



*Regarding using epidemiological and biomonitoring data to establish the bounds on [the] potential MCLG of [perchlorate] the [sic], the SAB was not provided the full extent of data on the epidemiologic, biomonitoring, water concentration, or physiologic data related to perchlorate, nor asked to complete each step in the new approach to developing an MCLG. ... The SAB recommends that EPA fully evaluate the breadth and depth of the data, data variability and uncertainty, and the utility of the data.*

The full database of perchlorate literature encompassing *in vitro*, animal, and human studies and reporting on a range of exposures from environmental levels up to therapeutic doses is needed to address the charge questions US EPA has asked of the SAB. The SAB recognizes this itself and also urges US EPA to not rely unduly on the narrow scope of research done since the NRC report.

- **Advice to US EPA to remove policy-based parameters from the PBPK model.** The Draft Report states:

*As noted above, the EPA needs to document and justify when selecting values other than average values in the absence of a full population analysis in order to be transparent about scientific, science policy, or regulatory policy choices involved.*

As we have commented in several submissions to US EPA and the SAB, certain parameters in the US EPA PBPK model are based on “science policy.” A model that has policy-based parameters can yield a non-science output. Further, there is a lack of transparency regarding changes to the model first presented in Merrill et al. (2003). We agree with the SAB that US EPA should revise the model to include only science-based parameters that allow for the model to produce the best available output from which US EPA and the scientific community can make informed decisions.

- **The Draft Report requests improved transparency in the PBPK model and MCLG documentation.** It states:

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

As we have commented, the US EPA White Paper lacks transparency in its description of the PBPK model. We agree that enhancing transparency would help in a process that the Draft Report describes as “...opaque despite the fact that it captures much scientific information.”

- **The Draft Report urges that any new assessment of perchlorate include exposure to other agents that have the same mechanism of action and to which the public is exposed to on a daily basis.** The Draft Report addresses the issue of other goitrogens qualitatively and advises US EPA to consider it in future work, particularly in future epidemiological studies (discussed in the Draft Report on page 21). The Draft Report also urges the inclusion of total goitrogen load in the PBPK model when it states, “The contributions to NIS of inhibition from other NIS inhibitors (e.g., thiocyanate, nitrate) also could be incorporated in the modeling, but may be addressed as qualitative uncertainties at this time.”

## 2.0 OPPORTUNITY FOR SCIENTIFIC ENHANCEMENT OF THE SECOND DRAFT DOCUMENT

The clarity of several components of the Draft Report can be increased or expanded upon.

- **The Draft Report continues to be silent regarding the dose-response of perchlorate.** We have raised this issue in previous comments. The importance of this concept is paramount. This concept has been understood for more than 500 years. As Paracelsus (1493–1541) stated (translated to English):

*All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.*

In other words, in order for harm to result from an exposure, the exposure must be of sufficient concentration and duration to exceed the chemical's dose-response threshold. Simply put, a greater dose will cause a greater response. The SAB report would be strengthened by clarifying which effects occur at which doses. This context will ensure that the reader is not misled into thinking that neurodevelopmental effects can occur at environmental levels of perchlorate.

The NRC assessment identified the dose of 0.4 mg/kg-d as a No Observed **Adverse** Effect Level (NOAEL), based on studies of therapeutic doses. The NRC found these studies to be important in determining a threshold for adverse effects because

*...one could consider treatment in the latter 12 months to be equivalent to administration of perchlorate to healthy people. Therefore, the results provide evidence that moderately high doses of perchlorate given chronically to people with a history of hyperthyroidism do not cause hypothyroidism.*

Clinical studies have delivered doses from approximately 0.007 mg/kg-d (Greer et al., 2002) to 9.2 mg/kg-d (Brabant et al., 1992) with no reports of induced hypothyroidism. Pregnant women with Graves' disease received doses of 600 to 1,000 mg/d (6.2 to 10.3 mg/kg-d, assuming a 70 kg individual) with the only adverse effect noted being slight thyroid enlargement in one infant that resolved soon after birth (NRC, 2005 citing Crooks and Wayne, 1960). Other clinical studies are summarized in NRC (2005).

There are numerous studies that report the doses of perchlorate needed to cause non-adverse and adverse effects. The concentrations reported in municipal water are at least an order of magnitude lower than the level that causes even a slight increase in IUI, a non-adverse effect. Thus, based on the best scientific data to date, at environmental levels, no effect is expected from perchlorate exposure. Given this, epidemiological studies evaluating environmental levels of perchlorate would not be expected to report any perchlorate related effects.

No effect is expected to occur at doses below the No Observed Effect Level (NOEL). With the exception of Amitai et al. (2007) which reported drinking water concentrations of  $\geq 340$  ppb<sup>2</sup>, epidemiological studies have reported exposure levels below the NOEL (equal to approximately 245 ppb in drinking water assuming a 70-kg adult drinking 2 L/d). It is not unexpected that most of these studies report no association between

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<sup>2</sup> Amitai et al. (2007) compared the neonatal T4 levels between "very high" ( $\leq 340$  ppb), "high" (42-92 ppb), and "low" ( $< 3$  ppb) exposure levels. The authors concluded "This study finds no change in neonatal T4 levels despite maternal consumption of drinking water that contains perchlorate at levels in excess of the Environmental Protection Agency (EPA) drinking water equivalent level (24.5 mg=L) based on the National Research Council reference dose (RfD) [0.7 mg=(kg \_ day)]."

environmental perchlorate and thyroid function (Pearce et al., 2010, 2011, 2012; Blount et al., 2009; Leung et al., 2012; Tellez et al., 2005; Amitai et al., 2007) with the few reported statistically significant associations due to chance.

It is unclear how the SAB could address the charge to the SAB without consideration of dose-response. For example, the White Paper asks “How can EPA use the available data to estimate reductions in adverse health effects (i.e., dose response) that are likely to result from reducing perchlorate levels in drinking water?” The SAB felt they could not address this question. However, a dose response assessment would clearly demonstrate the vast difference between doses that may lead to adverse effects and environmental doses of perchlorate.

- **The Draft Report should urge US EPA to be transparent in its scientific support for conducting a life stage assessment.** We agree that all life stages should be evaluated for environmental agents. However, by definition, the RfD accounts for sensitive subpopulations including pregnant women, infants, and children. For perchlorate, the RfD is derived by dividing a no observed effect level (NOEL) for a nonadverse effect by an uncertainty factor (10) to protect sensitive subpopulations. This assessment was conducted by the NRC in 2005. There is no new scientific information since 2005 that provides support and neither the Agency nor the SAB provide scientific support for conducting an additional life stage assessment.

- US EPA does not provide a scientific reference that provides evidence of an association between perchlorate and neurodevelopmental effects. Instead, US EPA states that, based on information about severe iodine deficiency, such effects are mechanistically plausible at sufficiently high doses. However, there are a number of other things that are at least plausible: (1) that any effects goitrogenic compounds might have on neurodevelopment would be almost exclusively driven by thiocyanates and nitrates given their prevalence in the diet; (2) that the doses of perchlorate that would be required to cause neurodevelopmental effects are in the therapeutic range and not in the environmental range; and (3) that the homeostasis provided by TSH secreted when circulating thyroid hormones are reduced would more than compensate for exposure to environmental levels of perchlorate.
- The Draft Report provides one measure in which infants are less sensitive than adults. It states

*Literature for iodide excretion indicates the rate is faster in neonate/infants than at later ages, which might then be expected to be the case for perchlorate (Malvaux et al. 1965; Oddie et al. 1966; Ponchon et al. 1966).*

As noted in previous comments, pharmaceutical agents similar to perchlorate exhibit clearance rates in infants and young children at least equal to, if not greater, than the adult (Appendix A). Increased clearance would decrease the biological half-life of perchlorate and decrease sensitivity.

- The SAB should clarify that by evaluating life stages through water intake and body weight in the standard MCLG calculation, US EPA will be “double counting” the uncertainty factors used to account for sensitive subpopulations. If the life-stage analysis is to be used, the starting point

should be the Greer point-of-departure (7 µg/kg-d) and not the current RfD, which already has been adjusted to account for sensitive subpopulations.

- **The Draft Report should recommend a level of Iodide Uptake Inhibition (IUI) that could reasonably result in changes of thyroid or pituitary hormones.** The PBPK model is based on IUI, which is nonadverse precursor to downstream thyroid hormone changes. This determination would require a review of the full database, including assessments by authoritative bodies (e.g., NRC, ATSDR).

Table A-4 of US EPA's White Paper presents Radio Active Iodine Uptake (RAIU) inhibition with a dose corresponding to the 95th percentile drinking water intake rate ranging from 0.11 (15 ppb water and no contribution from food in the average adult) to 3.4 (24.5 ppb water and contribution from food in the 7-d old bottle fed infant). Table A-3 presents RAIU inhibition with a dose of 7 µg/kg-d (the point of departure) ranging from 1.6 (average adult) to 12.5 (7-d old, breast-fed infant). This means that using US EPA's current model, even with a dose that is 10-times greater than the existing RfD (0.7 µg/kg-d), the maximum predicted IUI is only 12.5%. US EPA has previously used this information to discuss relative differences between life stages, but has not presented how this could be used to develop an MCLG.

Iodine uptake naturally fluctuates based on diet and other environmental changes. Perchlorate accounts for only 1-2% of the estimated total goitrogenic effect on IUI in a person's daily diet when nitrate and thiocyanate are present (US EPA OIG, 2010; Tarone et al., 2010; de Groef et al., 2006). Furthermore, up- and down-regulation of the sodium-iodine symporter (NIS) allows homeostasis of bodily functions.

We encourage the SAB to conduct an independent assessment of this parameter. For instance, the SAB may review:

- The determinations of authoritative bodies. NRC (2005) concluded:
 

*Given the compensation that is known to occur in people with iodide deficiency, as discussed earlier, it is highly likely that in people with a normal iodide intake the dose of perchlorate would have to reduce thyroid iodide uptake by at least 75% for a sustained period (several months or longer) for iodide uptake and thyroid hormone production to decline enough to cause adverse health effects (equivalent to reducing dietary iodide intake by 75%). In adults, that is likely to require sustained exposure to more than 30 mg of perchlorate per day (0.4 mg/kg per day for a 70-kg person), on the basis of the clinical studies in healthy subjects and the studies of long-term treatment of hyperthyroidism, both described in this chapter, and the studies of environmental exposure, described in Chapter 3 (Gibbs et al. 1998; Lamm et al. 1999; Crump et al. 2000). In pregnant women, infants and children, and people who have a low iodide intake or pre-existing thyroid dysfunction, the dose required to cause a decrease in thyroid hormone production may be lower. However, a dose that does not inhibit thyroid iodide uptake will not affect thyroid function, even in subjects with an abnormal thyroid gland or a very low iodide intake.*
- The literature on thyroid uptake determination. The range of normal RAIU (not RAIU inhibition as presented in the US EPA White Paper) has been reported to be 6-33% (Nelson et al., 1970), 4-27% (Hooper et al., 1980), and

10-35% (Balon et al., 2006). This is likely helpful information for the SAB to consider.

- The upregulation of NIS. In situations when IUI is increased—as is common with biological receptors under feedback control—there is up-regulation of the NIS (NRC, 2005). For example, as thyroid hormone decreases, thyroid stimulating hormone (TSH) stimulates the increase in the number and efficiency of NIS on the apical membrane of the thyrocyte leading to an increase in the amount of iodine that can be taken up. This is likely helpful information for the SAB to consider.

- **The Draft Report should be specific about what effects it considers to be adverse.** The Draft Report lists the SAB-defined adverse effects due to iodine deficiency or decreased thyroid hormone and presumes these could also be caused by perchlorate. The Draft Report states “These effects may range from changes in brain development and structure to impaired behavior, learning and memory, among others (Rovet and Willoughby 2010).”

This list is broad and nonspecific, and does not incorporate information on perchlorate dose-response and the sequence of events leading to these effects. We urge the SAB to give US EPA a more defined association of cause and effect. For example, a thyroid hormone decrease of “x”% could cause “y” response. The animal literature documents a number of specific neurodevelopmental endpoints that may be sensitive to thyroid hormone deficiency (e.g., hearing; Crofton, 2004), that may provide specific decreases in thyroid hormone associated with a sensitive neurodevelopmental effect.

The Draft Report suggests that any level of iodine deficiency would be exacerbated by exposure to perchlorate. However, the Draft Report would benefit by providing more specific information regarding the levels of iodine deficiency that are associated with neurodevelopmental effects and how exposure to environmental levels of perchlorate relates to this.

- **The Draft Report should define that a MCLG be based on the most sensitive population.** The Draft Report states “The SAB identified the sensitive subpopulation as hypothyroxinemic pregnant women.” In contrast, NRC (2005) defined the most sensitive subpopulation at the fetuses of potentially hypothyroid pregnant women. The PBPK model can determine IUI for many different life stages other than the hypothyroxinemic pregnant woman. The US EPA White Paper suggests that 7-day old infants have greater IUI than pregnant women with equivalent doses of perchlorate. Recall that IUI is not an adverse effect. The SAB should urge US EPA to consider the most sensitive subpopulation (pregnant women) or provide evidence why another subpopulation is more sensitive.
- **The Draft Report should enhance the discussion on the strengths and limitations of the epidemiological literature.** The SAB concluded that the current body of epidemiological literature “...is unsuitable for determining a cause and effect relationship or as the basis of an MCLG.” We agree with the Draft Report statement, however, there is an opportunity to determine if the body of epidemiological literature provides some useful and consistent scientific information.

The Draft Report would help US EPA if it recommended what epidemiological or other data would be required to conclude that there is no effect of perchlorate at environmental

doses. The SAB should define what characteristics a definitive study would have.

Appendix B of the Draft Report includes a critique of the epidemiological literature. We agree with the SAB's overall assessment of the poor reliability of data based on ecological and cross-sectional studies, but ask the SAB to review the following:

- The Draft Report states that “Ecological studies compare groups, not individuals.” Tellez et al. (2005) should not be included in this category as it includes individual measures of perchlorate exposure through individual tap water samples and urinary perchlorate measurements before and after childbirth. Individual outcomes were also reported (increased TSH and thyroglobulin (Tg) levels and decreased free thyroxine (T4) in either the mother during the early stages of gestation or the neonate at birth, or in growth retardation of the fetus).
- Cross-sectional studies (e.g., those based on NHANES) are unable to determine a causal relationship. Several of these studies that relied on the NHANES 2001-2002 dataset were limited in that they were conducted with an earlier release of the 2001-2002 dataset; the CDC has recently released an enhanced dataset of -thyroid measures for NHANES 2001-2002. This new dataset has been analyzed in Bruce et al. (2012) which reports “No evidence of functional thyroid abnormality...”
- **The Draft Report should further explain how the current epidemiological literature could be used to define a Relative Source Contribution (RSC).** The RSC accounts for the contribution from food in the standard MCLG calculation. In the White Paper, US EPA presents PBPK model results that already incorporate food intake, although the White Paper is unclear about the basis of the food intake rate, particularly in infants. If the PBPK model is used this way, no additional RSC is necessary. The Draft Report states that some of the epidemiological studies since 2005 “provide information for estimating perchlorate dose for drinking water and food intake levels within sensitive subgroups.” How would an RSC based on epidemiological data be applied in context of the Draft Report recommendation to use the PBPK? (We note that the point-of-departure from Greer—and the current RfD—do not need to be adjusted for RSC, because the subjects of that study ate a normal diet and therefore were exposed to perchlorate and other goitrogens in food)

### **3.0 ADDITIONAL SCIENTIFIC INFORMATION THAT WOULD ASSIST THE SAB.**

Given the amount of work the SAB has conducted and may need to conduct to arrive at a final report, we would be happy to provide basic scientific studies or lists of references for any number of topics (depending on copyright) the SAB is evaluating. We would encourage other groups to also provide information to the SAB and US EPA to encourage consensus among the scientific community.

In summary, this SAB has worked diligently towards addressing a number of questions posed by US EPA. If considered by US EPA, the SAB's recommendations will help US EPA as it aims to provide “...a meaningful opportunity for health risk reduction...” as required by the Safe Drinking Water Act. We appreciate the opportunity to provide the SAB with scientific information and remain available to answer any additional questions.

Sincerely,

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**APPENDIX A**

Clearance Rates

**SUMMARY OF CLEARANCE RATES FOR RENALLY EXCRETED, NON-METABOLIZED DRUGS IN ADULTS AND NEONATES: ONE COMPARTMENT MODEL**

<b>Drug</b>	<b>Age</b>	<b>Ratio of CL<sub>child</sub> to CL<sub>adult</sub> (child rate/adult rate)</b>	<b>% of adult C<sub>ss</sub> with same ADD</b>	<b>Reference*</b>
Gentamicin	0 – 1 d (n=27)	0.87 (.084 L/h/kg)/(.0966 L/h/kg)	115%	Johnson et al., 2006 citing Bass et al., 1998, Matzke et al., 1989/Wallace et al., 2002 <sup>3</sup>
	8 – 28 d (n=14)	1.2 (.118 L/h/kg)/(.0966 L/h/kg)	83%	
Gentamicin	1 – 84 d	1.0 (1.04 ml/kg/m)/(1.06 ml/kg/m)	100%	Ginsberg et al., 2002 citing Rodvold, 1993
Isepamicin	2 d	0.79 (1.1 ml/kg/m)/(1.4 ml/kg/m)	127%	Edginton et al., 2006 citing Scaglione et al., 1995, Radwanski et al., 1997*
	2 m	1.5 (2.14 ml/kg/m)/(1.4 ml/kg/m)	67%	
Ticarcillin	.08 – 2 y (n=16)	1.6 (3 ml/min-kg)/(1.9 ml/min-kg)	63%	Ginsberg et al., 2002 citing Reed, 1998*
Vancomycin	Premature, 4 – 17 d post-natal (n=11)	0.8 (.74 ml/kg/m)/(.96 ml/kg/m)	125%	Ginsberg et al., 2002 citing Jarret, 1993 and Cuttler, 1994*
<b>Geometric Mean (Range)</b>		<b>1.1 (0.79 – 1.6)</b>	<b>91% (63 – 127%)</b>	

d: day  
y: year  
m: minute  
ml: milliliter

kg: kilogram  
L: liters  
h: hour  
CL: clearance

C<sub>ss</sub>: steady-state serum concentration  
ADD: average daily dose

\* Values not verified from primary literature

**SUMMARY OF CLEARANCE RATES FOR RENALLY EXCRETED, NON-METABOLIZED DRUGS IN ADULTS AND CHILDREN APPROXIMATELY TWO YEARS OLD: ONE COMPARTMENT MODEL**

<b>Drug</b>	<b>Age</b>	<b>Ratio of CL<sub>child</sub> to CL<sub>adult</sub> (child rate/adult rate)</b>	<b>% of adult C<sub>ss</sub> with same ADD</b>	<b>Reference</b>
Gabapentin	3 – 6 y (n=8)	1.2 (4.8 ml/kg/m)/(3.9 ml/kg/m)	83%	Gatti et al., 2003
Gentamicin	2.25 y (n=17)	1.4 (.138 L/h/kg)/(.0966 L/h/kg)	71%	Johnson et al., 2006 citing Bass et al., 1998, Matzke et al., 1989/Wallace et al., 2002*
Gentamicin	.08 – 7.2 y	1.3 (1.57 ml/kg/m)/(1.25 ml/kg/m)	77%	Edginton et al., 2006 citing Assael et al., 1980, Ho et al., 1995, Kirkpatrick et al., 1999*
	1-5 y	2.2 (2.74 ml/kg/m)/(1.25 ml/kg/m)	45%	
Isepamicin	0.4 – 5.9 y	1.9 (2.64 ml/kg/m)/(1.4 ml/kg/m)	53%	Edginton et al., 2006 citing Scaglione et al., 1995, Radwanski et al., 1997*
Ticarcillin	.08 – 2 y (n=16)	1.6 (3 ml/min-kg)/(1.9 ml/min-kg)	63%	Ginsberg et al., 2002 citing Reed, 1998*
	2 – 12 y (n=23)	1.5 (2.83 ml/min-kg)/(1.93 ml/min-kg)	67%	
Vancomycin	1 – 5 y (n=12)	1.9 (.153 L/h/kg)/(.0786 L/h/kg)	53%	Johnson et al., 2006 citing Rodvold et al., 1997, Matzke et al., 1989/Wallace et al., 2002*
<b>Geometric Mean (Range)</b>		<b>1.6</b> (1.2 – 2.2)	<b>63%</b> (45 – 83%)	
<b>Geometric Mean w/o gabapentin<sup>†</sup></b>		<b>1.7</b>	<b>59%</b>	

y: year                      kg: kilogram                      CL: clearance                      ADD: average daily  
 m: minute                      L: liters                      C<sub>ss</sub>: steady-state                      dose  
 ml: milliliter                      h: hour                      serum concentration

\* Values not verified from primary literature

<sup>†</sup> Analyzed without gabapentin as the age range does not include our range of 1-3 year old.

## APPENDIX B

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