



OFFICE OF THE UNDER SECRETARY OF DEFENSE
3000 DEFENSE PENTAGON
WASHINGTON, DC 20301-3000

MAR 11 2009

ACQUISITION
TECHNOLOGY
AND LOGISTICS

U.S. Environmental Protection Agency
Attn: Perchlorate Comments for the OIG
c/o: OCPM (Mail code - 2491T) Room 3106
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Dear Mr. Roderick:

Enclosed please find the Department of Defense Consolidated Comments on the Office of External Review Draft Inspector General Scientific Analysis of Perchlorate, Assignment No. 2008-0010, December 30, 2008. The Department of Defense appreciates the opportunity to review this document. The enclosed technical comments are provided with the intent of bolstering the scientific credibility.

These comments represent those of the Department of Defense; all reviewing scientists are supportive of this report, agree with its overall conclusions, and the comments offered. We have identified the Service Component that originated each comment to address your request that the scientific/technical credentials of those offering comments be provided. The following individuals contributed to the enclosed executive summary and detailed comments:

Janis E. Hulla, PhD, DABT
US Army Corps of Engineers (USACE), [REDACTED]
[REDACTED]
PhD in Pharmacology [REDACTED]
Medicine, MS in Biochemistry, and BS in Microbiology [REDACTED]
[REDACTED] Diplomat of the American Board of Toxicology (DABT)

Ms. Vera Wang
Navy and Marine Corp Public Health Center (NMCPHC), [REDACTED]
[REDACTED]
Division Head, Toxicology/Human Health Risk Assessment
Environmental Programs Department
M.S. Biochemistry [REDACTED] (12 years experience in
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B.S. Industrial Chemistry, [REDACTED]
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Ms. Katharine Kurtz,
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Under Contract to the Navy and Marine Corp Public Health Center
(NMCPHC):

Mr. David Scarsella
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oncology/bioengineering). [REDACTED]

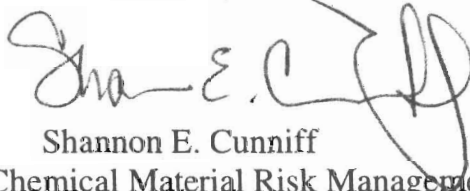
Under Contract to the U.S. Air Force:

Dr. Ivan Boyer, Ph.D. DABT
Noblis, Inc., under contract to the U.S. Air Force, [REDACTED]
[REDACTED]
Ph.D., Toxicology, [REDACTED]
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M.S., Toxicology, [REDACTED]
[REDACTED]
M.S., Biology, [REDACTED]
B.S., Biology / [REDACTED]

Mr. Andrew Rak
Noblis, Inc. under contract to U.S. Air Force, [REDACTED]
[REDACTED]
M.S., Environmental Toxicology, [REDACTED]
B.A., Environmental Science / [REDACTED]

We believe it is especially important that the public have understanding of and confidence in EPA's decision making regarding perchlorate and expect that the EPA program offices will consider, reflect, and to the extent practicable, harmonize the alternative analytical approaches offered by the OIG report when conducting their future decision making.

Sincerely,

A handwritten signature in black ink, appearing to read "Shannon E. Cunniff". The signature is fluid and cursive, with a large loop at the end.

Shannon E. Cunniff
Director, Chemical Material Risk Management

Enclosures A and B
As Stated

Attachment A

Title: Department of Defense Comments on the Office of Inspector General Scientific Analysis of Perchlorate, dated 30 December 2008

- Executive Summary - The OIG's analysis advances state-of-the-science environment health risk assessment toward meeting the vision outlined in the 2007 NAS report, "Toxicity Testing in the Twenty-First Century". The TIU cumulative risk assessment targets an important point of confluence, thyroid iodide uptake, in the toxicity pathway through which four environmental factors, ClO₄⁻, SCN⁻, I⁻ and NO₃⁻, might affect neurodevelopment. The analysts merge FDA's dietary survey data and CDC biomonitoring data with a) experimental determinations of relative iodide uptake inhibition potencies, b) hormone determinations from environmentally exposed population and c) linkages between hormone levels, iodine status and neurodevelopment affects. The approach is logical and incorporates the most recent risk assessment tools, advancements and recommendations.

- Major Issues –
 - The report would benefit from an analysis of the steps of a risk assessment to include a quantitative estimate of uncertainty in the approach.
 - The report needs to provide a balanced discussion of the issues stemming from questions about whether the reduction of iodide uptake in the thyroid should be considered to be an adverse (i.e., toxic) effect or precursor to an adverse effect.
 - There are some conclusions in the report that seem to contradict each other.
 - The relevant scientific literature should be cited to support the conclusions in the report.
 - The OIG report does not appear to consider the range of chemical risk assessments performed by the EPA. It needs to clearly define the context and scope of the conclusions regarding the use of "outdated" single chemical risk assessment approaches.
 - The report needs to identify and discuss the limitations of *in vitro* studies.
 - The OIG report should acknowledge or emphasize the substantial technical and legal limitations that often preclude a quantitative cumulative risk-based approach to the evaluation of risks from chemicals.
 - The OIG report should discuss the limitations and uncertainties associated with using the Banerjee et al. (1997) study, as well as the other epidemiological studies summarized in the report, as a basis for concluding that NIS inhibition, in general, will cause

severe hypothyroxinemia in pregnant women and mental deficits in children.

- The OIG report should provide a clear presentation of use of the scientific method in the design and interpretation of the results of epidemiological investigations.
- The treatment of [I-] as the unknown constant, X, in the derivation of the range of serum [I-] through which TIU is unchanged at a given ClO₄⁻ exposure level dismisses specific characteristics of thyroid physiology.
- The OIG report should evaluate the adequacy of using RDAs as thresholds for defining iodide deficiency.
- The OIG report should address the range of recommended iodide daily intake values and the potential impact of selecting alternate RDAs on the conclusions of the analysis, present a critical analysis of the most appropriate value for delineating the size of the iodide-deficient populations of concern, and the uncertainties associated with using an RDA for this purpose.
- When discussing percentage of total iodide uptake (%TIU) to be used as the LOAEL, the OIG report does not clearly distinguish between a measurement of effect and a measurement of exposure.

- Substantive Comments – See Table
- Editorial Comments – See Table
- List of Reviewers – with credentials

Janis E. Hulla, PhD, DABT

US Army Corps of Engineers (USACE), [REDACTED]

[REDACTED]
PhD in Pharmacology from the [REDACTED], MS
in Biochemistry, and BS in Microbiology from [REDACTED]
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[REDACTED]
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Ph.D., Toxicology, [REDACTED]
M.S., Toxicology [REDACTED]
M.S., Biology, [REDACTED]
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Mr. Andrew Rak
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M.S., Environmental Toxicology, [REDACTED]
B.A., Environmental Science [REDACTED]

Attachment B: Department of Defense Comments on the
Office of Inspector General Scientific Analysis of Perchlorate
December 30, 2008

EXTERNAL REVIEW DRAFT – FOR SCIENTIFIC REVIEW AND SCIENTIFIC COMMENT ONLY

Comments submitted by: Office of the Secretary of Defense Chemical and Material Risk Management Directorate	Organization: Department of Defense	Date Submitted: March 2009
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Comment No.	Section	Page & Paragraph (enter "Global" if report section-wide)	Comment	Suggested Action, Revision and References (if necessary)	Category*
1 DoD		Global	We would like to acknowledge the U.S. Environmental Protection Agency (U.S. EPA) Office of Inspector General's (OIG)' logical, scientific, and innovative cumulative risk assessment approach to total iodide uptake (TIU) inhibition as addressed in their External Review Draft Scientific Analysis of Perchlorate, dated December 2008. We appreciate the opportunity to participate in the public review and comment on the scientific nature of this work.		O
2 USACE		Global	The OIG's Analysis advances state-of-the-science environment health risk assessment toward	Include a quantitative estimate of uncertainty in the approach. NAS, "Toxicity Testing in the Twenty-First Century: A Vision and a	S/Major

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			meeting the vision outlined in the 2007 NAS report, "Toxicity Testing in the Twenty-First Century". The TIU cumulative risk assessment targets an important point of confluence, thyroid iodide uptake, in the toxicity pathway through which four environmental factors, ClO4-, SCN-, I- and NO3-, might affect neurodevelopment. The Analysts merge FDA's dietary survey data and CDC biomonitoring data with a) experimental determinations of relative iodide uptake inhibition potencies, b) hormone determinations from environmentally exposed population and c)	Strategy." Committee on Toxicity Testing and Assessment of Environmental Agents Washington, DC, National Academies Press, 2007. USEPA, "Concepts, Methods, and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures, and Effects: A Resource Document." Environmental Protection Agency Office of Research and Development, National Center for Environmental Assessment, Aug. 2007.	

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			<p>linkages between hormone levels, iodine status and neurodevelopment affects. The approach is logical and incorporates the most recent risk assessment tools, advancements and recommendations. However, absence of quantitative estimates of uncertainty is a missed opportunity to garner confidence in the approach. The discussion of "Approaches to Address this Public Health Issue", acknowledges that environmental health is just one component of the public health challenge and articulates a cogent strategy for the most effective and efficient federal risk</p>		

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			management.		
3 NMCPH		Global	<p>Iodide uptake inhibition (IUI) is the acronym U.S. EPA and other federal agencies have traditionally used to describe perchlorate competitive inhibition of iodide at the sodium iodide symporter (NIS). The U.S. EPA OIG's use of "total iodide uptake (TIU) inhibition" throughout this External Review Draft instead of total IUI may be confusing for some readers, thus requiring that the terminology be further clarified.</p> <p>The lack of iodine is a thyroid stressor, but cannot be described as a NIS</p>	<p>Consider addressing the use of the acronym TIU instead of IUI.</p> <p>Edit the use of the terms "iodine" and "iodide" throughout the document, and explaining the difference between them for the sake of all readers.</p>	E

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			inhibitor (as can perchlorate, thiocyanate, and nitrate).		
4 NMCPH		Global	Since the draft OIG report was released, U.S. EPA issued an Interim Drinking Water Health Advisory (Interim Health Advisory) for exposure to perchlorate of 15 µg/L in water and OSWER has also issued guidance pertinent to site clean up.	The different reports coming out of EPA – including the OIG report may further confuse the public about EPA's position. After the OIG report is released, it may be necessary for EPA to implement a comprehensive risk communication strategy to explain its decision. We recognize this is not an action the OIG can take	S
5 NMCPH		Global	Differences exist in the "key critical effect" selected for NIS uptake inhibition between (1) U.S. EPA Internal Draft Deliberative "Toxicological Review of Hydrogen Cyanide and Cyanide Salts", December 2008, which was based on	As a matter for EPA, but not necessarily for the OIG, differences may need to be resolved in the "key critical effect" selected and where it resides on the "continuum of change" from NOEL to LOAEL before finalizing the various draft EPA publications.	S

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			<p>an occupational exposure study (El Ghawabi, et al. (1975)) of thiocyanate as a metabolite, (2) U.S. EPA Pre-Decision Draft "Drinking Water: Preliminary Regulatory Determination on Perchlorate", December 2008, and (3) and the U.S. EPA OIG External Review Draft Scientific Analysis of Perchlorate.</p> <p>The OIG Scientific Analysis of Perchlorate developed a Lowest Observed Adverse Effect Level (LOAEL) based on their use of data derived from various occupational studies. This OIG cumulative risk assessment considers the total stress to the thyroid from four named</p>		

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			<p>stressors, perchlorate, thiocyanate, nitrate, and insufficient iodide. The OIG Scientific Analysis of Perchlorate states <i>"The first adverse effects in the fetus occur before the mother's thyroid performance shows any signs of stress (i.e., changes in thyroid hormone levels). Thus risk assessors should use neither maternal hypothyroidism nor hypothyroxinemia as the key biological event in a risk assessment. By contrast, the first adverse effects in the fetus occur when the maternal TIU is between 25 and 50% of normal,"</i> (page 6).</p> <p>The NAS used a no</p>		

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			observed effect level (NOEL), and only considered one chemical, perchlorate.		
6 AF	Overall	N/A	The Air Force acknowledges that this document is not intended to be a chemical risk assessment, but understands that it will likely play a role in informing future regulatory actions regarding perchlorate. In general the Air Force agrees with the findings and overall conclusions of the OIG report. Given the importance of the document we would like its findings and conclusions to be well supported, and offer the following technical	None	O

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			comments for consideration and incorporation in the document. In addition to technical comments on the OIG's report, the Air Force is also providing recommendations for further research to address some of the data gaps identified in the report.		
7 AF	Executive Summary	Page 6	The OIG report states: "...analysis of the scientific literature identified that the fetal thyroid is less able to adapt to a low TIU than the mother's thyroid." The text continues: "Therefore, the first adverse effect occurs to the fetus before the mother's thyroid performance shows any signs of stress (i.e.,	The report should cite the relevant scientific literature supporting the conclusion that "... the fetal thyroid is less able to adapt to a low TIU than the mother's thyroid." The OIG report should clarify that the premise for the conclusion that neither maternal hypothyroidism nor hypo-thyroxinemia should be used as the key biological event in a risk assessment is predicated on accepting the statement that "...the fetal thyroid is less able to adapt to a low TIU than the mother's thyroid."	S

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			<p>changes in thyroid hormone levels). Thus, risk assessors should use neither maternal hypothyroidism nor hypothyroxinemia as the key biological event in a risk assessment."</p> <p>Concern: References to the pertinent scientific literature are not provided.</p>		
8 AF	5.1.3	Page 48 - 49	Definitive statements in the OIG report indicating that hypothyroxinemia in the first 20 weeks of pregnancy produces mental deficits and attention deficit and hyperactivity disorders (ADHD) in off-spring are not adequately supported in the OIG report. The report	<p>The report should cite the peer-reviewed and published literature supporting these conclusions.</p> <p>The text should identify and discuss potential confounders and alternative explanations for observations that ADHD or mental deficits are associated with environmental exposures to chemicals.</p> <p>The last sentence of the quoted excerpt should be revised and expanded to explain that the associations observed between hypothyroxinemia and mental deficits or ADHD in epidemiological studies are not proven cause-and-effect relationships.</p>	S

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			<p>states:</p> <p>"...iodide deficiency (i.e., the lack of an adequate uptake of iodide by the thyroid) induces hypothyroxinemia, which is a thyroid condition characterized by a decrease T4 serum level and a normal or slightly elevated T3, without an increase in [thyroid stimulating hormone (TSH)] levels (i.e., TSH levels are normal)...The decrease in T4 in pregnant women with hypothyroxinemia in the first 20 weeks of</p>		

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			<p>pregnancy is associated with mental deficits and an increased frequency of ADHD in their children...Therefore, maternal hypothyroxinemia induces fetal brain damage through the same cause as maternal hypothyroidism – a decreased maternal supply of T4.”</p> <p>However, the OIG report does not cite the peer-reviewed, published literature supporting these conclusions or discuss other potential explanations</p>		

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			for the reported associations between environmental exposures to chemicals and mental deficits or ADHD.		
9 AF	5.1.4.1	Page 53	The OIG report identifies maternal hypothyroxinemia as the critical effect to be evaluated in a risk assessment of sodium/iodide symporter (NIS) inhibitors and states : "Maternal hypothyroxinemia (i.e., during pregnancy) is documented to be associated with mental deficits (e.g., ADHD) in the children... the OIG	The report should discuss the limitations and uncertainties associated with using the Banerjee et al. (1997) study, as well as the other epidemiological studies summarized in the report, as a basis for concluding that NIS inhibition, in general, will cause severe hypothyroxinemia in pregnant women and mental deficits in children.	S

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			<p>has identified the observed severe hypothyroxinemia in the Banerjee study [of] exposed workers to be an adverse effect (i.e., if severe hypothyroxinemia were to occur in pregnant woman population) from which an excess NIS inhibition RfD can be calculated from."</p> <p>Although cyanide-exposed electroplating workers examined in the epidemiological study of Banerjee et al. (1997) may have exhibited "severe hypothyroxinemia," this observation does not</p>		

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			provide a sufficient basis for OIG's conclusions that NIS inhibition, in general (including inhibition by thiocyanate, nitrate, and perchlorate), will cause severe hypothyroxinemia in pregnant women and mental deficits in their children. Note, for example, that cyanide has many well-known toxic effects, most of which can be explained by the inhibition of cellular respiration, rather than by the toxic action of its metabolite (i.e., thiocyanate).		
10 AF	8.1	Page 99	The OIG report states: "The IQ [Intelligence Quotient] level of children is associated with the amount	The text should be revised to clarify that the benefits of milk consumption on the mental development of children are not necessarily attributable to the iodide in milk.	S

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			of milk consumed... Milk is known to be a significant source of iodide in the diet." The conclusion inferred by these and other statements in this section, taken together, is not supported by references or citations to the current peer-reviewed literature. The basis for suggesting that the benefits of milk consumption on the mental development of children are solely attributable to the iodide in milk is unclear.		
11 AF	Executive Summary	Page 5	The OIG report states: "...the other common dietary NIS inhibitors, thiocyanate and nitrate, act through the same mechanism of toxicity." This	The text should be revised and elaborated to provide a balanced discussion of the issues stemming from questions about whether the reduction of iodide uptake in the thyroid should be considered to be an adverse (i.e., toxic) effect or precursor to an adverse effect.	S

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			<p>statement may be true only if the reduction of iodide uptake in the thyroid is considered an adverse effect; the NAS concluded that it is not. Critics of NAS's approach (e.g., Ginsburg and Rice, 2005) note that reduced iodide uptake is a "precursor to an adverse effect," on which EPA guidelines indicate an RfD can be based. In contrast, NAS indicated that reduced iodide uptake is a precursor, but not an "immediate precursor," to an adverse effect, and therefore their recommended RfD is based on a no observed effect level (NOEL), as opposed</p>		

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			to a no observed adverse effect level (NOAEL).		
12 AF	Executive Summary	Page 5	The OIG report concludes: "No increase in uncertainty factor value derives a perchlorate RfD that is low enough to prevent mental damage in children, by itself." Elsewhere, the report concludes that controlling exposure to perchlorate will not have a meaningful impact on adverse effects from perchlorate exposure. These conclusions appear to be contradictory.	The OIG report should clarify these conclusions because they appear to contradict each other.	S
13 AF	Entire Report	Global	The OIG report uses the term "lack of iodide," which literally means the total absence of iodide, throughout the report to mean "iodide deficiency."	The report should be revised to use the term "iodide deficiency", which more accurately describes the condition observed, or other, similar term rather than "lack of iodide."	E

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14 AF	Executive Summary	Page 5	<p>The OIG report does not correctly state the definition of the RfD. The RfD is defined on the EPA's Integrated Risk Information System (IRIS) web site as:</p> <p style="padding-left: 40px;">"An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors</p>	The report should explain how a useful RfD might be developed and applied as a non-static value (i.e., a dose that changes based on exposures to chemicals with the same target organ or mode of action).	S

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			<p>generally applied to reflect limitations of the data used."</p> <p>However, the OIG report (page 5) states: "...the perchlorate RfD is not a static value, but changes depending on the exposure level to the other three NIS stressors (i.e., thiocyanate, nitrate, or lack of iodide)."</p> <p>The idea that a useful perchlorate RfD can be a moving target is not consistent with the current concept of the RfD. No other RfDs have been developed using a non-static approach.</p>		
15 AF	2.3	Page 16	The OIG report does not appear to consider the	The OIG report should be revised to clearly define the context and scope of its conclusions regarding the use of "outdated" single	S

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			<p>range of chemical risk assessments performed by the EPA. The report states "...EPA has known that a single chemical risk assessment is an outdated approach to assessing risk. A single chemical risk assessment characterizes the potential adverse effect and quantifies the risk from only a single chemical pollutant. A single chemical risk assessment does not evaluate the combined effects from multiple chemicals acting through the same mechanism of toxicity."</p> <p>These statements are not necessarily applicable, for</p>	chemical risk assessment approaches.	

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			example, to all site-specific risk assessments conducted to inform remedial decisions. "Conventional" site-specific risk assessments under the Superfund-type site remediation programs typically involve assessing the risks from all of the contaminants (including their background concentrations) and complete exposure pathways (including food consumption, if appropriate) at a site. This total site risk assessment approach is achieved by adding together the "hazard quotients" of multiple chemical contaminants, which are calculated using the appropriate RfD for each		

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			chemical, to estimate an overall "hazard index." Further, the "single chemical" approach includes the incorporation of "relative potency factors" or "toxicity equivalency factors" for chemically related contaminants that likely share a common target or mechanism (e.g., organophosphate pesticides and polychlorinated biphenyls). Therefore, the OIG's general approach to "cumulative risk assessment" conceptually is similar to the "single chemical risk assessment" approach used in site-specific risk assessments. In their analysis, OIG incorporates		

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			<p>"lack of iodide" as a stressor that should be considered in the assessment of risks associated with NIS inhibitors or "goitrogens." However, the risk characterization in a "conventional single chemical risk assessment" equally offers risk assessors the opportunity to address the important role that iodide deficiency may play in determining the risks associated with these chemicals. Confidence in the results of any risk characterization, whether "cumulative" or "single chemical," directly depends on confidence in the data and assumptions used.</p>		

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16 AF	2.6.1	Page 27	There is still much to learn about interactions among numerous environmental stressors, including chemical contaminants. The OIG report states: "Numerous inorganic and synthetic chemicals have been documented to interfere with almost every major step in the production, transport, and peripheral tissue metabolism of thyroid hormones." Until our knowledge and confidence about these potential interactions grows substantially, and alternative "cumulative risk assessment" approaches are adequately verified and	The report should be revised to acknowledge or emphasize the substantial technical and legal limitations that often preclude a quantitative cumulative risk-based approach to the evaluation of risks from chemicals.	S /Major

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			validated, it is a mistake to characterize "conventional single chemical risk assessment" as outdated. For this reason, it is also premature to conclude that "...the only serious technical difficulty in implementing cumulative risk assessment is lack of experience and familiarity among the risk assessor community to embrace the use of cumulative risk assessment."		
17 AF	2.6	Page 23	The OIG report states "The <i>in vitro</i> modeling is required because as the complexity of the risk assessment increases (i.e., more factors evaluated), animal testing becomes neither practical	The OIG report should identify and discuss the limitations of <i>in vitro</i> studies. The report should note that the results of any <i>in vitro</i> study must be evaluated, corroborated, or interpreted using data from appropriate whole animal or epidemiological studies (e.g., pharmacokinetic and neurobehavioral toxicology data) before they can be used with an acceptable degree of confidence in a risk assessment. Conversely, it may be appropriate for the report to	S

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			nor sensitive enough to observe and define the relationship between an increasing number of stressors... no scientific techniques are available to measure subtle cognitive deficits in rat offspring." This statement implies that whole animal testing is infeasible and inadequate to produce the information needed to conduct risk assessments. The OIG report does not identify either the limitations of <i>in vitro</i> studies or the advantages of whole animal studies.	present conclusions about the inadequacies of the current <i>in vivo</i> models to "measure subtle cognitive deficits" without also concluding that the <i>in vitro</i> model will be able to overcome these difficulties.	
18 AF	2.6	Page 23	The OIG report sometimes uses the terms "effects" and "risks" incorrectly. For	The whole report should be revised to delineate clearly the difference between terms such as "risks" and "effects."	E

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			example, the report states: "...the Tonaccherra Model combines the risk from multiple chemicals into a single variable, the TIU, which measures the cumulative effect on the thyroid to the simultaneous exposure to all four NIS stressors." However, the Tonaccherra equation models the <u>effect</u> of multiple chemicals on a single target, namely the NIS. The model does not predict the attendant risks.		

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19 AF	6.1	Page 71	The OIG report should provide a clearer presentation of use of the scientific method in the design and interpretation of the results of epidemiological investigations. The report states: " when considered from a total goitrogen load, the experimental design of this epidemiological study is flipped: Taltal is the control group...y becomes the equivalent of comparing three control groups together."	The passage quoted from the OIG report should be deleted. Dependent and independent variables and controls are defined during the planning and designing phases of a study, not re-defined after the study is complete. Post-hoc re-analysis of data is generally discouraged.	S

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20 AF	8.1	Page 96	<p>The report states: "The neurodevelopmental hazard from the lack of iodide is a not threshold effect, but is better characterized by a dose-response relationship."</p> <p>In risk assessments, dose response curves are used to estimate threshold exposures for non-cancer effects and slope factors for cancer effects. A cause-and-effect relationship between exposure to a chemical and an adverse effect is determined first in the hazard assessment. If the mechanism of action suggests that there is no threshold (e.g., the one-hit hypothesis of carcinogenicity), then the toxicity value (e.g., the cancer slope factor) used in a risk assessment may be estimated by extrapolating</p>	<p>The report should be revised to clarify the relationship between dose-response curves and threshold dose concepts in risk assessments. The revised text should reflect that the threshold for an effect or response can be (and often is) estimated from a dose-response curve.</p>	S

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21 AF	9.4.1	Page 167	When discussing percentage of total iodide uptake (%TIU) to be used as the LOAEL, the OIG report does not clearly distinguish between a measurement of effect and a measurement of exposure. Defining %TIU as a measurement (or biomarker) of exposure would require better characterization of the relationships between exposures to the stressors, changes in TIU, and adverse effects of concern in the human population. In addition, appropriate approaches for addressing uncertainties would need to be developed and justified	The report should clearly indicate that the approach taken depends on defining the %TIU as a measure of effect, and discuss and evaluate the uncertainties associated with this approach.	S / Major

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			based specifically on these relationships and other factors, including data-derived expected or predicted variations in the susceptibilities and responses of individuals exposed to the stressors and the nature and expression of the measurements used to characterize exposures and responses.		
22 AF	9.4.2	Page 168	The OIG report appears to define the term No Observed Adverse Effect Level (NOAEL) incorrectly. The report states: "The traditional use of a NOAEL in a single chemical exposure a NOAEL is the lowest chemical exposure	The report should be revised to correct or clarify its usage of the term NOAEL.	E

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			level without adverse effects." The NOAEL is actually the <u>highest</u> exposure level with no observed adverse effects, as defined in EPA's online IRIS glossary.		
23 AF	9.4.1	Page 166	In the exposure assessment section, the OIG report estimates the size of the sensitive subpopulation based on the recommended daily allowance (RDA) for iodide. However, the OIG report does not evaluate the RDA, particularly of the adequacy of using the RDA as a threshold for defining iodide deficiency. The recommended iodide intakes for pregnant women listed in the report, range	The report should evaluate the adequacy of using RDAs as thresholds for defining iodide deficiency. The report should address the range of recommended iodide daily intake values and the potential impact of selecting alternate RDAs on the conclusions of the analysis. The report should present a critical analysis of the most appropriate value for delineating the size of the iodide-deficient populations of concern, and the uncertainties associated with using an RDA for this purpose	S / Major

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			from 200 ug/day to 375 ug/day; however, the variability and the uncertainty are not discussed.		
24 AF	Entire report	Global	<p>While it may not be the role of an OIG report to identify additional toxicological studies, we believe there are opportunities to better define the potential for perchlorate toxicity in exposed human populations, especially the proposed relationship between perchlorate and other "goitrogenic" anions.</p> <p>The report could be expanded to identify and recommend additional studies that should be</p>	<p>Future research that could reduce critical uncertainties include:</p> <ul style="list-style-type: none"> • The observed and proposed associations between thyroidal and neurodevelopmental effects and the combined ("cumulative") intake of I⁻, ClO₄⁻, SCN⁻ and NO₃⁻ should be characterized through additional experimental investigation. • The variability in the capacity of the hypothalamic-pituitary-thyroid axis to compensate for I⁻ deficiency when the intake of each of the "goitrogenic" anions is varied should be determined experimentally to elucidate the compensatory mechanisms involved (including potentially the up-regulation of the NIS during pregnancy and fetal and neonatal development). • The pharmacokinetics (i.e., relative rates of absorption, distribution, metabolism, and elimination) of I⁻, ClO₄⁻, SCN⁻ and NO₃⁻ during combined exposure to these chemicals should be investigated. These studies are warranted to describe likely pharmacokinetic interactions among these 	S

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			performed to better define the potential for perchlorate to cause adverse effects in exposed human populations, including confirmation and elucidation of the proposed relationships among perchlorate and other "goitrogenic" anions.	<p>ions, in addition to the competitive interactions at the level of the NIS observed <i>in vitro</i>, for example, by Tonacherra et al. (2004). Well-designed and executed whole animal studies are needed to support the development of pharmacokinetic models.</p> <p>The kinds of studies listed above would be especially likely to reduce the significant uncertainties in the cumulative risk assessment attributable to inadequate data in these and other areas.</p>	