FERC Online service, please e-mail *FERCOnlineSupport@ferc.gov* or call (866) 208–3676 (toll free). For TTY, call (202) 502–8659.

Kimberly D. Bose,

Secretary.

[FR Doc. E8–24157 Filed 10–9–08; 8:45 am]

BILLING CODE 6717–01–P

DEPARTMENT OF ENERGY

Federal Energy Regulatory Commission

[Docket No. ER08–1522–000]

WG Energy LLC; Supplemental Notice That Initial Market-Based Rate Filing Includes Request for Blanket Section 204 Authorization

October 6, 2008.

This is a supplemental notice in the above-referenced proceeding of WG Energy LLC's application for market-based rate authority, with an accompanying rate tariff, noting that such application includes a request for blanket authorization, under 18 CFR Part 34, of future issuances of securities and assumptions of liability.

Any person desiring to intervene or to protest should file with the Federal Energy Regulatory Commission, 888 First Street, NE., Washington, DC 20426, in accordance with Rules 211 and 214 of the Commission's Rules of Practice and Procedure (18 CFR 385.211 and 385.214). Anyone filing a motion to intervene or protest must serve a copy of that document on the Applicant.

Notice is hereby given that the deadline for filing protests with regard to the applicant's request for blanket authorization, under 18 CFR Part 34, of future issuances of securities and assumptions of liability, is October 27, 2008.

The Commission encourages electronic submission of protests and interventions in lieu of paper, using the FERC Online links at *http://www.ferc.gov.* To facilitate electronic service, persons with Internet access who will eFile a document and/or be listed as a contact for an intervenor must create and validate an eRegistration account using the eRegistration link. Select the eFiling link to log on and submit the intervention or protests.

Persons unable to file electronically should submit an original and 14 copies of the intervention or protest to the Federal Energy Regulatory Commission, 888 First St., NE., Washington, DC 20426.

The filings in the above-referenced proceeding are accessible in the Commission's eLibrary system by clicking on the appropriate link in the above list. They are also available for review in the Commission's Public Reference Room in Washington, DC. There is an eSubscription link on the Web site that enables subscribers to receive e-mail notification when a document is added to a subscribed dockets(s). For assistance with any FERC Online service, please e-mail *FERCOnlineSupport@ferc.gov* or call (866) 208–3676 (toll free). For TTY, call (202) 502–8659.

Kimberly D. Bose,

Secretary.

[FR Doc. E8–24160 Filed 10–9–08; 8:45 am]

BILLING CODE 6717–01–P

DEPARTMENT OF ENERGY

Federal Energy Regulatory Commission

[Docket No. PR08–30–000]

Enterprise Texas Pipeline LLC; Notice of Petition for Rate Approval

October 6, 2008.

Take notice that on September 30, 2008, Enterprise Texas Pipeline LLC (Enterprise Texas) filed a petition for rate approval pursuant to section 284.123(b)(2) of the Commission's regulations. Enterprise Texas requests that the Commission approve an incremental rate of $0.6370 per MMBtu for service on the Sherman Extension commencing on September 30, 2008.

Any person desiring to participate in this rate proceeding must file a motion to intervene or to protest this filing must file in accordance with Rules 211 and 214 of the Commission's Rules of Practice and Procedure (18 CFR 385.211 and 385.214). Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a notice of intervention or motion to intervene, as appropriate. Such notices, motions, or protests must be filed on or before the date as indicated below. Anyone filing an intervention or protest must serve a copy of that document on the Applicant. Anyone filing an intervention or protest on or before the intervention or protest date need not serve motions to intervene or protests on persons other than the Applicant.

The Commission encourages electronic submission of protests and interventions in lieu of paper using the ''eFiling'' link at *http://www.ferc.gov*. Persons unable to file electronically should submit an original and 14 copies of the protest or intervention to the Federal Energy Regulatory Commission, 888 First Street, NE., Washington, DC 20426.

This filing is accessible on-line at *http://www.ferc.gov*, using the ''eLibrary'' link and is available for review in the Commission's Public Reference Room in Washington, DC. There is an ''eSubscription'' link on the Web site that enables subscribers to receive e-mail notification when a document is added to a subscribed docket(s). For assistance with any FERC Online service, please e-mail *FERCOnlineSupport@ferc.gov* or call (866) 208–3676 (toll free). For TTY, call (202) 502–8659.

Comment Date: 5 p.m. Eastern Time Friday October 17, 2008.

Kimberly D. Bose,

Secretary.

[FR Doc. E8–24152 Filed 10–9–08; 8:45 am]

BILLING CODE 6717–01–P

ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OW–2008–0068; FRL–8727–6]

RIN 2040–ZA02

Drinking Water: Preliminary Regulatory Determination on Perchlorate

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

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 November 10, 2008.

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* Web site 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

SUPPLEMENTARY INFORMATION:

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:

(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 1, 2007, FR notice of preliminary regulatory determinations for 11 contaminants, EPA also presented information on several contaminants

[1] The MCLG is the ''maximum level of a contaminant in drinking water at which no known off 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 heath 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.

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

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 perchlorate 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 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 100 µg/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 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

[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.

[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).

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

Notes:

[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.

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

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)	[e] 16.6 M	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
25 µg/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 1 analytical 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 U.S. 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 U.S. 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, 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 U.S. 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 U.S. 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 U.S. 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 (*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 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 U.S. 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 U.S. 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

[11] Murray *et al.,* (2008) compared estimated average iodine intakes with U.S. 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.

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	2,063	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	1,185	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 U.S. 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:

$$HRL = [(RfD \times BW)/DWI] \times RSC$$

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

TABLE 5—RELATIVE SOURCE CONTRIBUTIONS REMAINING FOR WATER BASED ON TDS FOR VARIOUS SUBGROUPS—Continued

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)
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

Subpopulation	Body weight [a]	Drinking water consumption [a]	Source of RSC derivation	RSC (percent)	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 U.S. 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]

Table 8 also shows the exposure to each subpopulation in µg/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	[d] 0.52	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	[d] 0.74	1.27	0.73	(d)	1.48	0.84

[12] The model does not exactly match the average measured inhibition at each exposure concentration. At the point of departure (7 µg/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—PREDICTED PERCENT RADIOACTIVE IODIDE UPTAKE (RAIU) INHIBITION AND CORRESPONDING PERCHLORATE INTAKE FROM WATER AT 15 μG/L WITH AND WITHOUT FOOD INTAKE—Continued

	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
Bottle-fed infant:							
Infant—7 d	3.6	[e] 0.84	3.53	2.0	1.42 μg/L	3.87	2.2
Infant—60 d	5	[e] 1.14	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 U.S. 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.

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