

**Science Advisory Board (SAB) Draft Advisory Report (November 9, 2012)
For Discussion to Assist Meeting Deliberations**

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The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for
Perchlorate

Dear Administrator Jackson:

Perchlorate is both a naturally occurring and man-made chemical that is used to produce rocket fuel, fireworks, flares, and explosives, and can be present in bleach and fertilizers. The Environmental Protection Agency identified perchlorate as a potential drinking water contaminant because it may have an adverse health effect and has been detected in public water systems.

In 2005, at the request of the EPA and other federal agencies, the National Research Council published a comprehensive report *Health Implications of Perchlorate Ingestion*. The NRC concluded that perchlorate could affect thyroid function by inhibiting the transport of iodide into the thyroid, which can lead to thyroid hormone deficiency. Decreased levels of thyroid hormone can have adverse effects in sensitive populations such as people with thyroid disorders, pregnant women, fetuses, and infants.

The NRC recommended the use of inhibition of iodide uptake, a precursor non-adverse effect, to derive a reference dose for perchlorate. The RfD was based on the no observed effect level of 7 $\mu\text{g}/\text{kg}/\text{day}$, corresponding to a radioactive iodide uptake inhibition of 1.8 percent, and application of an uncertainty factor of 10 to account for differences in sensitivity between the healthy adults and the most sensitive population, namely fetuses of pregnant women who might have hypothyroidism or iodide deficiency. The NRC concluded that this RfD should be protective of the health of sensitive populations, but acknowledged that it might need to be adjusted either up or down based on the results of new research. The RfD of 0.7 $\mu\text{g}/\text{kg}/\text{day}$ was adopted by EPA in 2005.

In 2009, EPA identified perchlorate as a drinking water contaminant and initiated the process to develop a Maximum Contaminant Level Goal and National Primary Drinking Water Regulation under the Safe Drinking Water Act. The MCLG is a non-enforceable goal defined under the SDWA as “the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety.”

The EPA developed a white paper that identifies and summarizes relevant perchlorate studies available since the publication of the NRC 2005 report. The agency also is evaluating the available

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1 physiologically based pharmacokinetic models for perchlorate, as well as literature related to sensitive
2 life stages that are likely to be at greater risk of adverse health effects. The EPA's Office of Water
3 requested that the SAB provide advice on how the agency should consider recent information on
4 sensitive life stages including: epidemiological and biomonitoring studies; the agency's PBPK modeling
5 efforts; and approaches to use and integrate this information in deriving an MCLG.

6
7 The SAB reviewed the recent information and EPA's white paper and concludes that it is important for
8 the EPA to consider sensitive life stages explicitly in the development of a MCLG for perchlorate. The
9 mode of action of perchlorate toxicity is well understood and involves the potential for disturbance of
10 thyroid homeostasis: perchlorate limits the access of iodide to the thyroid, which in turn can lead to
11 production of less thyroid hormone. Interference with the thyroid and available thyroid hormones is
12 known to produce adverse effects on neurodevelopment in humans, with the fetus and infants most
13 vulnerable. Although adverse neurodevelopmental effects of perchlorate in infants and children have not
14 been reported in the literature, their risk can be reasonably inferred from perchlorate's mode of action.
15 The NRC in 2005 concluded that the first adverse effect in the continuum of effects from perchlorate
16 exposure would be hypothyroidism. In considering new information and health endpoints of potential
17 concern, the SAB finds that hypothyroxinemia, also known as subclinical hypothyroidism, is more
18 appropriate to consider in evaluating the potential adverse health effects for pregnant women, fetuses
19 and infants than the more pronounced decreases in thyroid hormone associated with hypothyroidism.

20
21 The SAB recommends that the EPA derive a perchlorate MCLG that addresses sensitive life stages
22 through physiologically-based pharmacokinetic/pharmacodynamic modeling based upon its mode of
23 action rather than the default MCLG approach using the RfD and specific chemical exposure
24 parameters. The SAB finds that this approach is a more rigorous way to address differences in biology
25 and exposure between adults and sensitive life stages than is possible with the default approach for
26 deriving an MCLG.

27
28 The SAB applauds the agency's efforts in developing models to better inform differences in adverse
29 health effects of perchlorate in different life stages. The SAB urges the EPA to expand the modeling
30 approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental
31 outcomes from perchlorate exposure. Incorporating these components into the model offers the
32 opportunity for much greater scientific rigor in establishing quantitative relationships between
33 perchlorate exposure and adverse effects at sensitive life stages. The SAB recognizes that full
34 implementation of this approach may take years to develop. As an interim approach the agency could
35 use the existing model to estimate iodide uptake inhibition and empirical observations to relate iodide
36 uptake inhibition to thyroid hormone perturbation. Specifically, the thyroid clinical literature could be
37 evaluated to identify the degree of iodide uptake inhibition required for onset of hypothyroxinemia in
38 the pregnant woman. This information, together with modeling to link iodide uptake inhibition to
39 perchlorate exposure, would provide the basis for an MCLG that addresses directly the most sensitive
40 life stages for perchlorate effects.

41
42 The agency should incorporate the appropriate studies related to ingestion of perchlorate,
43 pharmacokinetics of perchlorate, and the effects (dynamics) of perchlorate from the entire body of
44 literature available. In developing the pharmacodynamic aspect of this model, the EPA should take

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1 advantage of available data on potential adverse health effects due to thyroid hormone perturbations,
2 regardless of the cause of those perturbations, to document and support parameters used in the model.

3
4 The SAB notes that as perchlorate research continues, studies in animals may provide important insights
5 into neurobehavioral consequences of perchlorate exposure. A physiologically-based
6 pharmacokinetic/pharmacodynamic framework is well suited to help place these findings in the context
7 of human perchlorate exposure.

8
9 The SAB appreciates the opportunity to provide the EPA with advice and looks forward to the agency's
10 response.

11
12 Sincerely,
13

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NOTICE

This report has been written as part of the activities of the EPA Science Advisory Board (SAB), a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The SAB is structured to provide balanced, expert assessment of scientific matters related to problems facing the agency. This report has not been reviewed for approval by the agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names of commercial products constitute a recommendation for use. Reports of the SAB are posted on the EPA website at <http://www.epa.gov/sab>.

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**U.S. Environmental Protection Agency
Science Advisory Board
Perchlorate Advisory Panel**

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Acronyms and Abbreviations

1		
2		
3	µg	Microgram (one-millionth of a gram)
4	ADHD	Attention Deficit Hyperactivity Disorder
5	BBDR	Biologically Based Dose Response
6	BW	Body Weight
7	DWI	Drinking Water Ingestion Rate
8	EPA	U.S. Environmental Protection Agency
9	FDA	Food and Drug Administration
10	fT4	Free thyroxine
11	GW	Gestational Week
12	HPT	Hypothalamus-Pituitary-Thyroid
13	HRL	Health Reference Level
14	I ⁻	Iodide
15	IQ	Intelligence Quotient
16	IUI	Iodide Uptake Inhibition
17	kg	Kilogram
18	K _m	Michaelis Constant
19	L	Liter
20	MCL	Maximum Contaminant Level
21	MCLG	Maximum Contaminant Goal Level
22	MOA	Mode of Action
23	Na	Sodium
24	NHANES	National Health and Nutrition Examination Survey
25	NIS	Sodium (Na)/Iodide (I) Symporter
26	NOEL	No Observed Effect Level
27	NPDWR	National Primary Drinking Water Regulation
28	NRC	National Research Council
29	PBPK	Physiologically Based Pharmacokinetic
30	PBPK/PD-IUI	Physiologically Based Pharmacokinetic/Pharmacodynamic-Iodide Uptake Inhibition
31	POD	Point of Departure
32	PPBK/PD	Physiologically-Based Pharmacokinetic Pharmacodynamic
33	PWS	Public Water System
34	RAIUI	Radioactive Iodide Uptake Inhibition
35	RfD	Reference Dose
36	RSC	Relative Source Contribution
37	SAB	Science Advisory Board
38	SDWA	Safe Drinking Water Act
39	T3	Triiodothyronine
40	T4	Thyroxine or Tetraiodothyronine
41	TDS	Total Dietary Study
42	TgAb	Thyroglobulin antibody
43	TH	Thyroid Hormones

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1	TPOAb	Thyroid Peroxidase Antibody
2	TRH	Thyrotropin Releasing Hormone
3	TSH	Thyroid Stimulating Hormone or
4	TSH-RAb	Thyroid Stimulating Hormone Receptor Antibody
5	UCMR	Unregulated Contaminant Monitoring Rule
6	UF	Uncertainty factor
7	µmU	Micromolar Units
8		

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1. EXECUTIVE SUMMARY

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3
4 In 2005, at the request of EPA and other federal agencies, the National Research Council (NRC)
5 published a comprehensive report “*Health Implications of Perchlorate Ingestion.*” The NRC concluded
6 that perchlorate could affect thyroid function because it is an ion that competitively inhibits the transport
7 of iodide into the thyroid and that a prolonged decrease of thyroid hormone can have adverse effects in
8 sensitive populations (people with thyroid disorders, pregnant women, fetuses, and infants).
9

10 The NRC recommended the use of a precursor, non-adverse effect (i.e., inhibition of iodide uptake) to
11 derive a reference dose (RfD) for perchlorate. An RfD is defined by EPA as “an estimate (with
12 uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population
13 (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects
14 during a lifetime.” The RfD was based on the no observed effect level of 7 µg/kg/day in healthy adults,
15 corresponding to a radioactive iodide uptake inhibition (RAIUI) of 1.8 percent, and application of an
16 intraspecies uncertainty factor (UF) of 10. The UF is intended to account for differences in sensitivity
17 between the healthy adults and fetuses of pregnant women who might have hypothyroidism or iodide
18 deficiency as the most sensitive population,. The NRC acknowledged that the RfD may need to be
19 adjusted upward or downward based on future research. The RfD of 0.7 µg/kg/day was adopted by EPA
20 in 2005.
21

22 In 2009, EPA identified perchlorate as a drinking water contaminant and initiated the process to develop
23 a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation
24 (NPDWR) under the Safe Drinking Water Act (SDWA). The MCLG is a non-enforceable goal defined
25 under the SDWA as “the level at which no known or anticipated adverse effects on the health of persons
26 occur and which allows an adequate margin of safety.” The SDWA specifies that the enforceable
27 Maximum Contaminant Level be set as close to the MCLG as feasible using the best available
28 technology, treatment techniques, and other means (considering cost). SDWA further requires that when
29 proposing any NPDWR that includes an MCL, the Administrator must analyze “[t]he effects of the
30 contaminant on the general population and on groups within the general population such as infants,
31 children, pregnant women, the elderly, individuals with a history of serious illness, or other
32 subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure
33 to contaminants in drinking water than the general population.”
34

35 The EPA developed a white paper that identifies and summarizes recent epidemiological and
36 biomonitoring studies and physiologically based pharmacokinetic (PBPK) models for perchlorate. The
37 agency is evaluating these studies in addition to the data and information used by the NRC to consider
38 sensitive life stages that comprise groups within the general population that are likely to be at greater
39 risk of adverse health effects. EPA’s Office of Water requested that the SAB provide advice on how the
40 agency should consider recent information on sensitive life stages, epidemiological and biomonitoring
41 studies and the agency’s PBPK modeling efforts. The agency also is seeking advice on approaches to
42 use and integrate this information in deriving an MCLG for perchlorate.

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1
2 In summary, the SAB finds that there is sufficient information to derive an MCLG for perchlorate and
3 recommends that the agency use a mode of action approach (MOA) and physiologically based
4 pharmacokinetic /pharmacodynamic iodide uptake inhibition (PBPK/PD-IUI) modeling to integrate this
5 information in a robust and transparent analysis. The SAB recognizes that this is a novel approach as
6 compared to previous MCLG derivations that use the RfD and exposure factors. However, PBPK/PD-
7 IUI modeling provides a more rigorous tool to integrate the body of information available on
8 perchlorate, and this approach may better address different life stage susceptibilities to perchlorate than
9 the default MCLG approach.

10 ***Sensitive Life Stages***

11
12 The SAB concludes that a sensitive life stage analysis is critical to derive an MCLG for perchlorate. The
13 specific adverse effects of inadequate iodide uptake — and the consequence of low thyroid hormone
14 levels on brain development — vary at different life stages. The fetus and infant are more susceptible to
15 perchlorate exposure effects than is the adult as thyroid hormone is required for normal brain
16 development. Thus, deficits in brain function become permanent if thyroid hormone deprivation occurs
17 even transiently during early life, whereas the effects of transient thyroid hormone deprivation on the
18 adult brain are measurable but are readily reversible. Additionally, the tissue-specific expression
19 patterns of the sodium iodide symporter (NIS), the molecular target of perchlorate, vary depending on
20 life stage. Although no data exist on the long-term adverse neurodevelopmental effects of perchlorate
21 *per se*, the human and animal data on the adverse effects of thyroid hormone perturbations (a down-
22 stream effect from iodide uptake inhibition) on the developing brain support the need for a life stage
23 approach. The evidence suggests that the most sensitive life stages for the potential permanent adverse
24 effects of perchlorate on brain development are the fetus and infants of hypothyroxinemic, ,
25 niminalyiodide deficient, pregnant women.

26 ***Physiologically Based Pharmacokinetic Pharmacodynamic Modeling***

27
28 The EPA should utilize an MOA framework for developing the MCLG that links the steps in the
29 proposed mechanism leading from perchlorate exposure through iodide uptake inhibition to thyroid
30 hormone changes and finally neurodevelopmental impacts. Within this MOA framework, the PBPK/PD
31 IUI model provides a tool for integrating exposure (e.g., different drinking water consumption rates)
32 with the biological changes occurring at the different lifestages to obtain predictions for perchlorate
33 pharmacokinetics and resulting iodine uptake inhibition to address these initial steps of the MOA
34 framework.

35
36 Extension of the current PBPK/PD-IUI model to describe the pharmacodynamic changes in thyroid
37 hormone levels would provide a key tool for linking these early events with subsequent events as
38 reported in the literature on iodide deficiency, changes in thyroid hormone levels and their relationship
39 to neurodevelopmental outcomes during sensitive early life stages.

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1 ***Epidemiological Data***

2
3 The SAB concludes that the available epidemiological data published since the NRC 2005 report are
4 insufficient to guide causal inference with regard to the association between perchlorate exposure and
5 thyroid dysfunction in pregnant women, neonates or the general population. Limitations concerning
6 study design, exposure assessment, sample size and statistical modeling have led to inconsistent results.
7 Thus, the current body of epidemiologic evidence cannot provide validation of a safe level of
8 perchlorate in drinking water.

9
10 None the less, the SAB finds that these epidemiology data may be are useful. These data provide support
11 for analyses to: estimate the size of potentially sensitive subgroups in the United States (U.S.); estimate
12 the extent to which the general U.S. population and sensitive subgroups are exposed to perchlorate, as
13 well as other compounds with the comparable MOA (i.e., goitrogens); and estimate the relative source
14 contribution of perchlorate in drinking water among sensitive subgroups not addressed in the Food and
15 Drug Administration's total diet study.

16
17 ***Integration of Information Using PBPK/PD Modeling***

18
19 The SAB recommends integrating the body of information on perchlorate to derive an MCLG based on
20 the MOA previously identified for perchlorate. The recommended approach relies on the use of a
21 PBPK/PD model that associates perchlorate intake via drinking water with percent iodide uptake
22 inhibition.

23
24 The SAB notes that the EPA developed a PBPK/PD model for perchlorate that builds on the models
25 reviewed by the NRC and can be used in its present form to derive an MCLG based on iodide uptake
26 inhibition. The limitation of the model in its current state, similar to the limitations of the standard
27 MCLG approach, is that the current model describes a precursor event and does not explicitly predict
28 subsequent events or adverse outcomes. However, the SAB recommends that the EPA expand the
29 PBPK/PD approach past IUI to explicitly incorporate predictions on thyroid hormone perturbations of
30 potential adverse neurodevelopmental outcomes from perchlorate exposure. This approach permits
31 assessment of the predicted exposure-response relationship for perchlorate exposure and alterations in
32 thyroid hormone levels (e.g., decreases in serum free T4). The SAB recognizes that such an effort will
33 require resources and time, likely on the order of one to several years. In the interim, the EPA could use
34 the existing model to estimate IUI and develop empirical relationships for each of the steps beyond
35 perchlorate-mediated IUI. The thyroid clinical literature should be evaluated to identify the degree of
36 iodide inhibition (percentage IUI) required for the onset of hypothyroxinemia in the pregnant woman.

37
38 The agency should incorporate the appropriate studies related to ingestion of perchlorate,
39 pharmacokinetics of perchlorate, and the effects (dynamics) of perchlorate from the entire body of
40 available literature. In developing the pharmacodynamic aspect of this model, the EPA should take
41 advantage of available data on potential adverse health effects due to thyroid hormone level
42 perturbations regardless of the cause of those perturbations to document and support parameters used in

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1 the model. The SAB notes that as perchlorate research continues, studies in animals may provide
2 important insights into neurobehavioral consequences of perchlorate exposure.

3

4 The SAB recommendations represent an important and novel opportunity that should be implemented
5 carefully with attention to data quality and methodological rigor. At each step, EPA should critically
6 evaluate available data and describe the strengths and limitations. The SAB concludes that a stepwise
7 “integrated” approach is a logical way forward allowing multiple sources of information to be integrated
8 into the MCLG derivation.

9

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3 **2. INTRODUCTION**

4
5
6 **2.1. Background**

7 Perchlorate is both a naturally occurring and man-made chemical that is used to produce rocket fuel,
8 fireworks, flares, and explosives, and can be present in bleach and fertilizers. The Environmental
9 Protection Agency identified perchlorate as a potential drinking water contaminant because it may have
10 an adverse health effect and has been detected in public water systems.

11 In 2005, at the request of EPA and other federal agencies, the National Research Council (NRC)
12 published a comprehensive report *Health Implications of Perchlorate Ingestion* (2005). The NRC
13 concluded that perchlorate can affect thyroid function because it is an ion that competitively inhibits the
14 transport of iodide into the thyroid by a protein known as the sodium /iodide symporter (NIS).
15 Significant inhibition of iodide uptake results in intra-thyroid iodine deficiency, decreased synthesis of
16 key thyroid hormones triiodothyronine (T3), thyroxine (T4), and increased thyroid stimulating hormone
17 or thyrotropin (TSH). The NRC also concluded that a prolonged decrease of thyroid hormone can have
18 adverse effects in sensitive populations (e.g., people with thyroid disorders, pregnant women, fetuses,
19 and infants).

20 The NRC recommended the use of a precursor, non-adverse effect (i.e., inhibition of iodide uptake) to
21 derive a reference dose (RfD) for perchlorate. An RfD is defined by EPA as “an estimate (with
22 uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population
23 (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects
24 during a lifetime.” The RfD was based on the no observed effect level of 7 µg/kg/day in health adults,
25 corresponding to a radioactive iodide uptake inhibition RAIU of 1.8 percent, and application of an
26 intraspecies uncertainty factor (UF) of 10 to account for differences in sensitivity between the healthy
27 adults and the most sensitive population, namely fetuses of pregnant women who might have
28 hypothyroidism or iodide deficiency. The NRC acknowledged that the RfD may need to be adjusted
29 upward or downward based on future research. The RfD of 0.7 µg/kg/day was adopted by EPA in 2005
30 (U.S. EPA 2005).

31 The EPA has initiated the process to develop an MCLG and NPDWR for perchlorate under the SDWA
32 (U.S. EPA 2011). The MCLG is a non-enforceable goal defined under the SDWA (§1412.b.4.B) as “*the*
33 *level at which no known or anticipated adverse effects on the health of persons occur and which allows*
34 *an adequate margin of safety.*” For perchlorate, the NPDWR likely will specify an enforceable
35 Maximum Contaminant Level (MCL) and monitoring and reporting requirements for public water
36 systems. The SDWA (§1412.b.4.B and D) specifies that the enforceable MCL be set as close to the
37 MCLG as feasible using the best available technology, treatment techniques, and other means
38 (considering cost).
39

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1 EPA generally derives an MCLG using the following formula as a default:
2

$$3 \text{ MCLG } (\mu\text{g/L}) = \frac{\text{RfD} (\mu\text{g/kg bw/day}) \times \text{BW} (\text{kg})}{\text{DWI} (\text{L/day})} \times \text{RSC}$$

4 Where:

5 *RfD* is the reference dose for a contaminant ($\mu\text{g/kg/day}$).

6 *BW* is body weight in kg. A default body weight (70 kg) is typically used.

7 *DWI* is drinking water ingestion rate in L/day. A default intake (2 L/day) is typically used.

8 *RSC* is the relative source contribution. The RSC is derived as the percentage of the RfD

9 remaining for drinking water after other sources of exposure to perchlorate (e.g., food) have been
10 considered. The EPA is relying on a total Diet Study developed by the Food and Drug
11 Administration (FDA) for perchlorate. (U.S. EPA 2012)

12
13 The regulatory schedule established by SDWA requires EPA to publish a proposed MCLG and NPDWR
14 within 24 months of making a determination to regulate a contaminant and promulgate a final regulation
15 within 18 months of the proposal. SDWA further requires that when proposing any NPDWR that
16 includes an MCL, the Administrator must analyze “[t]he effects of the contaminant on the general
17 population and on groups within the general population such as infants, children, pregnant women, the
18 elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely
19 to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the
20 general population¹.”

21
22 EPA developed a white paper (2012) that identifies available information published since the NRC
23 report (2005). The white paper presents epidemiological and biomonitoring studies and physiologically
24 based pharmacokinetic (PBPK) modeling² that the agency is evaluating, in addition to the data and
25 information used by the NRC, to consider sensitive life stages that are likely to be at greater risk of
26 adverse health effects than the general population.

27
28 EPA’s Office of Water requested the Science Advisory Board’s (SAB) advice on how best to consider
29 the sensitive life stages, the available epidemiological studies, and PBPK modeling, and integrate this
30 information in deriving an MCLG for perchlorate. The SAB formed an ad-hoc panel, the Perchlorate
31 Advisory Panel, to perform this task. The Panel met on July 18-19, 2012, to hear EPA technical
32 presentations, public comments on the draft White Paper and to discuss response to the Charge to the

¹SDWA uses the term subpopulation to refer to groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other groups that can be identified and characterized and are likely to experience elevated health risks. In 2005 EPA started using the term life stages to refer to age-defined groups. All life stages are subpopulations but not all subpopulations are life stages. In this document, the term life stage is used predominantly because of the focus on infants and very young children.

² The EPA white paper and Charge to the SAB refer to the current model as a PBPK model. The SAB notes that the current model predicts iodide uptake inhibition which is a pharmacodynamic step in the mode of action.

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1 SAB (76 FR 78256-78257). The Panel held a follow-up teleconference on September 25, 2012 to
2 discuss an initial draft SAB report.
3

4 **2.2. Charge to the Science Advisory Board**

5
6 The EPA Charge to the SAB seeks advice and recommendations on approaches to derive an MCLG for
7 perchlorate. The EPA identified recent studies on life stage information for infants and children,
8 epidemiologic and biomonitoring data since the NRC report (2005), and physiologically based
9 pharmacokinetic modeling that address the iodide uptake inhibition and the decreased synthesis of
10 thyroid hormones. The agency is seeking advice on how to consider these studies and models in terms of
11 different life stages and adverse effects, approaches to include the information in deriving an MCLG,
12 and what are the strengths and limitations of the biomonitoring and epidemiological studies. The Charge
13 also asks the SAB how best to integrate the total body of information to derive a health-protective
14 MCLG. Charge questions are included at the beginning of each section of this Report and the full
15 Charge is included as Appendix A.

16
17
18

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3. RESPONSE TO CHARGE QUESTIONS

The specific charge questions focus on how the EPA should consider various life stage factors, PBPK modeling, and epidemiological and biomonitoring studies published since the NRC 2005 Report in MCLG development. A fourth set of charge questions addresses the related issue of how this and the other available information should be integrated into development of a health protective MCLG and how reductions in adverse health effects from lowering perchlorate concentrations in drinking water can be estimated.

Responses to charge questions on different life stages identified the hypothyroxinemic pregnant woman, her fetus and infants as the most sensitive population to perchlorate, and iodide deficiency, decreased thyroid hormone biosynthesis, and other key factors as important considerations in addressing perchlorate risk. The SAB also noted the agency's progress in using PBPK models to better understand the potential impacts of perchlorate exposure during different life stages. In review of the epidemiological and biomonitoring studies, the SAB identified data of value in assessing risk of perchlorate exposure, but found that limitations and inconsistent results in the epidemiological and biomonitoring studies precluded their use in deriving the MCLG.

When considering how to integrate the disparate information and analyses into the derivation of an MCLG, the SAB found that the default algebraic approach provides limited ability to address the various exposure and biological factors affecting sensitivity to perchlorate at different life stages. The SAB concluded that, from a scientific standpoint, it would be more appropriate to base the MCLG derivation on the perchlorate mode of action, using PBPK/PD modeling to relate perchlorate concentrations in drinking water to its biological effects rather than the default approach.

3.1. Sensitive Life Stages

Charge Questions:

There are currently no data available to directly link perchlorate to neurobehavioral effects in infants and children. How should EPA consider the following life stage factors in deriving an MCLG?

- *Life stage specific differences in body weight and food and drinking water intake;*
- *Differences in greater severity and permanence of potential adverse effects in neonates, infants and young children compared to adults;*
- *Shorter half-life and lower reserves for thyroid hormone in infants compared to adults; and*
- *Intrauterine exposure to perchlorate and impact on thyroid status in fetuses.*

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3.1.1. Rationale for Considering Life Stages in Deriving an MCLG

The SAB finds that there is a critical need to consider sensitive life stages in deriving an MCLG for perchlorate. The SAB recognizes that studies directly linking perchlorate to neurobehavioral effects in infants and children are lacking. However, the SAB notes that there are scientifically sound human clinical and rodent toxicology reports that describe the biology linking iodide deficiency, changes in thyroid hormone production, and developmental neurobehavioral effects. The mechanisms of perchlorate inhibition of sodium/iodide symporter (NIS)-mediated iodide uptake into the thyroid are also well-documented (Dohan et al. 2007; Tran et al. 2008; Paroder-Belenitzky et al. 2011). Therefore, the SAB concludes that these two streams of information — biology of iodide deficiency and perchlorate inhibition of iodide uptake — are complementary and sufficient for the EPA to consider specific life stage factors in deriving an MCLG for perchlorate. The SAB also notes that the specific adverse effects of inadequate iodide uptake and low thyroid hormone levels on brain development vary at different life stages, but are especially critical during the earliest stages of brain development.

The thyroid hormones (TH) triiodothyronine (T3) and tetraiodothyronine or thyroxine (T4) are the only iodine-containing hormones in the body. To synthesize these hormones, once iodide is transported by NIS from the bloodstream into the interior of the cell, iodide is oxidized and covalently incorporated into specific tyrosyl residues on a large precursor molecule called thyroglobulin, found in the colloid of the thyroid (Carrasco 1993). After endocytosis of iodinated thyroglobulin and proteolysis, the resulting T3 and the more abundant T4 both are transported from the thyroid via the bloodstream to various essential target organs. One of the primary target organs is the brain, which has a well-defined need for TH for its normal development (Zoeller and Rovet 2004). A deficit of TH leads to poor brain development that may ultimately cause intellectual and behavioral impairments in the developing child (Morreale de Escobar et al. 2000). Since the iodide needed for T3 and T4 production cannot be synthesized within the body, it must be obtained through the diet, and this requires a constant and sufficient supply of iodide to ensure normal thyroid function (Carrasco 1993). In addition, the need for iodide is substantially increased during pregnancy to support the increased production of maternal TH that occurs during this period (Glinioer 2004). Children who experienced iodide or TH insufficiency during critical earlier stages of brain development (viz., gestation and infancy) are at risk of neurological, mental, and growth impairments (Glinioer and Delange 2000; Glinioer and Rovet 2009).

Dietary iodide is transported from the bloodstream into the thyroid via the NIS, an intrinsic plasma membrane protein consisting of 643 amino acids (Dai et al. 1996; Smanik et al. 1996; Riesco-Eizaguirre and Santisteban 2006). This transport process is the first and key rate-limiting step in the biosynthesis of T3 and T4. NIS is also expressed in the salivary glands and stomach, two tissues where active iodide transport also takes place. Notably, NIS is highly expressed in the placenta and lactating breast, allowing iodide to be supplied to the fetus and the breast-feeding infant (Tazebay et al. 2000; De La Vieja et al. 2000; Dohan et al. 2003).

Perchlorate inhibits iodide uptake and therefore interferes with TH production. Perchlorate acts by specifically inhibiting NIS-mediated transport of iodide into the thyroid, placenta, lactating breast, and all other NIS-expressing tissues. Although perchlorate has long been known to act as a competitive NIS

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1 inhibitor, recent studies show that perchlorate is actually an actively transported NIS substrate (Dohan et
2 al. 2007; Tran et al. 2008; Paroder-Belenitzky et al. 2011). Consequently, a primary downstream effect
3 of perchlorate exposure is reduction in the levels of T3 and T4 that are ultimately needed by the
4 developing brain. Clearly, in the presence of perchlorate, less iodide may be available for TH
5 biosynthesis. The extent of inhibition of iodide uptake is dependent upon the relative concentrations of
6 the two anions and their respective Michaelis constants (K_m) for transport.

7
8 Although evidence is lacking that directly links perchlorate intake to altered brain development in
9 humans, animal evidence is suggestive of perchlorate intake having an impact on mammalian brain
10 development (Gilbert and Sui 2008). Likewise, studies of children born to women with mild to moderate
11 reductions in TH during pregnancy (hypothyroxinemia) (Man et al. 1991; Pop et al. 1999; Pop et al.
12 2003; Kooistra et al. 2006) and children born to women with clinical (Smit et al. 2000, Mirabella et al.
13 2000) or subclinical hypothyroidism (Haddow et al. 1999) show reduced intelligence quotients (IQ),
14 selective cognitive deficits, as well as behavioral abnormalities. Similar observations have been made in
15 offspring of women with iodide deficiency during pregnancy (Pharoah et al. 1984; Vermiglio et al.
16 2004).

17
18 It is important to note that changes in brain development caused by perchlorate exposure and observed at
19 any level of biological organization, including the molecular, cellular, or whole organism behavioral
20 levels, could be considered adverse due to the difficulty in associating changes in brain development
21 (e.g., altered expression patterns of TH-regulated brain genes) with later functional effects (e.g., specific
22 intellectual abilities, sociobehavioral effects). In addition, molecular effects during development can be
23 irreversible, although they may be later modified via various enrichment and intervention approaches.

24 ***Recommendation:***

25 The SAB recommends that the EPA consider the sensitive life stages of the pregnant and lactating
26 woman and her fetus and infant in modeling levels of perchlorate exposure and effects.

27 **3.1.2. Life Stage Specific Differences in Body Weight and Intakes**

28 Specific differences in body weight, food intake, and drinking water consumption are important factors
29 for the understanding of perchlorate-induced iodide uptake inhibition (IUI) at different life stages.
30 The factors specified in this subpart of the charge question are a reflection of the default formula applied
31 by the EPA to develop an MCLG from an RfD, which is frequently applied for chronic toxicities for
32 which adult body weight and intake dominate exposures. The challenge in the case of perchlorate is that
33 the developing nervous system is of interest and thus, exposures during specific periods of development
34 (e.g., *in utero* or early postnatal) need to be considered. During these periods, many changes occur in
35 biology beyond body weight and food or water intake. For example, evidence is available from the
36 literature on other drug and chemical exposures showing differing absorption and metabolism rates with
37 age and body weight (Kearns et al. 2003; Bartelink et al. 2006; Anderson and Lynn 2009). In addition,
38 since NIS is expressed in tissues other than the thyroid, such as the salivary glands, stomach, lactating
39 breast, and placenta, one might anticipate developmental differences in pharmacokinetics and
40 pharmacodynamics for perchlorate and iodide uptake inhibition.

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1 **Recommendation:**

2 The SAB notes that the EPA developed a PBPK model that considers life stage differences in thyroid
3 NIS inhibition and has continued to develop this model (U.S EPA 2009 and 2012). Using the PBPK
4 modeling approach (see Sections 3.2 and 3.4), life stage specific differences in body weight and food
5 and drinking water intakes have been and should be explicitly incorporated in the modeling of each life
6 stage and documented. Additionally, differences in other parameters characterizing the biological
7 system in the model, such as organ weight (volumes), blood flows, or NIS activity have been
8 incorporated and over time may need to be updated if more information becomes available in the
9 literature.

10
11 The SAB acknowledges that NIS expression is accounted for in different tissues and at different stages
12 of development in the current PBPK model for RAIU inhibition calculations. In addition, the current
13 PBPK model addresses the movement of perchlorate into relevant organs that can interfere with the
14 availability of thyroid hormones for brain development, such as the mammary gland, placenta, and
15 thyroid gland. In the longer term, new models for the hypothalamic pituitary thyroid axis need to also
16 include these same competitive inhibition equations for both anions for NIS-bearing organs or tissues.

17 **3.1.3. Differences in Potential Adverse Effects to Neonates, Infants and Young Children**

18 The SAB finds that neonates, infants, and children are significantly more sensitive than adults are to the
19 potential effect of decreased TH levels on brain development, and that these effects are significantly
20 longer lasting in the former population.

21
22 It is well established that TH is essential for normal brain development (Bernal and Nunez, 1995,
23 Anderson 2001). A broad and diverse literature, based primarily on rodents, has shown that T3 and T4
24 are translocated into the brain through the blood-brain barrier by specific transporters (Patel et al. 2011).
25 From here, T4 enters glia where it is metabolized to T3 by local deiodinases. T3 is then transported via
26 specific transporters (Kester et al. 2005) into target brain cells, binds to nuclear thyroid hormone
27 receptors and regulates expression of key brain genes fundamental to critical neurodevelopmental
28 processes (Bernal 2007, Anderson et al. 2003) including neurogenesis, neuronal migration, axon and
29 dendritic growth, synaptogenesis, and myelination (Chan and Rovet 2003). Thyroid hormones regulate
30 these developmental processes throughout gestation and early life (Zoeller and Rovet, 2004), with the
31 temporal sensitivity of thyroid hormone deprivation differing depending on brain region. Therefore the
32 consequences of TH insufficiency, regardless of cause, will vary depending on when the deficiency
33 occurs (Royland et al. 2008). Furthermore, since different brain regions vary in development as to their
34 timing of need for TH (Thompson and Potter 2000; Morreale de Escobar *et al*, 2004), the specific
35 consequences of TH insufficiency or iodide deficiency will also differ regionally within the brain
36 (Schweizer et al 2008).

37
38 Importantly, the adult brain is also sensitive to altered thyroidal status, however, the changes in brain
39 chemistry and function are reversible upon return to euthyroid status, therefore changes in thyroidal
40 status are less deleterious on brain function in the adult life stage (Bauer et al 2008).

41
42 Finally, as human neurodevelopment occurs along a continuum through gestation to childhood, it is also

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1 important to consider that the human thyroid develops during gestation and does not begin secreting
2 thyroid hormones until the fourth month of gestation (Ballabio et al. 1989; Obregon et al. 2007),
3 meaning that earlier in development the fetal brain is totally reliant on the maternal TH supply .
4

5 The SAB recognizes that it is essential to obtain robust data in order to best assess the long-term effects
6 of perchlorate exposure on thyroidal iodide uptake, and resultant impact on thyroid function, as
7 measured by TSH and free T4 levels, in both human and animal models. In contrast to the dearth of
8 studies of perchlorate effects on neurodevelopment, the literature on iodide deficiency, maternal
9 hypothyroxinemia, and congenital hypothyroidism is robust and provides key data identifying the range
10 of thyroidal perturbation attributable to reductions in iodide availability to the thyroid gland or to TH
11 production itself. The importance of these broad areas of research for interpreting the results of
12 perchlorate studies is that the ultimate mechanism of perchlorate toxicity is known: perchlorate limits
13 the access of iodide to the thyroid, which in turn means less TH for the developing brain. These data can
14 be compared to the known neurodevelopmental effects of mild, moderate and severe iodide deficiency
15 on human and animal brain development. The SAB finds that while the currently available studies are
16 insufficient to draw unequivocal conclusions regarding the impact of perchlorate exposure on human
17 brain development, studies from the other two areas are invaluable. Indeed, recent studies based on
18 newly available neuroimaging data show a direct impact of these deficiencies on the human brain
19 (Willoughby 2011; Wheeler et al. 2011; Wheeler et al 2012).

20 **3.1.4. Thyroid Hormone Reserve Differences**

21 It is reported that fetuses and infants have lower reserves of TH and a shorter half-life TH than do adults
22 (Brent 2010). However, the key evidence linking these features to perchlorate levels, iodide levels, and
23 outcome is lacking. According to Brent (2010), it is possible that gestational exposure to perchlorate can
24 have an impact on fetal TH production and brain development, without necessarily altering maternal TH
25 levels, and that this effect can be compounded by iodine insufficiency. A study by Blount et al (2009)
26 measuring perchlorate and iodine levels from multiple compartments (e.g., maternal urine, maternal
27 serum, cord blood serum, amniotic fluid) in women undergoing cesarean section surgery showed that at
28 time of birth, perchlorate levels were high, including in cord blood, but there was no evidence of either
29 inhibition of iodine transport across the placenta or impact on infant growth. While the absence of effect
30 may be due to the high levels of iodine in the study population, since most women were taking iodine-
31 fortified prenatal vitamins, it is also possible that later developmental effects may become evident but
32 are more subtle than those measured by Blount (Brent 2010) and that perchlorate effects will be
33 observed in breast milk once the infant starts to feed (Blount et al. 2009). Nevertheless, the EPA should
34 consider lower TH reserves and shorter retention or half-lives in comparison with the non-pregnant
35 adult.

36 ***Recommendation:***

37 The EPA, when determining safe levels of perchlorate in drinking water, should consider the shorter
38 half-life and lower reserves of TH and metabolic differences in specific sensitive life stages. It is critical
39 that the EPA consider these two key features in making comparisons with the non-pregnant adult, based
40 on the Greer et al study (2002). Additionally, this issue may be studied in animals using appropriate
41 experimental designs.

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1

2 **3.1.5. Intrauterine Exposure to Perchlorate and Thyroid Status Impact in Fetuses**

3 The SAB finds that intrauterine perchlorate exposure has the potential to affect the developing fetus in
4 several ways. First, it can lead to less iodide for the fetal thyroid. In addition, it can mean less maternal
5 TH because her iodide supply has been reduced. In early pregnancy, prior to the onset of fetal thyroid
6 function, the main disruption will be less maternal TH, whereas later in gestation, when the fetal thyroid
7 needs iodide to make its own TH, both maternal and fetal supplies of TH will be reduced. This
8 hypothyroxinemia (i.e., low TH levels) will likely have an impact on the fetal brain, affecting those
9 pathways that have the highest need for TH at the time. In addition, maternal hypothyroxinemia in
10 pregnancy can lead to adverse reproductive and pregnancy outcomes, including preterm delivery (Casey
11 et al. 2005).

12

13 Although the fetal thyroid develops in the first trimester of pregnancy, it does not secrete TH until the
14 second trimester, and is not centrally regulated by the hypothalamus and pituitary (which secrete
15 thyrotropin releasing hormone (TRH) and TSH) until the third trimester (Thorpe-Beeston et al. 1991;
16 Obregon et al. 2007). Furthermore, the fetal thyroid continues to grow throughout gestation (Costa et al.
17 1986), as does its capacity to secrete hormone (Williams et al. 2004). Nevertheless, autopsy evidence
18 indicates that the fetal brain appears to need TH very early in gestation, given findings of TH receptors
19 and measurable quantities of maternally derived TH in fetal brain as early as the first trimester (Kilby et
20 al. 2000). Since substantial quantities of maternal TH are also observed both in fetal compartments
21 throughout gestation (Calvo et al. 2002) and in neonatal serum at term (Vulsma et al. 1989), an adequate
22 maternal supply of TH to the fetus is necessary until the end of pregnancy. After birth, small amounts of
23 TH may be transferred from the mother to the infant via breast milk (Rovet 1990). This dual maternal–
24 fetal/child system typically allows for normal brain development, unless either the maternal or the child
25 TH supplies are inadequate.

26

27 Women with inadequate levels of TH during pregnancy due to clinical or subclinical hypothyroidism or
28 hypothyroxinemia are unable to provide the fetus with sufficient TH (Moleti et al. 2011). It is well
29 established that the offspring of these women are at risk for poor outcomes, including mild to severe IQ
30 reductions, specific cognitive and motor deficits, learning disabilities, and behavioral problems (Man et
31 al. 1991; Haddow et al 1999; Pop et al 1999; Smit et al. 2000; Mirabella et al 2000; Kooistra et al. 2006;
32 Heinrichs et al. 2010). Even the least severe TH inadequacy, maternal hypothyroxinemia, when
33 occurring during gestation, has been associated with neurological impairment (Morreale de Escobar et
34 al. 2004). Furthermore, iodide deficiency during pregnancy and early neonatal life is also associated
35 with impaired development of the brain and suboptimal outcome since pregnant and lactating women
36 from iodide-deficient areas provide insufficient iodide through the placenta or breast milk to their
37 offspring (Zimmerman 2009). Finally, children who are TH-deficient due to congenital hypothyroidism
38 or iodide deficiency also show suboptimal to poor neurodevelopmental outcomes, which depend on the
39 severity and duration of the TH or iodide deficiency (Rovet and Daneman 2003, Vermiglio et al. 2004).
40 Because most TH-mediated brain development only becomes complete by the age of two years, the
41 fetus, infant, and young child are especially vulnerable to the effects of both TH and iodide deficiency.
42

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1 Since perchlorate inhibits iodide transport into the thyroid, exposure to perchlorate can have a direct
2 impact on the maternal thyroid, the fetal thyroid, and the child's thyroid throughout its development.
3 Perchlorate is likely to have a downstream effect on the developing brain similar to that observed in
4 studies of iodide and TH deficiency. However, no data exist in humans directly examining the relation
5 between perchlorate exposure, its thyroidal impact, and the developing brain. Nevertheless, a recent
6 study with perchlorate-exposed rodents showed subtle and specific brain and learning impairments that
7 directly reflect the perchlorate-dosing regimen (Axelstad et al. 2008)

8
9 From studies of the developing human thyroid, it is expected that in early pregnancy, when the fetus
10 relies entirely on the maternal supply of TH to meet its brain needs, perchlorate exposure will lead to
11 reduced TH from the mother, and this will have an impact on the brain functions that are developing at
12 this time. Once the fetal thyroid starts to function in the second trimester, the fetus will require its own
13 supply of iodide in order to make TH. Thus, perchlorate actively transported through the placenta via
14 NIS may block fetal iodide uptake into the thyroid and lead to lowered TH production. This lowered
15 fetal TH production, along with the already reduced maternal TH supply, will likely lead to a state of
16 fetal hypothyroxinemia throughout pregnancy. However, the critical data on these effects do not exist.

17
18 After birth, perchlorate exposure can reduce the infant's capacity to synthesize TH by blocking iodide
19 supply in two possible ways: through the water added to formula preparations or through breast milk.
20 Notably, breast-fed infants exposed to perchlorate may also receive less TH in the milk than non-
21 exposed infants because their mother's TH production has been compromised by her reduced iodide
22 supply due to the perchlorate. Therefore, the infant's own capacity to produce TH will be reduced. Older
23 infants and young children may be affected by perchlorate in dairy milk and certain foods, in addition to
24 drinking water.

25
26 Overall, these findings signify that perchlorate exposure at different sensitive life stages may lead to
27 reduced TH and this in turn can adversely affect brain development in gestation and infancy. Moreover,
28 the effects may be particularly profound if exposure occurs during a critical window of development.
29 Although some literature does exist examining perchlorate levels in relation to maternal and neonatal
30 TH levels, the findings are contradictory; furthermore, the evidence is often limited methodologically
31 and/or the statistical approach is inadequate (see epidemiology section). Nevertheless, the findings show
32 that the fetus and infant are definitely more susceptible to effects of perchlorate exposure than is the
33 adult. Exposure may be more harmful for fetuses and infants given that their brains are undergoing rapid
34 TH-dependent development, in contrast to the adult brain, which is fully developed. Although no data
35 exist on the long-term adverse neurodevelopmental effects of perchlorate *per se*, the data on the adverse
36 effects of iodine deficiency and TH perturbations (a downstream target) on the developing brain justify
37 the need for a life stage approach.

38 ***Recommendation:***

39 It is important that future studies monitor maternal iodide and thyroid hormone levels throughout
40 pregnancy in relation to perchlorate exposure and reproductive/pregnancy outcomes. Future studies may
41 also measure fetal integrity directly by obtaining measurements such as fetal heart rate, ultrasound
42 measures of fetal thyroid, fetal movement, growth, and response to stimulation (Allen and Lipkin 2005).

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1 In addition, in light of advances in neuroimaging of the fetus and neonate, future research could obtain
2 direct measurements of fetal brain in relation to perchlorate exposure at different levels.

3 **3.2. Physiologically-Based Pharmacokinetic Modeling**

4 *Charge Questions:*

5 *How should EPA consider PBPK modeling to derive an MCLG for perchlorate?*

6

7 *What are the strengths and limitations of the two PBPK model results described in this effort?*

8 **3.2.1. Considering PBPK Modeling to Derive an MCLG for Perchlorate**

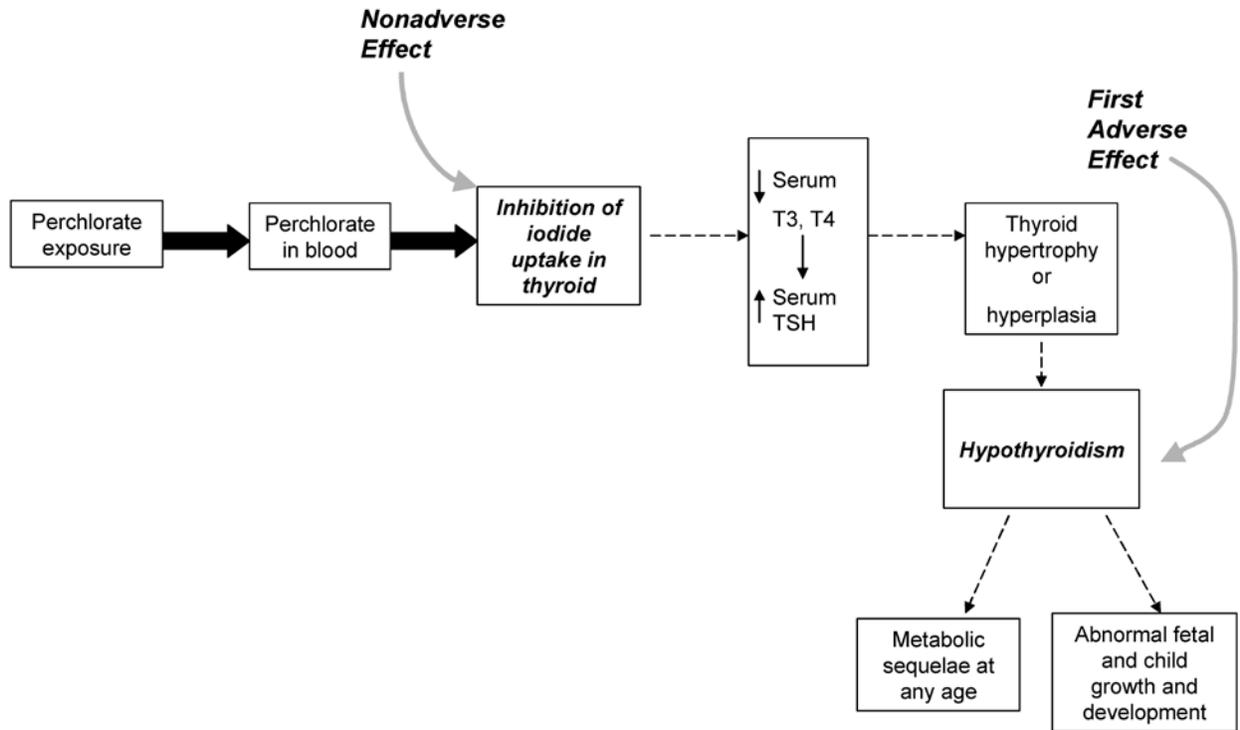
9

10 The NRC committee made a recommendation to use inhibition of iodide uptake by the thyroid arising
11 from competitive inhibition of the NIS by perchlorate as the first step in the MOA for perchlorate
12 leading to all subsequent events (See Figure 1) (NRC 2005). The NRC indicated this effect of
13 perchlorate was relevant for perchlorate risk assessment and provided a health-protective and
14 scientifically valid approach, which has been incorporated by EPA in the derivation of the perchlorate
15 RfD of 0.7 µg/kg/day. The physiologically based pharmacokinetic/pharmacodynamic-iodide uptake
16 inhibition (PBPK/PD-IUI) model links perchlorate exposure in food and water with perchlorate
17 concentrations in plasma and tissue and resulting NIS inhibition assessed by radioactive iodide uptake
18 (RAIU) studies. The continuum of events in the MOA after NIS inhibition would include possible
19 changes in serum TH levels, which have been linked with neurodevelopmental changes in iodine-
20 deficient individuals during early life stages as discussed in the previous section. Using the MOA
21 framework, the model provides a key tool for assessing the potential for the upstream step (iodide
22 uptake inhibition) at different lifestages or in sensitive populations. This MOA framework should be a
23 good way to determine the MCLG using the percent IUI as a surrogate for the adverse effect.

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1
2 **Figure 1. NRC suggested mode of action for perchlorate toxicity in humans indicating the first adverse effect in the**
3 **continuum. (Reprinted with permission from Health Implication of Perchlorate Ingestion, 2005 by the NAS. Courtesy**
4 **National Academy Press.)**

5
6 Research scientists at the toxicology laboratory at Wright-Patterson Air Force Base developed a series of
7 physiological models to describe the effect of perchlorate on the inhibition of thyroidal uptake of
8 radiotracer iodide (Fisher et al. 2000, Clewell et al. 2003a, b; Merrill et al. 2003, 2005). These models
9 included the adult rat, pregnant rat and fetus, and the lactating rat and rat pup, and the adult human. The
10 PBPK/PD-IUI models described the uptake, distribution and urinary elimination of both perchlorate and
11 radiotracer iodide anions. Serum levels of perchlorate and radiotracer iodide are predicted to describe
12 active transport of perchlorate and radiotracer iodide into cells containing the NIS protein, such as the
13 thyroid gland, small intestine, placenta, and mammary tissue (Merrill et al. 2005). Both anions,
14 perchlorate and iodide, compete for active uptake by NIS-containing tissues. The inhibition of thyroidal
15 uptake of radiotracer iodide by perchlorate is recognized as the primary mode of action for perchlorate
16 leading to potential disruption of the hypothalamic-pituitary-thyroid (HPT) axis by depleting the thyroid
17 gland of iodide used in synthesizing thyroid hormones. RAIU inhibition for the thyroid gland is
18 measured for different doses of perchlorate. Later the PBPK/PD-IUI human model for perchlorate and
19 radiotracer iodide was extended to human life stages (Clewell et al. 2007) to make RAIU inhibition
20 predictions in the sensitive sub-population (i.e., the fetus, infant and child). The human PBPK/PD-IUI
21 life stage model was the subject of an EPA-sponsored peer review and underwent modest revisions in
22 response to the reviewers comments (U.S. EPA 2008). This peer reviewed model was used for the
23 predictions of RAIU inhibition presented in the EPA white paper (2012) provided to the SAB. This

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1 modeling approach starts to answer questions about sensitivity of life stages to RAIU inhibition that
2 otherwise are only qualitative justifications for the uncertainty factor (UF) of 10 used in the RfD to
3 protect sensitive populations.

4
5 Future mathematical modeling development should describe HPT axis events after RAIU inhibition in
6 human life stages. The current model does not describe thyroid hormone levels or the dietary iodide
7 intake that is the source of iodide for synthesis of the thyroid hormones. Expansion of the model to
8 incorporate these aspects has been accomplished in the adult rat (McLanahan et al. 2008, 2009) and
9 ongoing efforts were reported for the pregnant dam and fetus (Lumen et al. 2012). Lumen and
10 coworkers described the serum pharmacokinetics of perchlorate and dietary iodide in the near term
11 pregnant dam and fetus, thyroid stores, iodide, and total serum T4 from which fT4 is calculated, and
12 total T3. The competitive inhibition of each anion (perchlorate and dietary iodide) on the other for
13 uptake by the NIS is described for the thyroid gland and placenta. Serum fT4 levels in the mother and
14 fetus were predicted at steady state for a range of dietary iodide intakes ranging from mild iodide
15 deficiency (75 µg/day) to sufficient iodide intake (250 µg/day) with no perchlorate intake (exposure)
16 and for a range of perchlorate intakes (0.00001 to 1.0 mg/kg/d). The authors predicted the exposure
17 conditions for perchlorate, under varying dietary iodide diets, that would result in serum maternal fT4
18 levels associated with hypothyroxinemia (decrease in serum T4 and no change in serum TSH) and for
19 the onset of hypothyroidism (increase in serum TSH and decrease in serum fT4 levels). This biologically
20 based dose response (BBDR) model for the HPT axis in the pregnant woman and fetus provides a
21 quantitative approach to better understand the adverse health consequences (hypothyroxinemia and
22 hypothyroidism) using an MOA-based analysis of perchlorate exposure for a range of dietary iodide
23 intakes. A substantial enhancement in this modeling effort reported by Lumen et al. (2012) would be to
24 perform Monte Carlo analysis to address variability in the human population. The contributions to NIS
25 of inhibition from other NIS inhibitors (e.g., thiocyanate, nitrate) also could be incorporated in the
26 modeling, but may be addressed as qualitative uncertainties at this time.

27
28 Documenting the MOA framework and the PBPK/PD-IUI model to make them accessible to both
29 modelers and non-modelers will be an important challenge for the EPA. By comparison with the simple
30 algebraic default equation describing an MCLG as a function of a few terms (e.g., RfD, body weight,
31 water intake, and source contribution), the proposed analysis could appear opaque despite the fact that it
32 captures much scientific information. The model documentation would describe model structure, data
33 used to establish that structure and estimate parameter values, sensitivity of model outputs such as NIS
34 inhibition to parameters, and characterization of the model strengths and limitations. Publications on
35 model evaluation and documentation (Clark et al. 2004; Chiu et al. 2007; Thompson et al. 2008) as well
36 as the World Health Organization International Programme on Chemical Safety PBPK Guidance (IPCS,
37 2010) provide useful approaches for developing documentation. This documentation would also
38 reference the published literature on the model and the 2008 EPA peer review of the PBPK/PD-IUI
39 model and its subsequent revisions.

40
41 ***Recommendations:***

42 The SAB recommends that the EPA utilize an MOA framework for developing the MCLG that links the
43 different steps in the proposed mechanism leading from perchlorate exposure through NIS inhibition to
44 thyroid hormone changes and finally neurodevelopmental impacts. Within this MOA framework, the

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1 PBPK/PD-IUI model provides a tool for integrating exposure (e.g., different drinking water
2 consumption rates) with the biological changes occurring at the different lifestages to obtain predictions
3 for perchlorate pharmacokinetics and resulting symporter inhibition to address these initial steps of the
4 MOA framework.

5
6 Extension of the PBPK/PD-IUI model to describe changes in thyroid hormone levels should be
7 expeditiously incorporated as this would provide a key tool for linking early events with subsequent
8 events as reported in the literature on iodide deficiency, changes in thyroid hormone levels, and their
9 relationship to neurodevelopmental outcomes during these sensitive early life stages.

10
11 Development of a clear communications strategy, including documentation of the MOA framework and
12 the PBPK model, will facilitate stakeholder and public understanding of approach used in the
13 development of the MCLG.

14 **3.2.2. Strengths and Limitations of EPA's PBPK Model Results**

15 The two analyses EPA presented in the white paper address different aspects of the model and its use in
16 developing an MCLG (US EPA 2012). The first analysis (Table A3 in the EPA white paper (2012))
17 evaluates the predicted RAIU inhibition for the same perchlorate dose (7 µg/kg/day) that arises from
18 biological variations captured in the PBPK model for different lifestages. This analysis helps support the
19 use of the UF in deriving the RfD as it predicts greater inhibition at fetal and neonatal/infant lifestages as
20 compared to the adult. The second analysis (Table A4 in the EPA white paper (2012)) evaluates the
21 combined effects of life stage-dependent differences in exposure (e.g., drinking water consumption)
22 with the biological variability by assessing the predicted RAIU inhibition at fixed drinking water
23 exposure concentrations.

24
25 Some strengths and limitations of the first analysis of life stage dependent biological variability were
26 identified. A limitation of the first analysis is the selection of the urinary excretion rate for perchlorate.
27 Literature for iodide excretion indicates the rate is faster in neonate/infants than at later ages, which
28 might then be expected to be the case for perchlorate (Malvaux et al. 1965; Oddie et al. 1966; Ponchon
29 et al. 1966). The values in the model need to be reassessed and justified. While the model addresses life-
30 stage variations, it is a model of the average human at each life stage. Extension of the model to a full
31 population description would be useful, but it is recognized that this would be a major effort. In the
32 absence of a full population analysis, it is important for the EPA to document and justify when model
33 parameter values are selected that either represent an upper or lower bound rather than the average (e.g.,
34 using upper bound drinking water intake) or when given uncertainty in the experimental literature they
35 select a specific value (e.g., the highest or lowest urinary clearance rate) rather than using an average
36 value. An approach of a sensitivity analyses for PBPK model predictions could be useful for identifying
37 key parameters to make such population analyses more tractable or to evaluate and demonstrate the
38 impact of selection of particular parameter values. The human biological modeling uses life-stage
39 specific uptake rates mediated by NIS levels but does not reflect changes in NIS in response to TSH
40 regulation if they occur since the model does not currently include thyroid hormones to permit such a
41 feedback description nor potential effects of chronic perchlorate exposure. A strength of the analysis is
42 that the EPA evaluated the model's capability to describe both perchlorate transport into breast milk as

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1 well as to assessing the expected impact of NIS inhibition on iodide transfer to breast milk, so that
2 predictions for inhibition in breast-fed infants account for both these aspects.

3
4 The second analysis would share these same strengths and limitations because it combines the biological
5 variability with life-stage dependent differences in exposures. Data for water and diet consumption at
6 the different lifestages that inform the exposure modeling appear somewhat variable in extent across the
7 lifestages.

8
9 The major strength and limitation of the current model as noted above is that it provides a tool to link
10 perchlorate exposure with impacts on iodide uptake, but goes no further in the MOA. This early step
11 would usefully be extended to represent the consequences of those changes on thyroid hormone levels at
12 different life stages under varied conditions of basal iodide intake and thyroid hormone status.

13 ***Recommendation:***

14 The SAB finds the second analysis is the most valuable for asking what extent of NIS inhibition would
15 be predicted for different potential MCLG concentrations; it provides perspective on the protection
16 offered by different perchlorate concentrations. Since it uses 90th percentile drinking water consumption
17 rates, it starts to address population issues in exposure, although most of the biological aspects of the
18 model are for an average individual. As noted above, the EPA needs to document and justify when
19 selecting values other than average values in the absence of a full population analysis in order to be
20 transparent about scientific, science policy, or regulatory policy choices involved.

21
22 Limited data have been available for perchlorate in plasma and breast milk so checking the availability
23 of new data in the literature would usefully inform alternative parameterization or characterization of the
24 uncertainty in the current model parameters. There is widespread sensitivity to information on potential
25 impacts of breast and bottle-feeding for infants, so care in communications about these topics will be
26 beneficial.

27
28 The choices for urinary clearance values for perchlorate and iodide at the different life stages should be
29 reviewed and the current or revised values documented and justified to clarify the selections as
30 appropriate for a model of the average individual at each life stage in light of uncertainties in the
31 scientific literature.

32
33 **3.3. Epidemiological Studies**

34 ***Charge Question:***

35 *How should EPA consider the post-NRC epidemiology data in deriving an MCLG?*

36
37 The SAB finds that the epidemiological data published since NRC 2005 report the are useful for
38 estimating the size of potentially sensitive subgroups in the United States, estimating the extent to which
39 the U.S. general population and sensitive subgroups are exposed to perchlorate and other goitrogens, and
40 estimating the relative source contribution of perchlorate in drinking water among sensitive subgroups
41 not included in the Food and Drug Administration (FDA) total diet study (Murray et al. 2008).

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1
2 The SAB concludes that these epidemiological data are insufficient to guide causal inference of an
3 association between perchlorate exposure and thyroid dysfunction in pregnant women, neonates or the
4 general population. Limitations concerning study design, exposure assessment, sample size, and
5 statistical modeling have resulted in inconsistent findings. The current body of epidemiologic evidence
6 cannot provide validation of a safe level of perchlorate in drinking water.
7

8 The SAB provides specific comments on how the agency could use the exposure and biomonitoring
9 studies published since the NRC report (2005). The SAB identifies research components that the EPA
10 and others should consider when planning analyses based on existing data or when developing new
11 studies to improve the agency's understanding of the effect of perchlorate exposure in hypothyroxinemic
12 populations. The SAB also provides specific comments in Appendix B on the strengths and weaknesses
13 of recent studies identified by EPA and others.

14 **3.3.1. Using Exposure and Biomonitoring Studies**

15 Manuscripts published since the 2005 NRC report are informative for providing an estimate of the size
16 of potentially sensitive subgroups in the U.S., estimating exposure to perchlorate and other goitrogens,
17 including among sensitive subgroups, and estimating the relative source contribution of perchlorate in
18 drinking water among sensitive subgroups.

19 ***Prevalence of Sensitive Subgroups***

20 Epidemiologic studies can be used to identify sensitive subgroups. However, methodological
21 considerations (see review of epidemiologic literature in Appendix B) limit the scientific conclusions
22 that can be drawn from the studies published to date. The National Health and Nutrition Examination
23 Survey (NHANES) is a cross-sectional, population-based survey that over-sampled some subgroups to
24 produce a relatively representative sample of the U.S. population (CDC 2004). NHANES can be used to
25 estimate the population prevalence of potentially sensitive subgroups, including pregnant women who
26 are iodide insufficient and pregnant women with detectable thyroid antibodies.
27

28 Iodine is critical for the formation of TH. Iodine deficiency occurs when iodine falls below
29 recommended levels. According to the WHO guidelines, urinary iodine levels > 100 ug/L are considered
30 "adequate" among the general population (WHO 1994). However, among pregnant women the demand
31 for iodine is greater; therefore, in this population group, urinary iodine levels <150 ug/L are considered
32 "insufficient" (Andersson et al. 2007). Caldwell et al. (2005) used iodine measured in spot urine samples
33 from NHANES 2001-2002 to characterize iodine levels in the U.S. population (2005). Among women
34 age 15 to 44, 37.2% have iodine levels <100 ug/L. Using the 2005-6 and 2007-8 NHANES samples,
35 Caldwell et al. (2011) reported that the proportion of women ages 15-44 with urinary iodine <100 ug/L
36 remains relatively constant at 38.1%. Among pregnant women, however, 56.7% have urinary iodine
37 concentrations less than the recommended 150 ug/L.
38

39 The thyroid antibodies — thyroglobulin antibody (TgAb), thyroid stimulating hormone receptor
40 antibody (TSH-RAb), and thyroid peroxidase antibody (TPOAb) — can interfere with TH synthesis via
41 humoral and cell-mediated mechanisms leading to clinical or subclinical hypothyroidism (Sinclair

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2006). Individuals with hypothyroidism may be more susceptible to additional thyroid disruption, such as that occurring when exposed to perchlorate. Hollowell et al. (2002) estimated the prevalence of thyroid antibodies in the NHANES 1988-1994 sample (2002). In the overall study population, 13.0% and 11.5% had detectable TPOAb and TgAb, respectively. Among the disease-free population, 11.3% (TPOAb) and 10.4% (TgAB) were antibody-positive. Antibody-positive participants were more likely to be female and among females, antibody prevalence increased significantly with age. Using NHANES data, it would be possible to estimate the proportion of women of childbearing age and the proportion of pregnant women (with imprecision due to the small number of pregnant women typically represented in NHANES) that are thyroid antibody-positive.

Estimating Perchlorate Exposure and Exposure to Other Goitrogens

Biomonitoring and exposure studies published since the NRC report can be used to identify subgroups with the highest exposures to perchlorate. NHANES studies can produce population estimates of perchlorate exposure, including among potentially sensitive subgroups.

Blount et al. (2006) provides information for estimating perchlorate exposure and dose using spot urine samples among a representative sample of n=2820 males and females ≥ 6 years of age in NHANES 2001-2002. Perchlorate was detectable in all samples, indicating widespread exposure. Children ages 6-11 had the highest concentrations of urinary perchlorate (geometric mean: 5.40 ug/L, adjusted for race/ethnicity, sex, age, fasting time and urinary creatinine).

Huber et al. (2011) provides information for estimating perchlorate exposure and dose in pregnant women. The authors used data from a random subset of NHANES 2001-2002 that measured perchlorate in n=2708 spot urine samples (creatinine adjusted), including 116 pregnant women. Compared to non-pregnant women aged 15-44 years, pregnant women had significantly higher average daily perchlorate doses (geometric mean: 0.06 ug/kg/day vs. 0.051 ug/kg/day). These data, however, may be imprecise because they are estimated from a single spot urine sample and because during pregnancy, creatinine adjustment for urinary dilution is less effective (Mendez et al. 2010). Huber et al. also examined the EPA Unregulated Contaminant Monitoring Regulation (UCMR) data, which provides data on perchlorate levels in public drinking water sources. In the UCMR data the estimated perchlorate contribution from food was 86% and from drinking water was 14%.

Some potentially sensitive subgroups, such as infants, are not represented in NHANES. Exposure information for these missing subgroups can be inferred from exposure and biomonitoring studies specifically targeting these groups. While these studies are often comprised of highly selected study subjects and may not be representative of the U.S. population, the paucity of epidemiologic data on potentially sensitive subgroups makes these targeted studies useful nonetheless. Some of the studies published since the NRC report may inform dose parameters for PBPK/PD models.

Information for estimating perchlorate exposure and dose among infants less than 6 months of age is available in four studies (Kirk et al. 2005; Dasgupta et al. 2008; Schier et al. 2010; Valentin-Blasini et al. 2011). Kirk et al. (2005) reported average perchlorate concentrations of 2.0 ug/L (range: 0.0 to 11.0 ug/L) and 10.5 ug/L (range: 1.4 to 92.2 ug/L) in dairy milk and breast milk, respectively (2005). Using

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1 these data, the authors estimate that the majority of breast-fed infants would exceed the NRC RfD (0.7
2 ug/Kg/day). Dasgupta et al. (2008) measured perchlorate in repeated milk and urine samples from a
3 small number of lactating women (n=13) (2008). Based on these data, the authors estimated that 9 of 13
4 infants exceeded the NRC perchlorate RfD. Schier et al. (2010) estimated perchlorate intake from four
5 varieties of infant formula: bovine-based with lactose, bovine-based without lactose, soy-based, and
6 elemental. The authors reported that bovine formula with lactose had the highest concentrations of
7 perchlorate (geometric mean: 1.72 ug/L), which could lead to estimated daily doses at 1 and 6 months of
8 age that exceeded the perchlorate RfD. Valentin-Blasini et al. (2011) directly measured perchlorate
9 exposure in the urine of breast- and formula-fed infants age 1-377 days by collecting up to four samples
10 per infant (n=205 samples from 92 infants) . The highest average perchlorate concentrations were
11 among breast-fed infants (geometric mean: 2.65 ug/L vs. 1.3 ug/L for bovine-based formula and 0.35
12 ug/L for soy-based formula). Correspondingly, the highest average estimated perchlorate doses
13 (geometric means for breast-fed, bovine-based formula fed, and soy-based formula fed, respectively:
14 0.922 ug/kg/day, 0.103 ug/kg/day, and 0.027 ug/kg/day) were among breastfed infants. Based on these
15 estimates, 16% of all infants (and 31% of breast-fed infants) had at least one perchlorate exposure dose
16 exceeding the RfD. There was, however, a great deal of intra-individual variability of perchlorate
17 concentrations across repeated samples (intraclass correlation coefficient (ICC) = 0.07). These authors
18 also reported concurrent urinary levels of nitrate, thiocyanate, and iodide concentrations.

19
20 In addition to perchlorate, NHANES provides an opportunity to evaluate the extent to which the U.S.
21 population, including sensitive subgroups, may be co-exposed to other goitrogens with comparable
22 MOAs, such as thiocyanate and nitrate. The ion chromatography coupled with tandem mass
23 spectrometry method used to measure perchlorate in urine in the NHANES sample from 2001-2002
24 provides simultaneous measurement of nitrate, thiocyanate and iodide (Valentin-Blasini et al. 2007).
25 While the geometric mean concentrations of all four compounds are reported in Blount et al. (2006) and
26 Mendez and Eftim (2012), these data have not yet been described in detail in a peer-reviewed
27 publication (English et al. 2011). Ultimately, while data from epidemiologic studies are insufficient for
28 evaluating the causal association between perchlorate exposure and thyroid dysfunction because of the
29 methodological issues described in Appendix B, these studies may be useful for understanding
30 perchlorate exposure and co-exposure to other goitrogens among pregnant women and infants.

31
32 ***Estimating the relative source contribution***

33 The relative source contribution (RSC) is the proportion of an individual's daily perchlorate reference
34 dose remaining for drinking water after considering exposure from other sources. For perchlorate, food
35 is the only other important exposure pathway. The EPA used the FDA total diet study by Murray et al.
36 (2008) to estimate the drinking water RSC (Table A-2, US EPA 2012) based on estimated perchlorate
37 intake from food among n=14 age/sex subgroups of the U.S. population. RSC estimates ranged from
38 44% to 89%, although the total diet study did not provide intake estimates for all potentially sensitive
39 subgroups (e.g., pregnant or lactating women, infants less than 6 months of age). Studies outlined above
40 provide information for estimating perchlorate dose for drinking water and food intake levels within
41 sensitive subgroups.

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1 **3.3.2. Epidemiologic Studies of Associations between Perchlorate Exposure and Thyroid**
2 **Dysfunction**

3 The SAB finds that epidemiologic studies published since the 2005 NRC report are insufficient to guide
4 causal inference concerning an association between perchlorate exposure and thyroid dysfunction, or to
5 support derivation of an MCLG. Methodological and statistical issues limiting the applicability of these
6 studies to the Charge question include (1) use of ecological measures of perchlorate exposure based on
7 community drinking water concentrations, (2) cross-sectional study designs, (3) small sample size, (4)
8 misspecified statistical models and (5) inconsistent treatment of creatinine, iodide status, thyroid
9 antibodies and co-exposures to other goitrogens. These issues are discussed in detail in Appendix B.
10

11 **3.3.3. Recommendations for Future Analyses and Studies**

12 Existing exposure and biomonitoring studies are useful for understanding the prevalence of sensitive
13 subgroups. Additional analyses of NHANES data can be undertaken to estimate the prevalence of
14 sensitive subgroups not previously described, including the proportion of thyroid-antibody positive
15 pregnant women. The typically small number of pregnant women in NHANES, however, may limit the
16 precision of these analyses. In addition to perchlorate, urinary concentrations of other goitrogens are also
17 available in NHANES data.
18

19 It may be possible to pool data from existing studies with similar design and analytic measures to
20 alleviate some of the methodological and statistical issues discussed in Appendix B. However, *post-hoc*
21 pooled analyses should be undertaken with caution and with careful consideration of potential sources of
22 heterogeneity across studies.

23 ***Recommendations***

24 Prospective studies of individual urinary biomarkers of perchlorate exposure and thyroid function and
25 child neurobehavioral development are recommended. Studies that evaluate hypothyroxinemia
26 endpoints during pregnancy may offer a better picture of the role of perchlorate as a contributor to
27 meaningful health outcomes in susceptible populations, specifically endpoints directly related to
28 neurodevelopment.
29

30 Additionally, future studies may benefit from improved statistical methods. Investigating non-linear
31 patterns of effect across low, moderate and high exposures categories may be informative. Careful and
32 thorough consideration of appropriate control variables may reduce bias and improve the precision of
33 estimated perchlorate effects. For instance, directed acyclic graphs are useful tools for graphically
34 depicting assumptions about causal relations among variables, which can then inform statistical
35 modeling strategies (Greenland et al. 1999). Rather than adjusting models for characteristics of
36 potentially vulnerable populations, it may be more informative to stratify the analysis by the
37 characteristic. For instance, iodide deficient pregnant women may be more susceptible to the effect of
38 perchlorate than iodide sufficient pregnant women. Stratification highlights this differential
39 susceptibility instead of providing an average effect over all iodide levels. Such studies, however, would
40 require large sample sizes to see these divergent effects.
41

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1 Finally, co-exposures to other goitrogens should be consistently measured in future studies and
2 consideration should be given to conducting sensitivity analyses to address uncertainties of modeling co-
3 exposures to compounds with the same (or different) modes of action. Studies of the variability of
4 perchlorate, iodide, nitrate, and thiocyanate in spot urine samples also should inform methods for
5 minimizing measurement error.
6

7 **3.4. Integration of Information**

8 *Charge Questions:*

9 *How can EPA best use the total body of information to derive a health protective MCLG, while*
10 *considering the results of epidemiology and biomonitoring data in establishing bounds on potential*
11 *values?*

12
13 *How can EPA use the available data to estimate reductions in adverse health effects (i.e., dose*
14 *response) that are likely to result from reducing perchlorate levels in drinking water?*

15 **3.4.1. Integrating Information to Derive a MCLG**

16 The EPA white paper describes a process for deriving an MCLG for perchlorate that incorporates an
17 RfD and RSC (U.S. EPA 2012). The SAB recommends that the EPA integrate the body of information
18 on perchlorate to derive an MCLG using the MOA previously identified for perchlorate rather than the
19 default algebraic approach. The MOA approach relies on the use of a PBPK/PD model that relates
20 perchlorate intake via drinking water with percent iodide uptake inhibition. The SAB recommends that
21 EPA use a PBPK/PD- IUI approach and where possible expand this approach to relate the percent IUI
22 with TH perturbations and potential adverse neurodevelopmental outcomes.
23

24 The SAB recommendation represents an important and novel opportunity that should be implemented
25 carefully with attention to data quality and methodological rigor. At each step, EPA should critically
26 evaluate available data and describe the strengths and limitations. The SAB concludes that a stepwise
27 “integrated” approach is a logical way forward allowing multiple sources of information to be integrated
28 into the MCLG derivation. The SAB also recommends that EPA undertake the necessary literature
29 review and critical analysis to fully test the feasibility and utility of the approach. The SAB also
30 recommends that EPA incorporate into the MCLG development the recent recommendations from the
31 National Academy of Sciences to improve the scientific basis and clarity of assessment documents
32 (NRC 2009, 2011).
33

34 This SAB advisory report presents specific recommendations for considering sensitive life stages, PBPK
35 modeling, and the epidemiological and biomonitoring data that were presented to the SAB to derive an
36 MCLG. While the charge to the SAB focused on scientific literature published since the release of
37 NRC’s 2005 report, clearly the agency needs to consider the entire literature related to ingestion of
38 perchlorate, pharmacokinetics of perchlorate, and the effects (dynamics) of perchlorate (such as Clewell
39 et al. 2001; 2003a, b). In addition, the SAB finds that EPA should also consider available data on
40 potential adverse health effects due to thyroid hormone level perturbations regardless of the cause of
41 those perturbations.

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1
2 A summary the three previous sections provides the foundation for an approach to derive the MCLG for
3 perchlorate using the entire body of available information.
4

5 *Sensitive Life Stages:* The most important SAB recommendations are the focus on *subtle*
6 changes in thyroid hormone levels in pregnant women – specifically, hypothyroxinemia
7 (defined as “fT4 levels below the 10th percentile and concomitant TSH values <2.0
8 µmU/L”). Hypothyroxinemic pregnant women should be considered the sensitive life
9 stage; this would replace pregnant women with clinical hypothyroidism as the sensitive
10 life stage as defined by the NRC (2005). As discussed in section 3.1, the SAB finds that
11 the sensitive subpopulation of concern is pregnant hypothyroxinemic women and the
12 adverse effect is impacts on neurodevelopment of the fetus, neonate, infant, and child,
13 born to these women.
14

15 *Epidemiology and Biomonitoring Data:* The key conclusion of the SAB was that the data
16 in the scientific literature since the 2005 NRC report were insufficient to provide the
17 basis for an MCLG. However, a consideration of the full literature and/or other combined
18 analyses (such as meta-analysis or pooled analysis) might provide important information
19 that could be used to support an MCLG based on pregnant hypothyroxinemic women,
20 and their fetuses and infants , as the sensitive subpopulation.
21

22 *PBPK Modeling:* The current PBPK/PD-IUI model can link perchlorate exposure in food and
23 water with perchlorate concentrations in plasma and tissue and resulting NIS inhibition assessed
24 by RAIU studies. The continuum of events in the MOA after NIS inhibition would include
25 possible changes in serum thyroid hormone levels, which have been associated with
26 neurodevelopmental changes in offspring of iodine-deficient women. Work to extend the
27 PBPK/PD-IUI model with links to serum thyroid hormone levels was presented at the Society of
28 Toxicology 2012 meeting (Lumen et al. 2012) and a manuscript is in preparation (personal
29 communication with Dr. Jeffery Fisher, September 29, 2012).
30

31 The SAB recognizes that an MOA that links the different steps in the proposed mechanism leading from
32 perchlorate exposure through NIS inhibition to thyroid hormone changes and finally
33 neurodevelopmental impacts has been determined. The SAB finds that this framework provides a strong
34 foundation for the EPA to develop the MCLG. Within this MOA framework, the PBPK/PD-IUI model
35 provides a tool for integrating exposure (e.g., different drinking water consumption rates) with the
36 biological changes occurring at the different lifestages to obtain predictions for perchlorate
37 pharmacokinetics and resulting NIS inhibition to address these initial steps of the MOA framework.
38

39 In order to ensure that the model is predictive of actual adverse health outcomes, the EPA will need to
40 examine the literature on the associations between reduced iodide uptake, subtle changes in thyroid
41 hormone levels as defined by hypothyroxinemia, and adverse neurodevelopmental outcomes in children,
42 including literature not specifically designed to include perchlorate (i.e., iodide deficiency, thyroid
43 hormone levels, hypothyroxinemia).
44

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1 The SAB recognizes the existence of a large amount of scientific research on perchlorate and also
2 thyroid hormone perturbations and potential adverse health outcomes (unrelated specifically to
3 perchlorate). As a result, the SAB recommends that EPA explore the use of the literature beyond that
4 which focuses on perchlorate.

5
6 The SAB notes that the recommendation to use the MOA and PBPK/PD mathematical model is a novel
7 and alternative approach to developing the MCLG. The SAB emphasizes the need for transparency in
8 approaches for identifying and/or excluding model input data, compiling datasets for purposes of
9 identifying and bounding numerical estimates needed for the MCLG and transparency and robust
10 explanation of the approach and modeling used for the derivation of the MCLG.

11
12 Regarding using epidemiological and biomonitoring data to establish the bounds on potential MCLG of
13 the, the SAB was not provided the full extent of data on the epidemiologic, biomonitoring, water
14 concentration, or physiologic data related to perchlorate, nor asked to complete each step in the new
15 approach to developing an MCLG. Therefore, the SAB finds that it is premature to provide specific
16 guidance on bounding estimates. The SAB recommends that EPA fully evaluate the breadth and depth
17 of the data, data variability and uncertainty, and the utility of the data. The SAB further notes the
18 importance of incorporating metrics and statistics, such as 95th percentiles and ranges of values rather
19 than point estimates (see Section 3.2).

20
21 The SAB notes that in applying the framework to the epidemiological data, the the agency should
22 consider the available evaluation tools such as Strengthening the Reporting of Observational Studies in
23 Epidemiology (STROBE)³ or Grading of Recommendations Assessment, Development and Evaluation
24 (GRADE 2012). The SAB recommends that as the EPA integrates information, if they consider the
25 general frameworks for evaluating quality of studies used to support the MCLG derivation (as discussed
26 briefly in Appendix C).

27
28 ***Steps In A Mode of Action Modeling Approach***

29 The SAB recommends the following MOA- based approach for using PBPK/PD modeling and
30 additional clinical and toxicological data to inform the derivation of a health-protective MCLG
31 recognizing the sensitive population as the fetuses, infants, and children of hypothyroxinemic women.
32 The effects of concern are neurodevelopment outcomes in the offspring. The SAB presents this
33 approach as a series of steps to progressively improve the scientific rigor in the evaluation of different
34 life stages considered for the MCLG and recognizes that the steps described here may require an
35 increased level of effort and additional data. The approach is discussed below and summarized in Figure
36 2. The SAB recommended approach follows the solid arrows in the diagram and an alternative approach
37 follows the dashed arrows in the figure.

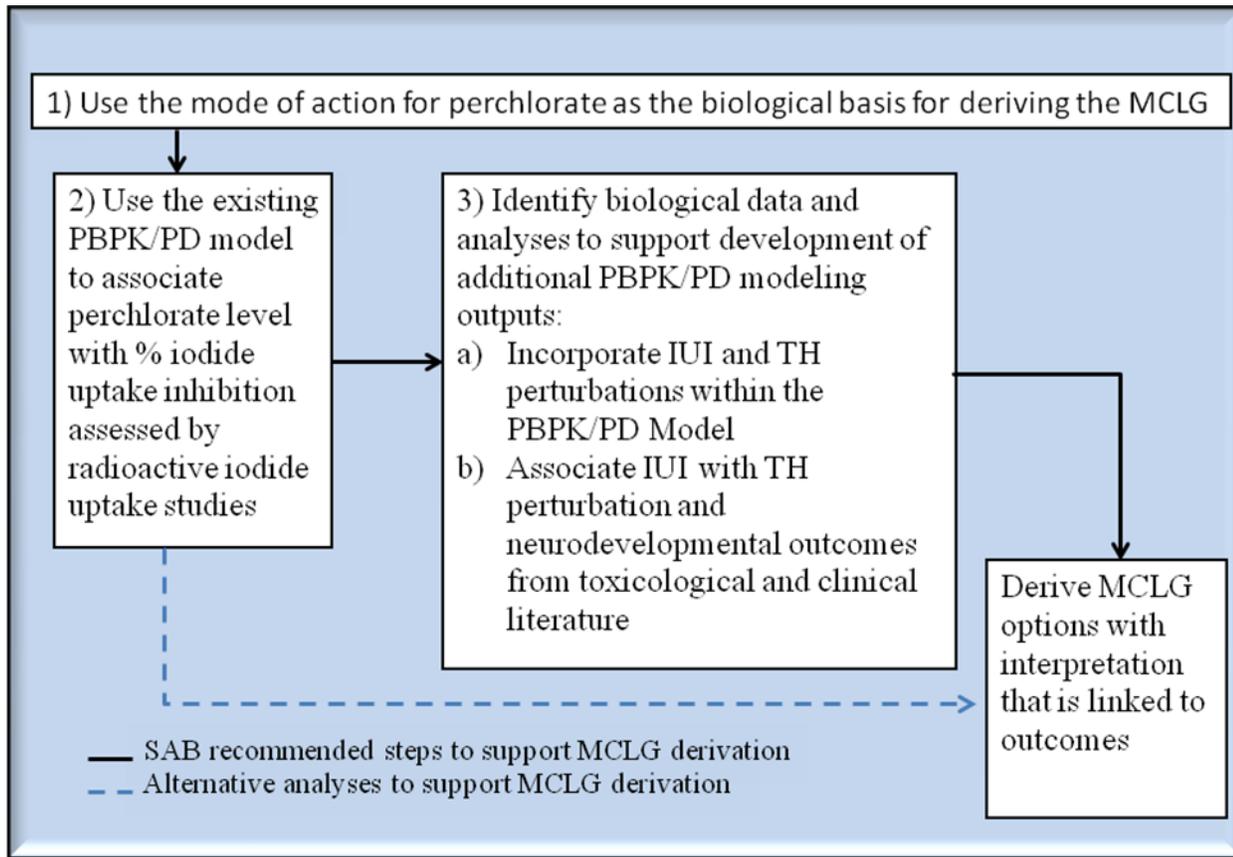
38

³ Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
<http://www.strobe-statement.org/index.php?id=available-checklists> [accessed July 30, 2012].

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1
2 Figure 2. Steps in a mode of action and modeling approach to derive MCLG for perchlorate.

3
4 Step 1. Use the MOA for perchlorate (See Figure 1 Section 3.2.) as the biological basis for deriving the
5 MCLG. This MOA links perchlorate exposure to NIS inhibition to thyroid hormone changes and
6 neurodevelopmental impacts.

7
8 Step 2. Use the existing PBPK/PD-IUI model to link perchlorate exposure in water with perchlorate
9 concentrations in plasma and tissue and resulting NIS inhibition assessed by RAIU studies. The model
10 in its current form addresses important aspects of biological life stage sensitivities, but limitations
11 should be clearly stated or the model should be adjusted (e.g., iodide and perchlorate clearance in the
12 early postnatal period as noted in Section 3.2). While the preferred MOA approach would link IUI with
13 subsequent events (e.g., thyroid hormone perturbations), using predictions of IUI from the current
14 PBPK/PD-IUI model is consistent with the derivation of the RfD. This would be the most rapid analysis
15 for EPA to implement since the model predicts percent IUI for the relevant life stages and has already
16 been subject to a peer review. The NRC report proposed that by minimizing IUI, one would minimize
17 subsequent events and adverse health consequences. The limitation of using either the RfD in the default
18 algebraic equation or IUI predicted by the model is that both describe a precursor event and neither
19 explicitly provides predictions for subsequent events and adverse outcomes. The advantage of the
20 PBPK/PD-IUI model approach over the algebraic calculation is that it explicitly predicts IUI at the
21 relevant lifestages that this SAB panel considered important.

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1
2 Step 3. The SAB urges the EPA to expand the PBPK/PD model to address as many of the downstream
3 MOA outcomes as possible. The agency should identify literature and conduct analyses to support the
4 model outputs for the downstream steps. While incorporating these subsequent steps into the PBPK/PD-
5 IUI model is the preferred approach, the SAB recognizes the additional effort required. An interim
6 approach is to obtain data from the clinical and toxicological literature to describe empirical
7 relationships to the downstream effects not provided by the models output. Benefits and limitations to
8 both approaches are described below.

- 9
- 10 a) The SAB recommends that the EPA extend the PBPK/PD-IUI model to incorporate predictions
11 of thyroid hormone perturbations. Such an extension of the model would need to explicitly
12 address dietary iodide intake (both adequate and insufficient intake) and thyroid hormone
13 production at different life stages for women and children with adequate and insufficient iodide
14 intakes. This approach would permit assessment of the predicted exposure-response relationship
15 for perchlorate exposure and alterations in thyroid hormone levels (e.g., decreases in serum free
16 T4). To establish what magnitude of decrease in T4 would be relevant, EPA would need to
17 document the relationship between the levels of maternal serum biomarkers, e.g. fT4 and TSH,
18 associated with adverse effects on neurodevelopment of infants. Examples of useful literature to
19 support this step may include the Haddow et al. (1999) and Pop et al. (1999) studies. The
20 assumption of this approach is that the source of the decreased iodide for thyroid hormone
21 synthesis (e.g., lack of dietary intake or competition by perchlorate) does not impact the
22 subsequent events driven by thyroid hormone levels. Such an effort will require resources and
23 time, likely up to several years. The SAB notes that similar modeling efforts are underway at
24 other federal agencies and collaboration with these researchers could facilitate development
25 thereby reducing the level of effort.
- 26
- 27 b) An interim approach is to use the existing PBPK/PD-IUI model to estimate IUI and then develop
28 empirical relationships for each of the steps beyond perchlorate-mediated IUI. Use the thyroid
29 clinical literature to identify the degree of symporter inhibition (percentage IUI) required for
30 onset of hypothyroxinemia in the pregnant woman. The relevant literature for this step may
31 include the clinical literature on iodine deficiency as well as other literature on
32 hypothyroxinemia. If one could establish equivalence between perchlorate-mediated IUI and
33 reduced iodide intake as observed by measured urinary iodide, one could utilize the relationship
34 between urinary iodide and thyroid hormones levels described in Silva and Silva (1981) for
35 varying levels of iodide intake in pregnant women. Again, the relationship between changes in
36 thyroid hormone levels and neurodevelopmental outcomes just discussed would be required to
37 complete the linkages. This approach will require resources and time, perhaps less than required
38 for explicitly expanding the PBPK/PD-IUI model to include thyroid hormone levels, but that
39 depends upon being able to identify data to provide the needed empirical relationships for steps
40 between IUI and neurodevelopment.

41
42 As a check on the predictions from either of these approaches, the agency could compare model
43 predictions with epidemiological data. As previously discussed, the post-2005 epidemiological studies
44 have significant limitations for the purposes of MCLG derivation and have limited utility for evaluating

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1 the PBPK-PD-IUI model outputs. However, it may be possible to gain information on perchlorate
2 exposure and thyroid hormone perturbations from an examination of the raw data, i.e., a pooled analysis.
3 If a pooled analysis is pursued, the SAB advises exploring the recent Pearce et al. (2010, 2011, and
4 2012) studies as the source material, although there may be other relevant studies as well.

5
6 Pooled analyses are challenging and the data to be combined must be carefully evaluated to ensure that
7 such an analysis is appropriate. Methodological issues particular to pooled analysis of biomarkers
8 studies are presented by Taioli and Bonassi (2002). Section 3.3.3 identifies several model specification
9 considerations (e.g., non-linearity of effects across exposure categories, assessment of effect
10 modification, and assessment of confounding) that would be relevant to a pooled analysis, if conducted.
11 (Further information on model misspecification in the epidemiological literature the SAB reviewed is
12 found in Appendix B). A pooled analysis requires substantial effort.

13
14 The discussion immediately above identifies three potential next steps to identify and apply biological
15 data in support of the PBPK/PD-IUI modeling to derive a MCLG for perchlorate. In Table 1, the SAB
16 provides rough estimates of the time requirements for each potential next step.

**Table 1. Potential Next Steps in an Integrated Approach to
Derive a MCLG for Perchlorate, with Estimated Time Requirements**

Potential Next Steps	Short-term (estimated up to 1 year)	Medium-term (estimated 1 – 2 years)	Long-term (estimated more than 2 years)
Use existing literature to identify empirical linkages between existing PBPK model to downstream changes (TH, neurodevelopment)	●		
Extend PBPK/PD-IUI model to predict TH		●	
Pooled analysis of existing epidemiological studies			●

3.4.2. Estimating Reductions In Adverse Health Effects

21 The SAB finds that the epidemiological studies provided to the panel are inadequate for quantitatively
22 estimating reduction in adverse health effects realized in regulating perchlorate in drinking water.
23 Specifically, the epidemiological studies provided are not adequate to support quantitative dose-response
24 modeling and related adverse health effects reduction analyses. To move toward the goal of quantitative
25 dose-response and reduction in adverse health effects assessment for perchlorate, the agency must first:
26 define:
27

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- Define the adverse effect. The SAB recognizes neurodevelopmental effects in the infant as the potential adverse effects of perchlorate. These effects may range from changes in brain development and structure to impaired behavior, learning and memory, among others (Rovet and Willoughby 2010). These effects have been observed in studies of iodine deficiency or altered thyroid hormone function – conditions consistent with the MOA for perchlorate. Changes in brain development and structure have been observed in studies of animals where maternal hypothyroxinemia or thyroid hormone deficiency were modeled (for example, Lavado-Autric et al. 2000; Auso et al. 2004). Impaired learning, cognition and motor development have been observed in studies of children whose mothers were iodine deficient or hypothyroxinemic (for example, Zoeller and Rovet 2004; Henrichs et al. 2010; Li et al. 2010; Suarez-Rodriguez et al. 2012). For the purposes of deriving a MCLG for perchlorate, SAB recommends that the EPA focus on measurements relevant to these adverse effects including iodine deficiency and hypothyroxinemia; and

- Define the sensitive population. The SAB identified the sensitive subpopulation as hypothyroxinemic pregnant women.

EPA may be able to begin to estimate reduction in adverse health effects from reducing perchlorate levels in drinking water by examining shifts in the distribution of exposure to the sensitive subpopulation - hypothyroxinemic pregnant women – if relevant data are available.

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APPENDIX A

Charge to EPA Science Advisory Board

LIFE STAGE CONSIDERATIONS AND INTERPRETATION OF RECENT
EPIDEMIOLOGICAL EVIDENCE TO DEVELOP A MAXIMUM
CONTAMINANT LEVEL GOAL FOR PERCHLORATE

Background

On February 11, 2011 (U.S. EPA, 2011a), EPA published a determination to regulate perchlorate under the Safe Drinking Water Act (SDWA) because:

- perchlorate may have an adverse effect on the health of persons;
- perchlorate is known to occur or there is a substantial likelihood that it will occur in public water systems with a frequency and at levels of public health concern; and,
- in the sole judgment of the Administrator, regulation of perchlorate presents a meaningful opportunity for health risk reduction for persons served by public water systems.

EPA has initiated the process to develop a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for perchlorate. The MCLG is a non-enforceable goal defined under the SDWA (§1412.b.4.B) as “*the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety.*” For perchlorate, the NPDWR will likely specify an enforceable Maximum Contaminant Level (MCL) and monitoring and reporting requirements for public water systems. The SDWA (§1412.b.4.B and D) specifies that the enforceable MCL be set as close to the MCLG as feasible using the best available technology, treatment techniques, and other means (taking cost into consideration).

The regulatory schedule established by SDWA requires EPA to publish a proposed MCLG and NPDWR within 24 months of making a determination to regulate a contaminant and promulgate a final regulation within 18 months of the proposal. As part of this proposed rulemaking, EPA also must develop a Health Risk Reduction and Cost Analysis that includes an assessment of the quantifiable and non-quantifiable health risk reduction benefits likely to occur as a result of treatment to remove the perchlorate. SDWA further requires that when proposing any NPDWR that includes an MCL, the Administrator must analyze “[t]he effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a

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1 *history of serious illness, or other subpopulations that are identified as likely to be at greater risk of*
2 *adverse health effects due to exposure to contaminants in drinking water than the general population⁴.”*
3

4 In 2005, at the request of EPA and other federal agencies, the NRC published a comprehensive
5 report “*Health Implications of Perchlorate Ingestion*” (NRC, 2005). The NRC concluded that
6 perchlorate can affect thyroid function because it is an ion that competitively inhibits the transport of
7 iodide into the thyroid by a protein known as the sodium (Na)/iodide (I) symporter (NIS). Significant
8 inhibition of iodide uptake results in intra-thyroid iodine deficiency, decreased synthesis of key thyroid
9 hormones (Triiodothyronine, T3 and Thyroxine, T4), and increased thyroid stimulating hormone or
10 thyrotropin (TSH). The NRC also concluded that a prolonged decrease of thyroid hormone is potentially
11 more likely to have adverse effects in sensitive populations (people with thyroid disorders, pregnant
12 women, fetuses, and infants).
13

14 The NRC recommended the use of a precursor, non-adverse effect (i.e., inhibition of iodide
15 uptake) to derive a reference dose (RfD) for perchlorate. An RfD is defined by EPA as “an estimate
16 (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human
17 population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious
18 effects during a lifetime.” The NRC identified a clinical study involving 37 healthy men and women by
19 Greer *et al.* (2002) as the critical study and determined an RfD of 0.7 µg/kg/day for perchlorate. The
20 RfD was based on the No Observed Effect Level (NOEL) of 7 µg/kg/day corresponding to a radioactive
21 iodide uptake (RAIU) inhibition of 1.8 percent and application of an intraspecies uncertainty factor (UF)
22 of 10 to account for differences in sensitivity between the healthy adults in the Greer *et al.*, (2002) study
23 and the most sensitive population, fetuses of pregnant women who might have hypothyroidism or iodide
24 deficiency. The NRC also acknowledged that the RfD may need to be adjusted upward or downward on
25 the basis of future research. The RfD of 0.7 µg/kg/day was adopted by EPA in 2005 (U.S. EPA, 2005a).
26 EPA believes that this RfD is the most scientifically defensible endpoint available at this time for
27 assessing risk from perchlorate exposure.
28

29 In October 2008, EPA published a preliminary determination not to regulate perchlorate in
30 drinking water using a health reference level (HRL) of 15 µg/L, which was derived from the RfD of 0.7
31 µg/kg/day, using a default body weight (70 kg), a default drinking water consumption rate (2 L/day),
32 and a perchlorate-specific relative source contribution (RSC) of 62% for a pregnant woman (U.S. EPA,
33 2008). The RSC is the percentage of the RfD remaining for drinking water after the other sources of
34 exposure to perchlorate (e.g., food) have been considered. In January 2009, EPA issued an interim
35 health advisory (15 µg/L perchlorate in drinking water) to provide guidance to state and local officials in

⁴SDWA uses the term *subpopulation* to refer to groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other groups that can be identified and characterized and are likely to experience elevated health risks. In 2005 EPA started using the term *life stages* to refer to age-defined groups. All life stages are subpopulations but not all subpopulations are life stages. In this document, the term *life stage* is used predominantly because of the focus on infants and very young children.

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1 their efforts to address perchlorate contamination while EPA was continuing to review scientific issues
2 (U.S. EPA, 2009a).

3
4 In August 2009, EPA published a supplemental request for comment with a new analysis that
5 derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used
6 the RfD of 0.7 µg/kg/day and life stage-specific body weight and exposure information (i.e., drinking
7 water intake, RSC) (U.S. EPA, 2009b). The HRLs ranged from 1 µg/L to 47 µg/L. In February 2011,
8 EPA published the Final Regulatory Determination to regulate perchlorate under SDWA. The Final
9 Regulatory Determination stated that EPA was evaluating the potential alternative HRLs and considered
10 them to be levels of public health concern for the purposes of final determination (U.S. EPA, 2011a).

11
12 **Charge to the SAB**

13
14 The purpose of this white paper is to seek guidance from the SAB on how best to consider and
15 interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report,
16 physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health
17 information to derive an MCLG for perchlorate.

18
19 **Specific Charge Questions**

20
21 ***Issue I - Sensitive Life Stages***

22
23 While studies directly demonstrating the adverse effects of perchlorate in humans are not
24 available, potential effects can be inferred from the mode of action for perchlorate and the literature on
25 thyroid hormone decrements and neurological deficits in various life stages. Perchlorate blocks the
26 transport of iodide into the thyroid gland leading to iodide deficiency and decreased synthesis of thyroid
27 hormones, T3 and T4. Transfer of iodide from blood into the thyroid gland is essential for the synthesis
28 of the thyroid hormones. In its deliberations on the health effects of perchlorate in drinking water, the
29 NRC committee considered pregnant women who might have hypothyroidism or iodide deficiency and
30 their fetuses to be particularly sensitive populations to perchlorate mediated health effects (NRC, 2005).

31
32 Based on the discussion in Section IV of the white paper, pregnant women and their fetuses,
33 neonates, infants (breast-fed and bottle-fed) and young children have been identified as life stages of
34 concern for adverse effects due to perchlorate. Significant thyroid perturbations *in utero* are well known
35 to cause neurological deficits in infants and children (NRC, 2005). High turnover rate of thyroid
36 hormones, and low storage capacity in the fetus and neonate make these in particular, sensitive life
37 stages for thyroid hormone perturbations. Furthermore, infants and children, in general, are more
38 susceptible to xenobiotics effects because of low urinary clearance of contaminants, and higher food
39 consumption and drinking water intake per body weight relative to adults (USEPA, 2011b). As in the
40 thyroid gland, perchlorate is actively taken up into mammary tissue via NIS. Perchlorate also
41 competitively inhibits the uptake of iodide into the mammary gland, reducing the amount of available
42 iodide in breast milk. Therefore, breast-fed infants also represent a population of particular concern as
43 they experience a double hit – exposure to perchlorate accumulated in breast milk in addition to a

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1 deficiency of iodine in the breast milk. (Kirk *et al.*, 2005; Dasgupta *et al.*, 2008; Valentin-Blasini *et al.*,
2 2011).

3
4 **There are currently no data available to directly link perchlorate to neurobehavioral effects in**
5 **infants and children. How should EPA consider the following life stage factors in deriving an**
6 **MCLG?**

- 7
8 • **Life stage specific differences in body weight and food and drinking water intake;**
9
10 • **Differences in greater severity and permanence of potential adverse effects in neonates,**
11 **infants and young children compared to adults;**
12
13 • **Shorter half-life and lower reserves for thyroid hormone in infants compared to adults;**
14 **and**
15
16 • **Intrauterine exposure to perchlorate and impact on thyroid status in fetuses.**

17
18 *Issue II - Physiologically-Based Pharmacokinetic Evidence*

19
20 The NRC relied on information on inhibition of RAIU in a small group of healthy, iodine
21 sufficient, adults, similar data are not available for other life stages. With the development of the PBPK
22 model (U.S. EPA, 2009b), it is now possible to provide estimates of the effect of perchlorate on RAIU in
23 different life stages as outlined in white paper Section VI.

24
25 The PBPK model predictions can be evaluated in two different ways. The first application is
26 based on a comparison of the relative RAIU inhibition sensitivity at a fixed dose (point of departure,
27 POD of 7 µg/kg/day identified by NRC) for different life stages. One exception in the first application
28 scenario with regard to dosing is that the breast-fed infants received a dose higher than the POD, but
29 lactating mothers received a dose equivalent to the POD. The second application involves comparing
30 RAIU inhibition at a fixed drinking water exposure level (15, 20 and 24.5 ppb) with and without
31 perchlorate contribution via food for various life stages. Thus, the doses for different life stages varied in
32 the second application scenario.

33
34 The findings from the first application indicate a greater sensitivity for RAIU inhibition for
35 fetuses and breast-fed infants compared to other life stages/sub populations (Table A-3 of the White
36 Paper). The findings from the second application indicate a RAIU inhibition of 2.2% or less for all life
37 stages when they are exposed to drinking water containing 15 µg/L perchlorate in addition to perchlorate
38 in food (Table A-4 of the White Paper). In the context of significance of RAIU inhibition, NRC
39 determined 1.8% RAIU inhibition was not significant at the POD/NOEL of 7 µg/kg/day for healthy
40 adults, but recommended that a 10-fold uncertainty factor be applied to the POD to protect the fetus of
41 the pregnant woman who might have hypothyroidism or iodine deficiency. However, the doses infants
42 receive when exposed to 15 µg/L perchlorate in water and perchlorate in food are up to 5 times higher
43 than the RfD.

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- 1 • **How should EPA consider PBPK modeling to derive an MCLG for perchlorate?**
- 2
- 3 • **What are the strengths and limitations of the two PBPK model results described in this**
- 4 **effort?**
- 5

6 ***Issue III – Epidemiological Evidence***

7

8 Since the NRC report (2005), a number of epidemiological studies have investigated the

9 association between perchlorate exposure and thyroid hormone perturbations. None evaluated the

10 neurodevelopmental outcomes. The studies reported findings for sensitive life stages of concern:

11 pregnant women, neonates and infants. Several of these studies investigated the association between

12 perchlorate exposure in drinking water and thyroid hormone levels in the US, Israel and Chile (Tellez *et*

13 *al.*, 2005, Amitai *et al.*, 2007, Steinmaus *et al.*, 2010). The study in Chile (Tellez *et al.*, 2005) reported

14 urinary and serum perchlorate levels in women during pregnancy and post partum (a longitudinal cohort

15 study). However, perchlorate assignment to subjects was based solely on geographical location. Other

16 studies that examined the association between perchlorate and thyroid hormone levels included urinary

17 perchlorate concentrations as biomarkers of exposure (Blount *et al.*, 2006; Pearce *et al.*, 2010, 2011).

18 Using NHANES 2001-2002 data, Blount *et al.* (2006) demonstrated a perchlorate-related increase in

19 TSH and decrease in T4 in women >12 years of age with urinary iodide <100 µg/L. Pearce *et al.* (2010,

20 2011) did not find an association between urinary perchlorate and thyroid hormone perturbations in first

21 trimester pregnant women. Differences in study designs, numbers and age of subjects, exposure

22 assessment approaches, and statistical methods may explain the mixed findings among these studies.

23 The studies published in the literature since the NRC (2005) review are described in Section VII and

24 Table A-5 of the white paper. The new epidemiological evidence may inform bounding of the possible

25 life stage-specific MCLG estimates derived in the White Paper (Table-1).

26

- 27 • **How should EPA consider the post-NRC epidemiology data in deriving an MCLG?**
- 28

29 ***Issue IV – Integration of Information***

30

31 The primary action of perchlorate exposure is on the thyroid gland, where perchlorate inhibits

32 the transport of iodide from the blood into the thyroid gland which in turn can lead to perturbations in

33 the synthesis of thyroid hormones. Perturbations in thyroid hormones during critical stages of

34 development lead to permanent neurological deficits in children (NRC, 2005). EPA generally derives an

35 MCLG on the basis of the RfD. EPA believes that the NRC derived RfD of 0.0007 mg/kg/day (0.7

36 µg/kg/day) for perchlorate is the most scientifically defensible endpoint available at this time for

37 deriving an MCLG. In deriving the RfD, the NRC applied an intraspecies factor of 10x to protect the

38 fetuses of pregnant women who might have hypothyroidism or iodide deficiency. The UF 10 can be

39 further subdivided into a $UF_{TK} = 10^{1/2} = 3.16$ (generally rounded to 3) to account for differences in

40 internal dosimetry due to toxicokinetic differences, and a $UF_{TD} = 10^{1/2} = 3.16$ (generally rounded to 3) to

41 account for differences in toxicodynamics. This convention is used by EPA in the absence of compound-

42 specific data as is the case with perchlorate.

43

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1 At a fixed dose of 7 $\mu\text{g}/\text{kg}/\text{day}$, the first application of PBPK model findings indicate 6.7x, 2.6x,
2 7.8x, and 1.1x greater sensitivity for RAIU inhibition for GW 40 fetuses, 7 day breast-fed infants, 7-day
3 bottle-fed infants and children from 6 months to 2-years, respectively, as compared to adults (Table A-3
4 of the White Paper). It was not possible to estimate sensitivity in younger than term fetus. The second
5 use of PBPK modeling indicates a RAIU inhibition of 2.2% or less for all life stages when they are
6 exposed to drinking water containing 15 $\mu\text{g}/\text{L}$ perchlorate in addition to perchlorate in food (Table A-4
7 of the White Paper). In the context of significance of RAIU inhibition, NRC determined 1.8% RAIU
8 inhibition not significant for healthy adults. However, the doses infants receive when exposed to 15 $\mu\text{g}/\text{L}$
9 perchlorate in water and perchlorate in food are up to about 5 times higher than the RfD.

10
11 As discussed previously the mixed pattern of observations in the epidemiologic studies which
12 investigated the association between perchlorate exposure and thyroid perturbations since the 2005 NRC
13 review is not surprising in light of their different study designs, numbers and age of subjects, exposure
14 assessment approaches, and statistical methods. In an ecological study, Steinmaus *et al.* (2010) found
15 increased TSH levels in neonates when the mothers were exposed to perchlorate concentrations above 5
16 $\mu\text{g}/\text{L}$ in drinking water. Using 2001-2002 NHANES data, perchlorate-related increases in TSH and
17 decreases in T4 were demonstrated in women >12 years of age with urinary iodide <100 $\mu\text{g}/\text{L}$ (Blount *et*
18 *al.*, 2006). The changes in thyroid hormone levels in the NHANES analyses were observed at a mean
19 perchlorate intake level of approximately 0.1 $\mu\text{g}/\text{kg}/\text{day}$ (including food and drinking water) reported by
20 Huber *et al.* (2011) for the NHANES populations, suggesting thyroid hormone perturbations at a
21 perchlorate intake level less than the RfD determined by NRC (2005). The perchlorate dose estimated
22 from Huber *et al.* (2011) is consistent with that reported from other biomonitoring studies and analyses
23 reported in Section VIII and Table A-6 of the White Paper. Other studies of pregnant women or
24 neonates did not report associations between residence in a city with perchlorate in drinking water
25 supplies or between urinary perchlorate at similar or higher exposure levels than those estimated for
26 Blount *et al.* (2006) (Tellez *et al.*, 2005; Amitai *et al.*, 2007; Pearce *et al.*, 2010, 2011). Together the
27 results of these studies may serve as a means to bound the drinking water exposure range of concern,
28 and assist in determining where within the range of potential MCLGs an appropriate regulatory value
29 can be set.

- 30
31 • **How can EPA best use the total body of information to derive a health protective MCLG,**
32 **while considering the results of epidemiology and biomonitoring data in establishing**
33 **bounds on potential values?**
34
35 • **How can EPA use the available data to estimate reductions in adverse health effects (i.e.,**
36 **dose response) that are likely to result from reducing perchlorate levels in drinking water?**

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APPENDIX B

Critique of Recent Epidemiological Data for Deriving a Perchlorate MCLG

Epidemiologic studies published since the 2005 NRC report are insufficient to guide causal inference with regard to the association between perchlorate exposure and thyroid dysfunction. This conclusion is based on methodological inconsistencies and limitations pertaining to study design, exposure assessment, samples size, and statistical modeling. Each of the issues are discussed in detail in this Appendix.

Study design

The prototypical epidemiologic study is a randomized controlled trial. When the primary study question is whether perinatal exposure to an environmental chemical adversely affects child cognitive and behavioral development, observational studies must suffice. The ideal observational study to identify potential effects of perinatal perchlorate exposure on child health is not difficult to conceive, although it would be large, expensive, logistically challenging, and take approximately 10 years to complete. Ideally, the study would, from the first trimester of pregnancy, prospectively collect serial urinary biomarkers of maternal prenatal perchlorate exposure, serial serum biomarkers of maternal prenatal thyroid function, including TSH, fT4, and thyroid antibodies, and serial urinary maternal prenatal biomarkers of the related compounds iodide, nitrate, and thiocyanate. To determine the relative source contribution of perchlorate in drinking water and perchlorate from other sources, such as food or prenatal vitamins, serial drinking water and dietary measures like a food frequency questionnaire, 24-hour dietary recall, or duplicate plate, must be included and coincide with the collection of exposure biomarkers. Once the child is born, perchlorate, iodide, nitrate, thiocyanate, and thyroid function must be serially monitored in the child. Breast milk, formula, and eventually early solid foods should be assayed for goitrogens. Beginning at birth the child's development must be tested and then monitored every 2 to 3 years by performance on standardized neurobehavioral assessments. The home environment should be evaluated by trained research personnel, the mother's IQ should be measured, and other known predictors of child IQ and behavior, for instance lead exposure, should be obtained. The study can conclude with a final round of cognitive and behavioral testing when the child reaches 7 – 9 years of age.

When even an observational study of perinatal perchlorate exposure and child development is such a massive undertaking, researchers look to other study designs, data collected for other purposes, and interim outcomes (e.g., maternal prenatal thyroid dysfunction rather than impaired child cognitive skills) to address the study question. Unfortunately, the epidemiologic studies of health effects of environmental perchlorate exposure are insufficient to guide causal inference even for the interim question of whether exposure to perchlorate results in thyroid dysfunction.

Thirteen epidemiological studies published since the monograph *Health Implications of Perchlorate Ingestion* (NRC 2005) and assessing thyroid function can be divided into 2 groups based on the level of measurement of the exposure. Four ecological studies present environmental measures of perchlorate in drinking water based on residential location (Tellez 2005; Buffler 2006; Amitai 2007; and Steinmaus

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1 2010). Nine studies present individual measures of urinary perchlorate exposure (Cao 2010; Pearce et al.
2 2010, 2011, 2012; Leung 2012; Blount 2006; Steinmaus 2007; Schreinemachers 2011; Mendez 2012).

3
4 Ecological studies compare groups, not individuals. Defining exposure based on group level
5 characteristics, such as water district, is a variation on the ecological study design. These types of
6 studies are often the first investigative hypothesis-testing tool. They can lend credence to a new
7 hypothesis and provide important preliminary data for planning future studies, but the ecological fallacy
8 precludes any causal interpretation. The ecological fallacy occurs when population level associations are
9 also assumed to occur at the individual level. For these studies, specifically, the fallacy occurs with the
10 assignment of exposure: someone with a residence in a city with high levels of perchlorate in drinking
11 water (person A) is assumed to be exposed to more perchlorate than someone with a residence in a city
12 with low levels of perchlorate in drinking water (person B). There are several reasons why this scenario
13 may be untrue. While ones' official residence at the time of exposure is defined for the study is located
14 in the high-exposure city, this may be a new residence (i.e., the subject may have moved during
15 pregnancy so the address listed on a birth certificate is not the address where the majority of the
16 pregnancy occurred). The subject may have an official residence, but actually spend the majority of time
17 at a different location. The subject may not drink tap water or used filtered tap water (i.e., under the
18 counter reverse osmosis filters remove perchlorate) or use a private well. Conversely, for the same
19 reasons why person A may not actually be exposed to high levels of perchlorate through drinking water,
20 person B may be exposed to higher than expected levels for someone with a residence in a city with low
21 levels of perchlorate in drinking water.

22
23 For perchlorate studies where exposure is an ecological measure based on drinking water source, there
24 are additional concerns that may lead to further exposure misclassification. First, drinking water
25 typically accounts for an estimated 20% of total perchlorate dose (Huber 2009). Consequently,
26 estimating total perchlorate exposure solely by drinking water source may be grossly inaccurate.
27 Second, perchlorate levels in drinking water may not be constant even though studies using ecological
28 exposure measures define them as such (e.g., person A either does or does not reside in a high exposure
29 location). Buffler et al. notes that in southern California, the proportion of Colorado River water used for
30 drinking water varies seasonally (2006). The Colorado River is a source of perchlorate exposure.
31 Consequently, the level of perchlorate in water supply systems reliant on Colorado River water may
32 change as more or less river water is diverted into the drinking water system. Categorical assignment of
33 high/medium/low exposure water districts may not be true over time and season.

34
35 Overall, the four studies examining ecological measures of perchlorate exposure in drinking water in
36 relation to thyroid function, regardless of whether or not they show an association, are of little value for
37 guiding decisions regarding a MCLG for perchlorate in drinking water.

38
39 Cross-sectional studies using individual level measures of both exposure and outcome are often the next
40 investigative tool for examining an association. With cross-sectional studies, there is an individual
41 measure of exposure and an individual measure of the outcome, but the exposure and outcome are
42 assessed at the same point in time so causality cannot be inferred. With a cross-sectional study, there is
43 no way to know whether the exposure preceded the outcome and consequently no way to determine

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1 whether the exposure is a causal factor in development of the outcome. Nonetheless, cross-sectional
2 studies may be useful for elucidating relationships.

3
4 Of the nine cross-sectional studies, four use NHANES data from 2001-2002 (Blount et al. 2006;
5 Steinmaus 2010; Schreinemachers 2011). Mendez and Eftim uses NHANES 2007 – 2008 (2012). Blount
6 observed biologically plausible and consistent associations between increased urinary perchlorate
7 concentration and increased TSH and decreased T4 among women with low urinary iodide
8 concentration. Steinmaus carried these analyses forward and observed that this relationship appeared to
9 be strengthened as urinary thiocyanate concentration increased. Mendez also showed inverse
10 associations between levels of perchlorate and T3 and T4. In these analyses, however, TSH, thyroid
11 antibodies, and iodine were adjusted for in the model although their role may be better treated as
12 stratification variables (see Statistical Model Misspecifications below). Schreinemachers used indirect
13 measures of thyroid function (HDL cholesterol, hemoglobin, hematocrit), which may be more relevant
14 to the thyroid's role in metabolic pathways rather than neurobehavioral development.

15
16 Only one of the five non-NHANES cross-sectional studies replicated the association between higher
17 urinary perchlorate concentration and higher TSH among infants with lower urinary iodide levels (Cao
18 2010). This study, however, measured thyroid hormones in urine, not serum and the correlation between
19 thyroid hormones in urine and serum is low (Cao 2010). Unexpectedly, higher urinary perchlorate was
20 also associated with higher T4. None of the remaining four cross-sectional studies observed associations
21 between urinary perchlorate levels and thyroid function in pregnant women (Pearce et al. 2010, . 2011,
22 2012) or in infants (Leung 2012).

23
24 Overall, there is little consistency in the study design, methods, or conclusions of the 9 cross-sectional
25 studies. Many of the studies suffer from a small sample size, several have poorly specified statistical
26 models (see discussion below), and there is inconsistent treatment of urinary creatinine, iodide status,
27 and presence of thyroid antibodies. Given these methodological concerns, the lack of concordance in
28 results is not surprising. A prospective study using individual level measures of both exposure and
29 outcome is needed to truly determine a causal link between perchlorate exposure and either thyroid
30 function or child neurobehavioral development. There are no prospective studies examining the
31 association between individual urinary biomarkers of perchlorate exposure and individual serum
32 biomarkers of thyroid function.

33
34 One final piece needed to fully interpret studies using spot urine specimens for determination of
35 perchlorate and iodide is an improved understanding of the temporal variability of urinary measures of
36 perchlorate, iodide, nitrate, and thiocyanate. Variability incorporates both daily variation in urine
37 excretion and variation in exposure due to a variable diet. A thorough review and synthesis of the
38 literature examining how well a single spot urinary measure of these compounds reflects long term
39 exposure patterns is advised.

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1 ***Misspecification of Statistical Models in Epidemiologic Studies***

2
3 Potential statistical model misspecification is an important consideration when interpreting the results of
4 seven studies published since the 2005 NRC report that have incorporated individual-level measures of
5 perchlorate exposure and serum thyroid hormone concentrations (Blount et al. 2006; Steinmaus et al.
6 2007; Mendez 2012; Pearce et al. 2010, 2011, 2012; Leung 2012). Concerns relate to: 1) modeling
7 perchlorate exposure as a linear term when the relationship with health outcomes may not be linear, 2)
8 proper assessment of suspected effect measure modifiers, 3) inappropriately controlling for causal
9 intermediates, 4) inadequate assessment of confounders leading to over-adjustment for factors suspected
10 to be associated with the thyroid hormone outcomes but not with perchlorate exposure, and 5) suitable
11 methods for modeling co-exposures to other goitrogens or thyroid hormone disrupters. These elements
12 are addressed in more detail as they relate to specific studies.

13
14 All epidemiologic studies of urinary perchlorate concentrations and thyroid function published after the
15 2005 NRC report have reported results of linear regression models or generalized additive mixed models
16 (GAMM) specifying perchlorate exposure as a linear term predicting continuous measures of thyroid
17 function (Mendez 2012). Approaches that assume a monotonic linear relationship between perchlorate
18 and thyroid hormone concentrations may fail to reveal other plausible patterns of association such as
19 effects that occur only after some exposure threshold is reached, low dose effects that plateau at some
20 point along the exposure continuum, or other possible U-shaped or inverted U-shaped patterns. Evidence
21 for non-linear associations with perchlorate was examined by adding a square of the log of perchlorate
22 to the linear regression models (Blount et al. 2006) and by using GAMM to determine whether
23 smoothing of the perchlorate term provided a better model fit (Mendez 2012). However, the extent to
24 which other patterns of association were explored in these and other studies is not evident. Furthermore,
25 hypothyroxinemia during the first trimester of pregnancy rather than overt thyroid disease is
26 increasingly of interest because hypothyroxinemia may result in irreversible neurodevelopmental
27 deficits in the offspring (Delahunty 2010). However, existing studies have not incorporated this
28 endpoint.

29
30 The seven studies that use individual-level biomarkers of exposure can be grouped according to their
31 target populations which include women during the first trimester of pregnancy (Pearce et al. 2010,
32 2011, 2012), infants at 1-3 months of age (Leung 2012), and the general U.S. population as represented
33 by NHANES data (Blount 2006; Steinmaus 2007; Mendez 2012). The three cross-sectional studies of
34 pregnant women by Pearce and colleagues (2010, 2011, 2012) have reported no observed associations
35 between urinary perchlorate concentrations and first-trimester thyroid hormone levels in populations
36 from California, Argentina, Wales, Italy, and Greece. While the studies were generally similar, the
37 outcome assessment in one of them differed from the others in that fT4 and TSH levels were assessed as
38 multiples of the median (Pearce et al. 2010). All of these studies used linear regression models adjusted
39 for urinary iodine and TPOAb as well as other factors selected for their suspected associations with
40 thyroid hormone status. Adjustment for iodine concentrations, TPOAb status and other indicators of
41 potential susceptibility, however, deserves careful consideration. The rationale provided for controlling
42 for both iodine and TPOAb titers is that women with low iodine or TPOAb may be more susceptible to
43 the effects of perchlorate exposure on thyroid function. If the effect of perchlorate is anticipated to differ

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1 across defined subgroups, it is appropriate to examine the factor as a potential effect measure modifier
2 by using stratification or interaction terms rather than adjusting for the factor as a control variable.
3 Otherwise, associations that may be present in defined subgroups could be obscured when these
4 subgroups are combined for analysis. While these studies examined correlations between urinary
5 perchlorate and thyroid hormones among women with urinary iodine concentrations < 100 µg/L,
6 multivariable regression analyses of perchlorate exposure were not examined for interactions with iodine
7 status. This evaluation was presumably limited by small sample sizes in the defined strata. The Pearce et
8 al. study of 134 pregnant women from California and 107 pregnant women from Argentina reported
9 examining a multivariable analysis restricted to TPOAb negative women from the combined study
10 populations (2011). Results were not shown but were reportedly similar to results obtained from the
11 unrestricted analyses of all women combined. Analyses among the potentially susceptible population of
12 TPOAb positive women were likely limited due to small numbers. The study of 134 pregnant women
13 from Greece reported examining and observing no interaction between urinary perchlorate and TPOAb
14 positivity, although the statistical power to detect such interactions was again limited by the small
15 sample size (Pearce et al. 2012).

16
17 It is noteworthy that Pearce et al. (2010) also controlled for smoking status defined as cotinine >500
18 ng/ml or thiocyanate concentrations (in separate models). The selected cotinine cutpoint of >500 ng/ml
19 would represent relatively heavy smoking and would not successfully control for more modest levels of
20 active smoking commonly indicated by urinary cotinine concentration of 15 ng/ml or 50 ng/ml.
21 However, if the effect of perchlorate on thyroid function is suspected to be greater among smokers than
22 non-smokers as reported by Steinmaus et al., then evaluation of potential interactions with smoking
23 would precede assessment of confounding (2007). Other potential confounders such as age, race, body
24 mass index (BMI), or creatinine concentrations were not considered in these models. Of particular note,
25 there was no evaluation of confounding or effect measure modification by gestational age to consider
26 the potential impact of changes in increasing fT4 and decreasing TSH concentrations that occur during
27 the first trimester due to increased circulating concentrations of human chorionic gonadotropin and
28 estrogen (de Escobar 2008). While the explanation for a potential association between perchlorate and
29 gestational age remains unclear, gestational age was identified as a confounding factor of the perchlorate
30 and thyroid hormone association among pregnant women in Greece (Pearce et al. 2012).

31
32 Another consideration is the potential bias that could be introduced by controlling for covariates that lie
33 on the causal pathway between perchlorate exposure and thyroid function. The mechanism by which
34 perchlorate may alter thyroid hormone status is by competitively inhibiting iodide uptake. This leads to
35 the question of whether urinary iodide concentrations would be a proxy for intra-thyroid iodine
36 deficiency, which lies on the causal pathway between perchlorate and thyroid hormone alterations.
37 Inappropriately controlling for a causal intermediate can distort results by underestimating the true
38 exposure effect, a result of partial or complete control of effects that occur through this pathway. Pearce
39 et al. 2010 controlled for urinary iodide concentrations in fT4 models, but reported that urinary iodide
40 concentrations were removed from the TSH models because iodide concentrations were not a significant
41 predictor of TSH and the model was not significant when urinary iodide was included (Pearce et al.
42 2011). All linear regression models in the remaining two Pearce et al. studies (2011, 2012) controlled for
43 urinary iodide. Results were not available to compare multivariable models with and without control for
44 these factors to determine if adjustment for iodide altered point estimates.

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1
2 According to power analyses provided in the Pearce et al. publications, the studies of first trimester
3 thyroid function were powered to detect stronger correlations than those observed; thus, the sample sizes
4 were not sufficient to confirm the absence of more modest associations (2010, 2010, 2012).

5
6 Three studies have evaluated urinary perchlorate associations with thyroid function in NHANES study
7 populations (Blount et al. 2006; Steinmaus et al. 2007; Mendez 2012) . The analysis by Blount et al. is
8 considered one of the most definitive studies to date, due to the large nationally representative sample
9 size and use of individual measures of urinary perchlorate concentrations. In the analysis of NHANES
10 2001-2002 data, Blount et al. observed no associations between perchlorate exposure and thyroid
11 function in men. However, in women with urinary iodine <100 µg/L, log-transformed urinary
12 perchlorate concentrations were positively associated with TSH concentrations and negatively
13 associated with T4 concentrations. In women with urinary iodine ≥ 100 µg/L, perchlorate remained
14 positively associated with TSH, but was not statistically associated with T4 concentrations. This was the
15 first study to separately evaluate associations among women with insufficient iodine intake (urinary
16 iodine <100 µg/L). The analysis by Blount et al. evaluated an extensive list of covariates selected on the
17 basis of known or suspected associations with T4 or TSH concentration. These included age,
18 race/ethnicity, BMI, estrogen use, menopausal status, pregnancy status, premenarche status, serum C-
19 reactive protein, serum albumin, serum cotinine, hours of fasting, urinary thiocyanate, urinary nitrate
20 and selected medication groups. Models were also controlled for log creatinine to adjust for variability
21 in urine dilution. The authors aimed to assess effects of perchlorate that were independent of other
22 factors known to alter thyroid function. However, when the aim is to estimate causal associations, the
23 goal is to control for those factors that may distort the true exposure-disease association due to mutual
24 associations with the perchlorate exposure and thyroid hormone function outcome. The impact of
25 unnecessarily adjusting for factors that are associated only with thyroid function (and, therefore are not
26 acting as confounders) is potential loss of precision.

27
28 Steinmaus et al. extended the NHANES 2001-2002 analyses reported by Blount et al. in 2006 to
29 examine interactions between perchlorate and smoking and between perchlorate and thiocyanate on
30 thyroid function (2007). In women with urinary iodine concentrations < 100 µg/L, the negative
31 association between log perchlorate and T4 was stronger in self-reported smokers, those with high
32 serum cotinine concentrations, and those with higher urinary thiocyanate levels than in those without
33 these characteristics. Similar interactions were not observed for log TSH. Although the T4 models were
34 adjusted for fasting time, kilocalories, BMI, c-reactive protein, nitrate, race, estrogen use, pregnancy and
35 menopause status, the authors reported that in most of the regression models only modest differences
36 were observed between the adjusted and unadjusted coefficients. As in the Blount et al. study, it is
37 unclear how some of the covariates may also be related to perchlorate exposure such as c-reactive
38 protein, estrogen use, and menopause status, but controlling for extraneous covariates that are not
39 confounders and not intermediates on the causal pathway would likely impact model precision but not
40 bias results.

41
42 While the previous NHANES analyses were limited to assessments of total T4 and TSH, Mendez and
43 Eftim's (2012) analysis of NHANES 2007-2008 data incorporated total and free T4 and T3
44 concentrations. The results of generalized additive mixed models (GAMM) indicated log-transformed

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1 perchlorate concentrations were negatively associated with total T4 and free T3 in both males and
2 females. In acknowledgment of the mutual effects of TSH, T3 and T4 levels on one another due to the
3 negative feedback loop in the hypothalamic-pituitary-thyroid axis, the regression models in this study
4 were controlled for TSH concentrations. However, TSH alterations may be a common effect of both the
5 exposure (perchlorate) as well as the outcome (T4 concentrations); thus, the observed associations
6 adjusted for TSH concentrations could be the result of collider-stratification bias, which is a form of
7 selection bias that can produce spurious associations when controlling for a shared effects (Schisterman
8 et al. 2009). Other covariates controlled in the analysis included thyroid antibodies and creatinine-
9 adjusted urinary iodine, thiocyanate and nitrate and other environmental contaminants such as phthalate
10 metabolites and bisphenol A. The covariates retained in final models were selected on the basis of
11 statistical significance of associations with thyroid hormone levels; thus, confounding of the perchlorate-
12 thyroid hormone association was not assessed directly, as in other studies, and overadjusting for non-
13 confounders could reduce the precision of the point estimates (Schisterman et al. 2009). Of note, urinary
14 iodine and thyroid antibodies were controlled in the analyses and were not assessed for potential effect
15 measure modification.

16
17 Uncertainties exist regarding the optimal method for considering co-exposures to other goitrogens such
18 as thiocyanate (including exposure occurring through tobacco exposure) and nitrate, which share the
19 same mode of action as perchlorate. Studies have predominantly addressed this concern by controlling
20 for urinary concentrations of other contaminants in multivariable models when the data are available for
21 thiocyanate (Blount 2006; Mendez 2012; Pearce et al. 2012, 2010; Leung et al. 2012), nitrate (Blount
22 2006; Steinmaus 2007), cotinine (Pearce et al. 2010) or self-reported smoking (Leung 2012). Some
23 studies, however, addressed the question by evaluating interactions between perchlorate and thiocyanate
24 (Steinmaus 2007; Pearce et al. 2012) and between perchlorate and smoking (Steinmaus 2007). These
25 inconsistencies emphasize the need for more in-depth evaluation of co-exposures, including
26 consideration of assessment of cumulative exposure.

27
28 The only study of infant thyroid function to incorporate individual measures of perchlorate exposure was
29 conducted by Leung et al. (2012). This cross-sectional study of 64 (partially or exclusively breast-fed)
30 infants ages 1-3 months reported no association between serum TSH or fT4 in infants and perchlorate
31 concentrations in breast milk, maternal urine, and infant urine. The multivariable linear regression
32 models controlled for thiocyanate (presumably measured in the same medium), maternal age, ethnicity,
33 smoking status, iodine-containing prenatal multivitamin use and supplemental infant formula use. The
34 effects of infant urinary perchlorate on infant serum fT4 and TSH were not statistically significant and
35 the small effect sizes were interpreted by the authors as clinically insignificant changes. The small
36 sample size, however, limits statistical power as well as precision of the point estimates.

37

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- 13
14

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APPENDIX C

General Comments on Integration of Information

1
2
3
4
5 Risk-based regulation that rests on
6 quantitative analyses is designed to
7 integrate disparate types of data and
8 information for hazard, exposure and
9 risk. For any given assessment, some of
10 the available data will be of poor or
11 lesser quality or of limited relevance,
12 precluding their use for quantitative
13 analyses. Therefore the agency must
14 employ transparent, rigorous review
15 criteria and clear presentation of
16 information to justify the data and
17 methods selected for use in developing
18 risk-based values such as MCLGs (NRC,
19 2011). The SAB considered the topic of
20 'integration of information' in this more
21 general sense and offers the following
22 recommendations for integration of the
23 available data and information to guide
24 its development of the perchlorate
25 MCLG.

Framework to Summarize Data Evaluation and Application

- 1) Critically evaluate the quality and content of each type of information in a transparent manner (may need to address each study or component of the larger 'dataset', e.g., life-stage specific intake estimates). Document:
 - a. Strengths
 - b. Limitations
 - c. Information on variability
 - d. Key uncertainties of the information
- 2) Define or describe the contribution of the information towards qualitative or quantitative understanding of perchlorate exposure, biological sensitivity, variability, toxicity and ultimately risk. Include discussion of how specific characteristics limit or support the contribution.

26
27 As EPA builds on the analyses presented in the White Paper and incorporates the panel's
28 recommendations, the agency should consider the advice of the NRC Committee in its Review of the
29 Draft IRIS Assessment on Formaldehyde (NRC 2011) to improve the clarity of assessment documents.
30 The agency needs an a priori approach for inclusion or exclusion and weighting of studies. Specifically
31 the panel recommends that EPA develop a structured framework to capture the key points of the
32 evaluation and application of each type of data or model used in the development of the perchlorate
33 MCLG, as well as the strengths, limitations and uncertainties associated with each. This framework
34 should be incorporated into the text, at the end of each relevant section. The text box below describes the
35 elements of such a framework discussed by the panel. These elements can be supplemented with
36 additional elements from the agency's guidance documents and current practices of data and weight of
37 evidence evaluation. In applying the framework to the epidemiological data, the panel recommends that
38 EPA take advantage of available evaluation tools such as Strengthening the Reporting of Observational
39 Studies in Epidemiology (STROBE)⁵ or Grading of Recommendations Assessment, Development and
40 Evaluation (GRADE)⁶, as appropriate.

⁵ Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
<http://www.strobe-statement.org/index.php?id=available-checklists> [accessed July 30, 2012].

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1
2 The draft framework also reflects the recommendations of the NRC as presented in Science and
3 Decisions: Advancing Risk Assessment (NRC 2009), specifically the necessity to estimate and
4 document the uncertainties in all aspects of an assessment including doses, exposures and outcomes.
5
6

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17

⁶ Grading of Recommendations Assessment, Development and Evaluation (GRADE)
<http://www.gradeworkinggroup.org/index.htm> [accessed July 30, 2012].