August 15, 2014

EPA-HSRB-14-02

Robert Kavlock, Ph.D.
Interim EPA Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: June 11, 2014 EPA Human Studies Review Board Meeting Report

Dear Dr. Kavlock,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) provide scientific and ethics reviews of three pre-Rule publications relating to oral ingestion of iodine. For each of these reports, the Agency charged the Board with specific scientific and ethics charges. These questions and the issue of the return of individual research results to study participants were discussed in the Board's meeting held on June 11, 2014. The Board's key responses to the charge questions are summarized in this letter and are detailed in the enclosed final meeting report.

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

Science

- The Board determined that the study was scientifically sound and does provide reliable data.
- The Board determined that the study would be relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine.

Ethics

- The Board concluded that the published report by Paul *et al* (1988) submitted for review meets the applicable requirements of 40 CFR part 26 subpart Q.

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

Science

- The Board concurred that the study is scientifically sound, providing reliable data. However, the lack of details in the analytic methods and less than robust statistical analysis weakened the HSRB's ability to evaluate all aspects of the study's scientific soundness. The Board did not find clear and convincing evidence that the conclusions drawn from this study are not reliable.
- The HSRB concluded that this study is relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine. However, the hormone levels and changes in T_4 observed in this study should be viewed as qualitative in nature. In contrast, the changes in thyroid function are sufficiently reliable to be used in a weight-of-evidence analysis.

Ethics

- The Board concluded that the published report by Gardner *et al* (1988) submitted for review meets the applicable requirements of 40 CFR part 26 subpart Q.

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

Science

Subject to several limitations, the Board concluded that:

- The study is scientifically sound and provides reliable data.
- This study would be relevant in a weight-of-evidence approach for establishing the reversibility of high dose iodine exposure.
- This study would be relevant in a weight-of-evidence approach for establishing that there are no sustained adverse effects from high dose iodine exposure.

Ethics

- The HSRB concurred that the published report by LeMar *et al* (1995) submitted for review meets the applicable requirements of 40 CFR part 26 subpart Q.

Sincerely,

Rebecca T. Parkin, PhD, MPH
Chair
EPA Human Studies Review Board

NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use. You may obtain further information about the EPA Human Studies Review Board from its website at http://www.epa.gov/osa/hsrb. You may also contact the HSRB Designated Federal Officer, via e-mail at ord-osa-hsrb@epa.gov

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

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HUMAN STUDIES REVIEW BOARD

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Jim Downing, Executive Director, Human Studies Review Board Staff, Office of the Science Advisor, United States Environmental Protection Agency, Washington, DC

*Participated via Adobe Connect.

INTRODUCTION

On June 11, 2014, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to three publications conducted before promulgation of the 2006 Human Studies Rule (U.S. Environmental Protection Agency (EPA), 2006). To conduct a quantitative risk assessment of oral exposure to iodine, the Agency must determine the toxic effects and point of departure for iodine exposure. EPA selected the three publications for HSRB review from larger sets of studies, examined by the Institute of Medicine (Institute of Medicine (IOM), 2001) and the Agency for Toxic Substances and Disease Registry (Agency for Toxic Substances and Disease Registry (ATSDR), 2004), concerning the ingestion of iodine for nutritional purposes.

The Board also discussed its Work Group's report on returning individual research results to study participants; this report was submitted to the HSRB during their April 8-9, 2014, meeting and was appended to that meeting's Final Report.

The four agenda items included in this meeting report are:

- 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
- 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
- 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
- HSRB Work Group Report on the Return of Individual Research Results

REVIEW PROCESS

The Board conducted a public meeting in Arlington, Virginia, on June 11, 2014; eight members were present in the meeting room and six members joined the meeting via Adobe Connect. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meeting" (EPA, 2014, pp. 30135-30137).

Following welcoming remarks from Agency officials, the Board heard presentations from EPA on each of the first three published reports listed above. The HSRB Chair introduced the discussion of the fourth report. This Final Report of the meeting describes the discussion, recommendations and rationale in response to each charge question for the first three reports; it summarizes the discussion and consensus of the Board regarding the fourth agenda item.

For each published report, Agency staff first presented their review of the science components of the publication and the Board asked the Agency presenters clarifying questions about the science. The staff then described their review of the ethical aspects related to the publication and the Board asked clarifying questions about the ethical issues. The Board solicited public

comments and next asked Agency staff to read the Charge Questions for the published report under consideration. The Board discussed the science questions first and then the ethics question. Upon conclusion of the discussion of each question, the Chair called for a vote to confirm concurrence on a summary statement in response to that question.

For their evaluation and discussion, the Board considered materials presented at the meeting, oral comments, a comment from the public, the original published reports, and the Agency's science and ethics reviews of the publications. A comprehensive list of background documents is available online at http://www.epa.gov/hsrb/. At the same website, a copy of the Work Group report is appended to the Final Report of the HSRB's April 8-9, 2104, meeting.

CHARGE TO THE BOARD AND BOARD RESPONSE

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

Overview of the Study

Paul *et al* (1988) conducted a study of euthyroid adults (9 males and 23 females 23-56 years old) to identify a tolerable upper limit for iodine consumption. While maintaining their usual diets over a 14-day period, the female participants took sodium iodide dissolved in water at one of three dosages (250, 500 or 1500 µg per day) along with 5 mg/day of ascorbic acid. In the same manner the male participants received only the 1500 µg per day dose. The authors found no change in weight and no symptoms of thyroid dysfunction in any of the study participants. Using the Student's paired t-test, they reported small but statistically significant ($p<0.01$) decreases in serum T_4 and T_3 concentrations and the free T_4 index, as well as small but statistically significant increases in serum thyrotropin (TSH) and thyrotropin-releasing hormone (TRH)-induced TSH. The changes were within normal ranges for TSH and TRH; the findings were not indicative of adverse effects.

This intentional exposure human toxicity study of iodine impacts on thyroid function was conducted among adult subjects. There is no information available about the population used to recruit these individuals. Subjects were told of the possible risks and were given the option to withdraw at any time. They provided written consent but were not paid for their participation in the study. Upon further investigation, no record of Institutional Review Board (IRB) review, approval or oversight was reported or found.

Science

Charge to the Board

- 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?

Board Response to the Charge

HSRB Recommendations

- The Board determined that the study was scientifically sound and does provide reliable data.
- The Board determined that the study would be relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine.

HSRB Detailed Recommendations and Rationale

Overall, the Board agreed with the Agency's scientific assessment of this study (Leshin, 2014a). The HSRB noted that its comments were in the context of the Agency's intended use of the study in a weight-of-evidence (WOE) approach. Most of the Board's discussion focused on limitations of the statistical analysis.

Is this study scientifically sound, providing reliable data?

1. Second treatment one year later
   Questions were raised about the authors' statement that "some of the women were studied at two dose levels at least one year apart" (Paul *et al*, 1988, p. 122). Why was this information included in the study when no rationale was given for this second treatment?

2. Statistical issues
   Based on the limited and inadequate descriptions regarding statistical design and the results reported in this study, it is difficult to assess the statistical validity of the findings thoroughly. For example, it is unclear how the total sample size of 32 can be reconciled with the values in column N of Table 1. However, the reported findings could be considered as statistically valid if we assume that (1) the duplicate assay values used in the study were treated as subsamples (not as true replications), and (2) the paired difference means were analyzed in comparing treatments (0 and 15 days on the same subject) and the reported *p-values* in Table 1 (Paul et al, 1988, p. 122) were associated with testing the null hypothesis from a paired t-test where the paired differences between 0 and 15 days means were compared (not based on the reported means for 0 and 15 days in Table 1).

If so, is this study relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine?

1. Tolerable upper limit
   The Board agreed with the authors' assertion (Paul *et al*, 1988, p. 123) that there are groups of individuals who are uniquely susceptible to the adverse effects of iodine, and consequently thought it is difficult to define an upper limit of normal for the daily iodine intake. This issue was emphasized because the EPA expressly desired to use this study in establishing a tolerable upper limit for the oral ingestion of iodine. The Agency explained that this study would be used as part of a WOE approach to establish such an upper limit. The Board

thought this was a reasonable approach and, if used in this fashion, the study could support an assessment of the risk of oral exposure to iodine.

Ethics

Charge to the Board

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

Board Response to the Charge

HSRB Recommendation

- The Board concluded that the published report by Paul *et al* (1988) submitted for review meets the applicable requirements of 40 CFR part 26 subpart Q.

HSRB's Detailed Recommendation and Rationale

The standard outlined in 40 CFR 26 subpart Q (U.S. Environmental Protection Agency (EPA), 2010) requires that EPA must not rely on data from a study that either involves a) intentional exposure of pregnant or nursing women or children or b) clear and convincing evidence of unethical conduct, defined specifically as one or more of the following: studies involving intentional serious harm to study participants; deficiencies in study conduct relative to prevailing ethical standards; or unethical recruitment such that informed consent is impaired. The Board concluded that there is no evidence that the published report by Paul *et al* (1988) submitted for review involved pregnant or nursing women, nor is there evidence of unethical conduct as defined above. Therefore, as defined by the regulation 40 CFR part 26 subpart Q, the study meets the requirements for use by EPA.

The article by Paul *et al*, published in February 1988 in *Metabolism*, is the report of a trial intended to test the effects of a small increase in dietary iodine on thyroid function in normal (euthyroid) volunteers. The investigation was not intended as a study of intentional exposure to a toxin, but rather was identified by the Office of Pesticide Programs (OPP) as a potential source of data for EPA decision-making.

The Board agreed with the OPP review (Sherman, 2014a) that the article fails to report on a number of facts relevant to ethical review. At the time that the study was carried out, the 1985 version of 45 CFR 46 (Williams, 2005)[1] required institutional review board (IRB) approval of human participant studies funded by the Department of Health and Human Services (DHHS) which includes the National Institutes of Health (NIH). The authors reported that the study was funded by NIH, which required documentation of IRB review as part of its grant-making procedures. However, the article does not mention IRB review and, when interviewed by phone by EPA's Jonathan Leshin (Sherman, 2014a, p. 7), the study's senior author, L.E. Braverman, had no memory of whether the study had undergone IRB review. Inquiries by EPA's Kelly

[1] For a timeline of the regulations related to the protection of human subjects in research, see http://history.nih.gov/about/timelines_laws_human.html#1983.

Sherman, found that the IRBs at the three institutions[2] where this work might have been reviewed have no records from that period. NIH's archived records from the period of the study do not include information on IRB review. The applicable regulations at 45 CFR Section 46.116 would also have required informed consent by participants and documentation with a consent form containing all required elements of consent, unless written documentation was waived by an IRB (45 CFR 46.117); however, no records regarding informed consent are available.

1. The Board concurred with the conclusions of the OPP's Ethics Review (Sherman, 2014a) that the reported research does not rely on data from intentional exposure of any human subject who is a pregnant or nursing woman or a child. There is no clear and convincing evidence that the conduct of the research was fundamentally unethical. There is no evidence that the research intentionally placed participants at risk of serious harm (based on the knowledge available at the time the study was conducted). Because the study most likely involved only minimal risk, the possibility of unethical conduct is significantly reduced. Regardless of risk level, it is still essential for study participants to be properly informed and given opportunity to consent. No information is available on the recruitment processes used for the study, nor is there any documentation regarding research participants' ability to give informed consent or the informed consent process itself.

    a. Assessment of risks and benefits: The authors stated that the quantity of iodine consumed by many Americans in their regular diet is greater than that necessary for maintenance of normal thyroid function, suggesting that knowledge of the effects of small incremental increases over the daily requirement of iodine would be beneficial for determining a normal, acceptable, and clearly excessive level of iodine intake, and thus would be of value to society. The authors did not address additional risks to human participants from ingesting small additional amounts of iodine, or any potential benefit to participants. They made no statement about the balance between risk and benefit. However the amounts of iodine ingested by participants at the maximum dose over a two-week period were described as being within the range of the average American's normal intake, suggesting that these amounts thus posed risk equivalent to the risks of everyday life, which meets the regulatory definition of minimal risk at 45 CFR 46.102(i).

    b. Voluntary and informed consent of all participants: No information is available about recruitment or enrollment of the 37 participants, either from the article or from the interview with co-investigator Braverman. It is not possible to tell whether participants from potentially vulnerable populations were recruited or whether the study protocol included mechanisms designed to minimize coercive recruitment and enrollment.

    To participate in the study, subjects needed to be healthy, non-pregnant, euthyroid adults. Women underwent pregnancy testing. Per Braverman (Sherman, 2014a, p. 7), any woman whose pregnancy test was positive would have been excluded, and no women participants were nursing (Sherman, 2014a, p. 8).

[2] University of Massachusetts Medical School, the Medical College of Virginia, and Beth Israel Hospital: These were the affiliations listed by the authors.

As stated above, no authoritative information was available about the study's informed consent materials or process, although senior investigator Braverman reported that participants gave informed consent and signed documents (Sherman, 2014a, p. 7).

c. Equitable selection of study participants: It is not possible to determine whether members of vulnerable populations were recruited or enrolled in the study. Per Braverman (Sherman, 2014a, p. 7), participants were not compensated for taking part in the study.

2. The Board recommended that the data within this article be considered acceptable for EPA reliance, contingent upon the determination of its scientific validity.

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

Overview of the Study

As in Paul *et al* (1988), this study was conducted to determine a tolerable upper limit for iodine consumption. Gardner *et al* (1988) examined 30 euthyroid males (ages 22-40) who had no history of thyroid disease, had not been on medications that affected thyroid function, or had a prior reaction to iodine. Each individual served as his own control. Over a 14-day period while maintaining his normal diet, each individual was randomly assigned to consume sodium iodide dissolved in water at 500, 1500 or 4500 µg/ml. The assigned dose was administered, along with 1 mg/ml ascorbic acid, twice a day in 0.5 ml solutions. Compared to baseline measures, post-administration measures of thyroid function revealed that at 1500 and 4500 µg/ml statistically significant ($p<0.02$) decreases in serum and free thyroxine (T_4) occurred. At all three dosages, basal and TRH-induced TSH were found to be significantly ($p<0.05$ or less) increased.

The study subjects were medical students or employees of the Medical College of Virginia, or were selected from a list of interested research candidates. The study protocol was reviewed and approved by the Virginia Commonwealth University (VCU) Committee on the Conduct of Human Research. Although each subject provided written consent and was compensated for their participation, there is no information about whether subjects were told they could withdraw at any time.

Science

Charge to the Board

- 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?

Board Response to the Charge

HSRB Recommendations

- The Board concurred that the study is scientifically sound, providing reliable data. However, the lack of details in the analytic methods and less than robust statistical analysis weakened the HSRB's ability to evaluate all aspects of the study's scientific soundness. The Board did not find clear and convincing evidence that the conclusions drawn from this study are not reliable.
- The HSRB concluded that this study is relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine. However, the hormone levels and changes in T_4 observed in this study should be viewed as qualitative in nature. In contrast, the changes in thyroid function are sufficiently reliable to be used in a weight-of-evidence analysis.

HSRB Detailed Recommendations and Rationale

While the authors are experienced researchers in this field and designed a reasonable study, the Board expressed some concern that this particular publication did not provide sufficient details in their analytic methodologies and in their rationale for the grouping of samples during analysis. Two additional limitations were the lack of statistical use of duplicate measurements and the finding that most of the mean thyroid response data did not correlate with the doses of iodine tested.

Is this study scientifically sound, providing reliable data?

1. Grouping
   The Board discussed the dose groups and the grouping of samples for analysis.

   a. The first of the uncertainties of the publication is the actual distribution of the subjects within the three dose groups. On p. 284, Gardner *et al* (1988) stated that "Thirty normal men between the ages of 22 and 40 years (mean age 27) were randomly assigned to receive 500, 1500 or 4500 µg iodide/day." However, the authors did not say in any text or table that these subjects were distributed evenly at 10 people per dose. This distribution is reasonable, but it is an assumption made in this review due to its omission within the text.

   b. It is unusual for an article to mention how the samples were grouped during their analysis, suggesting that batch-to-batch variability within one or more analytical methods might be an issue. No information was provided regarding the various analytic methods' variability. The methods used to measure serum hormone levels were cited but not provided for review; the methods used to measure serum iodide levels were not mentioned (only that the samples were analyzed by a commercial lab).

      In contrast to the grouping of samples by Paul *et al* in which "all serum samples for a given test were assayed in the same assay" (Paul *et al*, 1988, p. 122), in Gardner *et al:* "All samples from an individual man were analyzed in the same assay" (Gardner *et al*, 1988, p. 285). Analyzing all samples in the same assay has the advantage of eliminating

the effect of any batch-to-batch variability within the analytical method. By grouping all samples from a given individual together, batch-to-batch variability in the measurements by Gardner *et al* (1988) would not affect a given individual's change in hormone level, but it still could leave the values of the group means vulnerable to batch-to-batch variability.

2. Duplicate measurements

   The HSRB considered the use of the duplicate measurements, noting that the use of duplicate samples is very important, especially for finding small differences in a method with intrinsic variability. As above for Paul *et al* (1988), the authors of Gardner *et al* (1988) stated on p. 284 that serum hormone and T_3-charcoal uptake ratios "were measured in duplicate," but no paired data or information regarding the methods' precision or typical intra-personal variability was provided. Furthermore, the Student's paired t-test did not allow the duplicate data to be used. For statistical purposes, the duplicate data should have been considered as repeated measures.

If so, is this study relevant for quantitative use in support of an assessment of the oral risk of exposure to iodine?

1. Lack of correlation
   Board members raised concerns about the lack of correlation between iodine levels and effects measured in either thyroid function or hormone levels.

   a. The statistically significant changes in hormone levels reported in Table 2 are in the range of 8 to 14%; all of these endpoints fall within normal limits. The coefficient of variation in the standard error of the inter-personal mean T_4 levels on any day ranged from about ±5 to ±8%; but both the intra-personal variability and the method variability are unknown. Prior research trying to measure similarly small changes in cholinesterase enzyme activity with an imprecise assay has shown that neglecting the effect of method variability both within a person and from batch-to-batch could yield incorrect conclusions (Yager *et al*, 1976; Trundle and Marcial, 1988; Brock and Brock, 1990). It may be possible to estimate the statistical impact of method variability in this case if some quantitative information on its magnitude can be obtained.

   b. The Board noted a lack of an expected dose-response correlation within most of these authors' data. A correlation between dose and effect (a change in either hormone level or thyroid function in this case) is axiomatic in the field of toxicology. Because the authors did not provide individual data, the Board was restricted to observing the consistency of trends and testing for correlations among the mean values. The urinary iodine excretion reported in Table 1 (Gardner *et al*, 1988, p. 285) increased in relation to dose,[3] although even its correlation r^2 value of 0.996 is not statistically significant with only three mean values. In contrast, the statistically significant changes in mean serum thyroid hormone levels reported in Table 2 (Gardner *et al*, 1988, p. 286) (decreases in T_4 and free T_4 index) were not consonant with dose, either in their magnitude or in their level of

[3] This would be expected based on mass-balance considerations and as noted by the authors.

statistical significance; in fact, by both metrics, the changes in hormone levels at 4500 µg/day were less than at 1500 µg/day. It should be noted that an inverse dose response is what was expected and was not clearly established; i.e., as the dose of iodine increases, the levels of thyroxine T_4 and triiodothyronine T_3 should have decreased. Most (4 out of 5) of the changes in the mean TRH-stimulated TSH concentrations reported in Table 3[4] increased consistently with dose, except at 15 minutes; only the changes at 45 minutes were significantly correlated with dose at a $p < 0.01$.

The lack of a correlation between dose and response for either hormone levels or TSH response to TRH stimulation may be accounted for by fluctuations in baseline values among study participants. While such fluctuations may be taken into consideration as part of a different statistical analysis than has been used thus far, questions about the biological fidelity of the findings remain given that, despite findings of statistical significance in the dataset, all values reported fall well within the range of normal clinical values.

There seems to be some disagreement among studies about how typical such mixed results might be. On p. 287, Gardner *et al* (1988) state that "previous studies have demonstrated that pharmacological doses of 10 to 1000 mg/day for 2-11 weeks resulted in significant decreases in serum T_4 and free T_4 concentrations, and compensatory increases in serum TSH concentrations." However, on p. 123, Paul *et al* (1988)[5] state that such doses result "in a small increase in both basal serum TSH concentrations and the TSH response to TRH, *sometimes* [emphasis added] in association with decreased serum concentrations of T_4 and T_3."

Read in isolation, the statistical significance of changes in mean hormone levels observed by Gardner *et al* (1988) indicates that some change is probably occurring, but the lack of a dose-response correlation in this study weakens the attribution of dose to the significant differences in reported hormone levels. Despite the weak correlation of changes in mean thyroid function with dose, the generally coherent trends in these changes are in agreement with other studies, cited by Paul *et al* (1988) and Gardner *et al* (1988), at higher dose levels.

2. The large number of t-tests resulted in a higher than expected number of significant results. The statistical test results in this study should not be used quantitatively for supporting an assessment of the oral risk of exposure to iodine.

Ethics

Charge to the Board

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

[4] According to the authors, this indicated "a definite anti-thyroid effect" (Gardner *et al*, 1988, p. 287). One Board member stated that the acute TSH reaction may not be an indicator of such an effect.

[5] The authors cited two more than the four references noted by Gardner *et al* (1988) on p. 287.

Board Response to the Charge

HSRB Recommendation

- The Board concluded that the published report by Gardner *et al* (1988) submitted for review meets the applicable requirements of 40 CFR part 26 subpart Q.

HSRB's Detailed Recommendation and Rationale

The requirements in 40 CFR 26 subpart Q (U.S. Environmental Protection Agency (EPA), 2010), which guided this review, are listed above in the HSRB's review of Paul *et al* (1988) above. The Board concluded that there is no evidence that the study reported in Gardner *et al* (1988) submitted for review involved pregnant or nursing women or children, and there is no evidence of unethical conduct as defined above. The study therefore meets the requirements of 40 CFR part 26 subpart Q for use by EPA.

The article by Gardner *et al*, published in 1988 in *Clinical Endocrinology*, is the report of a trial intended to test the effects of very low dose iodine supplementation on thyroid function in normal (euthyroid) adult male volunteers. The investigation was not intended as a study of intentional exposure to a toxin, but rather was identified by the Office of Pesticide Programs as a potential source of data for EPA reliance.

In the Materials and Methods section of the article, the authors reported that the study was approved by VCU's IRB for the protection of human subjects ("The Committee on the Conduct of Human Research"), which at that time would have been operating under the 1985 version of 45 CFR 46 (Williams, 2005). They also reported that "each man gave informed written consent" (Gardner *et al*, 1988, p. 284).

When interviewed by OPP staff in February 2014, the article's first author, DF Gardner, reported that participants were given an opportunity to read the study protocol and asked if they understood, and then each man signed a written informed consent document. No additional information was requested from VCU's IRB, but it may be assumed that the Committee followed the regulatory requirements in place at the time the study was reviewed.

1. The Board concurred with the conclusions of the OPP's Ethics Review (Sherman, 2014b) that the reported research does not rely on data from intentional exposure of any human subject who was a pregnant or nursing woman or a child. There is no clear and convincing evidence that the conduct of the research was fundamentally unethical. There is no evidence that the research was conducted in a way that placed participants at increased risk of harm (based on the knowledge available at the time the study was conducted). Because recruitment processes were directed toward students and employees of the medical school where the study was conducted, the participants' ability to give informed consent may have been impaired by coercion.

    a. Assessment of risks and benefits: The authors reported that the quantity of iodine consumed by many Americans in their regular diet is greater than that necessary for maintenance of normal thyroid function, suggesting that knowledge of the effects of

small incremental increases over the daily requirement of iodine would be beneficial for determining a normal, acceptable, and clearly excessive level of iodine intake, and thus would be of value to society. The authors did not address additional risks to human participants from ingesting small additional amounts of iodine, or any potential benefit to participants. The Board found no statement of the balance between risk and benefit in the article. However, the amounts of iodine ingested by study participants were described as being within the range of the average American's normal intake, suggesting that the amounts thus posed minimal risk equivalent to the risks of everyday life.

b. Voluntary and informed consent of all participants: Participants were recruited from among students and employees of the Medical College of Virginia or a list of potential volunteers kept by the institution's Clinical Research Center. It is not possible to tell whether participants from potentially vulnerable populations were recruited, or whether the study protocol included mechanisms designed to minimize coercive recruitment and enrollment of students and employees who may have been in a subordinate position to the researchers.

   To participate in the study, subjects were required to be healthy, euthyroid adult men with no history of thyroid disease and who were not taking medications that affect thyroid function. No women and no children were enrolled.

   No authoritative information was available about the study's informed consent materials or process, although investigator Gardner reported that participants gave informed consent and signed consent documents.

c. Equitable selection of study participants: It is not possible to determine whether selection of study participants was equitable or whether members of vulnerable populations were recruited or enrolled in the study. According to investigator Gardner's telephone interview with EPA's Jonathan Leshin (Sherman, 2014b, p. 6), participants were compensated approximately $150-200 for taking part in the 2-week study that included multiple blood draws.

2. The Board recommended that the data within this article be considered acceptable for EPA decision making, contingent upon the determination of its scientific validity.

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

Overview of the Study

As in the above two studies (Paul *et al*, 1988; and Gardner *et al*, 1988), LeMar *et al* (1995) conducted a study of adults to identify a tolerable upper limit for iodine consumption, with a focus on effects of subchronic ingestion of iodine in water purification tablets (tetraglycine hydroperiodide). All seven males and one female (ages 35-47) in the study were euthyroid, had

no prior thyroid disease, had no chronic medical disorders, were not using medications which affected thyroid function, and had not had previous reactions to iodine. During the 90-day study period, the subjects maintained their normal diets; daily they self-administered four tablets (totaling 32,000 μg) dissolved in water or juice. Measures which decreased during the study period included 24-hour radioactive iodine uptake, mean serum T_4 and T_3 (triiodothyronine), while serum TSH, and TSH-20 (measured after 20 minutes) increased by the seventh day and remained elevated. Although no hypo- or hyper-thyroidism was found, thyroid volume increased an average of 37%. Among the 7 subjects for whom repeat measures were made (anywhere from 0.5 to 16.1 months after the study period), all thyroid volumes had returned to baseline levels. The authors stated that this result suggests that TSH-dependent thyroid enlargement is reversible following daily use of water purification tablets.

Participants in the study were employees of the hospital where the study was conducted (Fitzsimons Army Medical Center). The protocol was reviewed and approved by the hospital's IRB. All subjects were equitably selected; they signed a written consent form and were advised that they could withdraw at any time. They were not compensated for their participation.

Science

Charge to the Board

- 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?

Board Response to the Charge

HSRB Recommendations

Subject to the limitations noted below, the Board concluded that:

- The study is scientifically sound and provides reliable data.
- This study would be relevant in a weight-of-evidence approach for establishing the reversibility of high dose iodine exposure.
- This study would be relevant in a weight-of-evidence approach for establishing that there are no sustained adverse effects from high dose iodine exposure.

HSRB Detailed Recommendations and Rationale

The HSRB members discussed each charge question individually, carefully considering the wording of each query and their responses to each question. In particular, the Board disagreed with the word "sufficient" in the third question; no single study can be considered "sufficient" for establishing sustained adverse effects. A body of work is needed to evaluate a study in the context of other findings. Consequently, the HSRB requested permission from the Agency representatives to modify the wording of the third question; the request to change "sufficient" to "relevant" was granted.

Is this study scientifically sound, providing reliable data?

Subject to the limitations noted below, the Board concluded that the study is scientifically sound and provides reliable data.

If so, is this study relevant to establish the reversibility of high dose iodine exposure?

The weaknesses noted here decreased the Board's confidence that the LeMar *et al* (1995) paper can be used quantitatively. Following a detailed discussion, the HSRB decided that the study is relevant but not definitive by itself to establish the reversibility of high dose iodine exposure. Furthermore, the Board limited its response to the Agency's intended use of the data in a weight-of-evidence (WOE) approach. The HSRB determined that LeMar *et al* (1995) can be used qualitatively in a WOE approach, noting that the results are not sufficiently reliable for estimating reversibility quantitatively.

Board concerns related to the repeated measures study design and small sample size, the statistical methods used, and the thyroid volume reversibility data.

1. Repeated measures

   Based on the study description in LeMar *et al* (1995), the design of their experiment appears to have been a repeated measures study with either three or four unequally spaced time points, depending on whether or not baseline data are included in the analysis. Eight subjects, seven males and one female, participated in the experiment. It is commonly assumed that repeated measurements on a subject over time are correlated.

2. Statistical analysis

   The authors described their statistical analysis as "analysis of variance, followed by Student – Newman - Keuls multiple comparisons" (LeMar *et al*, 1995, p. 221). In general, the reported numerical estimates of the means do not contradict their statements regarding trends in the data. The HSRB's concern lies in the effect of the correlation and variance issues on the estimates of the standard errors and hence on the statistical significance of the results.

   The authors did not indicate the design on which their analysis was based nor did they indicate that any consideration was given to the correlation and unequal variance issues. Any analysis of their data should take into account the potential repeated measures correlation structure as well as the potential for unequal variances. Failure to account for either may impact the significance or non-significance of the reported results.

   a. The Board acknowledges that, at the time the study was conducted, explicitly adjusting for the correlation was not generally part of analysis of variance.

   b. The authors' numerical results provide evidence that, for at least some variables, the variance changed with time. For example, using the serum protein-bound iodine (PBI) data in Table 1 (LeMar *et al*, 1995, p. 221), the ratio of the largest to smallest variance is approximately 16 for the post-baseline data and about 108 if the baseline data are included.

In an attempt to judge the effect of the potential unequal variance problem, the worst case scenario (i.e., most likely to contradict the stated statistical significance of $p<0.05$; LeMar *et al*, 1995, p. 221) would be to compare the reported means using the largest reported standard error among the treatments as the standard error for all treatments in the multiple comparison procedure. Using the largest reported standard error generally confirmed the conclusions reached in the text regarding statistical significance.

The Board noted that the effects and potential corrective actions for unequal variances had been in the statistics literature since the 1950's. By the 1990's these methods were likely fairly well known outside the field of statistics and thus available at the time of the study analysis.

3. Thyroid volume reversibility

Since there was no indication that the post-experiment data on thyroid volume returning to normal were analyzed statistically, the results should be treated only as an observationally – and not a statistically – based indication of recovery.

a. Despite otherwise solid methods used by LeMar *et al* (1995, pp. 220-221), the paper contains a serious flaw in the thyroid volume data presented. The authors state that "The precision of the thyroid volume determined by this method was assessed in five [of 8] study participants, each examined on five separate occasions before the treatment period. Coefficients of variation for these thyroid volume measurements ranged from 3.6 to 13.2%" (LeMar *et al*, 1995, p. 221). However, in the next sentence they state: "The greatest volume for each of these five subjects was subsequently used as the pretreatment volume for that individual" (LeMar *et al*, 1995, p. 221). It is axiomatic in statistics that the most likely value for any single measurement is the mean for each subject. Thus, this decision to use the greatest volume for those five participants biased the results to decrease changes in thyroid volume during treatment (because these subjects' baseline volume appeared to be larger) and increase the likelihood for complete recovery to pretreatment volumes. The Board commented that the mean pretreatment volumes (both individually and collectively) were lower than the greatest volumes reported.[6]

b. Furthermore, the authors did not state that a goal of their study was to support the kinetics of either thyroid enlargement or recovery. The wide range of their recovery phase (from 0.5 to 16 months) suggests that this part of the research project was an unanticipated "add-on" to the study. Given that wide range and an average of 7.1 months for 7 of 8 subjects, the authors' observation that "the increase in thyroid volume was reversible" (LeMar *et al*, 1995, p. 222) is all the more remarkable. This bias weakens the usefulness of this study to "provide information on the effects of excess iodine in humans, which include a form of reversible thyroid gland volume increase and decreases in T_4 levels" (Leshin, 2014c, p. 5).

[6] In Figure 2 (LeMar *et al*, 1995, p. 222), the "recovery" volumes appear to be lower than the "Week 0" volumes.

Also, is this study sufficient to establish that there are no sustained adverse effects from high dose iodine exposure?

It is unlikely, from a scientific perspective, that any one study (i.e., LeMar *et al*, 1995) could be "sufficient to establish that there are no sustained adverse effects from high dose iodine exposure," as the Agency posed to the Board in this question. However, the Board recognizes and accepts that LeMar *et al* (1995) contributes significantly to scientific understanding about the lack of sustained adverse effects from high dose iodine exposure. The Board also recognizes that LeMar *et al* (1995) has been a key study on which daily maximum iodine intake levels have been established (e.g., in ATSDR, 2004). Therefore, the HSRB concluded that the study is relevant, but not sufficient, in a WOE approach for establishing whether there are sustained adverse effects for high dose iodine exposure.

Ethics

Charge to the Board

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

Board Response to the Charge

HSRB Recommendation

- The HSRB concurred that the published report by LeMar *et al* (1995) submitted for review meets the applicable requirements of 40 CFR part 26 subpart Q.

HSRB Detailed Recommendation and Rationale

The LeMar *et al* (1995) manuscript published in the *Journal of Clinical Endocrinology and Metabolism* describes a study designed to determine the effects of daily subchronic ingestion of iodine purification tablets (tetraglycine hydroperiodide) on thyroid size, function, and radioactive iodine uptake in eight healthy volunteers over a three month period. EPA's OPP has identified this study as a potential data source for EPA's human health risk assessments for products containing iodine. In addition to this manuscript, OPP also provided the HSRB with the transcript of a February 2014 interview between EPA representative Jonathan Leshin and a study co-investigator, Michael McDermott (Sherman, 2014c, p. 6).

The Agency's rules at 40 CFR part 26 subpart Q (U.S. Environmental Protection Agency (EPA), 2010) that are applicable to this review are stated above in the ethics review of the Paul *et al* (1988) study.

These rules identify three ethical issues that were discussed by the HSRB:

1. Subject profiles

    a. LeMar *et al* (1995, p. 220) reported that their study enrolled eight participants (seven men and one woman) between 35-47 years of age; thus, the study did not involve intentional exposure of any subjects who were children.

b. The manuscript makes no reference to the pregnancy or nursing status of the one female participant, but the co-investigator indicated in the interview that female participants were tested for pregnancy before study participation and that if a potential participant was pregnant, she was excluded from the study (Sherman, 2014c, p. 6). There is no indication that the subject became pregnant or was nursing in the course of the research.

c. In order to minimize risks to subjects enrolled in the study, all subjects were required to pass a physical exam prior to study activities, including thyroid level tests to verify euthyroid status. Subjects were also required to have no chronic medical conditions, not taking any medications affecting thyroid function, and not have had any reactions to iodine.

2. Introduction of intentional harm

a. The LeMar *et al* manuscript indicates that all participants provided their written informed consent prior to study participation and that the study had been approved by the institutional research committee (1995, p. 220). In his telephone conversation with EPA representatives, co-investigator McDermott confirmed that the study was reviewed and approved by the Fitzsimons Army Medical Center IRB. There was no evidence provided to the HSRB regarding the contents of informed consent processes, but applicable federal regulations at the time (Williams, 2005) specify required elements of informed consent, including a description of experimental procedures, potential risks to subjects, any potential benefits, and a notice that research participation is voluntary. Additionally, there was no documentation to verify IRB review and approval beyond the statements provided in the manuscript and by the co-investigator.

b. The authors described the research protocol (administration of water purification tablets) and the subjects' responses, including their serum and urine iodide levels, radioactive iodine uptake, and thyroid volume. Based on the data presented in LeMar *et al* (1995), the EPA Science Review, and the discussion of scientists during the HSRB meeting, the risks to subjects posed by this study of intentional exposure to free iodine do not appear to be unreasonable, unethical, or intentionally designed to seriously harm participants.

c. The HSRB considered whether the use of nuclear tracers in the RAIU procedures posed serious or unnecessary risks to participants, but after discussion among the group, the HSRB concluded that the small amount of radiation exposure (1-μCi) as described in the LeMar *et al* manuscript (1995, p. 221) did not pose unreasonable risks to study participants.

3. Prevalent ethical standards of the time

a. At the time in which this study was conducted (early 1990's) EPA's rules for the protection of human subjects at 40 CFR part 26 were not yet in effect. However, the study was supported by the United States Department of Defense, which adopted the Common Rule in 1991 (32 CFR part 219). As a result, the Common Rule provides the basic ethical regulatory framework for this investigation at the time of its conduct.

b. Common Rule provisions at the time required that a study such as this one undergo IRB review and approval prior to initiation. As noted above, the LeMar *et al* (1995) manuscript indicates that the investigation was reviewed and approved by an institutional review committee, and co-investigator McDermott indicated that the study had been under the oversight of the Fitzsimons Army Medical Center IRB. There was no official documentation provided to verify such IRB review and approval; the HSRB recommended that the EPA's OPP make an attempt to locate such records. However, given that Fitzsimons Army Medical Center is now closed, HSRB recommendations would not be contingent upon locating those records.

c. The Common Rule requires that participants in studies such as this must provide their informed consent prior to study participation. The Common Rule specifies elements that must be present in the consent process. Both the LeMar *et al* (1995) manuscript and the interview with co-investigator McDermott indicate that participants provided their informed consent prior to study participation. However, given the lack of IRB and investigator records regarding the conduct of this study, there is no documentation to indicate that the consent process met Common Rule requirements. As above, since the study location is now closed, HSRB recommendations are not contingent upon locating such records.

d. Common Rule regulations also address the issue of participant compensation. In the interview with EPA, co-investigator McDermott notes that participants were not compensated for their participation in this study. Lack of compensation in a study such as this is consistent with Common Rule standards of the time.

e. The manuscript does not describe participant recruitment practices and the interview with co-investigator McDermott provided little information on this matter. In the interview, McDermott stated: "We asked if anyone wanted to volunteer to take part in a study about iodine water purification tablets" (Sherman, 2014c, p. 6). While nothing provided to the HSRB indicates that participant recruitment was conducted in an ethical manner that was consistent with standards of the time, the information provided does not indicate that there were unethical recruitment practices taking place.

As with many of the points above, the HSRB's ability to assess the study was somewhat limited by the lack of documentation provided to support the use of this study by the EPA.

HSRB Work Group Report on the Return of Individual Research Results

Overview

On several occasions the HSRB has discussed the return of individual research results. The Board determined that the topic merited in-depth discussion by a smaller group of HSRB members and representatives of study participants and their medical providers. A Work Group was formed to deliberate about this issue; the group's workshop was held at EPA in January

2013. The Work Group membership, its process and report are included in Appendix A of the HSRB's April 8-9, 2014, Final Report.

The return of individual research results has been addressed for clinical studies and some community-based research but not for the types of laboratory or field studies within the HSRB's purview. The return of results is a timely, unresolved and evolving issue in the ethics profession.

The Work Group identified key ethical principles as the underpinnings of their deliberations: research participant's autonomy and right to know, and researchers' responsibilities to ensure trust and respect. The group also discussed the potential impacts of results on participants and sponsors, as well as on the HSRB and the Agency.

Discussion

The HSRB emphasized that the community and laboratory contexts in which the HSRB-related studies are conducted are quite different from the clinical settings that served as the foundations for the Work Group's report.

The Board decided that this topic should be considered in newer contexts; for example, in light of the recent report on handling incidental research findings (Presidential Commission for the Study of Bioethical Issues, 2013) and current risk communication knowledge.

One member noted that another committee with different expertise would be needed to discuss the "how" of returning results, whether the findings are aggregate or individual.

Board Consensus

Before deciding whether the HSRB will address this topic at a later meeting, the Board asked the Agency to determine whether returning results is a priority concern for study sponsors.

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