EPA obtained additional information about consent from Dr. Gardner, who explained that the typical procedure was to allow subjects to read the protocol, ask questions and then confirm their understanding. All participants signed the consent form. He believed that the subjects were paid approximately $150 to $200 for their participation, but it is unknown if they were told that they were free to withdraw at any time.

Ms. Sherman bypassed her discussion of standards for documentation, noting that the burden to find information falls on EPA. For the Standards of Conduct for human studies at the time the study was conducted, Ms. Sherman selected the Declaration Helsinki of 1983. Studies were required to be scientifically sound, have a clear purpose, undergo independent review and include prior informed consent. She omitted her discussion of the standards for EPA's reliance on studies.

Considering compliance in terms of EPA reliance on a study, CFR Section 26.1703 did not apply because the subjects were all adult males. Regarding CFR Section 26.1704, EPA concluded that there was no evidence of fundamental unethical behavior. The subjects were volunteers, they provided informed consent and general precautions were taken following normal medical procedures. On the second part of the regulation regarding whether there was convincing evidence that the study was deficient in terms of the prevailing ethical standards, EPA found no

clear and convincing evidence of this. The study was reviewed and approved by an IRB and involved informed consent. Some of the subjects were employees, so there was a potential for coercion, but those concerns were dealt with according to the IRB review. Ms. Sherman concluded that the study conduct was consistent with prevailing ethical standards at the time and that EPA can rely on it.

Board Questions of Clarification

Dr. Parkin asked for questions of clarification, and none were raised.

Public Comments

Mr. Downing remarked that there were no public comments.

Charge Questions

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

Charge to the Board—Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine?

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 provide his science review. Dr. Popendorf stated that, overall, he was comfortable with the report. However, he expressed concern regarding the lack of details about methods and that weakened his ability to conclude that it was scientifically sound and provided reliable data. If he were to vote at present, he would comment that there was no clear and convincing evidence that it was not sound. Regarding the 30 men randomly assigned to the research arms, there is an assumption that 10 people were in each group, but it is never stated explicitly. There also were no details about the commercial laboratory.

More substantively, on the positive side, all samples from an individual man were analyzed in the same assay, which is the preferred approach. The previous study looked at different points in time within the assay. His comment on the previous study would apply here regarding students' T-tests with duplicate samples. The effect of duplicate samples is important to look for small differences when an imprecise method with intrinsic variability is being used.

The major point that clearly affects the second charge question is that all of the urinary iodine excretion reported in Table 1 increased in relation to dose, as expected. However, the changes in thyroid hormone in Table 2 did not increase with dose either in their magnitude or in level of statistical significance. The data are statistically different, but if one examines the dose

relationship, it is not an increasing effect. The lack of a positive dose-response correlation weakens the attribution of dose with the significant differences that were reported.

Dr. Ramos agreed with Dr. Popendorf's observations. Additionally, he was surprised by the disregard for baseline values in the study given the observation that there was no dose-dependent response for either hormone levels or TSH response to TRH stimulation, which could be attributed to a lack of baseline values specified for the subjects in the study. Dr. Ramos disagreed with the conclusion about acute TSH response to TRH stimulation. He also commented that the statistical significance for some of the findings reported in the study were all within clinically acceptable normal limits.

Dr. Young stated that she did not understand the concern about the baseline. Dr. Ramos clarified the point, as noted by Dr. Popendorf, that there was no dose response. The lack of a dose response could be related to changes in baseline values in individuals that were not reported in the study. Dr. Young responded that the statistical method adjusts for differences in the baseline. Dr. Popendorf added that, toxicologically speaking, if one increased the dose—for instance, examining an effect on hormone levels or sensitivity to TRH—the expected result would be that the greater the dose, the bigger the response. This is a toxicological axiom. In this case, such a result is not demonstrated, possibly because of the baseline. The lack of a positive correlation between the response measured—that was statistically different—and the doses given weakens the logic of the dose-response attribution. Dr. Young responded that the problem was that, statistically, the authors were not treating the data as one study; they were treating it as three separate studies. The Board members discussed the unexpected absence of a dose response in subjects receiving the 4,500 µg/day dose. Dr. Popendorf stated that one would expect at the 4,500 µg/day level, the significance of the results should go down, indicating that the change is less at a higher than at a lower dose level. Dr. Ramos commented that the results raise questions about whether the lack of a dose response is impacted by differences in baseline values or some other factor. Dr. Young stated that it is unlikely to be due to differences in baseline data because of the way the analysis was performed. Drs. Ramos and Young agreed that the result was an unexpected finding.

Dr. Young added that the comments on the last report would apply to the Gardner *et al.* report as well. This is not the analysis that would be conducted today or in 1988. In particular, the analysis of the repeated measures presented in Table 3 of this report would have considered the fact that measurements were taken repeatedly from the same individual. Given all of these considerations, performing all of the T-tests is likely to lead to more significance than expected otherwise, so EPA could use these data as a guide without overly relying on the statistics.

Dr. Parkin asked for other comments, and there were none. She then turned to the ethics review.

Board Ethics Assessment

Dr. Parkin asked Dr. Heitman to present her ethics review. Dr. Heitman commented that the Board addressed the major ethics issues concerning the report in the first review. She agreed with Ms. Sherman's assessment on every point except on the issue of the standard of conduct at the time; it was less the Helsinki Declaration than the Belmont report and CFR 46. The Helsinki Declaration had no formal status regarding regulatory oversight or IRB approval in the United States. The Board can assume that any concerns regarding coercion or compensation would have

been addressed by the IRB review according to the IRB standards of the 1980s. On various ethics issues, the IRB review provides assurance. Due diligence is not needed because the journal would have confirmed documentation. In conclusion, Dr. Heitman asserted that the report meets the applicable requirements of 40 CFR Part 26 Subpart Q.

Dr. Galbraith agreed with Dr. Heitman's assessment. Dr. Popendorf questioned whether journals truly examine the validity of the IRB statements. Dr. Heitman responded that in 1988, when the report was published, it would have been a forward-thinking journal that required documentation, but that information was printed in the journal, so the editor would have taken responsibility to ensure that it happened.

Dr. Parkin asked for other comments on ethics, and hearing none, she took a vote.

On the first question, all voted "aye." Dr. Popendorf asked, however, if approval could be phrased in a way to indicate no evidence was available to suggest that it was not a sound study, and EPA agreed. The Board did not find evidence that the study contained fatal weaknesses within its methods or data. All voted "aye" and the statement passed. For the second and third questions, all HSRB members voted "aye."

Session 3: A published report by LeMar *et al.* (1995) of an intentional exposure human study measuring the effects of chronic tetraglycine hydroperiodide water purification tablet use on thyroid function

Background

Dr. John C. Kissel joined the meeting; he was not available for participation in Sessions 1 and 2. Dr. Parkin introduced Session 3 and invited Dr. Leshin to provide EPA's science assessment.

EPA Science Assessment

Dr. Leshin presented EPA's science review of the third publication, LeMar *et al.* The study was conducted at the Fitzsimmons Army Medical Center. The study objective was to determine the effects of subchronic ingestion of iodine purification tablets (tetraglycine hydroperiodide). The subjects included seven males and one female (not pregnant), ages 35 to 47. They were healthy, euthyroid, had no history of thyroid disease, no chronic medical disorders, and no use of medications known to affect thyroid function or previous reactions to iodine.

The test substance was tetraglycine hydroperiodide dissolved in water or juice, totaling 32,000 µg/day in four tablets, self-administered over the course of the day, for 90 days. Subjects maintained their normal diets. Some diets may have been higher in iodine than others, but the assumed average was 300 µg of dietary iodine per day.

Regarding the study methods, all subjects completed initial evaluations for the study. On day 0, baseline levels of T_4, T_3, and TSH were measured; stimulated TSH was measured after stimulation by TRH after 20 minutes (TSH-20). A 24-hour radioactive iodine uptake (RAIU) was recorded after dosing with 1 microcurie (µCi) of ^{131}I, with 10-minute counting times. Thyroid volume was measured in the recumbent position by ultrasound. Repeat serum iodine, T_3,

T_4, TSH, TSH-20 and urinary iodine measurements were collected on days 7, 28 and 90. RAIU was re-measured on days 7 and 90, and thyroid volume was reassessed on days 35 and 90. The endpoints were serum T_4, serum T_3, TSH, TSH-20, RAIU and thyroid volume.

The study concluded that the mean serum T_4 and T_3 decreased in response to iodine, with T_4 remaining below baseline throughout the study and T_3 recovering. The RAIU decreased during the study. Serum TSH and TSH-20 increased by day 7 and remained elevated. The average thyroid volume increase was 37 percent. No hypo- or hyperthyroidism was found in any subject. For the seven subjects with repeat volume determinations on average after 7 months, the thyroid size returned to baseline. This indicates that a reversible, TSH-dependent thyroid enlargement occurred in response to increased iodine load from daily use of water purification tablets.

Board Questions of Clarification—Science

Dr. Halanych asked how EPA determined that there was no hypo- or hyperthyroidism, and Dr. Leshin responded that the presumption was that the report would say if either had occurred.

Dr. Gbur noted that the report briefly mentions recovery data for the thyroid size, which did not appear to be a formal part of the study. The study design stopped at 90 days. Dr. Leshin stated that the thyroid volume was the only measure that was noninvasive and was easiest to measure. Dr. Ritter applauded the initiative to acquire additional information after the study.

EPA Ethics Review

Ms. Sherman explained that for this study, EPA was able to obtain additional information through conversation with Dr. Michael McDermott, one of the study investigators. Recruited subjects were employees of the hospital, including residents, fellows, civilians and military personnel. The female subject was tested for pregnancy, but EPA lacks definitive information about whether she was nursing. Dr. McDermott stated that for recruitment, the investigators sought volunteers and the subjects were not compensated. Subjects did provide informed consent. They were given an opportunity to read the protocol and ask questions, and they signed consent forms. The study was approved by the IRB. The only rule for the study was that subjects could drop out any time they wanted.

Regarding the standards of conduct, the study was conducted prior to 1995, before EPA's 40 CFR Part 26 rule took effect. FIFRA section 12(a)(2)(P) does not apply because the study did not involve the use of a pesticide. The Common Rule standards applied, including IRB oversight and prior approval; a fully voluntary, fully informed consent; a favorable risk-benefit balance; and equitable subject selection.

Regarding the standards to consider whether EPA can rely on the study, for CFR Section 26.1703, all subjects were adults, with the one female subject tested for pregnancy and no evidence of nursing. For CFR Section 26.1704, Ms. Sherman concluded that there was no convincing evidence of fundamentally unethical conduct. The study posed minimal risk and obtained informed consent from the subjects, and it was reviewed by an IRB. There was no clear, convincing evidence that the conduct was deficient with regard to ethical standards. Although the

subjects were employees and potentially faced coercion, the IRB reviewed the study, so EPA assumed no problems in this respect. Ms. Sherman concluded that EPA could rely on the study.

Board Questions of Clarification—Ethics

Dr. Halanych stated that she assumed a pregnancy test was performed at baseline. Ms. Sherman responded that she did not know the answer, but noted that it was an excellent question.

Dr. Kissel commented that it was not explicit in EPA's review or in the report that the purpose of the study was stated to the subjects. It may be obvious that the study was intended to evaluate iodine for use in drinking water disinfection, but it also can be used for defense prophylactically in a nuclear event. It was unclear that this information was communicated to the subjects. Ms. Sherman responded that the researchers explained the study procedures to the participants. The investigator commented that subjects were asked if they wanted to take part in a study about the purification of water with iodine. Dr. Kissel noted that in addition to the effects of iodine, subjects were given three oral doses of radioactivity. There was no mention of whether that was of concern. The radioactivity doses were not given for therapeutic purposes, yet subjects were exposed to internal doses of radiation.

Dr. Schonfeld commented that nuclear medicine is a well-respected field of medicine and often uses radioactive tracers. It is not unusual in some fields of medicine for patients to be given oral radioactive agents. Dr. Kissel responded that the subjects were not patients. Dr. Halanych added that with thyroid tests, the radioactivity test often is ordered, but she has never ordered it three times within 3 months.

Dr. Heitman added the presumption that the IRB record would have reviewed the exposure to any radioactivity. Many IRBs include radiation exposure review as part of the evaluation process. U.S. Department of Defense standards are stricter than those called for in the Common Rule. She presumed careful scrutiny over that issue.

Public Comments

Mr. Downing stated that there were no public comments.

Charge Questions

Ms. Sherman read the charge questions into the record.

Charge to the Board—Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study relevant to establish the reversibility of high-dose iodine exposure?
- Also, is this study sufficient to establish that there are no sustained adverse effects from high dose iodine exposure?

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. Ritter to provide his science review. Dr. Ritter commented that this study was fundamentally different than the first two. A key outcome relevant to the Board's understanding was the aspect of a long-term exposure at relatively high doses of iodine, not present in the first two papers, and the element of recovery after the exposure terminated. It appears that there is rapid recovery after exposure, but the charge questions do not relate to recovery. Asking if the study provides reliable data and uses an approach that is sound is a simpler question. It is testament that the study is sound that this report was selected by the NAS. It is difficult to argue that the report is not reliable, but the question of radioactivity Dr. Kissel raised was not applicable to the scientific question. Based on conversations with Ms. Sherman, the study is relevant to the needs of EPA, but whether it is definitive is harder to answer. The anticipated use by EPA, however, is unclear. He asked if the exposure is relevant to the use the Agency is considering.

Mr. Jordan noted that use patterns already discussed include incorporating cuprous iodide into fabric that could come into contact with people, even infants and children, via oral and dermal exposure pathways. Exposure could occur for extended periods. In addition to textile treatment, other use patterns include exposure via food pathways. For these reasons, it is useful to understand the nature of repeated exposure. This particular study addressed the reversible effects of iodine exposure, which helps to understand the adversity of the biological changes that might come from repeated exposure. Reversibility is one aspect of risk that EPA takes into account in making regulatory decisions.

Dr. Ritter responded that it helped to understand the context of how the data would be used by EPA. The study may not be definitive, but it certainly is relevant. No single study ever is sufficient by itself. He would prefer if the Board could say that the study is relevant to establishing that there are no sustained adverse effects from high-dose iodine exposure. He stated that there were only eight people involved in the study and asked if the Board's statisticians wanted to comment on that.

Dr. Young noted that in all of the studies, the sample size was quite small. If a significant effect is found, it is believable that it is truly there, because sample size affects power. If one does not see a significant effect, it may or may not be there. She had not emphasized the issue because the trends seemed to be what scientists were expecting. The means are all within the normal range. Dr. Ritter commented that he is not necessarily worried about the statistics, but the possibility of an outlier. Nothing indicated that the responses are not biologically representative, but the small set of samples was worrisome. Dr. Young stated that it was unlikely, but there could be outliers. With the exception of the second study, the patterns are what one would anticipate. One has to assume in the absence of evidence to the contrary that a reasonable review of the data took place. If an outlier were present, it would be prominent.

Dr. Kissel, reiterating his concern about population size, stated that his preformed answer to the third charge question would be "no," because a study of eight people cannot possibly be determinate for the population of the country. It is not a reasonable question as posed. Other than that, he had not heard any discussion as to what alternatives can be found. This report itself mentions prior human studies and animal studies. The question would be what happens at EPA if the Agency cannot use the study. He asked if there was so much other information available

from other studies that not approving this study would change the margin of exposure, reference dose or some other factor. He also stated that he was uncomfortable because it appeared as if the standard was for the Board to ask about human subjects compliance, and if there was no answer, the Board would decide there was no evidence of a problem and that would be good enough. Dr. Parkin asked that the issue be held for the ethics discussion.

Dr. Leshin stated that with regard to animal and humans differences, it is known that systemic and oral toxicity of iodine is different in animals and humans. Animal studies are not an acceptable replacement for human studies. The studies chosen for HSRB review were some of the best available studies selected for the NAS report. EPA chose the studies out of hundreds of publications as representative and the best fitting studies for the Agency's need. Dr. Ritter added that these studies were selected not only by the NAS, but also by other organizations. Dr. Parkin thanked him for the helpful addition.

Dr. Gbur stated that for their statistical analysis, the authors state that they used analysis of variance followed by mean separation, but that is not very informative. The standard errors in the various tables show large differences in the variances between time points, which have implications for statistical significance. The authors adopted a worst-case scenario. He stated that, in general, a significant difference in serum iodine would occur if all of the subjects received the largest doses. The question about the thyroid reducing to normal size following iodine exposure showed no statistical significance and can be viewed as anecdotal information. In terms of the charge questions, the data are reliable and the answer is "yes." However, on whether the study establishes the reversibility of a high dose for iodine exposure, the answer is "maybe."

Dr. Halanych questioned the meaning of the sustained adverse effects and whether 3 months represents a sustained effect. Dr. Leshin replied that the dosing is not sustained, but the question pertained to whether the effects are sustained. The body possesses a large number of compensatory regulatory effects. The regulation of T_3 occurs in an especially tight range. In response, Dr. Halanych stated that in thinking of how the thyroid is functioning over time, she would have preferred if there had been more information about people with high risk of thyroid cancer long-term from dietary iodine. She wondered if 10 or 20 years of impregnating clothing with iodine would produce thyroid cancer.

Mr. Jordan commented that, after listening to the Board's discussion, he realized that EPA's charge question might not be phrased as well as it should be. EPA is asking whether the Board members agree with the position that the study helps the Agency understand the reversibility of the effects of iodine on the thyroid and thyroid function, as well as providing general insights about the timeframe in which effects are reversible. If he were to rewrite the question, he would ask, "Is this study relevant to understanding whether doses of iodine in the range of 4 µg over a repeated period of time are reversible?" In addition, EPA regulates iodine tablets for water, such as for hiking the Appalachian Trail, and the study is valuable for thinking about the risks associated with that scenario. He noted that there is less risk from iodine tablets than from drinking unpurified water.

Dr. Heitman asked what constituted an adverse event or toxic effect, and if it was a term of art. Mr. Jordan cited several contexts. First, EPA regulations direct the Agency to seek Board review of human research in a toxicity study, which EPA interprets broadly so that the Agency can say to the public that anything that comes close to the definition is being reviewed by an

independent external panel of experts in science and research ethics. Second, there is an ethical obligation to report adverse effects to the governing IRBs so that they can determine whether to terminate or modify a research design. Third, when EPA discharges its regulatory responsibilities to determine under its statutes whether the use of a particular pesticide is safe, adversity is informed by the practical consequence for humans of a biological change, such as impairing or reducing a person's ability to function normally.

Dr. Ritter reiterated his point that the study is not sufficient; no study is singularly sufficient to answer the question of sustained effects. Dr. Popendorf made observations regarding the long-term recovery phase of this study. The only data provided were thyroid volume data. The study mentioned that the other thyroid function tests returned to normal, but it provided no data. There was a flaw in what was calculated; the authors stated that thyroid volume measurements in five of eight subjects were taken before treatment, and they provided the coefficient of variation (CV). They also stated that the greatest volume for the treatment for each of the five subjects was subsequently used as the pretreatment volume for that individual. They did not use the mean, but the highest volume, resulting in more change to see a significant difference and less likelihood of returning to the mean of the pretreatment normal for each individual. With the information provided, one cannot tell if there are no sustained adverse effects from high dose iodine exposure. If one assumed the study's highest CV is 13 percent, two standard deviations would all be in the same direction. The study goals and methods never mentioned recovery. It appears to have been an afterthought.

Dr. Young also agreed that the recovery was not purposeful, and she suggested rewording the question. Dr. Halanych commented that the researchers used the same method in baseline for all eight participants, but in five they checked if the methodology worked well. They tried their best to make ultrasound a useful tool. In response to a question from Dr. Gbur about the thyroid size variability, Dr. Halanych responded that it depends on the size of the person.

Dr. Popendorf offered a possible solution. The authors refer to long-term recovery in comparison to a reference in their manuscript. Perhaps the reference offers cleaner data that are more informative.

Dr. Parkin called for further questions, and seeing none, turned to the vote on EPA's charge questions to the Board. In response to the first charge question, the votes were "aye."

Dr. Parkin read the second question. Dr. Young asked if thyroid volume is the primary measure to assess reversibility. Dr. Leshin stated that it is a good measure because other measures, such as hormones, compensate over time. Thyroid volume is related to iodine exposure. As iodine exposure goes down, thyroid volume decreases. In response to a question from Dr. Gbur on the study's relevance, Dr. Leshin stated that it was relevant as part of the Agency's weight-of-evidence approach. Dr. Young stated that she would be more comfortable if that qualifier were added to the charge question. Dr. Parkin rephrased the second question accordingly, and the members all voted "aye."

Dr. Parkin read the third question, and Mr. Jordan provided alternative wording: "Is this study relevant to understanding whether high doses of iodine in the range of 32 µg/day produce effects that are reversible?" Dr. Parkin noted that 32 µg/day is not a range and suggested "approximately" instead. Mr. Jordan stated that the Board could say "no" to the last question, but articulate that the data are useful in specified ways within the study's limitations. Dr. Popendorf

agreed with that approach. Dr. Ritter suggested replacing "sufficient" with "relevant," and Mr. Jordan agreed with that suggestion. Dr. Young proposed adding "in a weight-of-evidence approach."

Dr. Parkin read the revised question: "Is this study relevant for establishing in a weight-of-evidence approach that there are no sustained adverse effects from high-dose iodine exposure?" All Board members voted "aye."

Board Ethics Assessment

Dr. Galbraith began by reemphasizing the applicable 40 CFR Subpart Q provisions that pertained to the study, such as not using children and a study conduct consistent with the ethical standards of the time. He also reviewed the basic facts of the study. There was no indication that subjects would have been withdrawn during certain time points if dangerous levels of iodine had been detected, but there also was no indication that they would not have been removed—there were no stopping rules in place. The study risks seemed reasonable. He concurred with the concern raised about using radioactive tracers.

In the 1990s, the Common Rule was in effect and provisions required IRB review and approval, which was included in the manuscript. There was no formal documentation from the IRB, and obtaining it would be difficult because the Army Medical Center closed in 1999. Both the manuscript and transcript indicate that the subjects provided informed consent, but there is no formal documentation available. The Common Rule specifies the elements of consent. Relying on the statement in the manuscript, consent was obtained and approved by an IRB, so certain elements can be assumed, such as the disclosure of risk, what to do in the event of injury, and voluntary participation. There was no compensation, which was unusual. Dr. Leshin clarified that the subjects could not be compensated because they were military members. There was a mix of civilian and military subjects, and if the military personnel were not compensated, the civilians also were not compensated.

Dr. Galbraith noted that the manuscript does not describe the recruitment processes. Regarding the specific charges of CFR Section 26.1703, the materials indicate that the researchers took appropriate steps to see that children were not involved. There was a pregnancy test for participation, but there is nothing to indicate that the female subject did not become pregnant or whether she was or was not nursing. Regarding CFR Section 26.1704, there is nothing to show that the research was deficient according to prevailing ethical standards at the time. Unfortunately, it will not be possible to reach out to the institution's IRB to glean further evidence. In Dr. Galbraith's opinion, the study's low risk is relevant to the Board's deliberations. Dr. Halanych concurred with Ms. Sherman's and Dr. Galbraith's reviews.

Dr. Dawson asked if the Board was satisfied that the risk from the radioactive tracer exposure three times during the study posed a reasonable risk. She stated that she needed evidence that the exposures were reasonable. "Minimal risk" is an ambiguous concept. Using a radioactive tracer for diagnostic purposes has benefits, but the subjects were not patients. In addition, she noted that the record retention period is 75 years. There may actually be records. Dr. Galbraith noted that he liked the point about the nuclear tracer being given three times in one study and asked for further information on that. Dr. Halanych stated that she is not a nuclear medicine physician but is trying to find out how much is in a radioactive test; it is definitely less than that used when trying to kill hyperthyroid.

Dr. Kissel commented further on IRB record keeping. He conducted human subjects research in the 1990s and could locate his consent forms because he has an electronic record. The idea that the hospital is closed and the paperwork is gone is not persuasive. He opined that Dr. McDermott was not responsive to the point of not fulfilling his ethical responsibilities. This sets a very bad precedent. HSRB members should not set a precedent for accepting that EPA tried but could not find out anything, so the study must be acceptable. There is no point in having a Board if that is the standard.

Dr. Dawson maintained that there was a big difference between reviewing whether a study was reviewed by someone and looking at the risks and benefits as an independent Board. If the Board did not evaluate the risks and benefits independent of an IRB, then she would agree with Dr. Kissel's statement that the Board was not doing its job. However, if all that the Board did was look for an IRB review and conclude its work was done, then it is not accomplishing anything either. An IRB review constitutes a solid piece of evidence, but if the Board's sole task was to look for an IRB review, there would be no point to the questions about risk, exposure and informed consent. The Board should rely on the expertise around the table or additional knowledge it can seek out as needed. The Board should look at both the risk issues and the human oversight procedures, but not make the oversight procedures the entire sum of the ethical analysis.

Dr. Kissel responded that he would like to see the human subjects forms to determine if they were informed about and understood the study. It is unclear how the Board can review what was done without records. Dr. Young referred to Ms. Sherman's earlier statement that the study is 20 years old. Ms. Sherman reiterated her statement that the regulatory standards were lower than they are today. The Board needs to decide if there is clear and convincing evidence that the study was fundamentally unethical or deficient compared to the standards at the time, the increased risks of the subjects, knowledge available at the time and such issues. That is what the current operational regulations say in deciding whether EPA can use a study, which comprise a different set of considerations than for new and proposed research.

Dr. Halanych noted that the typical radiation dose is 4 to 10 µCi for uptake scans to measure the size of the thyroid, and 30 to 100 µCi for treating thyroid cancer. The radiation is given all at once.

Dr. Parkin asked if the Board was ready vote on the question, or to modify the charge question. Dr. Halanych noted the possible need for new expertise on radioactivity. Dr. Leshin commented that the study used 1 µCi three times during the course of 90 days on the assumption that giving more all at once is more dangerous. Dr. Halanych responded that Dr. Leshin's statement satisfied her concerns. Dr. Dawson noted that some population studies exist showing cancer risk from exposure to iodine radioactive tracers, but there is no indication of undue risk.

Dr. Parkin called for a vote on the question of whether the study met the applicable requirements of 40 CFR Part Q. The majority voted "aye." Dr. Kissel voted "nay."

Discussion of HSRB Work Group on Return of Individual Research Results Report

Dr. Parkin introduced the final agenda item, providing the context and noting that there were no handout materials because they were distributed at the previous HSRB meeting, in April

2014, when the Board members agreed that they would hold another discussion of the report. At the last meeting, Dr. Sean Philpott-Jones (HSRB consultant, Icahn School of Medicine) provided a summary of the report for the work group convened in 2013 to address whether the Board could make recommendations about returning individual research results. The goal was to accomplish two results at today's meeting: (1) decide whether to accept the report's recommendations and (2) determine next steps on the issue, such as whether to drop, table or pursue the topic immediately.

A number of important concepts were raised at the last meeting. Members discussed the rights of participants in a study, the obligations of researchers to the participants, the importance of establishing trust and current IRB practices. Generally, IRBs do not allow researchers to recontact participants. A Presidential Commission (Commission) examined the return of results issue and the Common Rule and is expected to report its findings, although they have not yet been released. The Commission is posting new guidelines on their blog, including new guidelines for clinical researchers. The Commission's effort is not related to the Board's context, but it did introduce new concepts. One of them is a framework for defining individual findings. The Board has not separately defined types of findings. The Commission's framework distinguishes among primary findings, which are those that were part of the researchers' intent; incidental findings, either anticipated or not anticipated; and secondary findings, which were unsought by anyone but nevertheless resulted from a study. The Commission provides a whole new framework that the work group did not have an opportunity to consider because it was published after the work group's deliberations were completed.

Another concept is to ensure that researchers have a plan to talk about incidental individual results. The Board has not discussed any kind of implementation procedures, but the issue involves more than study sponsors simply putting a letter in a package. A more deliberative process is required for handling individual results.

Dr. Parkin found a different framework that was published in 2011 by Resnick *et al.* This paper recommended reasonable measures to minimize risks that were plausible and significant. The elements of "plausible and significant" referenced in the framework were not discussed by the work group. Resnick *et al.* discussed the possibility of individual results being provided with appropriate safeguards. The paper suggested having researchers available to advise individuals about results and to pursue follow-up with the research subjects. This requires additional human contact between the research team and the participants after the research is completed.

Dr. Parkin noted that several new concepts are available in the literature; this is a dynamic issue. The Board recognized that it was on the cutting edge when it convened a work group. In Dr. Parkin's view, the current question is how the Board would like to proceed with the work group report. Members simply can accept it as a report submitted by the work group without taking actions on the recommendations. The Board can discuss the minority report, which argues that subjects' right-to-know overrides the researchers' determination about whether the results are relevant and useful to participants. The minority report asserted that the sole consideration should be whether returning individual results would produce unintended harm. The minority report agreed with the opt-out option for aggregate results of the research, but did not agree with the work group's determination that opt-in was the way to deal with individual results; they also should be opt-out. A number of elements clearly are not resolved. Although the issues will not be resolved today, it would be appropriate to consider what to do with the report.

Dr. Parkin asked if the Board members preferred to vote on each recommendation, or to put aside the report and discuss the issues in a different framework.

Dr. Schonfeld asked if the work group had investigated the efforts of other federal agencies. For example, the U.S. Food and Drug Administration is thoroughly engaged with the issue, as are other agencies, and even though they have not all come to conclusions, it would be useful to review their efforts. Dr. Parkin responded that the work group included federal agency representatives who discussed some of their efforts. In addition, the work group conducted a thorough search of published literature at the time, which mostly pertained to research in a clinical framework, not a laboratory or field perspective. The work group has a different context, with a different relationship between researchers and participants than in other studies.

Dr. Heitman stated that one of the recent publications from the Presidential Commission addresses the issue of incidental findings and that it could be useful to review. Although the Commission does not speak as directly to non-medical issues, the publication will be a benchmark. Dr. Parkin noted that the work group had not read that publication; the guidance was published on May 8, 2014, after the work group completed its report.

Dr. Dawson commented that the exposure studies the Board addresses are very different from findings made in a clinical context. A fresh approach is required. At the previous meeting, members discussed briefly a number of issues regarding other kinds of communication—not just the provision of indicator measurements, but the overall context of the communication. That is a very different context than health discussions and does not easily fit into an individual's day-to-day experience. She suggested revisiting the issues with the new members, a proposal that Dr. Ramos seconded.

Dr. Parkin asked if the discussion should be conducted as a full group or through a new work group with different experts. Dr. Young noted that the Board had worked on the issue for 2 years, and the Board composition changes every year. At some point, the Board will have to approve or disapprove the report. Dr. Parkin suggested that one approach would be to examine the specific recommendations and accept them or not. If the Board rejects the recommendations, it then could decide if a different set of questions should be addressed by a new work group.

Dr. Schonfeld asked for clarification of the implications of the Board's decisions about the report. Would accepted recommendations become policy that researchers must meet? Dr. Parkin responded that the work group had discussed how Board reviews would change to support each recommendation that was accepted by the full HSRB. For example, if the Board accepted the recommendation that aggregate results should always be offered back to participants as opt-out, there would be a question of where the Board would expect sponsors to place that element in their documentation. The Board would need to review its own procedures.

Dr. Dawson suggested that new Board members be given a defined period of time to propose changes rather than overhauling the report. For example, the members could have until the next meeting to develop their input, and then the process could move to implementation. Dr. Parkin responded that the Board will not modify the work group's report, but if new members would like to make a statement at the next meeting, that would be appropriate. The report will be posted as an addendum to the minutes of the April 2014 HSRB meeting. The work group report will become a public document, but it cannot be modified. Dr. Dawson asked about creating an addendum for additional perspectives on the topic that could inform the discussion,

but Dr. Parkin replied that if the Board wrote a new statement, it would be a freestanding element. She noted that work on this issue goes back to 2009, and it has been difficult to work through. In her view, it would be fine if a subgroup convened to write another document for Board consideration. Mr. Downing suggested it could be a new work group.

Dr. Schonfeld reminded members of her general comments at the outset of the meeting regarding opportunities for collaborative efforts in different contexts. She recommended thinking about the topic in light of larger issues and where the Board might spend its energies amidst other priorities, either identified by the Board members or based on EPA's perspective on what might be the best way to take advantage of the Board's expertise. Dr. Schonfeld stated that the Board's duty could be considered discharged by the report. If there is good information in this work group report, it may lead to a revision or may be sufficient to address the question originally raised.

Dr. Parkin asked about the extent to which sponsors are still coming forward looking for advice about returning results in aggregate or to individuals. Ms. Sherman commented that in her recollection, one or two early Board members advised that researchers should return results, but now the advice is to not return research results, which sponsors approve. The work group's advice is to say that researchers are not under an obligation to return exposure results. Dr. Parkin noted that by virtue of publishing the April 2014 meeting minutes with the work group's conclusions, the set of recommendations will be on record without the Board endorsing them. The recommendations are that aggregate results should be returned, but the question about returning individual results is still open for debate. Sponsors will see those recommendations if they examine the minutes. The Board could pursue the topic more deeply or move on to other issues.

Dr. Dawson stated that the kind of recommendations she would like to make would address how and when results returned would be meaningful. Giving people a number without any context or other support to learn more can put individuals in a difficult situation if they are not familiar with the scientific matters being tested. She cautioned the Board members to be careful in the way they think about these issues. Dr. Parkin responded that it was clear to the work group that how to communicate was not part of the scope of the task. The work group was seeking the ethical foundations for whether researchers should return results, but could not come to a clear conclusion.

Dr. Young suggested that it would be useful to create another work group to talk about how to communicate, even with regard to aggregate results. If the work group thought individual results should be returned, it then could discuss how to do that. Dr. Halanych added that the issue of how to communicate is a stumbling block for many, because communication can be done so poorly.

Dr. Schonfeld recommended that a decision be made on whether the issue remains a priority because tackling how to communicate would be central to whether results should be returned. How to communicate would demand significant time. Dr. Parkin stated that she was comfortable with tabling the issue until EPA determines whether it remains a priority. She asked if that was agreeable to all of the Board members, and they responded affirmatively. She then asked for any other comments or additional thoughts.

Closing Remarks

Mr. Downing announced that the next meeting was scheduled for November 5–6, 2014, and the exact times will be posted in the *Federal Register*. Ms. Sherman added that the meeting will address old toxicity studies on nitrogen dioxide, a protocol from the Agricultural Handlers Task Force on a solid-pour protocol, and a final two-part study on the treatment of rights-of-way with handgun sprayers and backpack applications combined into a monograph.

Dr. Parkin thanked the Board members for their diligence and good work and stated that a report with writing timelines and instructions will be sent to the members. She also will leave as a final document a set of recommendations on the format for submitting comments and style issues. It was difficult to synchronize the last report. Mr. Downing added that a standardized approach would facilitate creating a final report.

Mr. Jordan thanked Dr. Parkin for her service, noting that she had managed the HSRB superbly well as Chair, ensuring that all topics were covered and everyone was heard. Mr. Downing stated that the April 2014 report had been received and a final draft would be sent out shortly for the Board's concurrence. Dr. Parkin explained that the process would occur via email. Mr. Downing noted that if a conference call is deemed necessary to address major issues, a public meeting must be announced in the *Federal Register* 15 days prior. He thanked the members for their participation and adjourned the meeting at 4:20 p.m.

Respectfully submitted:

Jim Downing
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

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

Rebecca Parkin, Ph.D., MPH
Professorial Lecturer, EOH and Epidemiology & 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

Liza Dawson, Ph.D.
Research Ethics Team Leader
Divisions of AIDS, National Institutes of Health (NIH)
National Institutes of Allergy & Infectious Diseases (NIAID)
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

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

Sidney Green, Jr., Ph.D., Fellow, ATS
Retired
Department of Pharmacology
Howard University College of Medicine
Silver Spring, MD

Members (continued)

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.
Professor Emeritus
Department of Biology
Utah State University
Logan, UT

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

Leonard Ritter, Ph.D., ATS
Professor Emeritus (Toxicology)
School of Environmental Sciences
University of Guelph
Guelph, Ontario, Canada

Linda J. Young, Ph.D.
Chief Mathematical Statistician and Director
USDA National Agricultural Statistics Service
Research and Development Division
Fairfax, VA

Attachment B

FEDERAL REGISTER NOTICE ANNOUNCING MEETING

[*Federal Register* Volume 79, Number 101 (Tuesday, May 27, 2014)]
[Notices]
[Pages 30135–30137]
From the *Federal Register* Online via the Government Printing Office [www.gpo.gov]
[FR Doc No: 2014–12172]

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ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–ORD–2014–0411; FRL–9911–45–OA]

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 (HSRB) to advise the Agency on the EPA ethical and scientific reviews of research with human subjects.

DATES: This public meeting will be held on June 11, 2014, from approximately 10:30 a.m. to approximately 4:00 p.m. Eastern Time. Comments may be submitted on or before noon (Eastern Time) on Friday, June 4, 2014.

ADDRESSES: The meeting will be held at the Environmental Protection Agency, Conference Center, Lobby Level, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA 22202.
Comments: Submit your written comments, identified by Docket ID No. EPA–HQ–ORD–2014–0411, by one of the following methods:
Internet: http://www.regulations.gov: Follow the website 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 West Building, located 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 online at 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 (CBI) 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: Seating at the meeting will be on a first-come basis. To request accommodation of a disability, please contact the persons listed under **FOR FURTHER INFORMATION CONTACT** at least ten business days prior to the meeting using the information under **FOR FURTHER INFORMATION CONTACT,** so that appropriate arrangements can be made.
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.
Web cast: This meeting may be webcast. Please refer to the HSRB Web site, http://www.epa.gov/hsrb/ for information on how to access the webcast. Please note that the webcast is a supplementary public process provided only for convenience. If difficulties arise resulting in webcasting outages, the meeting will continue as planned.

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

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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.**

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 last week of May 2014. 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 CONTACT.**

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–2014–0411 in the subject line on the first page of your request.
1. *Oral comments.* Requests to present oral comments will be accepted up to Friday, June 6, 2014. 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 at the meeting. 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, Friday, June 6, 2014, 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 by June 4, 2014. 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 June 11, 2014, EPA's Human Studies Review Board will consider scientific and ethical issues surrounding these topics:
    a. Published report by Gardner et al (1988) of an intentional exposure human study measuring the effects of low dose oral iodide supplementation on thyroid function
    b. Published report by Paul et al (1988) of an intentional exposure human study measuring the effects of small increases of dietary iodine on thyroid function
    c. Published report by LeMar et al (1995) of an intentional exposure human study measuring the effects of chronic tetraglycine hydroperiodide water purification tablet use on thyroid function
    d. Discussion of a report from the HSRB Work Group of the Return of Individual Research Results.
2. *Meeting minutes and reports.* Minutes of the meeting, summarizing the matters discussed and

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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.**

Dated: May 15, 2014.
Robert Kavlock,
Interim Agency Science Advisor.
[FR Doc. 2014–12172 Filed 5–23–14; 8:45 am]
BILLING CODE 6560–50–P

Attachment C

U.S. ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD
JUNE 2014 PUBLIC MEETING AGENDA

Environmental Protection Agency Conference Center
Lobby Level—One Potomac Yard (South Bldg.)
2777 S. Crystal Drive, Arlington, VA 22202

Wednesday, June 11, 2014

HSRB WEBSITE: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA–HQ–ORD–2014–0411

10:30 a.m. **Convene Public Meeting—**Jim Downing, Designated Federal Officer, Human Studies Review Board (HSRB), Office of the Science Advisor, EPA
Introduction of Board Members—Rebecca Parkin, Ph.D., M.P.H., HSRB Chair
Opening Remarks—Toby Schonfeld, Ph.D., Human Subjects Research Review Official, EPA
Welcome—Mr. Jack Housenger, Director, Office of Pesticide Programs (OPP), Office of Chemical Safety and Pollution Prevention, EPA

Session 1: **A published report by Paul *et al.* (1988) of an intentional exposure human study measuring the effects of small increases of dietary iodine on thyroid function**

10:45 a.m. **EPA Science Review—**Lt. Jonathan Leshin, Ph.D. (OPP, EPA)
11:00 a.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), EPA staff
11:15 a.m. **EPA Ethics Review—**Ms. Kelly Sherman (OPP, EPA)
11:25 a.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), EPA staff
11:35 a.m. **Public Comments**
11:40 a.m. **Board Discussion**

Charge to the Board—Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine?

Charge to the Board—Ethics:

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

Session 2: **A published report by Gardner *et al.* (1988) of an intentional exposure human study measuring the effects of low dose oral iodide supplementation on thyroid function**

12:05 p.m. **EPA Science Review—**Lt. Jonathan Leshin, Ph.D. (OPP, EPA)
12:20 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), EPA staff
12:30 p.m. **EPA Ethics Review—**Ms. Kelly Sherman (OPP, EPA)
12:40 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), and EPA staff
12:50 p.m. **Public Comments**
12:55 p.m. **Board Discussion**

Charge to the Board—Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine?

Charge to the Board—Ethics:

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

1:20 p.m. **Lunch**

Session 3: **A published report by LeMar *et al.* (1995) of an intentional exposure human study measuring the effects of chronic tetraglycine hydroperiodide water purification tablet use on thyroid function**

2:00 p.m. **EPA Science Review—**Lt. Jonathan Leshin, Ph.D. (OPP, EPA)
2:15 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), EPA staff
2:25 p.m. **EPA Ethics Review—**Ms. Kelly Sherman (OPP, EPA)
2:35 p.m. **Board Questions of Clarification—**Rebecca Parkin, Ph.D., M.P.H. (HSRB Chair), EPA staff
2:45 p.m. **Public Comments**
2:50 p.m. **Board Discussion**

Charge to the Board—Science:

- Is this study scientifically sound, providing reliable data?
- If so, is this study relevant to establish the reversibility of high-dose iodine exposure?
- Also, is this study sufficient to establish that there are no sustained adverse effects from high-dose iodine exposure?

Charge to the Board—Ethics:

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

3:20 PM **Discussion of HSRB Work Group on Return of Individual Research Results Report**

4:00 p.m. **Adjourn**