ENVIRONMENTAL PROTECTION AGENCY

 [EPA-HQ-OW-2008-0068; FRL-_____-_____]

RIN 2040-ZA02

**Drinking Water: Preliminary Regulatory Determination on Perchlorate**

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Notice.

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**SUMMARY:** This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present "a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). EPA included perchlorate on the first and second CCLs that were published in the *Federal Register* on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the *Federal Register* on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State

and local public health officials with technical information that they may use in addressing local contamination.

**DATES:** Comments must be received on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

**ADDRESSES:** Submit your comments, identified by Docket ID No. **EPA-HQ-OW-2008-0068**, by one of the following methods:

- www.regulations.gov: Follow the on-line instructions for submitting comments.

- Mail: Water Docket, Environmental Protection Agency, Mailcode: 2822T, 1200 Pennsylvania Ave., NW, Washington, DC 20460.

- Hand Delivery: Water Docket, EPA Docket Center (EPA/DC) EPA West, Room 3334, 1301 Constitution Ave., NW, Washington, DC. Such deliveries are only accepted during the Docket's normal hours of operation, and special arrangements should be made for deliveries of boxed information.

*Instructions:* Direct your comments to Docket ID No. **EPA-HQ-OW-2008-0068**. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at www.regulations.gov, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise

protected through www.regulations.gov or e-mail.  The www.regulations.gov website is

an "anonymous access" system, which means EPA will not know your identity or contact

information unless you provide it in the body of your comment.  If you send an e-mail

comment directly to EPA without going through www.regulations.gov your e-mail

address will be automatically captured and included as part of the comment that is placed

in the public docket and made available on the Internet.  If you submit an electronic

comment, EPA recommends that you include your name and other contact information in

the body of your comment and with any disk or CD-ROM you submit.  If EPA cannot

read your comment due to technical difficulties and cannot contact you for clarification,

EPA may not be able to consider your comment.  Electronic files should avoid the use of

special characters, any form of encryption, and be free of any defects or viruses.  For

additional instructions on submitting comments, go to Unit I.B of the

**SUPPLEMENTARY INFORMATION** section of this document.

*Docket:* All documents in the docket are listed in the www.regulations.gov index.

Although listed in the index, some information is not publicly available, e.g., CBI or

other information whose disclosure is restricted by statute.  Certain other material, such

as copyrighted material, will be publicly available only in hard copy.  Publicly available

docket materials are available either electronically in www.regulations.gov or in hard

copy at the Water Docket, EPA/DC, EPA West, Room 3334, 1301 Constitution Ave.,

NW, Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m.,

Monday through Friday, excluding legal holidays. The telephone number for the Public

Reading Room is (202) 566-1744, and the telephone number for the EPA Docket Center is (202) 566-2426.

**FOR FURTHER INFORMATION CONTACT:** Eric Burneson, Office of Ground Water and Drinking Water, Standards and Risk Management Division, at (202) 564-5250 or e-mail burneson.eric@epa.gov. For general information contact the EPA Safe Drinking Water Hotline at (800) 426-4791 or e-mail: hotline-sdwa@epa.gov.

**Abbreviations and Acronyms**

a. i. -- active ingredient

< -- less than

≤ -- less than or equal to

> -- greater than

≥ -- greater than or equal to

μ -- microgram, one-millionth of a gram

μg/g -- micrograms per gram

μg/kg -- micrograms per kilogram

μg/L -- micrograms per liter

ATSDR -- Agency for Toxic Substances and Disease Registry

AWWARF -- American Water Works Association Research Foundation

BMD -- bench mark dose

BMDL -- bench mark dose level

BW -- body weight for an adult, assumed to be 70 kilograms (kg)

CASRN -- Chemical Abstract Services Registry Number

CBI -- confidential business information

ChE -- cholinesterase

CCL -- Contaminant Candidate List

CCL 1 -- EPA's First Contaminant Candidate List

CCL 2 -- EPA's Second Contaminant Candidate List

CDC -- Centers for Disease Control and Prevention

CDPH - - California Department of Public Health

CFR -- Code of Federal Regulations

CMR -- Chemical Monitoring Reform

CWS -- community water system

DW -- dry weight

DWEL -- drinking water equivalent level

DWI -- drinking water intake

EPA -- United States Environmental Protection Agency

EPCRA -- Emergency Planning and Community Right-to-Know Act

FDA -- United States Food and Drug Administration

FQPA -- Food Quality Protection Act

FR -- Federal Register

FW -- fresh weight

g -- gram

g/day -- grams per day

HRL -- health reference level

IOC -- inorganic compound

IRIS -- Integrated Risk Information System

kg -- kilogram

L -- liter

$LD_{50}$ -- an estimate of a single dose that is expected to cause the death of 50 percent of the exposed animals; it is derived from experimental data.

LOAEL -- lowest-observed-adverse-effect level

MA DEP – Massachusetts Department of Environmental Protection

MCL -- maximum contaminant level

MCLG -- maximum contaminant level goal

mg -- milligram, one-thousandth of a gram

mg/kg -- milligrams per kilogram body weight

mg/kg/day -- milligrams per kilogram body weight per day

mg/L -- milligrams per liter

$mg/m^3$ -- milligrams per cubic meter

MRL -- minimum or method reporting limit (depending on the study or survey cited)

N -- number of samples

NAS -- National Academy of Sciences

NCEH -- National Center for Environmental Health (CDC)

NCFAP -- National Center for Food and Agricultural Policy

NCI -- National Cancer Institute

NCWS – non-community water system

ND -- not detected (or non-detect)

NDWAC -- National Drinking Water Advisory Council

NHANES -- National Health and Nutrition Examination Survey (CDC)

NIS -- sodium iodide symporter

NOEL -- no-observed-effect-level

NPDWR -- national primary drinking water regulation

NPS -- National Pesticide Survey

NQ  -- not quantifiable (or non-quantifiable)

NRC -- National Research Council

NTP -- National Toxicology Program

OA -- oxanilic acid

OW -- Office of Water

OPP -- Office of Pesticide Programs

PBPK – physiologically-based pharmacokinetic

PCR -- polymerase chain reaction

PGWDB -- pesticides in ground water data base

PWS -- public water system

RAIU -- radioactive iodide uptake

RED -- Reregistration Eligibility Decision

RfC -- reference concentration

RfD -- reference dose

RSC -- relative source contribution

SAB -- Science Advisory Board

SDWA -- Safe Drinking Water Act

SOC -- synthetic organic compound

SVOC -- semi-volatile organic compound

T3 -- triiodothyronine

T4 -- thyroxine

TDS -- Total Diet Study (FDA)

TRI -- Toxics Release Inventory

TSH -- thyroid stimulating hormone

TT -- treatment technique

UCMR 1 -- First Unregulated Contaminant Monitoring Regulation

UF -- uncertainty factor

US -- United States of America

USDA -- United States Department of Agriculture

USGS -- United States Geological Survey

UST -- underground storage tanks

VOC -- volatile organic compound

WHO – World Health Organization

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**SUPPLEMENTARY INFORMATION**

**I.  GENERAL INFORMATION**

*A.  Does this Action Impose Any Requirements on My Public Water System?*

Today's action seeks public comment on EPA's preliminary determination that a national primary drinking water regulation is not necessary for perchlorate, and thus imposes no requirements on public water systems.  After review and consideration of public comment, EPA will issue a final regulatory determination.

*B.  What Should I Consider as I Prepare My Comments for EPA?*

You may find the following suggestions helpful for preparing your comments:

1.  Explain your views as clearly as possible.

2.  Describe any assumptions that you used.

3.  Provide any technical information and/or data you used that support your views.

4.  If you estimate potential burden or costs, explain how you arrived at your estimate.

5.  Provide specific examples to illustrate your concerns.

6.  Offer alternatives.

7.  Make sure to submit your comments by the comment period deadline.

8.  To ensure proper receipt by EPA, identify the appropriate docket identification number in the subject line on the first page of your response.  It would also be helpful if you provided the name, date, and *Federal Register* citation related to your comments.

## II.  PURPOSE, BACKGROUND AND SUMMARY OF THIS ACTION

This section briefly summarizes the purpose of this action, the statutory requirements, previous activities related to the Contaminant Candidate List and regulatory determinations, and the approach used and outcome of this preliminary regulatory determination.

### A.  *What is the Purpose of This Action?*

The purpose of today's action is to present EPA's preliminary regulatory determination on perchlorate, the process and the rationale used to make this determination, a brief summary of the supporting documentation, and a request for public comment.

### B.  *Background on the CCL and Regulatory Determinations*

1.  Statutory Requirements for CCL and Regulatory Determinations.  The specific statutory requirements for the Contaminant Candidate List (CCL) and regulatory determinations can be found in section 1412(b) (1) of the Safe Drinking Water Act (SDWA).  The CCL is a list of contaminants that are not subject to any proposed or promulgated national primary drinking water regulations (NPDWRs), are known or anticipated to occur in public water systems (PWSs), and may require regulation under the SDWA.  The 1996 SDWA Amendments also direct EPA to determine, every five years, whether to regulate at least five contaminants from the CCL.  The SDWA requires EPA to publish a Maximum Contaminant Level Goal[1] (MCLG) and promulgate an NPDWR[2] for a contaminant if the Administrator determines that:

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[1]  The MCLG is the "maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, and which allows an adequate margin of safety.  Maximum contaminant level goals are non-enforceable health goals" (CFR 141.2).

[2]  An NPDWR is a legally enforceable standard that applies to public water systems.  An NPDWR sets a legal limit (called a maximum contaminant level or MCL) or specifies a certain treatment technique (TT) for public water systems for a specific contaminant or group of contaminants.

(a) the contaminant may have an adverse effect on the health of persons;

(b) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and

(c) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

While carrying out the process to make a determination, the law requires EPA to take into consideration the effect contaminants have on subgroups that comprise a meaningful portion of the general population (such as infants, children, pregnant women, the elderly, individuals with a history of serious illness or other subpopulations) that are identifiable as being at greater risk of adverse health effects than the general population.

If EPA makes a final determination that a national primary drinking water regulation is needed, the Agency has 24 months to publish a proposed MCLG and NPDWR. After the proposal, the Agency has 18 months to publish and promulgate a final MCLG and NPDWR (SDWA section 1412(b) (1) (E)).[3]

EPA published preliminary regulatory determinations for nine CCL 1 contaminants on June 3, 2002, (67 FR 38222 (USEPA, 2002a)), and final regulatory determinations on July 18, 2003 (68 FR 42898 (USEPA, 2003a)). EPA published preliminary regulatory determinations for eleven CCL 2 contaminants on May 1, 2007, (72 FR 24016 (USEPA, 2007)) and finalized these regulatory determinations on July 30, 2008 (73 FR 44251 (USEPA, 2008c)). As part of its May

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[3] The statute authorizes a nine month extension of this promulgation date.

1, 2007, FR notice of preliminary regulatory determinations for 11 contaminants, EPA also

presented information on several contaminants from the second CCL for which the Agency was

not yet making a preliminary regulatory determination, including perchlorate. Specifically, EPA

indicated that additional information was needed to more fully characterize perchlorate exposure

and determine whether it is appropriate to regulate perchlorate in drinking water (i.e., whether

setting a national primary drinking water standard would provide a meaningful opportunity to

reduce risk for people served by public water systems). The May 1, 2007, FR notice describes

how the Agency was considering additional information including FDA food data and CDC

human exposure data to determine whether to regulate perchlorate. (See the May 1, 2007, FR

notice at 24038 for a discussion regarding the information that EPA had on perchlorate as well as

the additional information that was needed before the Agency could make a preliminary

regulatory determination for perchlorate).

*C. What Comments and Information did EPA Receive Regarding Perchlorate in Response to the
May 1, FR Notice?*

Eight commenters on the Regulatory Determinations 2 Preliminary FR notice addressed

perchlorate. EPA received comments that supported and comments that opposed regulating

perchlorate. One of the commenters who encouraged regulation stated that perchlorate is known

to occur in public water supplies in a number of States and "while occurrence data does [*sic*] not

suggest that perchlorate occurs at levels of public health concern in the vast majority of public

drinking water supplies, and the population at risk appears to be small, that group does include a

sensitive subpopulation (pregnant women and developing fetuses) of significant concern."

Another commenter wrote "the contamination of water supplies by perchlorate is on-going" and

"perchlorate that has entered the soil and contaminated aquifers will likely lead to additional impacted sites." A commenter wrote that "a number of States are moving to regulate perchlorate and a patchwork of different regulations will confuse the public and the regulated water community."

The commenters opposed to regulating perchlorate also cited the available information to support their recommendation. One commenter wrote that "the extensive scientific record indicates that establishing a drinking water standard for perchlorate would not yield a meaningful opportunity to reduce risk to human health." Another commenter stated that perchlorate "does not appear, at this stage, to be a nationwide problem."

Several commenters also addressed EPA's assessment that additional investigation is necessary to ascertain total human exposure before a preliminary regulatory determination could be made. Commenters wrote that the principal study on which EPA's Reference Dose (RfD) is based already accounts for background sources of perchlorate and therefore EPA should not adjust the RfD to account for other non-drinking-water exposures.

EPA has considered the perchlorate comments submitted in connection with the May 1, 2007, notice in the development of today's action. EPA will consider these and any further comments submitted in response to this notice before preparing a final regulatory determination for perchlorate.

*D. What is EPA's Preliminary Regulatory Determination on Perchlorate and What Happens Next?*

EPA is making a preliminary regulatory determination in this notice that a national primary drinking water rule is not necessary for perchlorate because a national primary drinking water regulation would not provide a meaningful opportunity to reduce health risk. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. One of the analyses that EPA considered for this preliminary determination is a physiologically-based pharmacokinetic (PBPK) model that predicts radioactive iodide uptake (RAIU) inhibition in the thyroid for various sub-populations and drinking water concentrations. The model, which is described in section IV.B.5, has already been published in peer-reviewed articles (Clewell et al., 2007 and Merrill et al., 2005), but EPA subjected the model to intensive internal review prior to considering it for this regulatory determination and made several adjustments as a result. EPA believes it is appropriate to have these adjustments peer-reviewed. While the application of the model to non-adult subpopulations was part of the previously peer-reviewed articles, EPA will also ask the peer reviewers to comment on this issue to help EPA ensure that the model is appropriate for use in assessing health outcomes associated with perchlorate exposure for these populations. EPA intends to complete this review before publishing its final determination and will consider any comments from the reviewers. Additionally, EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with information that they may use in addressing local contamination.

Additionally, at the same time that EPA publishes a health advisory for perchlorate, the Agency will withdraw its existing January 2006 guidance regarding perchlorate and potential cleanup levels under the National Oil and Hazardous Substances Contingency Plan (National Contingency Plan, NCP) and will replace it with revised guidance. (See memorandum dated January 26, 2006, from Susan Parker Bodine to EPA Regional Administrators (US EPA, 2006).) Specifically, the January 2006 guidance, in part, addresses the use of preliminary remediation goals (PRGs) for perchlorate contaminated water at National Priority List (NPL) sites. The January 2006 guidance recommends a PRG of 24.5 ppb, assuming that all exposure comes from ground water at the site. The recommended PRG is based on the assumption that all exposure comes from ground water, because at the time the January 2006 guidance was issued there was insufficient information available on the levels of perchlorate in food to calculate a national relative source contribution (RSC). In the absence of such national data on the levels of perchlorate found in foods, the approach outlined in the January 2006 guidance was considered by the Agency to be the most scientifically defensible. In addition, because the recommended PRG generally is the starting point for determining appropriate site-specific cleanup levels, the guidance also indicates that the cleanup level at any site should be evaluated on a case-by-case basis, and modified accordingly, based on site-specific information, including exposure to non-water sources, such as foods. EPA now has sufficient data to calculate a national RSC and has used this RSC to calculate a health reference level (HRL) for drinking water as part of the basis for today's preliminary determination. When EPA issues the final regulatory determination for perchlorate, the final HRL will be the basis for the health advisory value in the health advisory document the Agency expects to issue at that time. Thereafter, it may be appropriate to use the

health advisory value as a "to be considered" (TBC) value in developing potential cleanup levels for perchlorate at Superfund sites. In addition, some State regulations may be applicable or relevant and appropriate requirements (ARARs) when establishing cleanup levels for perchlorate at Superfund sites.

## III. WHAT SCIENTIFIC DATA AND ANALYSES DID EPA EVALUATE IN MAKING A PRELIMINARY REGULATORY DETERMINATION FOR PERCHLORATE?

This section summarizes the health effects, occurrence, and population exposure evaluation information EPA used to support the preliminary regulatory determination for perchlorate. EPA's conclusions with respect to these data are discussed in Section IV.

### A. Evaluation of Precursor and Adverse Health Effects

Section 1412(b)(1)(A)(i) of the SDWA requires EPA to determine whether a candidate contaminant may have an adverse effect on public health. EPA described the overall process the Agency used to evaluate health effects information in the May 1, 2007, Federal Register Notice (72 FR 24016 (USEPA, 2007)). This section presents specific information about the potential for precursor and adverse health effects from perchlorate, including a discussion of an extensive report completed by the National Academy of Sciences (NAS) on the issue and other research published after that report.

1. NAS Review of Perchlorate Health Implications and EPA's Reference Dose.

In 2003, the National Research Council (NRC) of the NAS was asked to assess the current state of the science regarding potential adverse effects of disruption of thyroid function by perchlorate in humans and laboratory animals at various stages of life and, based on this

review, to determine whether EPA's findings in its 2002 draft risk assessment were consistent with the current scientific evidence.

In January 2005, the NRC published "Health Implications of Perchlorate Ingestion," a review of the state of the science regarding potential adverse health effects of perchlorate exposure and mode-of-action for perchlorate toxicity (NRC, 2005).

Perchlorate can interfere with the normal functioning of the thyroid gland by competitively inhibiting the transport of iodide into the thyroid. Iodide is an important component of two thyroid hormones, T4 and T3, and the transfer of iodide from the blood into the thyroid is an essential step in the synthesis of these two hormones. Iodide transport into the thyroid is mediated by a protein molecule known as the sodium (Na+)–iodide (I-) symporter (NIS). NIS molecules bind iodide with very high affinity, but they also bind other ions that have a similar shape and electric charge, such as perchlorate. The binding of these other ions to the NIS inhibits iodide transport into the thyroid, which can result in intrathyroidal iodide deficiency and consequently decreased synthesis of T4 and T3. There is compensation for low-levels of iodide deficiency, however, such that the body maintains blood serum concentrations of thyroid hormones within narrow limits through feedback control mechanisms. The compensation for decreased thyroid hormone is accomplished by increased secretion of the thyroid stimulating hormone (TSH) from the pituitary gland triggered by the reduced hormone levels, which has among its effects the increased production of T4 and T3 (USEPA, 2005b). The thyroid's ability to compensate in this way is limited, though, such that sufficiently high levels of perchlorate exposure result in a reduction of T4 and T3 blood levels (after thyroid iodine stores are depleted). Sustained changes in thyroid hormone and TSH secretion can result in thyroid

hypertrophy and hyperplasia (i.e., abnormal growth or enlargement of the thyroid) (USEPA, 2005b).

Children born with congenital hypothyroidism may suffer from mild cognitive deficits despite hormone remediation (Rovet, 2002; Zoeller and Rovet, 2004), and subclinical hypothyroidism and reductions in T4 (i.e., hypothyroxinemia) in pregnant women have been associated with neurodevelopmental delays and IQ deficits in their children (Pop et al., 1999, 2003; Haddow *et al.*, 1999; Kooistra et al., 2006; Morreale de Escobar, 2000, 2004). Animal studies support these observations, and recent findings indicate that neurodevelopmental deficits are evident under conditions of hypothyroxinemia and occur in the absence of growth retardation (Auso *et al.*, 2004; Gilbert and Sui, 2008; Sharlin *et al.*, 2008; Goldey *et al.*, 1995).

Results from studies of the effects of perchlorate exposure on hormone levels have been mixed. One recent study did not identify any effects of perchlorate on blood serum hormones (Amitai et al, 2007), while another study (Blount et al., 2006b) did identify such effects. The results of the Blount study are discussed further in Section III.A.2.

The data from epidemiological studies of the general population provide some information on possible effects of perchlorate exposure. Based upon analysis of the data available at the time NRC (2005) acknowledged that ecologic epidemiological data alone are not sufficient to demonstrate whether or not an association is causal, and that these studies can provide evidence bearing on possible associations. Noting the limitations of specific studies, the NRC (2005; chapter 3) committee concluded that the available epidemiological evidence is not consistent with a causal association between perchlorate and congenital hypothyroidism, changes in thyroid function in normal-birthweight, full-term newborns, or hypothyroidism or other

thyroid disorders in adults. The committee considered the evidence to be inadequate to determine whether or not there is a causal association between perchlorate exposure and adverse neurodevelopmental outcomes in children. The committee noted that no studies have investigated the relationship between perchlorate exposure and adverse outcomes among especially vulnerable groups, such as the offspring of mothers who had low dietary iodide intake, or low-birthweight or preterm infants (US EPA, 2005b).

The NRC recommended data from the Greer *et al.* (2002) human clinical study as the basis for deriving a reference dose (RfD) for perchlorate (NRC, 2005). Greer *et al.* (2002) report the results of a study that measured thyroid iodide uptake, hormone levels, and urinary iodide excretion in a group of 37 healthy adults who were administered perchlorate doses orally over a period of 14 days. Dose levels ranged from 7 to 500 µg/kg/day in the different experimental groups. The investigators found that the 24 hour inhibition of iodide intake ranged from 1.8 percent in the lowest dose group to 67.1 percent in the highest dose group. However, no significant differences were seen in measured blood serum thyroid hormone levels (T3, T4, total and free) in any dose group. The statistical no observed effect level (NOEL) for the perchlorate-induced inhibition of thyroid iodide uptake was determined to be 7 µg/kg/day, corresponding to an iodide uptake inhibition of 1.8 percent. Although the NRC committee concluded that hypothyroidism is the first adverse effect in the continuum of effects of perchlorate exposure, NRC recommended that "the most health-protective and scientifically valid approach" was to base the perchlorate RfD on the inhibition of iodide uptake by the thyroid (NRC, 2005). NRC concluded that iodide uptake inhibition, although not adverse, is the most appropriate precursor event in the continuum of possible effects of perchlorate exposure and would precede any

adverse health effects of perchlorate exposure.  The lowest dose (7 µg/kg/day) administered in

the Greer *et al.* (2002) study was considered a NOEL (rather than a no-observed-adverse-effect

level or NOAEL) because iodide uptake inhibition is not an adverse effect, but a biochemical

precursor.  The NRC further determined that, "the very small decrease (1.8 percent) in thyroid

radioiodide uptake in the lowest dose group was well within the variation of repeated

measurements in normal subjects."  A summary of the data considered and the NRC

deliberations can be found in the NRC report (2005).

The NRC recommended that EPA apply an intraspecies uncertainty factor of 10 to the

NOEL to account for differences in sensitivity between the healthy adults in the Greer *et al.*

(2002) study and the most sensitive population, fetuses of pregnant women who might have

hypothyroidism or iodide deficiency.  Because the fetus depends on an adequate supply of

maternal thyroid hormone for its central nervous system development during the first trimester of

pregnancy, iodide uptake inhibition from low-level perchlorate exposure has been identified as a

concern in connection with increasing the risk of neurodevelopmental impairment in fetuses of

high-risk mothers (NRC, 2005).  The NRC (2005) viewed the uncertainty factor of 10 as

conservative and protective of health given that the point of departure (the NOEL) is based on a

non-adverse effect (iodide uptake inhibition), which precedes the adverse effect in a continuum

of possible effects of perchlorate exposure.  The NRC panel concluded that no additional

uncertainty factor was needed for the use of a less-than chronic study, for deficiencies in the

database, or for interspecies variability.  EPA's Integrated Risk Information System (IRIS)

adopted the NRC's recommendations resulting in an RfD of 0.7 µg/kg/day, derived by applying

a ten-fold total uncertainty factor to the NOEL of 7 µg/kg/day (USEPA, 2005b).

The NRC emphasized that its recommendation "differs from the traditional approach to deriving the RfD." The NRC recommended "using a nonadverse effect rather than an adverse effect as the point of departure for the perhlorate risk asessement. Using a nonadverse effect that is upstream of the adverse effect is a more conservative, health-protective approach to the perchlorate risk assessment." The NRC also noted that the purpose of the 10-fold uncertainty factor is to protect sensitive subpopulations in the face of uncertainty regarding their relative sensitivity to perchlorate exposure. The NRC recognized that additional information on these relative sensitivities could be used to reduce this uncertainty factor in the future (NRC, 2005).[4]

2. Biomonitoring Studies

After the NRC report was released, several papers were published that investigated whether biomonitoring data associated with the National Health and Nutrition Examination Survey (NHANES) could be used to discern if there was a relationship between perchlorate levels in the body and thyroid function. These papers also help to evaluate populations that might be considered to be more sensitive to perchlorate exposure.

Blount *et al.* (2006b) published a study examining the relationship between urinary levels of perchlorate and blood serum levels of TSH and total T4 in 2,299 men and women (ages 12 years and older) who participated in CDC's 2001–2002 NHANES[5]. Blount *et al.* (2006b) evaluated perchlorate along with a number of covariates known or likely to be associated with T4 or TSH levels to assess the relationship between perchlorate and these hormones, and the

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[4] "There can be variability in responses among humans. The intraspecies uncertainty factor accounts for that variability and is intended to protect populations more sensitive than the population tested. In the absence of data on the range of sensitivity among humans, a default uncertainty factor of 10 is typically applied. The factor could be set at 1 if data indicate that sensitive populations do not vary substantially from those tested." (NRC 2005, p 173)

[5] While CDC researchers measured urinary perchlorate concentration for 2,820 NHANES participants, TSH and total T4 serum levels were only available for 2,299 of these participants.

influence of other factors on this relationship.  These covariates included gender, age, race/ethnicity, body mass index, serum albumin, serum cotinine (a marker of nicotine exposure), estimated total caloric intake, pregnancy status, post-menopausal status, premenarche status, serum C-reactive protein, hours fasting before sample collection, urinary thiocyanate, urinary nitrate, and use of selected medications.  The study found that perchlorate was a statistically significant predictor of thyroid hormones in women, but not in men.

After finding evidence of gender differences, the researchers focused on further analyzing the NHANES data for the 1,111 women participants.  They divided these 1,111 women into two categories, higher-iodide and lower-iodide urinary content, using a cut point of 100 µg/L of urinary iodide based on the median level the World Health Organization (WHO) considers indicative of sufficient iodide intake[6] for a population.  Hypothyroid women were excluded from the analysis.  According to the study's authors, about 36 percent of women living in the United States have urinary iodide levels less than 100 µg/L (Caldwell *et al.*, 2005).  For women with urinary iodide levels less than 100 µg/L, the study found that urinary perchlorate is associated with a decrease in (a negative predictor for) T4 levels and an increase in (a positive predictor for) TSH levels.  For women with urinary iodide levels greater than or equal to 100µg/L, the researchers found that perchlorate is a significant positive predictor of TSH, but not a predictor of T4.  The researchers state that perchlorate could be a surrogate for another unrecognized determinant of thyroid function.

Also, the study reports that while large doses of perchlorate are known to decrease thyroid function, this is the first time an association of decreased thyroid function has been

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[6] WHO notes that the prevalence of goiter begins to increase in populations with a median urinary iodide level below 100 µg/L (WHO, 1994).

observed at these low levels of perchlorate exposure.  The clinical significance of the variations

in T4/TSH levels, which were generally within normal limits, has not been determined.  The

researchers noted several limitations of the study (e.g., assumption that urinary perchlorate

correlates with perchlorate levels in the stroma and tissue and measurement of total T4 rather

than free T4) and recommended that these findings be affirmed in at least one more large study

focusing on women with low urine iodide levels.  It is also not known whether the association

between perchlorate and thyroid hormone levels is causal or mediated by some other correlate of

both, although the relationship between urine perchlorate and total TSH and T4 levels persisted

after statistical adjustments for some additional covariates known to predict thyroid hormone

levels (e.g., total kilocalorie intake, estrogen use, and serum C-reactive protein levels).  A

planned follow-up study will include additional measures of thyroid health and function (e.g.,

TPO-antibodies, free T4).  An additional paper by Blount *et al.* (2006c), discussed further in

Section III. C. 2. a., found that almost all participants in the NHANES survey, including the

participants in this group, had urinary levels of perchlorate corresponding to estimated dose

levels that are below the RfD of 0.7 µg/kg/day.

The Blount study suggested that perchlorate could be a surrogate for another

unrecognized determinant of thyroid function.  There are other chemicals, including nitrate and

thiocyanate, which can affect thyroid function.  Steinmaus *et al.* (2007) further analyzed the data

from NHANES 2001–2002 to assess the impact of smoking, cotinine and thiocyanate on the

relationship between urinary perchlorate and blood serum T4 and TSH.  Thiocyanate is a

metabolite of cyanide found in tobacco smoke and is naturally occurring in some foods,

including cabbage, broccoli, and cassava.  Increased serum thiocyanate levels are associated with

increasing levels of smoking. Thiocyanate affects the thyroid by the same mechanism as perchlorate (competitive inhibition of iodide uptake). Steinmaus et al. analyzed the data to determine whether smoking status (smoker or nonsmoker), serum thiocyanate, or serum cotinine were better predictors of T4 and TSH changes than perchlorate, or if the effects reflected the combined effects of perchlorate and thiocyanate

Of female subjects 12 years of age and older in NHANES 2001-2002, 1,203 subjects had data on blood serum T4, serum TSH, urinary perchlorate, iodine and creatinine. Subjects with extreme T4 or TSH (3 individuals) or with a reported history of thyroid disease (91) were excluded from further analyses. Of the remaining women, 385 (35 percent) had urinary iodine levels below 100 µg /l. Steinmaus, *et al*. evaluated serum cotinine as an indicator of nicotine exposure, with levels greater than 10 ng/ml classified as high and levels less than 0.015 ng/ml classified as low.

The authors found no association between either perchlorate or T4 and smoking, cotinine or thiocyanate in men or in women with urinary iodine levels greater than 100 µg/l. In addition, they found no association between cotinine and T4 or TSH in women with iodine levels lower than 100 µg/l. However, in women with urinary iodine levels lower than 100 µg/l, an association between urinary perchlorate and decreased serum T4 was stronger in smokers than in non-smokers, and stronger in those with high urinary thiocyanate levels than in those with low urinary thiocyanate levels. Although noting that their findings need to be confirmed with further research, the authors concluded that for these low-iodine women the results suggest that at commonly-occurring perchlorate exposure levels, thiocyanate in tobacco smoke and perchlorate

interact in affecting thyroid function, and that agents other than tobacco smoke might cause similar interactions (Steimaus et al. 2007).

EPA also evaluated whether health information is available regarding children, pregnant women and lactating mothers. The NRC report discussed a number of epidemiological studies that looked at thyroid hormone levels in infants. A more recent study by Amitai *et al.* (2007) assessed T4 values in newborns in Israel whose mothers resided in areas where drinking water contained perchlorate at "very high" (340 µg/L), "high" (12.94 µg/L), or "low" (<3 µg/L) perchlorate concentrations. The mean (± standard deviation) T4 value of the newborns in the very high, high, and low exposure groups was 13.8 ± 3.8, 13.9 ± 3.4, and 14.0 ± 3.5 µg/dL, respectively, showing no significant difference in T4 levels between the perchlorate exposure groups. This is consistent with the conclusions drawn by the NRC review of other epidemiological studies of newborns. The NRC (2005) also noted "no epidemiologic studies are available on the association between perchlorate exposure and thyroid dysfunction among low-birthweight or preterm newborns, offspring of mothers who had iodide deficiency during gestation, or offspring of hypothyroid mothers."

3.     Physiologically-based pharmacokinetic (PBPK) Models.

PBPK models represent an important class of dosimetry models that can be used to predict internal doses to target organs, as well as some effects of those doses (e.g,, radioactive iodide uptake inhibition in the thyroid). To predict internal dose level, PBPK models use physiological, biochemical, and physicochemical data to construct mathematical representations of processes associated with the absorption, distribution, metabolism, and elimination of compounds. With the appropriate data, these models can be used to extrapolate across and within

species and for different exposure scenarios, and to address various sources of uncertainty in health assessments, including uncertainty regarding the relative sensitivities of various subpopulations.

Clewell *et al.* (2007) developed multi-compartment PBPK models describing the absorption and distribution of perchlorate for the pregnant woman and fetus, the lactating woman and neonate, and the young child. This work built upon Merrill *et al.*'s (2005) model for the average adult. Related research that served as the basis for the more recent PBPK modeling efforts was discussed by the NRC in their January 2005 report on perchlorate.

The models estimated the levels of perchlorate absorbed through the gastrointestinal tract and its subsequent distribution within the body. Clewell *et al.* (2007) provided estimates of internal dose and resulting iodide uptake inhibition across all life stages, and for pregnant and lactating women. The paper reported iodide uptake inhibition levels for external doses of 1, 10, 100, and 1000 μg/kg/day. Results at the lower two doses indicated that the highest perchlorate blood concentrations in response to an external dose would occur in the fetus, followed by the lactating woman and the neonate. Predicted blood levels for all three groups (i.e., fetus, lactating women and neonates) were four- to five-fold higher than for non-pregnant adults. Smaller relative differences were predicted at external doses of 100 and 1000 μg/kg/day. The authors attributed this change to saturation of uptake mechanisms. The model predicted minimal effect of perchlorate on iodide uptake inhibition in all groups at the 1 μg/kg/day external dose (about one and one half times the RfD), estimating 1.1 percent inhibition or less across all groups. Inhibition was predicted to be 10 percent or less in all groups at an external dose of 10 μg/kg/day (about 14 times the RfD).

The results of the model extrapolations were evaluated against data developed in two epidemiologic studies performed in Chile, one studying school children (Tellez *et al.*, 2005) and another following women through pregnancy and lactation (Gibbs *et al.*, 2004). The model predicted average blood serum concentrations of perchlorate in the women from the Gibbs *et al.* (2004) study which were nearly identical to their measured perchlorate blood serum concentrations. The blood serum perchlorate concentrations predicted from the Tellez *et al.* (2005) study were within the range of the measured concentrations, and the concentrations of perchlorate in breast milk predicted from the model were within two standard deviations of the measured concentrations. The authors concluded that the model predictions were consistent with empirical results and that the predicted extent of iodide inhibition in the most sensitive population (the fetus) is not significant at EPA's RfD of 0.7 µg/kg-day.

The NRC recommended that inhibition of iodide uptake by the thyroid, which is a precursor event and not an adverse effect, should be used as the basis for the perchlorate risk assessment (NRC, 2005). Consistent with this recommendation, iodide uptake inhibition was used by EPA as the critical effect in determining the reference dose (RfD) for perchlorate. Therefore, PBPK models of perchlorate and radioiodide, which were developed to describe thyroidal radioactive iodide uptake (RAIU) inhibition by perchlorate for the average adult (Merrill *et al.*, 2005), pregnant woman and fetus, lactating woman and neonate, and the young child (Clewell *et al.*, 2007) were evaluated by EPA based on their ability to provide additional information surrounding this critical effect for potentially sensitive subgroups and reduce some of the uncertainty regarding the relative sensitivities of these subgroups.

EPA evaluated the PBPK model code provided by the model authors and found minor errors in mathematical equations and computer code, as well as some inconsistencies between model code files. EPA made several changes to the code in order to harmonize the models and more adequately reflect the biology (see USEPA, 2008b) for more information.

Model parameters describing urinary excretion of perchlorate and iodide were determined to be particularly important in the prediction of RAIU inhibition in all subgroups; therefore, a range of biologically plausible values available in the peer-reviewed literature was evaluated in depth using the PBPK models. Exposure rates were also determined to be critical for the estimation of RAIU inhibition by the models and were also further evaluated.

Overall, detailed examination of Clewell *et al.* (2007) and Merrill *et al.* (2005) confirmed that the model structures were appropriate for predicting percent inhibition of RAIU by perchlorate in most lifestages. Unfortunately, the lack of biological information during early fetal development limits the applicability of the PBPK modeling of the fetus to a late gestational timeframe (i.e., near full term pregnancy, ~GW 40), so EPA did not make use of model predictions regarding early fetal RAIU inhibition. Although quantitative outputs of EPA's revised PBPK models differ somewhat from the published values, the EPA evaluation confirmed that, with modifications (as described in USEPA, 2008b), the Clewell *et al.* (2007) and Merrill *et al.* (2005) models provide an appropriate basis for calculating the lifestage differences in the degree of thyroidal RAIU inhibition at a given level of perchlorate exposure. The results of EPA's model application are discussed in Section IV. B. 5.

*B. Evaluation of Perchlorate Occurrence in Drinking Water*

The primary source of drinking water occurrence data used to support this preliminary

regulatory determination is the data provided by public water systems in accordance with the

first Unregulated Contaminant Monitoring Regulation (UCMR 1).  The Agency also evaluated

supplemental sources of occurrence information.

1.  The Unregulated Contaminant Monitoring Regulation.  In 1999, EPA developed the UCMR

program in coordination with the CCL and the National Drinking Water Contaminant

Occurrence Database (NCOD) to provide national occurrence information on unregulated

contaminants (September 17, 1999, 64 FR 50556 (USEPA, 1999b); March 2, 2000, 65 FR 11372

(USEPA, 2000b); and January 11, 2001, 66 FR 2273 (USEPA, 2001b)).

EPA designed the UCMR 1 data collection with three parts (or tiers).  Occurrence data

for perchlorate are from the first tier of UCMR (also known as UCMR 1 List 1 Assessment

Monitoring).  EPA required all large[7] PWSs, plus a statistically representative national sample of

800 small[8] PWSs, to conduct Assessment Monitoring.[9]  Approximately one-third of the

participating small systems were scheduled to monitor for these contaminants during each

calendar year from 2001 through 2003.  Large systems could conduct one year of monitoring

anytime during the 2001–2003 UCMR 1 period.  EPA specified a quarterly monitoring schedule

for 1,896 surface water systems and a twice-a-year, six-month interval monitoring schedule for

1,969 ground water systems. The objective of the UCMR 1 sampling approach for small systems

was to collect contaminant occurrence data from a statistically selected, nationally representative

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[7]  Systems serving more than 10,000 people.
[8]  Systems serving 10,000 people or fewer.
[9]  Large and small systems that purchase 100 percent of their water supply were not required to participate in the UCMR 1 Assessment Monitoring or the UCMR 1 Screening Survey.

sample of small systems.  The small system sample was stratified and population-weighted, and included some other sampling adjustments, such as including at least 2 systems from each State. With contaminant monitoring data from all large PWSs and a statistical, nationally representative sample of small PWSs, the UCMR 1 List 1 Assessment Monitoring program provides a contaminant occurrence data set suitable for national drinking water estimates.

EPA collected and analyzed drinking water occurrence data for perchlorate from 3,865 PWSs between 2001 and 2005 under the UCMR 1.  EPA found that 160 (approximately 4.1 percent) of the 3,865 PWSs that sampled and reported had at least 1 analytical detection of perchlorate (in at least 1 sampling point) at levels greater than or equal to the method reporting limit (MRL) of 4 µg/L.  These 160 systems are located in 26 States and 2 territories.  Of these 160 PWSs, 8 are small systems (serving 10,000 or fewer people) and 152 are large systems (serving more than 10,000 people).  These 160 systems reported 637 detections of perchlorate at levels greater than or equal to 4 µg/L, which is approximately 11.3 percent of the 5,629 samples collected by these 160 systems and approximately 1.9 percent of the 34,331 samples collected by all 3,865 systems.  The maximum reported concentration of perchlorate was 420 µg/L, from a single surface water sample from a PWS in Puerto Rico.  The average concentration of perchlorate for those samples with positive detections for perchlorate was 9.85 µg/L and the median concentration was 6.40 µg/L.  A summary of the perchlorate occurrence statistics in UCMR 1 is shown in Table 1.

| Table 1.  UCMR 1 Occurrence of Perchlorate at Concentrations >= 4 µg/L[10] | | | | | | |
|---|---|---|---|---|---|---|
| System Size | Number of Samples | Samples w/Detects | Sampling Points Tested | Sampling Points w/ Detects | Sampled Systems | Systems w/Detects |

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[10] Table 1 shows perchlorate detectionsat levels greater than and equal to the MRL of 4 µg/L.

| | | | | | | |
|---|---|---|---|---|---|---|
| Small Systems | 3,295 | 15 | 1,454 | 8 | 797 | 8 |
| | | | | | | |
| Large System | 31,036 | 622 | 13,533 | 379 | 3,068 | 152 |
| | | | | | | |
| Total System | 34,331 | 637 | 14,987 | 387 | 3,865 | 160 |

Footnotes:
1. For both large and small systems, at 3,865 systems with data, there were 34,331 samples taken at 14,987 (entry) points resulting in 637 (1.86%) sample detects representing 387 (2.58%) of the entry/sample points in 160 (4.14 %) of the systems.
2. For 3,068 large systems with data, there were 31,036 samples taken at 13,533 entry points resulting in 622 (2.00%) detections representing 379 (2.80%) entry/sample points in 152 (4.95%) of the systems
3. For 797 small systems with data, there were 3,295 samples taken at 1,454 entry points, resulting in a total of 15 ( 0.455%) detections representing 8 (0.55%) entry/sample points at 8 (1%) of the systems.

Table 2 presents EPA's estimates of the population served by water systems for which the highest reported perchlorate concentration was greater than various threshold concentrations ranging from 4 µg/L (MRL) to 25 µg/L. The fourth column of Table 2 presents a high end estimate of the population served drinking water above a threshold. This column presents the total population served by systems in which at least one sample was found to contain perchlorate above the threshold concentration. EPA considers this a high end estimate because it is based upon the assumption that the entire system population is served water from the entry point that had the highest reported perchlorate concentration. In fact, many water systems have multiple entry points into which treated water is pumped for distribution to their consumers. For the systems with multiple entry points, it is unlikely that the entire service population receives water from the one entry point with the highest single concentration. Therefore, EPA included a less conservative estimate of the population served water above a threshold in the fifth column in

Table 2. EPA developed this estimate by assuming the population was equally distributed among all entry points. For example, if a system with 10 entry points serving 200,000 people had a sample from a single entry point with a concentration at or above a given threshold, EPA assumed that the entry point served one-tenth of the system population, and added 20,000 people to the total when estimating the population in the last column of Table 2. This approach may provide either an overestimate or an underestimate of the population served by the affected entry point. In contrast, in the example above, EPA added the entire system population of 200,000 to the more conservative population served estimate in column 4, which is likely an overestimate.

| Table 2. UCMR 1 Occurrence and Population Estimates for Perchlorate Above Various Thresholds | | | | |
|---|---|---|---|---|
| Thresholds[a] | PWSs with at Least 1 Detection > Threshold of Interest | PWS Entry or Sample Points with at Least 1 Detection > Threshold of Interest[b] | Population Served by PWSs with at Least 1 Detection > Threshold of Interest[c] | Population Estimate for Entry or Sample Points Having at Least 1 Detection > Threshold of Interest[d] |
| 4 µg/L | 4.01% (155 of 3,865) | 2.48% (371 of 14,987) | 16.6 M[e] | 5.1 M |
| 5 µg/L | 3.16 % (122 of 3,865) | 1.88 % (281 of 14,987) | 14.6 M | 4.0 M |
| 7 µg/L | 2.12 % (82 of 3,865) | 1.14 % (171 of 14,987) | 7.2 M | 2.2 M |
| 10 µg/L | 1.35 % (52 of 3,865) | 0.65 % (97 of 14,987) | 5.0 M | 1.5 M |
| 12 µg/L | 1.09 % (42 of 3,865) | 0.42 % (63 of 14,984) | 3.6 M | 1.2 M |
| 15 µg/L | 0.80 % (31 of 3,865) | 0.29 % (44 of 14,987) | 2.0 M | 0.9 M |
| 17 µg/L | 0.70 % (27 of 3,865) | 0.24 % (36 of 14,987) | 1.9 M | 0.8 M |
| 20 µg/L | 0.49 % (19 of 3,865) | 0.16 % (24 of 14,987) | 1.5 M | 0.7 M |
| 25µg/L | 0.36 % (14 of 3,865) | 0.12 % (18 of 14,987) | 1.0 M | 0.4 M |

Footnotes:
[a]All occurrence measures in this table were conducted on a basis reflecting values *greater than* the listed thresholds.
[b]The entry/sample-point-level population served estimate is based on the system entry/sample points that had at least 1 analytical detection for perchlorate greater than the threshold of interest. The UCMR 1 small system survey was designed to be representative of the nation's small systems, not necessarily to be representative of small system entry points.
[c]The system-level population served estimate is based on the systems that had at least 1 analytical detection for perchlorate greater than the threshold of interest.
[d]Because the population served by each entry/sample point is not known, EPA assumed that the total population served by a particular system is equally distributed across all entry/sample points. To derive the entry/sample point-level population estimate, EPA summed the population values for the entry/sample points that had at least 1analytical detection greater than the threshold of interest.
[e]This value does not include the population associated with 5 systems serving 200,000 people that measured perchlorate at 4 µg/L in at least one sample.

2. Supplemental Occurrence Data. The Agency also evaluated drinking water monitoring data for perchlorate in California and Massachusetts. EPA considers these State data to be supplemental for purposes of this regulatory determination, because they are not nationally representative. EPA believes these State's monitoring results are generally consistent with the results collected by EPA under UCMR 1. The California Department of Public Health (CDPH) last updated its perchlorate monitoring results on July 10, 2008 (CDPH, 2008). The Massachusetts's Department of Environmental Protection (MA DEP) last updated its draft report on *The Occurrence and Sources of Perchlorate in Massachusetts* in April, 2006 (MA DEP, 2005).

C. *Evaluation of Perchlorate Exposure from Sources Other than Drinking Water*

An important element of EPA's regulatory determination process is to consider the contaminant exposure that individuals are likely to receive from sources other than drinking

water.  An individual's total exposure to a contaminant is more relevant to his or her risk for adverse health effects than is exposure to the contaminant from drinking water alone.

Because there are significant sources of perchlorate exposure other than through the drinking water route, EPA determined that data on exposure to perchlorate from these sources is critical to the evaluation of whether or not there is a meaningful opportunity for health risk reduction through a national primary drinking water rule for perchlorate.  Dietary studies pose a particular challenge because there is great variety in the American diet and many foods must be analyzed to enable a comprehensive dietary exposure estimate.  However, EPA believes that two recent studies provide a sound basis for evaluating total perchlorate exposure.  These are the Food and Drug Administration (FDA) Total Diet Study and an analysis of NHANES/UCMR data conducted by EPA and CDC.

FDA's Total Diet Study (TDS) combines nationwide sampling and analysis of hundreds of food items along with national surveys of food intake to develop comprehensive dietary exposure estimates for a variety of demographic groups in the US.  CDC's NHANES data base measured perchlorate in the urine of a representative sample of Americans.  EPA and CDC used data from the NHANES data base and UCMR monitoring to estimate perchlorate exposure from food and water together, and food alone, for different sub-populations.  This section of the notice provides details on the results of these studies.  Because the sources of exposure encompassed by each of these studies overlap, EPA has considered them both in making a regulatory determination in an effort to provide the most comprehensive basis for the preliminary determination.

In this section, EPA also provides a brief review of other dietary and biomonitoring studies that, while not directly incorporated into our determination, tend to reinforce the results of the primary exposure studies.

1. Food Studies.  The FDA, the United States Department of Agriculture (USDA), and other researchers have studied perchlorate in foods.  The most recent and most comprehensive information available on the occurrence of perchlorate in the diet has been published by FDA.  This section describes two perchlorate studies released by FDA. – the *Total Diet Study* and FDA's *Exploratory Survey Data on Perchlorate in Food*.

a. *FDA Total Diet Study, 2005 and 2006.*  Since 1961, FDA has periodically conducted a broad-based food monitoring study known as the *Total Diet Study* (TDS).  The purpose of the TDS is to measure substances in foods representative of the total diet of the US population, and to make estimates of the average dietary intake of those substances for selected age-gender groups.  A detailed history of the TDS can be found at the following Web site: http://www.cfsan.fda.gov/~comm/tds-toc.html.

Murray *et al.* (2008) briefly describe the design of the current TDS.  Dietary intakes of perchlorate were estimated by combining analytical results from the TDS with food consumption estimates developed specifically for estimating dietary exposure from TDS results.  While the perchlorate data for TDS foods were collected in 2005-2006, the food consumption data in the current TDS food list is based on results (Egan *et al.*, 2007) from the USDA's 1994–96, 1998 *Continuing Survey of Food Intakes by Individuals* (94-98 CSFII), which includes data for all age groups collected in 1994-96, and for children from birth through age 9 collected in 1998.  Although over 6,000 different foods and beverages were included in the food consumption

surveys, these foods and beverages were collapsed into a set of 285 representative foods and

beverages by aggregating the foods according to the similarity of their primary ingredients and

then selecting the specific food consumed in greatest quantity from each group as the

representative TDS food for that group.  The consumption amounts of all the foods in a group

were aggregated and assigned to the representative food for that group.  It is these 285

representative foods and beverages that are on the current TDS food list.   This approach to

estimating dietary intakes assumes that the analytical profiles (e.g., perchlorate concentrations)

of the representative foods are similar to those of the larger group of foods from the original

consumption survey to which they correspond. This approach provides a reasonable estimate of

total dietary exposure to the analytes from all foods in the diet, not from the representative TDS

foods alone.  The sampled TDS foods are purchased at retail from grocery stores and fast-food

restaurants.  The foods are prepared table-ready prior to analyses, using distilled water when

water is called for in the recipe.  The analytical method developed and used by FDA to measure

perchlorate in food samples has a nominal limit of detection (LOD) of 1.00 ppb and a limit of

quantitation (LOQ) of 3.00 ppb (Krynitsky *et al.*, 2006).

     Murray *et al.* (2008) reports that FDA included perchlorate as an analyte in TDS baby

foods in 2005 and in all other TDS foods in 2006.  Iodine was analyzed in all TDS foods from

five market baskets surveyed in late 2003 through 2004.  Using these data collectively, FDA

developed estimates of average dietary perchlorate and iodine intake for 14 age-gender groups.

To account for uncertainties associated with samples with no detectable concentrations of

perchlorate or iodine (non-detects or NDs), FDA calculated a lower-bound and upper-bound for

each estimate of average dietary exposure, assuming that NDs equal to zero and the LOD,

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respectively.  Specifically, FDA multiplied these upper- and lower-bound concentrations by the

average daily consumption amount of the representative food for the given subpopulation group

to provide a range of average intakes for each TDS food.

Table 3 summarizes the FDA estimated upper- and lower-bound average dietary

perchlorate intakes (from food) for 14 age-gender groups on a per kilogram of body weight per

day basis to enable direct comparison to the perchlorate RfD.  Murray *et al.* (2008) reports that

average body weights for each population group were based on self-reported body weights from

respondents in the 94–98 CSFII.

**Table 3.  Lower- and Upper-bound (ND = 0 and LOD) Perchlorate Intakes from FDA's TDS Results for 2005–2006.**

| Population Group | | Average Perchlorate Intake from Food (µg/kg/day) | |
|---|---|---|---|
| | | Lower-bound | Upper-bound |
| Infants | 6-11 mo | 0.26 | 0.29 |
| Children | 2 yr | 0.35 | 0.39 |
| Children | 6 yr | 0.25 | 0.28 |
| Children | 10 yr | 0.17 | 0.20 |
| Teenage Girls | 14-16 yr | 0.09 | 0.11 |
| Teenage Boys | 14-16 yr | 0.12 | 0.14 |
| Women | 25-30 yr | 0.09 | 0.11 |
| Men | 25-30 yr | 0.08 | 0.11 |
| Women | 40-45 yr | 0.09 | 0.11 |
| Men | 40-45 yr | 0.09 | 0.11 |
| Women | 60-65 yr | 0.09 | 0.10 |
| Men | 60-65 yr | 0.09 | 0.11 |
| Women | 70+ yr | 0.09 | 0.11 |
| Men | 70+ yr | 0.11 | 0.12 |

Based on their analysis of TDS data, FDA reports that detectable levels of perchlorate were found in at least one sample in 74 percent ( 211 of 286) of TDS foods (Murray *et al.*, 2008). The average estimated perchlorate intakes for the 14 age-gender groups range from 0.08 to 0.39 µg/kg/day, compared with the RfD of 0.7 µg/kg/day. Though not shown here, Murray *et al.* (2008) reports that average estimated iodine intakes for the 14 age-gender groups range from 138 to 353 µg/person/day, and for all groups exceed the relevant US dietary reference values used for assessing the nutritional status of populations.[11]

The results of the TDS dietary intake assessment provide an estimate of the average dietary perchlorate intakes by specific age-gender groups in the US. However, Murray *et al.* note that the current TDS design "does not allow for estimates of intakes at the extremes (i.e., upper or lower percentiles of food consumption) or for population subgroups within the 14 age/sex groups that may have specific nutritional needs (e.g., the subgroups of pregnant and lactating women within the groups of women of child bearing age)." Nevertheless, Murray *et al.* stated that: "These TDS results increase substantially the available data for characterizing dietary exposure to perchlorate and provide a useful basis for beginning to evaluate overall perchlorate and iodine estimated dietary intakes in the US population."

*b. FDA Exploratory Survey Data on Perchlorate in Food, 2003–2005.* Prior to including perchlorate in the TDS, FDA conducted exploratory surveys from October 2003 to September 2005 to determine the occurrence of perchlorate in a variety of foods. In May 2007, FDA provided an estimate of perchlorate exposure from these surveys

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[11] Murray *et al.* (2008) compared estimated average iodine intakes with US Dietary Reference Intakes for iodine (NAS, 2000). The reference values cited by Murray *et al.* (2008) are as follows: 130 µg/person/day for infants, 65 µg/person/day for children 1–8 years, 73 µg/person/day for children 9–13 years, and 95 µg/person/day for the remainder of population.

(http://www.cfsan.fda.gov/~dms/clo4ee.html).  Using the data from these exploratory studies and food and beverage consumption values from USDA's 94–98 CSFII, FDA estimated mean perchlorate exposures of 0.053 µg/kg/day for all ages (2+ years), 0.17 µg/kg/day for children (2–5 years), and 0.037 µg/kg/day for females (15–45 years).  There are uncertainties associated with the preliminary exposure assessment because the 27 foods and beverages selected represent only about 32 to 42 percent of the total diet depending on the population group.  Additionally, the overall goal of the sampling plan was to gather initial information on occurrence of perchlorate in foods from various locations with a high likelihood of perchlorate contamination.  With the preceding caveats in mind, the results of these exploratory studies are generally consistent with the more complete results of the 2005-2006 TDS.  For the purpose of developing a national estimate of dietary perchlorate exposure, the results of FDA's exploratory studies are superseded by the results of the TDS.

   *c. Other Published Food Studies.*

   Since publication of EPA's May 2007 notice, Pearce *et al.* (2007) published an analysis of perchlorate concentrations in 17 brands of prepared ready to eat and concentrated liquid infant formula.  Perchlorate concentrations in the 17 samples ranged from 0.22 to 4.1 µg/L, with a median concentration of 1.5 µg/L.  The researchers did not estimate the dose infants would consume at the concentrations observed in the study.  FDA also included sampling and analysis of infant formula in their 2008 TDS analysis, discussed above.

   Studies, such as those published by Kirk *et al.* (2003, 2005) and Sanchez *et al.* (2005a, 2005b) have examined perchlorate in milk and produce.  These studies and others were

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summarized in EPA's May 2007 notice describing the status of EPA's evaluation of perchlorate (72 FR 24016 (USEPA, 2007)).

2. Biomonitoring Studies. Researchers have also begun to investigate perchlorate occurrence in humans by analyzing for perchlorate in urine and breast milk. For example, CDC has included perchlorate in its National Biomonitoring Program, which develops methods to measure environmental chemicals in humans. With this information, the CDC can obtain data on levels and trends of exposure to environmental chemicals in the US population.

*a. Urinary Biomonitoring.* In the largest study of its kind, Blount *et al.* (2006c) measured perchlorate in urine samples collected from a nationally representative sample of 2,820 US residents as part of the 2001–2002 NHANES. Blount *et al*. (2006c) detected perchlorate at concentrations greater than 0.05 µg/L in all 2,820 urine samples tested, with a median concentration of 3.6 µg/L and a 95th percentile of 14 µg/L. Women of reproductive age (15–44 years) had a median urinary perchlorate concentration of 2.9 µg/L and a 95th percentile of 13 µg/L. The demographic with the highest concentration of urinary perchlorate was children (6–11 years), who had a median urinary perchlorate concentration of 5.2 µg/L. Blount *et al.* (2006c) estimated a total daily perchlorate dose for the NHANES participants aged 20 and older (for whom a creatinine correction method was available) and found a median dose of 0.066 µg/kg/day (about one tenth of the RfD) and a 95th percentile dose of 0.234 µg/kg/day (about one third of the RfD). Eleven adults (0.7 percent) had estimated perchlorate exposure greater than perchlorate's RfD of 0.7 µg/kg/day (the highest calculated exposure was 3.78 µg/kg/day). Because of daily variability in diet and perchlorate exposure, and the short residence time of perchlorate in the body, these single sample measurements may overestimate long-term average

exposure for individuals at the upper end of the distribution and may underestimate the long-term average exposure for individuals at the lower end of the distribution. Blount *et al.* did not estimate daily perchlorate dose for children and adolescents due to the limited validation of estimation methods for these age groups at that time (Blount *et al.*, 2006c).

In a recent unpublished, but peer reviewed, study, EPA and CDC investigators merged the data sets from NHANES and UCMR 1 to identify the NHANES participants from counties which had a perchlorate detection during the UCMR survey (USEPA, 2008a). The study assumes, based on previous analyses of perchlorate pharmacokinetics, that urine is the sole excretion pathway other than in lactating women. Since all NHANES participants' urine contained perchlorate, separating out those who had a higher potential for additional exposure via drinking water from those who had a lower potential for drinking water exposure left the remainder of participants whose exposure was expected to be primarily from food.

The advantage of a urinary biomonitoring study is that it analyzes the perchlorate actually ingested in the diets of a large number of individuals rather than using estimators of perchlorate ingestion from a variety of foods for a diverse population. The methodology provides a novel opportunity to use public water system occurrence and human biomonitoring data to directly inform EPA's decision. The approach is reasonable for estimating perchlorate intake at various percentiles from food and to gain an understanding of the relative contribution from water. A limitation is in the use of NHANES's spot urine testing, and creatinine corrections for a population with diverse physiological characteristics, to calculate the daily perchlorate dose. The cross sectional study attempts to capture a representative exposure, but was limited by the need to match up drinking water occurrence data with biomonitoring data on a county-wide basis,

even though county and public water system service area boundaries often do not coincide. There also may have been some temporal mismatch between the occurrence and biomonitoring data.

As noted, the primary goal of the study was to derive the dose of perchlorate coming from food alone by eliminating possible sources of water contribution. Individuals' data were placed into one of three bins based on likelihood of perchlorate being in their tap water. The bins were further sorted by age and sex. Bin I was comprised of NHANES 2001-2002 data for individuals residing in the same counties as public water systems that had at least one positive measurement of perchlorate during the sample period, as measured in UCMR 1. Therefore, this bin represented those who were more likely to be exposed to perchlorate in both food and water. For the most part, the average perchlorate level in urine for all age groups was the highest in this bin, and the creatinine-corrected average dose for all individuals in this group was 0.101 µg/kg/day, with a geometric mean of 0.080 µg/kg/day.

In contrast, Bin III was comprised of data for individuals considered less likely to have exposure to perchlorate via drinking water, as defined in one of three ways: (1) they resided in counties where there were no quantified detections of perchlorate in public drinking water systems sampled as part of UCMR (i.e., UCMR 1 results were below the minimum reporting limit of 4 µg/L); or (2) they self-reported that they had not consumed tap water in the previous 24 hours regardless of where they resided (i.e., they may have resided in a county with a positive UCMR finding, but did not drink tap water); or (3) again, not considering the UCMR status of the county, their response to NHANES indicated they used a reverse osmosis filter which may be effective for removing perchlorate. Bin III thus represents results of urinary perchlorate from

individuals who were less likely to experience perchlorate exposure via tap water, and were thus more likely to have their perchlorate exposure caused solely by intake from food. The average creatinine-corrected perchlorate dose for these individuals was 0.090 µg/kg/day, with a geometric mean of 0.062 µg/kg/day.

Finally, Bin II included individuals residing in counties which had not been sampled in UCMR. As such, there is no information on potential perchlorate in their public drinking water. The average creatinine-corrected perchlorate dose for these individuals was 0.072 µg/kg/day, with a geometric mean of 0.053 µg/kg/day. The results for Bin II are somewhat anomalous, and may suggest either that drinking water concentrations are even lower in these non-monitored counties than in the Bin III counties or that food exposure for these counties was lower than for the counties in either Bin I or III. In any case, EPA's analysis to determine the RSC did not focus on Bin II, as discussed below.

A summary of selected results for individuals in Bins I and III is shown in Table 4. The estimates of daily perchlorate intake presented in Table 4 from the NHANES-UCMR analysis are somewhat higher than those of Blount *et al.* (2006). The Blount *et al.* (2006) estimates were limited to adults 20 years of age and older because application of the set of creatinine excretion equations used by Blount *et al.* to estimate perchlorate dose was limited to adults. Mage *et al.* (2007) provides an expanded set of equations that allows for estimating daily creatinine excretion rates for children, as well as for adults. Since children tend to have higher exposure on a per body weight basis than adults, it is not surprising that the estimates based on both adults and children are somewhat higher than the Blount estimates based on adults alone. The mean total exposure for people that are more likely to be exposed to perchlorate in food and water (Bin

I) was calculated to be 0.101 µg/kg/day.  The average exposure for people more likely to be

exposed to perchlorate from food alone (Bin III) was 0.090 µg/kg/day.

**Table 4.  Estimated Daily Perchlorate Intakes (µg/kg/day) for Two Bins Based on UCMR 1 Occurrence Data**

| Group | Bin* | Number of people | Average (Mean) | Geometric Mean | 50th percentile | 90th percentile |
|---|---|---|---|---|---|---|
| Total | I | 320 | 0.101 | 0.080 | 0.075 | 0.193 |
| | III | 2063 | 0.090 | 0.062 | 0.058 | 0.167 |
| Age:  6-11 | I | 52 | 0.152 | 0.132 | 0.131 | 0.237 |
| | III | 270 | 0.150 | 0.118 | 0.124 | 0.280 |
| Age: 12-19 | I | 100 | 0.109 | 0.078 | 0.070 | 0.286 |
| | III | 608 | 0.080 | 0.061 | 0.060 | 0.158 |
| Age:  20 or more | I | 168 | 0.091 | 0.074 | 0.071 | 0.186 |
| | III | 1185 | 0.085 | 0.057 | 0.055 | 0.143 |
| Females: 15-44 | I | 57 | 0.081 | 0.062 | 0.071 | 0.141 |
| | III | 505 | 0.093 | 0.055 | 0.052 | 0.143 |
| Pregnant Females | I | 8 | 0.097 | 0.086 | 0.060 | 0.121 |
| | III | 98 | 0.123 | 0.064 | 0.056 | 0.263 |

*Bin I was comprised of individuals residing in counties which had at least one positive measurement of perchlorate somewhere in the public drinking water supply.  Bin III was comprised of individuals considered less likely to have exposure to perchlorate via drinking water based on a three part test (see text).

Using Bin III as the dose most closely representing only dietary perchlorate exposure,

one can compare results from the FDA TDS, shown previously in Table 3.  For example, for

females 14-16, women 25–30, and women 40-45 years old, the FDA mean food dose was 0.09–

0.1 µg/kg/day.  In the EPA-CDC biomonitoring study of NHANES-UCMR, the mean food dose

for women of child-bearing age (15–44 years old) was 0.093 µg/kg/day.  The results from

calculating likely food intakes (TDS study) and from urinalysis from actual intakes

(NHANES/UCMR) are in close agreement where comparisons can be made.

*b. Breast Milk.*  A number of studies have investigated perchlorate in human breast milk.

The most recent study included measurements from 49 healthy Boston-area volunteers (10–250

days postpartum, median 48 days; Pearce, *et al.*, 2007).  Perchlorate was found in all samples,

ranging from 1.3–411 µg/L, with a median concentration of 9.1 µg/L and a mean concentration of 33 µg/L.  No correlation was found between perchlorate and iodine concentrations in breast milk.  EPA notes that the Boston-area public water systems did not detect perchlorate in drinking water samples collected for the US EPA's Unregulated Contaminant Monitoring Rule from 2001 to 2003, nor did Boston area systems detect perchlorate in samples collected in response to the Massachusetts DEP 2004 emergency regulations for perchlorate (see Section III.B of this notice).

Kirk *et al.* (2005) analyzed 36 breast milk samples from 18 States (CA, CT, FL, GA, HI, MD, ME, MI, MO, NC, NE, NJ, NM, NY, TX, VA, WA, WV) and found perchlorate concentrations in all samples ranging from 1.4 to 92.2 µg/L, with a mean concentration of 10.5 µg/L.  Kirk *et al.* (2007) later did a smaller study involving 10 women, which included 6 samples on each of 3 days in a temporal study.  Half the women were from Texas, but the others were from CO, FL, MO, NM, and NC.  They found significant variation in all samples (n=147), with a range, mean, and median perchlorate concentration of 0.5–39.5 µg/L, 5.8 µg/L, and 4.0 µg/L, respectively.

Téllez *et al.* (2005) reported maternal parameters for participants from a study conducted in Chile.  Breast milk samples indicated that a significant amount of perchlorate leaves the body of the nursing mother through breast milk, in addition to urine.  However, the breast milk perchlorate levels were highly variable and no significant correlations could be established between breast milk perchlorate and either urine perchlorate or breast milk iodide concentrations for the individuals evaluated in these Chilean cities (Téllez *et al.*, 2005).

Blount et al (2007) also suggests breast milk as an excretion pathway and the NHANES-UCMR study authors observed a difference between the urinary perchlorate concentration of

breast feeding women versus pregnant women with an overall mean concentration of 0.130

µg/kg/day for 117 pregnant women compared to a concentration of 0.073 µg/kg/day for the 24

breast-feeding women (USEPA, 2008a).

Dasgupta *et al.* (2008) analyzed breast milk samples and 24 hour urine samples from 13

lactating women from Texas for perchlorate and iodine.  For breast milk, they found perchlorate

concentrations ranging from 0.01 to 48 µg/L, with a median concentration of 7.3 µg/L and a

mean concentration of 9.3 µg/L (457 total samples).  For iodine, concentrations ranged from 1 to

1,200 µg/L, with a median concentration of  43 µg/L and a mean concentration of 120 µg/L (447

total samples). For urine they found perchlorate concentrations ranging from 0.6 to 80 µg/L, with

a median concentration of 3.2 µg/L and a mean concentration of 4.0 µg/L (110 total samples).

For iodine, concentrations ranged from 26 to 630 µg/L, with a median concentration of 110 µg/L

and a mean concentration of 140 µg/L (117 total samples)

## IV.  PRELIMINARY REGULATORY DETERMINATION FOR PERCHLORATE

In making preliminary regulatory determinations, EPA uses the criteria mandated by the

1996 SDWA Amendments.  EPA has found that perchlorate, at sufficiently high doses, may have

an adverse effect on the health of persons, and that perchlorate is found in a small percentage of

public water supply systems.  However, EPA has determined that regulation of perchlorate in

drinking water systems does not present a meaningful opportunity to reduce health risk for

persons served by public water systems.  This section describes how EPA has evaluated these

three criteria in light of the data presented in Section III to make a preliminary regulatory

determination for perchlorate.

*A. May Perchlorate Have an Adverse Effect on the Health of Persons?*

Yes.  Perchlorate interacts with the sodium iodide symporter, reducing iodine uptake into the thyroid gland and, at sufficiently high doses, the amount of T4 produced and available for release into circulation.  Sustained changes in thyroid hormone secretion can result in hypothyroidism.  Thyroid hormones stimulate diverse metabolic activities in most tissues and individuals suffering from hypothyroidism experience a general slowing of metabolism of a number of organ systems. In adults, these effects are reversed once normal hormone levels are restored (NRC, 2005).

In fetuses, infants, and young children thyroid hormones are critical for normal growth and development.  Irreversible changes, particularly in the brain, are associated with hormone insufficiencies during development in humans (Chan and Kilby, 2000 and Glinoer, 2007) . Disruption of iodide uptake presents particular risks for fetuses and infants (Glinoer, 2007 and Delange, 2004).  Because the fetus depends on an adequate supply of maternal thyroid hormone for its central nervous system development during the first trimester of pregnancy, iodide uptake inhibition from perchlorate exposure has been identified as a concern in connection with increasing the risk of neurodevelopmental impairment in fetuses of high-risk mothers (NRC, 2005).  Poor iodide uptake and subsequent impairment of thyroid function in pregnant and lactating women have been linked to delayed development and decreased learning capability in infants and children with fetal and neonatal exposure (NRC, 2005)

The NRC recommended basing the RfD on a precursor to an adverse effect rather than an adverse effect *per se*.  The precursor event precedes a downstream adverse effect in the dose response continuum.  In this case, NRC used prevention of iodide uptake inhibition, a precursor

to adverse thyroid effects, to establish a level at which no adverse effects would be anticipated in exposed populations. This approach is consistent with the Agency's policy on the use of precursor events when appropriate in establishing the critical effect upon which an RfD is based (U.S. EPA, 2002c).

Based on the information above, EPA finds that perchlorate, at sufficiently high doses, may have an adverse effect on the health of persons.

*B. Is Perchlorate Known to Occur or is there a Substantial Likelihood that Perchlorate Occurs at a Frequency and at a Level of Public Health Concern in Public Water Systems?*

No. EPA has found that perchlorate occurs infrequently at levels of health concern in public water systems. Specifically, EPA established a Health Reference Level (HRL) as the level of concern and evaluated the information on the occurrence of perchlorate in public water systems presented in Section III.B in relation to this HRL. The HRL is a benchmark against which EPA compares the concentrations of a contaminant found in public water systems to determine if it is at a level of public health concern. For past regulatory determinations for non-carcinogens, EPA has calculated an HRL using the Agency's reference dose (RfD) as follows:

HRL = [(RfD x BW)/DWI] x RSC

Where:

RfD = Reference Dose

BW = Body Weight for an adult assumed to be 70 kilograms (kg)

DWI = Drinking Water Intake for an adult, assumed to be 2 L/day

RSC = Relative Source Contribution, or the remaining portion of the reference dose available for drinking water after other sources of exposure have been considered (e.g., food, ambient air)

In addition, EPA has used a RSC default value of 20 percent for screening purposes to estimate the HRL for past regulatory determinations because it has lacked adequate data to develop an empirical RSC.  In the absence of such data, EPA has determined that it is appropriate to use a conservative value that is more likely to understate than to overstate the amount of contaminant that can be safely ingested through drinking water.  For its two previous sets of regulatory determinations, EPA did not find contaminants at frequencies and levels of concern in comparison to the conservative screening-level HRL.  Therefore, it was not necessary for the Agency to further evaluate the RSC in making regulatory determinations for these contaminants.

However, the Agency believes that sufficient exposure data are available for perchlorate to enable EPA to estimate a better informed RSC and HRL that is more appropriate for fetuses of pregnant women (the most sensitive subpopulations identified by the NRC).  These exposure data include the further analysis by EPA of the UCMR data and the CDC's NHANES biomonitoring data, as well as the FDA's Total Diet Study.  The following sections describe EPA's analyses of each of these data sources to estimate RSCs and HRLs for this sensitive subpopulation.

1.  Total Diet Study for Estimation of an RSC.  The results of FDA's recent evaluation of perchlorate under the TDS were presented in Section III.C.1 of this notice.  The TDS estimates are representative of average, national, dietary perchlorate exposure, for the age-gender groups that were selected.  EPA used FDA's dietary exposure estimates to calculate RSC values by subtracting the dietary estimates from the RfD (0.7 µg/kg/day), dividing this difference by the RfD, and multiplying the result by 100 (to convert it to a percentage).  Because EPA believes

that dietary ingestion is the only significant pathway for non-drinking-water perchlorate

exposure, the resulting RSCs represent the amount of perchlorate exposure (as a percentage of

the RfD) that the average individual within a subgroup would have to ingest via drinking water

in order to reach a level of total perchlorate exposure that equals the RfD.  These RSCs,

displayed as percentages, are presented in Table 5.

**Table 5.  Relative Source Contributions Remaining for Water Based on TDS for Various Subgroups**

| Population Group | Total Perchlorate Intake from Food (µg/kg/day) | RfD that Remains (µg/kg/day) | RSC Remaining for Drinking Water (as a percentage of the RfD) |
|---|---|---|---|
| Infants, 6–11 mo | 0.26–0.29 | 0.41-0.44 | 59%–63% |
| Children, 2 yr | 0.35–0.39 | 0.31-0.35 | 44%–50% |
| Children, 6 yr | 0.25–0.28 | 0.42-0.45 | 60%–64% |
| Children, 10 yr | 0.17–0.20 | 0.50-0.53 | 71%–76% |
| Teenage Girls, 14–16 yr | 0.09–0.11 | 0.59-0.61 | 84%–87% |
| Teenage Boys, 14–16 yr | 0.12–0.14 | 0.56-0.58 | 80%–83% |
| Women, 25–30 yr | 0.09–0.11 | 0.59-0.61 | 84%–87% |
| Men, 25–30 yr | 0.08–0.11 | 0.69-0.62 | 84%–89% |
| Women, 40–45 yr | 0.09–0.11 | 0.59-0.61 | 84%–87% |
| Men, 40–45 yr | 0.09–0.11 | 0.59-0.61 | 84%–87% |
| Women, 60–65 yr | 0.09–0.10 | 0.60-0.61 | 86%–87% |
| Men, 60–65 yr | 0.09–0.11 | 0.59-0.61 | 84%–87% |
| Women, 70+ yr | 0.09–0.11 | 0.59-0.61 | 84%–87% |
| Men, 70+ yr | 0.11–0.12 | 0.58-0.59 | 83%–84% |

The subpopulation that is the most sensitive to perchlorate exposure is the fetus of an

iodine-deficient pregnant woman.  The FDA TDS does not estimate the dietary intake of

perchlorate specifically for pregnant women (nor can it specifically address iodine-deficient

women); but it does present dietary estimates for three groups of women of childbearing age

(Teenage girls 14–16, Women 25–30 and Women 40–45).  The calculated RSCs range from 84

to 87 percent for women of childbearing age.  Murray *et al* (2008) suggested that perchlorate

intake rates for pregnant and lactating women are "likely to be somewhat higher than those of

women of childbearing age as a whole."   If this is true, an RSC derived based upon the TDS

mean dietary intake for women of childbearing age may underestimate the relative source

contribution from food for pregnant women.

2.  Urinary Data for Estimation of an RSC.  As described in Section III.C.2 of this notice, EPA

and CDC researchers analyzed NHANES urinary data in conjunction with UCMR occurrence

data at the CDC's National Center for Environmental Health (NCEH) to evaluate exposure to

perchlorate.  These data were partitioned to provide an estimate of what portion of the overall

exposure likely came from food alone. In this analysis, EPA and CDC researchers were able to

characterize the distribution of actual perchlorate exposure as seen in their urine for pregnant

women.  This means that the analysis could determine not only the mean exposure, but also the

exposure of highly exposed individuals.  Results of this analysis, presented in Table 6, indicate

that for pregnant women, exposure to perchlorate from food is 0.263 µg/kg/day at the 90th

percentile, representing nearly 38 percent of the RfD, and thus leaving an RSC for water of 62

percent.

**Table 6.  Dose Remaining for Water, and Fraction of RfD (RSC) Based On NHANES-UCMR Analysis Calculations of Perchlorate in Food)**

| Group | Mean Food Dose (µg/kg/day) | RfD that Remains (µg/kg/day) | RSC as % of RfD | Median Food Dose (µg/kg/day) | RfD that Remains (µg/kg/day) | RSC as % of RfD | 90th Percentile Food Dose (µg/kg/day) | RfD that Remains (µg/kg/day) | RSC as % of RfD |
|---|---|---|---|---|---|---|---|---|---|
| Total population | 0.090 | 0.61 | 87 | 0.075 | 0.625 | 89 | 0.167 | 0.533 | 76 |
| Ages 6-11 | 0.150 | 0.55 | 79 | 0.124 | 0.58 | 83 | 0.280 | 0.42 | 60 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Ages 12-19** | 0.080 | 0.62 | 89 | 0.060 | 0.64 | 91 | 0.158 | 0.542 | 77 |
| **Ages 20 +** | 0.085 | 0.615 | 88 | 0.055 | 0.645 | 92 | 0.143 | 0.557 | 80 |
| **Female 15-44** | 0.093 | 0.607 | 87 | 0.052 | 0.65 | 93 | 0.143 | 0.557 | 80 |
| **Pregnant** | 0.123 | 0.58 | 82 | 0.056 | 0.64 | 91 | 0.263 | 0.437 | 62 |

3. HRL Derivation. EPA believes the NHANES-UCMR analysis is the best available

information to characterize non-drinking water exposures to perchlorate for the most sensitive

subpopulation. The FDA *Total Diet Study* provides a nationally representative estimate of the

mean dietary exposure to perchlorate for 14 age and gender groups, including women of

childbearing age. However, this study does not provide specific estimates for the most sensitive

subpopulation, the iodine-deficient pregnant woman and her fetus. Also, this study estimates

only mean exposures, so it does not account for the perchlorate exposure of highly exposed

individuals. The NHANES-UCMR analysis provides a distribution of exposure (not just a mean)

specific to almost 100 pregnant women who are not likely to have been exposed to perchlorate

from their drinking water, although it also does not separate out iodine-deficient pregnant women

because of data limitations. Table 7 presents the HRLs developed for the most sensitive

subpopulation using the TDS data and the NHANES-UCMR data. EPA notes that the mean

RSC for pregnant women estimated from the NHANES-UCMR data is very close to, but slightly

lower than, the mean for women of childbearing age estimated from the TDS data. This shows

close agreement between the two data sets and is consistent with the suggestion in *Murray et al*

that food exposures for pregnant women are likely to be somewhat higher than for women of

childbearing age as a whole. (Note that higher food exposure equates to a lower RSC because a

smaller fraction of the RfD is left to be allocated to drinking water.) While the *means* are

available (and in close agreement) from both data sets, EPA believes it is more protective to

estimate the HRL for drinking water by subtracting the 90th percentile exposure in food from the reference dose to assure that the highly exposed individuals from this most sensitive subpopulation are considered in the evaluation of whether perchlorate is found at levels of health concern. The NHANES-UCMR data allow for the calculation of the 90th percentile food exposure, which results in an HRL of 15 µg/L for the pregnant woman.

**Table 7. Health Reference Levels for Pregnant Women Using TDS Data and NHANES-UCMR Data**

| Sub population | Body Weight [a] | Drinking Water Consumption [a] | Source of RSC Derivation | RSC | HRL |
|---|---|---|---|---|---|
| Women of Childbearing Age | 70 kg | 2 liters | TDS mean (Table 5) | 84 - 87% | 21 µg/L |
| Pregnant Women | 70 kg | 2 liters | NHANES-UCMR mean (Table 6) | 82% | 20 µg/L |
| Pregnant Women | 70 kg | 2 liters | NHANES-UCMR 90th percentile (Table 6) | 62% | 15 µg/L |
| Footnotes: [a]Default values used by EPA in the derivation of HRLs. | | | | | |

4. Frequency of Exposure at Health Reference Level. The number of pregnant women potentially exposed to perchlorate in public drinking water above these HRLs can be estimated from the UCMR data. Using the data presented in Table 2, approximately 0.8 percent of the systems had one or more detections of perchlorate at or above 15 µg/L, the HRL determined for pregnant women in this analysis. These systems serve a total of 2.0 million persons in their entire service area, of which 1.0 million are females, and thus might become pregnant at some point during their lives. However, not all water system customers are living in households that are served water from the entry point(s) that tested positive. Table 2 also provides a more

refined estimate of the potentially exposed population by factoring in an estimate of the portion of the system population served by each entry point (as described in Section III.B.1. of this notice). Using this second approach, which is likely to be more accurate, the number of people served by entry points which exceed the HRL is 0.9 million, of which 0.45 million are females. EPA estimates that at any one time, 1.4 percent of the population from Table 2 served by water systems (or entry points) that detected perchlorate at levels greater than 15 µg/L (Table 7) are pregnant women. This estimate is based on the number of live births (4,059,000, Ventura *et al.*, 2004) as a percentage of the total US population in 2000 (281,421,906, U.S. Census Bureau, 2002). Therefore, a best estimate of about 16,000 pregnant women (with a high end estimate of 28,000) could be exposed at levels exceeding the HRL at any given time.

Based on this analysis, EPA concludes that perchlorate occurs infrequently at levels of health concern in public water systems. There are a small percentage of public water systems (0.8 percent) where drinking water above the HRL, in combination with perchlorate from food, may result in exposures to pregnant women at levels that exceed the EPA reference dose for perchlorate. However, as explained in section IV.C, these exposures to perchlorate in drinking water at concentrations above the HRL do not rise to the level of a meaningful opportunity for public health risk reduction through a national primary drinking water regulation.

5. Consideration of Sensitive Subpopulations

In making a regulatory determination, the SDWA requires EPA to take into consideration the effect of contaminants on subgroups that comprise a meaningful portion of the general population that are identifiable as being at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population.

As noted above, in past regulatory determinations, EPA has calculated a screening level

HRL based on drinking water consumption and body weight information for adults in general,

combined with default assumptions about RSC, in the absence of robust empirical data. For this

preliminary perchlorate determination, EPA has improved on this approach by using body

weight, drinking water and food exposure data for pregnant women, in order to protect the most

sensitive subpopulation identified by the NRC (i.e., the fetuses of these women). In addition,

EPA has used 90th percentile rather than mean food exposure data to ensure that the HRL

protects highly exposed pregnant women and their fetuses. However, infants, developing

children, and people with iodine deficiency or thyroid disorders were also identified as sensitive

subpopulations by the NRC. Because infants and children eat and drink more on a per body

weight basis than adults, eating a normal diet and drinking water with 15 µg/L of perchlorate

may result in exposure that is greater than the reference dose in these groups. To address this

concern, the potential effect of this intake on inhibition of iodide uptake in these subgroups (i.e.,

relative sensitivity) was evaluated using PBPK modeling, as discussed in Section III.A.3.

Because the NRC (NRC, 2005) found that the inhibition of iodide uptake by the thyroid, which is

a non-adverse precursor to any adverse effect, should be used as the basis for perchlorate risk

assessment, evaluating iodide uptake inhibition is important for determining whether the HRL of

15 µg/L (derived for pregnant women) is also an appropriate health reference level for the other

sensitive subpopulations. Reducing some of the uncertainty regarding the relative sensitivities of

these subpopulations will help to address the concerns that some groups may be exposed above

the reference dose (calculated using group-specific body weight and intake information),

particularly if PBPK modeling predicts that at the HRL, these groups do not experience

precursor effects (RAIU inhibition) that exceed the no effect level from which the reference dose was derived.

a. Published PBPK Models. The Clewell *et al.* (2007) and Merrill *et al.* (2005) PBPK models predict the distribution and elimination of perchlorate after it is ingested. The models also predict the level of RAIU inhibition that would result from different levels of perchlorate exposure for different subpopulations, including children and infants.

Clewell *et al.* (2007) predicted that at a perchlorate dose of 0.001 mg/kg/day (1 µg/kg/day), approximately one and one half times the RfD, iodide uptake inhibition in the most sensitive populations, i.e., fetuses and infants, was no greater than 1.1 percent. This is below the level (1.8 percent) of inhibition at the NRC identified no-effect level (NOEL) in healthy adults and recommended as the point of departure for calculating the RfD, applying a 10-fold intraspecies uncertainty factor. The fact that for all subpopulations the predicted RAIU at a level slightly above the RfD is still below the RAIU at the NOEL is consistent with the NRC's conclusion that the RfD would protect even the most sensitive sub-populations. However, because the Clewell model does not account for reduced urinary clearance that occurs in young infants, EPA modified the model as discussed in Section III.A.3 to address this and other limitations.

b. Results of EPA's Application of the Published Models. EPA evaluated the published models (Clewell *et al.*, 2007, and Merrill *et al.*, 2005) and used them to further explore the relationship between water concentrations and iodide uptake inhibition in different subpopulations. As noted in Section III.A.3 and discussed in more detail in EPA's description of the model (USEPA, 2008b), EPA determined that it was appropriate to make several changes to

the models' computer codes in order to harmonize them and more adequately reflect the biology. EPA considered in detail the data currently available for parameters determined to be particularly important to the models' predictions, and modified the model parameters describing exposure as well as urinary excretion of perchlorate and iodide. These modifications resulted in predicted RAIU inhibition rates that were up to 1.5 times the predicted inhibition rates in the earlier versions of the model. EPA believes its revisions have improved the predictive power of the model and has used its results as the basis for the following discussion.

Consistent with both the unmodified Clewell model and the NRC's conclusions, EPA's analysis identified the near-term fetus (gestation week 40 fetus) as the most sensitive subgroup, with a percent RAIU inhibition that was 5-fold higher than the percent inhibition of the average adult at a dose equal to the point of departure (7 µg/kg/day). After correcting the model for reduced urinary clearance in infants, the same analysis shows that the predicted percent RAIU inhibition is approximately 1- to 2-fold higher for the breast-fed and bottle-fed infant (7-60 days) than for the average adult, and is slightly lower for the 1-2 year old child than for the average adult. While uncertainty remains regarding the model's predictions, EPA believes that it is a useful tool, in conjunction with appropriate exposure information, for evaluating the relative sensitivity of particular subpopulations (infants and children) that can inform our assessment of whether the HRL is an appropriate health reference level for all subpopulations (not just pregnant women).

EPA thus applied the adjusted model to the HRL of 15 µg/L to determine the predicted percent RAIU inhibition (Table 8). Iodide uptake inhibition levels for all other subpopulations, including infants and children, were estimated to be not greater than 2.0 percent at the 15 µg/L

drinking water concentration and not greater than 2.2 percent when also considering perchlorate in food. The highest iodide update inhibition level (2.2 percent) was seen for the 7 day bottle fed infant; all other subpopulations, including the 60 day bottle fed infant as well as the 7 and 60 day breast fed infant had inhibition levels below 1.4 percent when also considering perchlorate in food. The 2.2 percent inhibition level for 7-day old bottle fed infants is comparable to the 1.8 percent inhibition level that the NRC identified as a no effect level in healthy adults and recommended as the point of departure for calculating the RfD. [12]

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[12] The model does not exactly match the average measured inhibition at each exposure concentration. At the point of departure (7 ug/kg/day), the model predicts a value of 2.1 percent for adults, rather than the 1.8 percent from the Greer *et al.* (2002) study. Thus, the model slightly over-predicts the level of inhibition for this group at this exposure level, though this relationship may not hold true for other sub-groups and exposure levels. In any event, the difference between the average measured value of 1.8 percent and the model-predicted value of 2.1 percent is well within the statistical uncertainty in the data.

Table 8 also shows the exposure to each subpopulation in ug/kg of body weight. EPA notes that for some subgroups, the modeled exposure exceeds the RfD, though not for the most sensitive subgroup (i.e., pregnant women and their fetuses) from which the HRL was derived. EPA has used these exposure estimates as one input into the PBPK model to reduce the uncertainty associated with the relative sensitivities of other subgroups, particularly infants and children. EPA believes use of the model enhances its assessment beyond considering exposure alone by predicting the resulting iodide uptake inhibition that may result from that exposure. As noted above, the NRC concluded that the "most health protective and scientifically valid approach" was to base the point of departure for the RfD on the inhibition of iodide uptake by the thyroid (NRC, 2005), a non-adverse precursor effect. The predicted RAIU inhibition for all subgroups is comparable to or less than the RAIU at the NOEL selected by the NRC. Therefore EPA believes the HRL of 15 µg/L, derived for pregnant women, is also an appropriate health reference level for other sub-populations, against which to evaluate monitored levels of perchlorate occurrence in drinking water systems.

Table 8.  Predicted percent radioactive iodide uptake (RAIU) inhibition and corresponding perchlorate intake from water at 15 µg/L

with and without food intake.

| | Body Weight (kg) [a] | 90th Percentile Water Intake (L/day) [b] | Perchlorate Intake from only water at 15 µg/L (µg/kg-day) | Percent RAIU Inhibition from only water at 15 µg/L | TDS estimated perchlorate intake from food (µg/kg-day) [c] | Perchlorate Intake from food and water at 15 µg/L (µg/kg-day) | Percent RAIU Inhibition from food and water at 15 µg/L |
|---|---|---|---|---|---|---|---|
| Average adult | 70 | 2.24 | 0.48 | 0.15 | 0.10 | 0.58 | 0.18 |
| Non-pregnant woman | 66 | 2.11 | 0.48 | 0.21 | 0.10 | 0.58 | 0.26 |
| Pregnant woman | | | | | | | |
|  Mom -- GW 13 | 69 | 2.18 | 0.50 | 0.49 | 0.10 | 0.60 | 0.59 |
|  Mom -- GW 20 | 71 | 2.34 | 0.50 | 0.49 | 0.10 | 0.60 | 0.59 |
|  Mom -- GW 40 | 78 | 2.57 | 0.50 | 0.47 | 0.10 | 0.60 | 0.57 |
| Fetus -- GW 40 [g] | 3.5 | -- | -- | 0.90 | -- | -- | 1.1 |
| Breast-fed infant | | | | | | | |
|   Mom -- 7 d | 74 | 2.96 | 0.60 | 0.18 | 0.10 | 0.70 | 0.21 |
|   Infant -- 7 d | 3.6 | 0.52 [d] | 1.36 | 1.1 | -- [d] | 1.59 | 1.3 |
|   Mom -- 60 d | 72 | 2.96 | 0.61 | 0.17 | 0.10 | 0.71 | 0.20 |
|   Infant -- 60 d | 5 | 0.74 [d] | 1.27 | 0.73 | -- [d] | 1.48 | 0.84 |
| Bottle-fed | | | | | | | |

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| | Body Weight (kg) [a] | 90th Percentile Water Intake (L/day) [b] | Perchlorate Intake from only water at 15 µg/L (µg/kg-day) | Percent RAIU Inhibition from only water at 15 µg/L | TDS estimated perchlorate intake from food (µg/kg-day) [c] | Perchlorate Intake from food and water at 15 µg/L (µg/kg-day) | Percent RAIU Inhibition from food and water at 15 µg/L |
|---|---|---|---|---|---|---|---|
| infant | | | | | | | |
| Infant -- 7 d | 3.6 | 0.84[e] | 3.53 | 2.0 | 1.42 µg/L | 3.87 | 2.2 |
| Infant -- 60 d | 5 | 1.14[e] | 3.42 | 1.3 | 1.42 µg/L | 3.74 | 1.4 |
| Child | | | | | | | |
| 6-12 mo[f] | 9.2 | 1.03 | 1.68 | 0.46 | 0.275 | 1.96 | 0.53 |
| 1-2 yr[f] | 11.4 | 0.64 | 0.84 | 0.23 | 0.370 | 1.21 | 0.33 |

[a] Calculations for a 70 kg "average" adult are shown, while the body weight (BW) for the non-pregnant woman is from US EPA 2004 (based on CSFII 94-96,98) and BWs for the child are mean values from Kahn and Stralka (2008). BWs for pregnant and breast feeding moms, fetuses, bottle and breast fed infants are predicted weights (functions of age or gestation week) using growth equations from Gentry et al. (2002) as implemented in the PBPK models (Clewell *et al.* 2007; non-pregnant value is BW at day 0 of gestation).

[b] Water intake levels for adults other than the lactating mother are based on normalized 90th percentile values for total water intake (direct and indirect) multiplied by the age- or gestation-week-dependent BW, as follows: 0.032 L/kg-day for average adult and non-pregnant woman; 0.033 L/kg-day for the pregnant woman. A fixed ingestion rate was used for the lactating mother because, while her BW is expected to drop during the weeks following the end of pregnancy, the demands of breast-feeding will be increasing. Values are from Kahn and Stralka (2008), except values for women are from U.S. EPA (2004).

[c] The dietary values used correspond to the midpoint of the range of lower- and upper-bound average perchlorate levels for each subgroup, as identified from the FDA TDS in Murray *et al.* (2008), except for the bottle-fed infant. EPA used 1.42 µg/L as the concentration of perchlorate in infant formula. This is based on an average of available FDA TDS data, with ½ LOD included in the average for the samples in which perchlorate was not detected.

[d] The breast-fed infants are assumed to have no direct exposure via food or water. The prediction for breast-fed infants in this table results from the dose from both food and water to the mother providing breast milk to the infant. Breast-fed infant

"water intake" is the breast milk ingestion rate obtained by fitting an age-dependent function to the breast-milk ingestion data (L/kg-day) from Arcus-Arth *et al.* (2005). Urinary clearance rates for the lactating woman equal to that of the average adult were used, consistent with data presented in Delange (2004).

[e] For the bottle-fed infant, normalized total water intake (direct and indirect, L/kg-day) was described as a smooth function of infant age fit to the results from Kahn and Stralka (2008), and multiplied by BW(age). For the 7-day-old infant, the data used to fit the function included the 90th percentile community water-consumers only intake (0.235 L/kg-day, N=40) for the < 1 month old infant. For the 60-day-old infant, the 90th percentile community water-consumers only intake (0.228 L/kg-day, N=114) for the 1- to <3 months-old infant was used.

[f] For the 6- to 12-month and 1- to 2-year-old children, EPA set the water ingestion based on published exposure tables and selected the age at which the model-predicted BW (from growth equations) matched the exposure-table mean. This approach resulted in model predictions for a 9.6-month old child (to represent 6- to 12-month-old children) and a 1.3-year old (to represent 1- to 2-year-old children).

[g] Due to data limitations, RAIU inhibition is calculated only for fetuses at GW 40.

c. Modeling Uncertainties

EPA recognizes that there are uncertainties associated with this modeling, as there are for any modeling effort.  For example, this analysis does not take into account within-group variability in pharmacokinetics, uncertainty in model parameters and predictions, or population differences in pharmacodynamics (PD) of receptor binding and upregulation.  Also, the NRC identified fetuses of pregnant women that are hypothyroid or iodine deficient as the most sensitive subpopulation.  The model  predictions of RAIU inhibition in the various subgroups are average inhibition for typical, healthy individuals, not for hypothyroid or iodine deficient individuals.  However, EPA did not rely on this analysis for determining the HRL.  Rather, the HRL of 15 µg/L was calculated directly from the RfD to protect the most sensitive subpopulation, the fetuses of  pregnant women, using high end exposure assumptions (e.g,, estimated 90th percentile drinking water consumption and estimated 90th percentile perchlorate dietary (food) exposure).  The PBPK modeling was used to provide information on the potential effects of exposure at the HRL for other subgroups, such as infants and children.

In addition, the predicted inhibitions are averages for the subgroup as a whole, given the exposure assumptions used in the model.  Thus, some members of a group would be expected to have RAIU inhibition greater than indicated in Table 8 for a particular perchlorate concentration, while others would have lesser inhibition.  EPA was able to partially address this variability by using 90th percentile water consumption rates and mean body weights in the analysis to consider the highly exposed portions of the various subgroups. Most members of the subgroups would be expected to have exposures less than those indicated in Table 8.

There is also some uncertainty regarding the water intake rates, particularly for infants. EPA described water intake by infants as a smooth function fit to the 90th percentile community water-consumers intake-rate data (intake per unit BW) of Kahn and Stralka (2008), which is then multiplied by the age-dependent BW to account for the changes occurring over the first weeks of life. This resulted in an estimated 90th percentile water intake rate of 0.84 L/day for the 7-day bottle fed infant and used by EPA in PBPK model simulations. General information on water and formula intake for 7-day old infants is also available in guidelines for healthy growth and nutrition of the American Academy of Pediatrics (AAP, 2008). The values estimated using the guidelines from the AAP (0.126 L/kg-day assuming 80% is the percent water used in preparation of formula) for 7-day-old infants are close to the mean consumers-only intake rate for the 1-30 day-old infants from Kahn and Stralka (2008; 0.137 L/kg-day N=40).

However, FDA has suggested an alternate approach, using the caloric intake requirement of a 7-day old infant as the basis for calculating consumption (FDA, 2008). This would likely yield a lower estimate of intake than the 0.84 L/day EPA has used in the model. If intake is lower, this would yield a lower prediction of RAIU inhibition, as can be seen from the value predicted for the 7-day old breast fed infant (1.4 percent). EPA plans to ask specifically for feedback on the consumption estimates for 7-day old bottle-fed infants when the model revisions are peer reviewed.

There is also uncertainty regarding the appropriate duration of exposure (i.e., days, weeks, months) to compare to the perchlorate RfD, which EPA defines as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of

deleterious effects during a lifetime." Reference values, like the RfD, are derived based on an

assumption of continuous exposure throughout the duration specified, while intake levels may

rapidly change day to day or during certain life stages. For comparability with the RfD,

continuous perchlorate exposure was assumed in EPA's modeling analysis. Using perchlorate

levels predicted for a continuous exposure (constant rate of introduction to the stomach), rather

than incorporating changes in exposure and other input parameters over time (i.e., simulating the

timing and quantity of specific ingestion events during the day), substantially reduced the effects

of parameter uncertainty in the modeling. RAIU inhibition, on the other hand, is evaluated as the

change in thyroid uptake of a pulse of iodide (radiolabeled, from an IV injection) at a time 24

hours after the pulse is administered. Thus, it represents the inhibition on a given day. This was

true in the Greer study on which the RfD is based, and it is also true in the model. For all

lifestages except the developing infant, the day-to-day variation in RAIU inhibition at the levels

under consideration will have little or no effect. However, the effects of short-term inhibition in

the infant (and fetus) may be of greater consequence than in the adult, although infants may also

have less short-term variability in their diet and intake levels than adults. To address this

concern, we present the results for the infant at both 7 days and 60 days after birth. The model

predicts a fairly smooth variation in effect between these two ages.

     d. Summary of Modeling Analysis. In deciding whether to regulate perchlorate, EPA

focused attention on the most sensitive subpopulation, a pregnant woman and her fetus. EPA

calculated an HRL of 15 µg/L for pregnant women using RSC information derived from an

analysis of NHANES and UCMR data. EPA also conducted PBPK modeling to evaluate

predicted biological outcomes associated with drinking water concentrations at the health

reference level for different sensitive subpopulations. For pregnant women, EPA assumed a 90th

percentile water ingestion rate of 0.033 L/kg-day, a food intake rate that represented the midpoint

of the range of average perchlorate dietary exposures reported in Murray et al. (2008), and used

the Clewell *et al.* (2007) PBPK model-fitted body weight. EPA believes that the model-fitted

body weight provides a more realistic weight for the pregnant woman than EPA's 70 kg default

assumption for adults. In addition, rather than using the default assumption of 2L/day water

ingestion, EPA used a 90th percentile water ingestion rate normalized for body weight and based

on data specifically for pregnant women (USEPA 2004b). Using these assumptions, the model

predicted that the pregnant woman's dose of perchlorate would not exceed the reference dose if

she consumed drinking water with a concentration of 15 µg/L or less, which is consistent with

the derivation of the HRL from the reference dose, based on average body weight, 90th percentile

water consumption, and 90th percentile food exposure for pregnant women. The model further

predicted that the percent inhibition in the fetus of a pregnant woman consuming drinking water

with 15 µg/L perchlorate (in combination with a normal diet) is 1.1 percent, below the 1.8

percent that the NRC determined to be a no-effect level in healthy adults. EPA evaluated other

subpopulations to estimate iodide uptake inhibition and determined that 7-day old bottle-fed

infants were predicted to have a 2.2 percent inhibition level, after also accounting for food

exposure, and all other subpopulations, including 60-day old bottle-fed infants, 7 and 60 day old

breast-fed infants, and children, were predicted to have levels of inhibition of 1.4 percent or less,

after accounting for food. All of these levels are comparable to or below the 1.8 percent no

effect inhibition level from the Greer study.

Based on the health protective approach for deriving the RfD (i.e., use of a NOEL rather than a NOAEL as the point of departure), the conservative assumptions used in deriving the RSC and corresponding HRL (use of 90th percentile food exposure data specifically from pregnant women), and the PBPK modeling analysis of RAIU inhibition in potentially sensitive subpopulations, EPA believes drinking water with perchlorate concentrations at or below the HRL of 15 µg/L is protective of all subpopulations.   Based upon the HRL and the analysis of drinking water occurrence , EPA concludes that perchlorate does not occur at a frequency and level of health concern to warrant a national drinking water regulation.

*C. Is There a Meaningful Opportunity for the Reduction of Health Risks from Perchlorate for Persons Served by Public Water Systems?*

The Agency does not believe that a national primary drinking water regulation for perchlorate presents a meaningful opportunity for health risk reduction for persons served by public water systems. EPA has found that perchlorate occurs infrequently above levels of health concern. Only 31 out of 3,865 systems (0.8 percent) detected perchlorate in drinking water above the HRL of 15 µg/L. EPA's best estimate is that 0.9 million people (with an upper bound estimate of 2 million people) may be consuming water containing perchlorate at levels that could exceed the HRL for perchlorate and the Agency estimates that fewer than 30,000 of them are pregnant women at any given time.

EPA's RfD was derived by applying a 10 fold uncertainty factor to the dose corresponding to a non-statistically significant mean 1.8 percent decline in RAIU in healthy adults following two weeks of daily exposure to perchlorate (Greer et al., 2002). Because iodide uptake inhibition is not an adverse effect but a precursor biochemical change, this point of departure (7 ug/kg/day) is a NOEL which provides for a more conservative and health-protective approach to perchlorate hazard assessment. After taking perchlorate in the diet into consideration, at the HRL of 15 µg/L for perchlorate in drinking water, the models predicted that the percent RAIU inhibition in fetuses would be 1.1 percent, while the inhibition in all other subgroups except the 7-day old bottle fed infant would be no greater than 1.4 percent. For the 7-day old bottle fed infant, the predicted inhibition is 2.2 percent. All of these values are comparable to or below the percent inhibition at the NOEL in the Greer study.

Based on these analyses, EPA has determined that a national primary drinking water regulation for perchlorate would not present a meaningful opportunity for health risk reduction for persons served by public water systems.

## V.    EPA'S NEXT STEPS

EPA requests comment on this preliminary determination that a national primary drinking water regulation for perchlorate would not present a meaningful opportunity for health risk reduction for persons served by public water systems.  EPA also requests comment upon the scientific data and supporting analyses for this determination.  In past regulatory determinations, EPA has qualitatively but not quantitatively evaluated the health effects of exposure at the HRL on infants and children.  Because the evaluation of the potential impacts of exposure at the HRL of 15 µg/L on infants and children is a novel approach, EPA specifically requests comment on its use of the revised PBPK model to evaluate these potential impacts.

EPA will respond to the public comments it receives on the preliminary determination and will review the comments from the peer review of its model application.  After considering comments, EPA plans to issue a final regulatory determination for perchlorate by December 2008.  EPA also plans to publish a health advisory for perchlorate at the time of the final determination to provide information to Federal, Regional, State, and local public health officials regarding potential health risks from perchlorate-contaminated drinking water.

## VI.  REFERENCES

AAP, 2008: American Academy of Pediatrics,  Bright futures guidelines for health supervision of infants, children, and adolescents (2008)

http://brightfutures.aap.org/pdfs/Guidelines_PDF/6-Promoting_Healthy_Nutrition.pdf

Amitai Y, Winston G, Sack J, Wasser J, Lewis M, Blount BC, Valentin-Blasini L, Fisher N, Israeli A, and Leventhal A. (2007). Gestational exposure to high perchlorate concentrations in drinking water and neonatal thyroxine levels. Thyroid. 17(9): 843-850.

Arcus-Arth, A., G. Krowech, and L. Zeise. 2005.  Breast milk and lipid intake distributions for assessing cumulative exposure and risk.  Journal of Exposure Analysis and Environmental Epidemiology 15(4): 357–365.

Auso E., R. Lavado-Autric, E. Cuevas, F.E. Del Rey, G, Morreale De Escobar, and P. Berbel. 2004.  A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. Endocrinology. 145: 4037-47.

Blount, B.C., L. Valentín-Blasini, D.L. Ashley. 2006a. Assessing human exposure to perchlorate using biomonitoring. *Journal of ASTM International*. Vol. 3, No. 7. pp. 1–6.

Blount, B.C., J.L. Pirkle, J.D. Osterloh, L. Valentín-Blasini, and K.L. Caldwell. 2006b. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. *Environmental Health Perspectives*. Vol. 114, No. 12. pp. 1865–1871.

Blount, B.C., L. Valentín-Blasini, J.D. Osterloh, J.P. Mauldin, and J.L. Pirkle. 2006c. Perchlorate Exposure of the US Population, 2001–2002. *Journal of Exposure Science and Environmental Epidemiology*. Advance online publication 18 October 2006. Available on the Internet at: http://www.nature.com/jes/journal/vaop/ncurrent/pdf/7500535a.pdf.

Blount, B.C., L. Valentin-Blasini. 2006. Analysis of perchlorate, thiocyanate, nitrate and iodide

in human amniotic fluid using ion chromatography and electrospray tandem mass

spectrometry. *Analytica Chimica Acta*. Vol. 567, No. 1. pp. 87–93.

CDPH. 2008.  California Department of Public Health. "Perchlorate in California Drinking

Water: Update and Overview."  Available on the Internet at:

http://www.cdph.ca.gov/certlic/drinkingwater/Pages/Perchlorate.aspx.  Updated July 8, 2008.

Caldwell K.L., Jones R., and Hollowell J.G. 2005. Urinary iodine concentration: United States

National Health and Nutrition Examination Survey 2001–2002. *Thyroid*. Vol. 15, pp. 692–

699.

Chan, S. and M. D. Kilby. 2000. Thyroid hormone and central nervous system development. J

Endocrinol 165(1): 1-8.

Clewell, R.A., E.A. Merrill, J.M. Gearhart, P.J. Robinson, T.R. Sterner, D.R. Mattie, and H.J.

Clewell, III. 2007.  Perchlorate and radiodide kinetics across life stages in the human: using

PBPK models to predict dosimetry and thyroid inhibition and sensitive subpopulations based

on developmental stage.  *Journal of Toxicology and Environmental Health.  Part A.*  70:5

408-428.

Dasgupta, P.K., A.B. Kirk, J.V. Dyke, and S.I. Ohira.  2008.  Intake of  Iodine and Perchlorate

Excretion in Human Milk.  Environ. Sci. Technol.  Advance online publication accessed

September 18, 2008.

Delange, F. 2004.  Optimal iodine during pregnancy, lactation and the neonatal period.

International Journal of Endocrinology and Metabolism 3:1-12.

Egan, S.K., Bolger, P.M., and Carrington, C.D. 2007. Update of US FDA's Total Diet Study

Food Lists and Diets. J Expo Sci Environ Epidemiol. pp. 1-10. (As cited in Murray *et al.*, 2007)

FDA, 2008: Food and Drug Administration. Volume of feeds for infants. Memorandum from Benson M. Silverman, M.D., Staff Director, Infant Formula/Medical Foods Staff, Center for Food Safety and Applied Nutrition, to P. Michael Bolger.

Gibbs *et al.*, 2004  J.P. Gibbs, L. Narayanan and D.R. Mattie, Crump *et al.* Study among school children in Chile: subsequent urine and serum perchlorate levels are consistent with perchlorate in water in Taltal, *J*. Occup. Environ. Med 46 (2004) (6), pp. 516–517.

Gilbert, M.E. and L. Sui. 2008. Developmental exposure to perchlorate alters synaptic transmission in hippocampus of the adult rat.  Environ Health Perspect 116: 752-60.

Glinoer, D. 2001. Potential consequences of maternal hypothyroidism on the offspring: evidence and implications. Horm Res 55(3): 109-14.

Glinoer, D. 2007. Clinical and biological consequences of iodine deficiency during pregnancy. Endocr Dev 10: 62-85.

Goldey, E.S., L.S. Kehn, G.L. Rehnberg, and K.M. Crofton. 1995.  Effects of developmental hypothyroidism on auditory and motor function in the rat. Toxicology and Applied Pharmacology 135:67-76.

Greer, M.A., G. Goodman, R.C. Pleuss, and S.E. Greer. 2002.  Health effect assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodide uptake in humans. Environ Health Perspect Vol. 110. pp. 927–937.

Haddow, J.E., G.E. Palomaki, *et al.* 1999.  Maternal thyroid deficiency during pregnancy and

subsequent neuropsychological development of the child.  New England Journal of Medicine

341(8): 549-55.

Kahn, H., and K. Stralka. 2008.  Estimated daily average per capita water ingestion by child and

adult age categories based on USDA's 1994-96 and 1998 continuing survey of food intakes

by individuals. Journal of Exposure Analysis and Environmental Epidemiology (accepted for

publication).

Kirk, A.B., E.E. Smith, K. Tian, T.A. Anderson, and P.K. Dasgupta. 2003.  Perchlorate in Milk.

Environmental Science and Technology. Vol. 37, No. 21. pp. 4979–4981.

Kirk, A.B., P.K. Martinelango, K. Tian, A. Dutta, E.E. Smith, and P.K. Dasgupta. 2005.

Perchlorate and iodide in dairy and breast milk. Environmental Science and Technology.

Vol. 39, No. 7. pp. 2011–2017.

Kirk, A.B., J.V. Dyke, C.F. Martin, and P.K. Dasgupta. 2007. Temporal patterns in perchlorate,

thiocyanate and iodide excretion in human milk. Environ Health Perspect

Online Vol. 115, No. 2. pp. 182–186.

Kooistra, L., S. Crawford, A.L. van Baar, E.P. Brouwers, and V.J. Pop. 2006. Neonatal effects of

maternal hypothyroxinemia during early pregnancy. Pedeatrics; 117; 161-167.

Krynitsky, A.J., R.A. Niemann, A.D. Williams, M.L. Hopper. 2006. Streamlined sample

preparation procedure for determination of perchlorate anion in foods by ion

chromatography-tandem mass spectrometry.  Analytica Chimica Acta Vol 567. pp. 94-99.

(As cited in Murray *et al.*, 2007)

Mage, D.T., R.H. Allen, A. Kodali. 2007. Creatinine corrections for estimating children's and

adult's pesticide intake doses in equilibrium with urinary pesticide and creatinine
concentrations. J. Expos Sci Enviro Epidem. 18, pp. 360 – 368.

Massachusetts Department of Environmental Protection (MA DEP). 2005.  The occurrence and
sources of perchlorate in Massachusetts. Draft Report. Available on the Internet at:
http://www.mass.gov/dep/cleanup/sites/percsour.pdf.  Updated April 2006.

Merrill, E.A., R.A. Clewell, P.J. Robinson, A.M. Jarabek, T.R. Sterner, and J.W. Fisher. 2005.
PBPK model for radioactive iodide and perchlorate kinetics and perchlorate-induced
inhibition of iodide uptake in humans.  Toxicological Sciences 83: 25-43.

Morreale de Escobar, G., M.J. Obregon, and F. Escobar del Rey.  2004.  Is neropsychological
development related to material hypothyroidism or to maternal hypothyroxinemia?  The
Journal of Clinical Endocrinology & Metabolism Vol. 85. No. 11.

Morreale de Escobar, G., M.J. Obregon, and F. Escobar del Rey.  2004.  Role of thyroid
hormone during early brain development. European Journal of Endocrionlogy 151: U25-U37.

Murray, C.W III, S.K. Egan, H. Kim, N. Beru, P.M. Bolger. 2008. US Food and Drug
Administration's Total Diet Study: Dietary Intake of Perchlorate and Iodine. Journal of
Exposure Science and Environmental Epdimiology, advance online publication January 2,
2008.

National Research Council (NRC). 2005. *Health Implications of Perchlorate Ingestion*. National
Academies Press, Board on Environmental Studies and Toxicology. January 2005. 276 p.

Pearce, E.N., A.M. Leung, B.C. Blount, H.R. Bazrafshan, X. He, S. Pino, L. Valentin-Blasini,
L.E. Braverman. 2007. Breast milk iodine and perchlorate concentrations in lactating Boston-
area women. J Clin Endocrin Metab Vol. 92, No. 5, pp. 1673-1677.

Pop, V.J., J.L. Kuijpens , A.L. van Baar , G. Verkerk , M.M. van Son, J.J. de Vijlder, T. Vulsma, W.M. Wiersinga. H.A. Drexhage, and H.L. Vader. 1999. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf).  Feb;50(2):149-55.

Pop, V.J.,  E.P. Brouwers, H.L. Vader, T. Vulsma , A.L. van Baar , and J.J. de Vijlder JJ. 2003. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf). Sep;59(3):282-8.

Rovet, J.F., 2002. Congenital hypothyroidism:  an analysis of persisting deficits and associated factors.  Child Neuropsychology Vol. 8, No. 3. pp. 150-162.

Sanchez , C.,  Blount, B., L Valentin-Blasini, L.,  Krieger, R.  Perchlorate, thiocyanate, and nitrate in edible cole crops (Brassica sp.) produced in the lower colorado river region. Bull Environ Contam Toxicol. 2007 Oct 26.

Sanchez, C.A., R.I Krieger, N. Khandaker, R.C. Moore, K.C. Holts, and L.L. Neidel. 2005a. Accumulation and perchlorate exposure potential of lettuce produced in the lower Colorado River region. Journal of Agricultural and Food Chemistry Vol. 53. pp. 5479–5486.

Sanchez C.A., K.S. Crump, R.I. Krieger, N.R. Khandaker, and J.P. Gibbs. 2005b. Perchlorate and nitrate in leafy vegetables of North America. Environmental Science and Technology Vol. 39, No. 24, pp 9391–9397.

Sharlin, D.S., D. Tighe, *et al.* 2008.  The balance between oligodendrocyte and astrocyte production in major white matter tracts is linearly related to serum total thyroxine. Endocrinology 149(5): 2527-36.

Steinmaus, C., M.D. Miller, R. Howd. 2007. Impact of smoking and thiocyanate

on perchlorate and thyroid hormone associations in the 2001-2002 National Health and Nutrition Examination Survey. Environ Health Perspect 115(9):1333-8.

Téllez, R.T., P.M. Chacón, C.R. Abraca, B.C. Blount, C.B. Van Landingham, K.S. Crump, and J.P. Gibbs. 2005. Chronic environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid Vol. 15, No. 9. pp. 963–975.

U.S. Census Bureau, 2002. U.S. Summary: 2000. U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau. C2KPROF/00-US. July 2002.

USEPA. 1997a. Announcement of the Draft Drinking Water Contaminant Candidate List; Notice. *Federal Register*. Vol. 62, No. 193. p. 52193, October 6, 1997.

USEPA. 1998a. Announcement of the Draft Drinking Water Contaminant Candidate List; Notice. *Federal Register*. Vol. 63, No. 40. p. 10273, March 2, 1998.

USEPA. 1999b. Revisions to the Unregulated Contaminant Monitoring Regulation for Public Water Systems. *Federal Register*. Vol. 64, No. 180. p. 50556, September 17, 1999.

USEPA. 2000b. Unregulated Contaminant Monitoring Regulation for Public Water Systems: Analytical Methods for Perchlorate and Acetochlor; Announcement of Laboratory Approval and Performance Testing (PT) Program for the Analysis of Perchlorate; Final Rule and Proposed Rule. *Federal Register*. Vol. 65, No. 42. p. 11372, March 2, 2000.

USEPA. 2001b. Unregulated Contaminant Monitoring Regulation for Public Water Systems; Analytical Methods for List 2 Contaminants; Clarifications to the Unregulated Contaminant Monitoring Regulation. *Federal Register*. Vol. 66, No. 8. p. 2273, January 11, 2001.

USEPA. 2002a. Announcement of Preliminary Regulatory Determinations for Priority

Contaminants on the Drinking Water Contaminant Candidate List. *Federal Register*. Vol. 67,

No. 106. p. 38222, June 3, 2002.

USEPA. 2002b. Perchlorate Environmental Contamination: Toxicological Review and Risk

Characterization. EPA/635/R-02/003. National Center for Environmental Assessment,

Office of Research and Development, U.S. EPA.

USEPA. 2002c. A review of the reference dose and reference concentration processes. Risk

Assessment Forum, Washington, DC; EPA/630/P-02/0002F. Available from:

<http://www.epa.gov/iris/backgr-d.htm>.

USEPA. 2003a. Announcement of Regulatory Determinations for Priority Contaminants on the

Drinking Water Contaminant Candidate List. *Federal Register*. Vol. 68, No. 138. p. 42897,

July 18, 2003.

USEPA. 2004a. Drinking Water Contaminant Candidate List 2; Notice. *Federal Register*. Vol.

69, No. 64. p. 17406, April 2, 2004.

USEPA. 2004b. Estimated Per Capita Water Ingestion and Body Weight in the United States–An

Update Based on Data Collected by the United States Department of Agriculture's 1994–

1996 and 1998 Continuing Survey of Food Intakes by Individuals. EPA-822-R-00-001.

Office of Science and Technology, Office of Water, U.S. EPA.

USEPA. 2005a. Notice - Drinking Water Contaminant Candidate List 2; Final Notice. *Federal

Register*. Vol. 70, No. 36. p. 9071, February 24, 2005.

USEPA. 2005b. "Integrated Risk Information System (IRIS), Perchlorate and Perchlorate Salts."

February 2005. Available on the Internet at: http://www.epa.gov/iris/subst/1007.htm.

Accessed February 2, 2005.

USEPA 2006. Assessment Guidance for Perchlorate. Memorandum from Susan Bodine,

Assistant Administrator of the Office of Solid Waste and Emergency Response, to EPA

Regional Administrators. Available on the Internet at:

http://www.epa.gov/fedfac/pdf/perchlorate_guidance.pdf. Accessed August 20, 2008

USEPA. 2007. Drinking Water: Regulatory Determinations Regarding Contaminants on

the Second Drinking Water Contaminant Candidate List – Preliminary

Determinations. *Federal Register.* 72 FR 24016. May 1, 2007.

USEPA, 2008a Evaluation of Perchlorate Exposure from Food and Drinking Water:

Results of NHANES Biomonitoring Data and UCMR 1 Occurrence Data Merge.

USEPA. 2008b. Inhibition of the Sodium-Iodide Symporter by Perchlorate: Evaluation of

Lifestage Sensitivity Using Physiologically-Based Pharmacokinetic Modeling. {NOTE:

Final title/reference info for the document will be provided before publication.}

USEPA. 2008c. Drinking Water: Regulatory Determinations Regarding Contaminants on

the Second Drinking Water Contaminant Candidate List – Final

Determinations. *Federal Register.* 73 FR 44251. July 30, 2008.

Ventura SJ, Abma JC, Mosher WD, Henshaw S. Estimated pregnancy rates for the United States,

1990–2000: an update. National vital statistics reports; vol 52 no 23. Hyattsville, Maryland:

National Center for Health Statistics. 2004.

Zoeller, R.T., and J. Rovet. 2004. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. J Neuroendocrinology 16: 809-18.

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