THE AMERICAN COUNCIL
ON SCIENCE AND HEALTH PRESENTS

SPECIAL REPORT

Perchlorate in Drinking Water
Scientific Collaboration in Defining Safety

Prepared for the
American Council on Science and Health (ACSH)
New York, NY

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January 2002

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January 2002

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Table of Contents

Table of Contents *(continued)*

Executive Summary

Since the mid-1990s, there has been an increasing amount of research effort aimed at evaluating the potential human health risk of perchlorate (ClO_4) because of its presence at trace levels in some water systems. Concern over potential effects on the thyroid gland in humans from perchlorate exposure and whether environmental levels pose a risk to human health have surfaced recently. In response to this concern, a broad collaborative effort spanning both private and government sectors has been engaged in extensive toxicological testing of perchlorate to add to our knowledge about how and under what exposure conditions perchlorate may cause effects in laboratory animals and in humans. The collaboration between the U.S. Environmental Protection Agency (EPA), the Department of Defense (Air Force) and an inter-industry Perchlorate Study Group (PSG) is unique in its focus on development of state-of-the art science for accurately determining what constitutes a safe level for humans.

Because of its mission to identify significant public health threats and to bring sound scientific analysis to environmental health concerns, the American Council on Science and Health (ACSH) has (a) evaluated the allegations of health risk from perchlorate as alleged by the Environmental Working Group (EWG); (b) reviewed the current regulatory process that is ongoing with respect to the establishment of a safe environmental exposure level; and (c) highlighted some of the recent scientific studies that have further characterized the toxicity of perchlorate in both animals and humans.

With respect to the EWG's Report entitled "Rocket Science" which alleges human health risk from perchlorate in drinking water, ACSH concludes the following:

- The EWG report encompasses a selective and limited use of the scientific data for perchlorate and does not represent the totality of our current knowledge regarding its toxicity.

- Many of the claims of health risk are not supported through the inclusion of scientific references and as such cannot be construed to represent the scientific facts.

- The EWG report mischaracterizes the current regulatory efforts

underway aimed at defining a safe exposure level and fails to recognize the scientific process at work.

- The EWG report has prematurely forecast what it believes to be a safe environmental exposure level without consideration of the significant amount of toxicological data that have been generated in the last few years or without regard for the scientific process at work.

In reviewing the history of the regulatory response in establishing a safe level for perchlorate in the environment, the ACSH concludes the following:

- Over the course of the last 10 years, the EPA has worked to define a safe exposure level for perchlorate in the environment, although a final value has not been established owing to data gaps for perchlorate.

- There has been a concerted effort to identify those studies and data gaps that would facilitate the establishment of a safe exposure level and significant testing has resulted in a much improved toxicological database for perchlorate.

- There has been a cooperative strategy and effort amongst both government and industry groups aimed at improving the scientific database for perchlorate for the protection of public health.

- As a result of the extensive toxicological testing, the EPA is expected to release its proposed Reference Dose (RfD, the safe exposure level for humans) in 2002, at which time all interested parties and stakeholders can publicly comment on the level.

In reviewing the recent scientific studies that have enhanced our knowledge of perchlorate's toxicity, ACSH concludes that:

- Both animal and human studies have appreciably contributed to our understanding of dose-response relationships for perchlorate such that the process of defining a protective RfD will be accompanied by less uncertainty and increased confidence.

- Both animal and human studies have contributed to our knowledge about the mechanism of action by which perchlorate exerts toxicity and under what exposure conditions. This knowledge will aid in the identification of sensitive subpopulations and in our increased ability to set a safe level for all humans.

- Because the number and types of toxicological studies that have been conducted for perchlorate has increased significantly, there is less uncertainty that accompanies the establishment of a safe exposure level and as such, the need for conservatism in the absence of knowledge has been reduced.

It is the intent of this ACSH report to provide readers with a perspective on how the concern over perchlorate arose, what the regulatory response has been over the last 10 years, and how the scientific process can be extremely beneficial in establishing safe exposure levels for humans in order to safeguard public health.

INTRODUCTION

What is Perchlorate?

Perchlorate is an anion that is both naturally occurring (e.g., such as in nitrate-mining regions of Chile) and man-made. It may be present in ground and surface waters as a result of the breakdown of ammonium, potassium, magnesium, or sodium salts that contain perchlorate (Crump et al., 2000; EPA, 1998). Ammonium perchlorate is manufactured primarily for use as an oxidizing agent in some military applications, principally as an ingredient in solid propellants for rockets and missiles. Because of its reducing capacity, it can undergo chemical reactions, which result in the release of gaseous products and it can thus act as a thrust booster. To this day, perchlorate remains an important component of the rocket delivery systems used in NASA and other space programs (EPA, 1998). In addition to its military applications, perchlorate has been used in airbags, stick matches and fireworks.

The Use of Perchlorate in Medicine

Normal thyroid function, which is dependent on an adequate supply of iodine, is important for growth and development. Normal thyroid function is especially important in fetal development, as hypothyroidism (deficiency of thyroid activity) during gestation often results in mental retardation (cretinism) in the neonate. If sufficient inhibition of iodine occurs, thyroid hormone production is depressed, which causes hypothyroidism. Perchlorate acts by inhibiting iodide uptake in the thyroid, and as a result of this, it was used to treat hyperthyroidism (excessive thyroid activity) due to Graves disease in the 1950s and 60s (Wolff, 1998; Stanbury and Wyngaarden, 1952; Trotter, 1962). Perchlorate has also been used to treat thyroid gland disorders resulting from overaccumulation of iodine, a side effect observed in some medical treatments (Bartalena et al., 1996). It is precisely because of its known action on the thyroid gland that the concern over human exposure to perchlorate from environmental sources arose. Clinical use of perchlorate in treating disease involves doses up to 400 milligrams on a daily basis, a level which is thousands of times greater than potential environmental exposures (Wolff, 1998).

The Current Concern

Because perchlorate has been detected at low levels in some water supply systems, primarily in the Western U.S., there has been some concern about whether its presence in the environment poses a health risk to humans. The U.S. EPA, in an effort to evaluate the potential risk and to establish a safe oral exposure level, has been actively engaged in testing and research on the toxicity of perchlorate over the past few years. Much of the current focus and debate centers on what exactly is an acceptable exposure level and on what scientific basis the EPA will establish its final Reference Dose (RfD) for humans. When the EPA releases its proposed RfD in early 2002, there will be an extensive peer review of the value to determine whether or not the RfD appropriately reflects the scientific database and knowledge that has developed for perchlorate.

Chapter I. EVALUATING THE EWG REPORT ON PERCHLORATE IN DRINKING WATER

Because of its interest in distinguishing significant health risks from those that are miniscule or hypothetical, the American Council on Science and Health (ACSH) undertook a review of the Environmental Working Group (EWG) report entitled "Rocket Science" in which allegations are made that perchlorate contamination in drinking water supplies in California and elsewhere may pose a health risk to humans, particularly infants and children. The EWG is an environmental organization based in Washington D.C. whose stated mission is the protection of public health and the environment through the reduction of pollution in air, water, and food. The EWG does not conduct primary research but states that their focus is on computer-assisted research with the goal of turning data into usable information. There are serious allegations contained in the EWG report, ranging from potential harm to millions of Americans, to the claim that federal regulators, specifically the Environmental Protection Agency (EPA), are dragging their feet in establishing new standards for perchlorate in drinking water. The EWG has been openly critical of the scientific effort that has taken place in the last five years, one which has demanded significant investment in human resources and millions of dollars in testing costs. Much of the criticism is misplaced and suffers from a lack of knowledge about the actual studies and scientific information derived from the extensive testing. However, before evaluating what we know about perchlorate and its toxicity, it is important, first, to review the basis of these allegations.

The Premise Behind the EWG Report—Water Contamination by Perchlorate

The basis for the EWG concern stems from the detection of perchlorate in some water supplies (e.g., groundwater, surface water), primarily in California, and the association between perchlorate and thyroid effects (EWG, 2001). The data provided in the EWG report describes wells containing various quantities of perchlorate; however, more questions arise than are addressed by these data. For example, how were the samples for analysis obtained, and who analyzed the data? How many samples per well were obtained? Were background levels of perchlorate evaluated in wells or other drinking water supplies in areas not known to be affected by perchlorate? If so, what were these levels? Most

importantly, what do we know about human exposure to these contaminated wells?

The EWG report gives the impression that the presence of perchlorate in water is a new phenomenon, but, in reality, it was the advance of analytical technology that now permits the detection of perchlorate at lower levels. It is likely that perchlorate has been present in water supplies for some time, albeit at previously undetectable levels and without any evidence of human harm (Soldin et. al., 2001). While the health effects, if any, of current levels of perchlorate in water need to be addressed, it is premature to equate this finding with one of high risk as portrayed in the EWG report. As with virtually all chemical substances, it is the dose that determines the relative risk and it is imperative that this cornerstone principle of toxicology be included in any assessment of perchlorate. Mere detection of a chemical in the environment cannot be equated with increased risk, but must be evaluated in terms of the hazard, dose-response, and human exposure, all steps in the characterization of health risk.

Selective and Limited Use of the Scientific Database for Perchlorate

Perchlorate has been well characterized toxicologically and continues to be extensively evaluated in numerous toxicity tests. The EWG report does not reflect the weight of scientific evidence available for perchlorate and selectively cites studies that support its presumption that any perchlorate in water poses a health risk. The EWG report singles out the one study (Brechner et al., 2000) in which the authors reported altered thyroid hormone levels in infants whose mothers consumed drinking water presumably containing perchlorate. Relative to this study, both Goodman (2001) and Crump and Weiss (2001) have reevaluated the data reported by Brechner et al. (2000) and because of differing opinion on the study implications, have called into question the conclusions by Brechner et al. (2000). Yet EWG fails to consider these concerns. The EWG report cites some other human studies that have not shown associations between perchlorate and toxicity, but suggests that these studies were biased because they “were all sponsored by various industry groups with a stake in the outcome of EPA’s scientific review of perchlorate…” Instead of assessing the science and the credibility of each study, the EWG report criticizes those studies conducted through a collaborative effort involving the EPA, Department of Defense, and the Perchlorate Study Group (an inter-industry scientific group).

Similar to its limited discussion of the human data, the EWG report glosses over much of what is known about the toxicity of perchlorate in animals. The animal toxicity database for perchlorate is considerably more extensive than portrayed in "Rocket Science." While some recently completed studies have not yet been formally published, their existence and contents are public knowledge (EPA, 1998; TERA, 2001). Yet, these studies are not discussed in the EWG report. Much of the recent animal data that have been developed represent mechanistic analyses of how perchlorate may affect hormonal status and thyroid function, and such research certainly will be included by the EPA in the process of determining a safe level for perchlorate in drinking water.

Scientific Basis for Health Claims Not Documented

In their report, the EWG authors make statements of fact without providing some context or scientific support in the form of primary citations. Because of this, it is impossible for the reader to know whether statements regarding perchlorate contamination, perchlorate toxicity, and risk to humans are based on credible evidence or are conjectural. In fact, a critical review of the literature on perchlorate shows that few of these statements can be scientifically supported. There is no way for readers to independently evaluate the basis for the statements and to review the studies on which the claims are based. Examples of unsupported, unqualified statements include:

- "More serious, however, are the effects of thyroid hormone disruption in the developing fetus and child. Small changes in maternal thyroid hormone levels during pregnancy have been associated with reduced IQs and attention deficit in children." *No citation provided and this statement is completely unsupported.*

- "This effect [impairment of thyroid function] has been known for decades, but recent research has found that perchlorate can affect human thyroid hormone levels at extremely low concentrations." *No citation provided and this statement is completely unsupported.*

- "Fetuses, infants, and children with thyroid damage may suffer mental retardation, loss of hearing and speech, or deficits in motor skills. At higher levels of exposure, perchlorate is known to cause cancer." *It is well known that thyroid abnormalities can produce severe developmental deficits, but there is no evidence that perchlo -*

rate exposure at current environmental levels has produced thyroid abnormalities in humans. Likewise, while exposure of laboratory animals to levels of perchlorate high enough to cause severe thyroid abnormalities also produces thyroid lesions of a type that could progress to thyroid cancer, there is no evidence that perchlorate exposure at current environmental levels has caused any cancer in humans. Throughout much of their report, the EWG fails to discuss dose-response in general, and dose-response for perchlorate in par - ticular and merely resorts to references of "effects" on the thyroid without concomitant discussion of the corresponding doses.

In addition, there are statements that either overestimate the risk or generalize the scientific facts about perchlorate. For example,

- "Too much perchlorate can impair proper functioning of the thyroid gland, which controls growth, development and metabolism." *How much is too much? Are the perchlorate levels in drinking water, and more importantly, the exposure levels to humans, considered to be "too much?" Obtaining answers to these questions has been one of EPA's highest priorities during the past five years, manifested as an ambitious research program undertaken by the Perchlorate Study Group and the Department of Defense at the request of EPA.*

Many statements within the report are subjective and sensationalistic, are not qualified or supported by scientific studies and evidence, and go beyond what we currently know about perchlorate and the risk to humans. In addition, some statements contain implicit assumptions and definitions which are not stated clearly in the report, so there is no way to know exactly what the authors mean or how they believe the statements apply to perchlorate. A straightforward discussion of the existing science and identification of areas of uncertainty would be more useful in defining the potential risk from perchlorate in the environment.

Mischaracterizing EPA's Effort and Level of Understanding

The EWG report does not accurately depict the current regulatory effort aimed at establishing a safe level for perchlorate in drinking water. For example, the report implies that the EPA has not adequately considered the sensitivity of children with respect to perchlorate. This is noted in the following description taken from "Rocket Science."

> "Although children are at far more risk from the effects of thyroid hormone disruption than adults [no citation], federal and state regulators have consistently ignored children in their calculations."

But this assertion is simply not true. For years, the EPA and others involved in the risk assessment process have included what is known as an intraspecies uncertainty factor (typically a factor of 10) to consider the potential vulnerability of sensitive subpopulations (NRC, 1983; EPA, 1998). In addition, EPA and others specifically review the results of tests designed to determine the outcome of perchlorate exposure to the fetus or young animal, and routinely use an additional uncertainty factor to lower the RfD when such data are missing. Thus, the claim that children are not considered by the EPA as potentially more sensitive than other humans is not valid. Further, a significant amount of the research in the last few years that was conducted by the Department of Defense and Perchlorate Study Group at the request of EPA has been specifically focused on understanding the effects in developing infants and children.

The EWG report also contains the following statement: "Despite weighty evidence to the contrary, the EPA apparently doesn't consider significant changes in thyroid hormone levels to be a problem for developing children." Again, there is no apparent basis for this statement if one simply considers the approach adopted by the EPAin their Draft "Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization Based on Emerging Information." The EPA states that the testing strategy for perchlorate includes studies to specifically address the potential sensitivity of young children. Some of the studies are designed to "identify other target tissues in young adult rats…," to "evaluate the potential for functional and morphological effects in offspring from the mother exposed during pregnancy and lactation," to "evaluate the potential for perchlorate to cause birth defects…," and to "evaluate the potential for perchlorate to cause…toxicity in the young offspring" (EPA, 1998). In addition, the EPA specifically states that "other potentially adverse and permanent effects from decreased thyroid hormone include effects during development in utero…" which clearly demonstrating that the EPA is mindful of the potential sensitivity of the developing young (EPA, 1998). The EPA, in fact, selected thyroid follicular cell hypertrophy in rat pups as the critical effect on which it based its provisional RfD (EPA, 1998). Thus, the EWG has mischaracterized the EPA's attention and

commitment to protection of the young when evaluating the toxicity of perchlorate. This process of ignoring the truth and the scientific evidence while making serious allegations and drawing erroneous conclusions typifies the EWG's assessment of perchlorate's risk to humans.

Forecasting a Safe Level for Perchlorate Prematurely

The EWG report repeatedly asserts that the EPA RfD, although not yet final, will not be sufficient to protect children or other humans. For example, the EWG report states:

> "These standards, [official state or federal drinking water standard for perchlorate] however, will not be adequate to protect the public, particularly children."

How could this be known in view of the fact that a final RfD has not been established?

Another example of this premature forecasting is seen in the statement:

> "But it's unlikely that those standards will protect the public, particularly children."

Again, the EWG report appears to assume that an EPA-based standard will not meet their definition of safety. To gain some insight into what the EWG considers to be an adequate standard, it is helpful to review their risk assessment for perchlorate (EWG, 2001). In their assessment, the EWG uses more conservative input values for body weight and drinking water consumption which the EWG authors claim were ignored by the EPA (EWG, 2001). The use of these revised EWG input values is inappropriate since effects on infants and children are already addressed and accounted for during the selection of a no-effect level and uncertainty factors. In addition, the EWG's proposed safe drinking water level uses uncertainty factors with a weak scientific basis and which go beyond standard risk assessment practice. Finally, there is subjectivity and bias in the EWG contention that a combined uncertainty factor of 1000 is needed, as opposed to the level of 100 proposed by the Agency in its 1998 draft risk assessment. Perhaps a factor of 1000 would have been appropriate years ago, but by 1998, significant amounts of perchlorate data existed, replacing the need for such conservatism in the risk assessment. With the new information provided by the

studies that have been completed since 1998, an even lower safety factor may very well be justified.

Failure to Recognize the Scientific Process at Work

Throughout the EWG report, it is apparent that there is a lack of appreciation of the current research underway aimed at better characterizing the toxicological effects of perchlorate and at what dose levels these effects occur. The EWG report seeks the rapid development and promulgation of an RfD, rather than a scientifically supported, objective analysis. The image conveyed by the EWG authors is that the EPA is working with the Department of Defense and PSG to delay the setting of standards, to raise the permissible drinking water level for perchlorate, and to ignore the potential sensitivity of children when considering the establishment of a safe level. In actuality, however, the partnership offers a unique approach for conducting a legitimate scientific investigation. For the first time, regulation parties are, without obligation under any environmental law, committing their resources to conduct toxicity studies to the exact specification of a regulatory agency. The results of the studies were supplied directly to the EPA and not even shared among the parties that funded them.

While the EWG claims that the EPA is dragging its feet in setting a standard for oral exposure, it apparently doesn't recognize the scientific process at work. The sole intent of the current research effort is to contribute knowledge to the scientific database for perchlorate, to address current questions of concern, to fill data gaps that are important when assessing potential risk to humans, and ultimately to reduce the uncertainty in the derivation of a safe exposure level for humans. The final RfD will identify the most sensitive effect or early precursor to an effect appropriate to human exposures, and will include uncertainty factors appropriate and reflective of the scientific database. The EWG mischaracterizes the current collaborative effort underway as one intended to put people at risk by reducing the total uncertainty factor in the development of an RfD for perchlorate. This is absolutely false. The effort underway is aimed at getting the science right and reducing the uncertainty inherent in the RfD through the accumulation of additional scientific data.

What we need now is a return to basics—an understanding that the issue at hand involves a water contaminant that is present at trace levels,

levels that previously were not detectable by available technology. We must not forget one of the major tenets of toxicology and risk – the dose makes the poison. We must put into perspective what the environmental presence of perchlorate means for human health and determine whether the levels present pose a risk to humans. This will be done if science and objective analysis are permitted to proceed and are not derailed by those who wish to place policy decisions ahead of scientific investigation and knowledge.

Chapter II. PERCHLORATE AS AN ENVIRONMENTAL CONCERN—THE REGULATORY RESPONSE

Perchlorate in the Environment

The EPA first became aware of perchlorate in water systems in 1985 when well samples confirmed the presence of perchlorate in the low parts per million (ppm) range (EPA, 1998). At the time, there was insufficient toxicity information to address questions about potential risk to exposed humans. By the early 1990s, perchlorate was found in monitoring wells at a California Superfund site and the EPA increased its efforts to establish a health-based reference dose (RfD) in order to provide some perspective of the risk associated with its environmental presence (EPA, 1998).

Analytical technology advancements in the mid 1990s enabled the detection of perchlorate in water systems at levels as low as four parts per billion—four-thousandths of a part per million—through the use of an ion chromatographic method. It was this increase in our detection ability that led to concerns over what the presence of perchlorate meant for human health. Characterization of perchlorate's environmental presence has occurred primarily in California as a result of the manufacturing and commercial user base that exists in the region. Outside of California, perchlorate contamination has been confirmed in 13 states.

Presently, perchlorate concentrations in wells and surface water vary widely (EPA, 1998). Water suppliers in both northern and southern

California have detected perchlorate in 144 public water supply wells, with roughly 25% of these above the provisional action level in California of 18 ppb. The types of water systems in which perchlorate has been detected include agricultural wells, monitoring wells, city water systems, and in some private wells. From a public health standpoint, it will be important to accurately characterize the extent and variability of perchlorate contamination in the U.S. and identify any hotspots in order to characterize potential human exposure.

Provisional RfD's for Perchlorate

The EPA issued a provisional RfD in 1992 (Dollarhide, 1992) and a revised provisional RfD in 1995 (Dollarhide, 1995) based on a review of the data available at the time. Under ideal circumstances, an RfD is based on a database that covers an array of toxicological endpoints during various critical life stages, from developing fetus through adult and reproductive stages. For perchlorate, such a database was not available.

The 1992 provisional RfD for perchlorate (0.0001 mg/kg/day) was based on discharge of iodine from the thyroid in humans (Stanbury and Wyngaarden, 1952), and included a combined uncertainty factor of 1000 (a factor of 10 for intraspecies variability [i.e., sensitive humans such as children, the elderly, persons with chronic disease], 10 for the fact that the study upon which the RfD was based was less than a chronic study, and 10 for toxicity database deficiencies). In 1995, the EPA reduced the database deficiency uncertainty factor from 10 to 3 in light of additional toxicity information for perchlorate. Thus, the total uncertainty factor was reduced to 300 (i.e., 10 x 10 x 3) and the RfD was 0.0005 mg/kg/day.

In 1997, an independent external peer review resulted in the determination that the toxicity database for perchlorate was insufficient for a rigorous quantitative risk analysis (TERA, 1998a). In short, the provisional 1995 RfD still suffered from database gaps critical to the development of a robust RfD. A significant finding from this review was that developmental toxicity, notably neurological development affected by hypothyroidism during pregnancy, could be a critical effect of perchlorate, and one that had not been adequately evaluated. Studies to address this concern have since been completed (TERA, 2001). In order to move the risk assessment for perchlorate forward, another external peer review group recommended and prioritized a set of toxicity studies to

address key data gaps and to reduce uncertainty inherent in the extrapolation of animal data to humans (TERA, 1998b).

Identification of Data Needs for a Robust RfD

To support the development of an RfD for perchlorate, key research gaps and data needs had to be addressed. Not only were various toxicological endpoints of interest (e.g., neurodevelopmental, immunological) not available for perchlorate, but mechanistic data (e.g., toxicodynamics and toxicokinetics) on how perchlorate operates within the body and which are useful in estimating the potential risk to humans were also not available. Because an RfD is intended to protect the entire population from all effects associated with a particular chemical, the objective of a sufficient database is to ensure that all potential target organs have been evaluated and the critical effect identified. While it is generally recognized that perchlorate's target organ is the thyroid, little data concerning other potential target tissues or effects existed prior to 1995. This was an important factor in the EPA's decision to develop additional data.

Cooperative Efforts

Beginning in 1997, a collaborative effort between the Air Force and PSG resulted in the formation of a panel of risk assessment experts, which recommended additional studies for perchlorate to further characterize its toxicity. Based on the recommendations of this panel, the Air Force and PSG began to conduct toxicological studies. Shortly thereafter, the EPA formed the Interagency Perchlorate Steering Committee (IPSC), whose membership included the Department of Defense (Air Force), EPA, PSG, as well as government representatives from the Agency for Toxic Substances and Disease Registry (ATSDR) the National Institute for Environmental Health Sciences (NIEHS) and interested state, tribal, and local governments. This testing effort involved a unique collaboration between government, private sector, and non-profit independent review groups, all aimed towards bettering the science for the protection of public health.

Advancing the Science—EPA's Draft RfD of 1998

In 1998, following the completion of the eight additional studies that were critical to the development of the perchlorate database, the EPA

issued its draft RfD. The testing strategy and resultant data confirmed that the target tissue for perchlorate is the thyroid gland, as indicated by alterations of the principal thyroid hormones and by thyroid histopathological effects in both young and adult rats. Identification of the target organ for perchlorate was also confirmed by the absence of effects in other organs or systems. The EPA used histopathological evidence from a neurodevelopmental study (Argus, 1998) from postnatal day five pups (rats) as the critical effect and study for RfD derivation.

The EPA selected a combined uncertainty factor of 100, which was decreased from the 1995 provisional RfD, because additional toxicological data had been developed and the magnitude of individual factors could therefore be reduced. The EPA proposed an RfD of 0.0009 mg/kg/day, which, if one assumes a 70 kg person and the assumed consumption of two liters of water per day, equates to 32 ppb in drinking water as a safe level (EPA, 1998). We should note that actual water consumption is much less than two liters per day, as this value basically represents the water content of all foods and beverages. Before this derived RfD could become final, it was necessary to obtain an independent peer review of the value and the scientific reasoning behind it.

External Review of the Draft RfD

The EPAcontracted the Research Triangle Institute (RTI) RTI, an independent research organization, to coordinate a scientific peer review of its Draft RfD for perchlorate and a set of supporting toxicological and ecological studies. The peer review was sponsored by EPA's Office of Solid Waste and Emergency Response (OSWER) and Office of Water (OW), while the Draft Toxicological Review Document was prepared by EPA's National Center for Environmental Assessment (NCEA). The RTI selected ten independent scientists familiar with the regulatory and risk assessment processes to be peer reviewers of the draft RfD as well as the eight studies that were important to the development of the RfD. The peer review panel convened in 1999 at a workshop open to the public (RTI, 1999).

Among the key findings of the Peer Review panel were the following:

- The additional studies considered adequately delineated the hazards of perchlorate in an appropriate manner.

- Perchlorate does not appear to produce toxic effects to most organs and is not mutagenic. Any toxicity as a result of perchlorate's influence on hormone levels and subsequent sequelae, appears to be a consequence of its inhibition of iodide transport into the thyroid gland.

- Because thyroid hormones are essential for normal development of the central nervous system, the panel suggested that the effects of perchlorate on mental development during the fetal period and during the first few weeks of life be closely evaluated by histopathological, morphological, and behavioral assessments.

- Increases in TSH are a more sensitive index of an antithyroid effect and can be observed even when it is not possible to observe a clear decline in serum thyroid hormones (T3 and T4).

- Thyroid cell hyperplasia is a more indicative biomarker for the adverse effect of perchlorate than is thyroid cell hypertrophy.

- Infant exposure to perchlorate, possible alterations in maternal hormones in the mother's milk, and the potential for perchlorate transfer from mother to pup via milk, should be investigated.
- Use of pharmacokinetic and toxicokinetic data for perchlorate in rats and humans should be used for building a predictive risk assessment for humans.

- Risk assessments that estimate human risk from data on human populations should be more accurate than ones that rely on animal data.

- Additional studies on healthy human adult volunteers are encouraged.

- EPA is encouraged to adopt a mode of action approach for assessing both non-cancer and cancer risks of perchlorate as this represents a move in the direction of harmonization of each type of risk and also permits a more logical use of available toxicological and biological data.

In commenting on the actual RfD value proposed by the EPA, the peer review panel determined that the use of a specific uncertainty factor must wait for all relevant studies to be completed. The panel did note, however, that if appropriate human data are generated, the attendant

uncertainty factor could be small, perhaps considerably less than the current value of 100. Based on the lack of demonstrated adverse effects in the animal studies, the peer review panel felt that the RfD proposed by the EPA (0.0009 mg/kg/day), is likely to be conservative. This is a significant finding by an independent group of expert scientists and gives some indication of where this group feels the RfD should stand conclusion than a panel of recognized researchers deserves more explanation of their rationale.

What has occurred over the past 10 years in response to the initial finding of perchlorate in some water systems has been a systematic, collaborative, and iterative process in which a progressive scientific investigation has occurred resulting in the development of a robust database for perchlorate. The degree of collaboration is uncommon and the development of the science in such a timely manner is rare indeed.

The EWG characterizes the history of the development of the RfD as a series of steps in which higher and higher numbers are derived, and they imply that the movement from the provisional RfD to the 1998 proposal results in less protective levels. This displays a lack of understanding of the process of risk assessment and regulation. It is typical and reasonable that a provisional number based on a poor database, as was available in 1995 and earlier was set at a very conservatively low level, because there are many uncertainties still existing that are addressed by the uncertainty factors discussed above. As additional studies are conducted, especially when they are designed to support the assessment of health risks for regulatory purposes, these uncertainties are addressed, and the need for additional uncertainty factors is replaced by scientific knowledge. If, as in the case of perchlorate, the new studies do not uncover more uncertainties or toxic effects that were not previously known, then it is common for the estimated safe level to increase as it becomes more grounded in fact and less shrouded in uncertainty. The new studies on perchlorate reaffirm the critical and exclusive role of the thyroid gland in mediating any effect and add considerably to our understanding of the potential for perchlorate to cause harm. The mischaracterization of this process by the EWG illustrates either a fundamental ignorance of the risk assessment process or a blatant disregard for the scientific foundations or risk assessment. Regardless of whether it is due to ignorance or bias, the EWG fails to enter into an objective and qualified scientific discussion about perchlorate, which is the only discussion that is underway, and is discussed in the following section.

Chapter III. ASSESSING THE SCIENCE BEHIND THE RFD

The risk assessment for perchlorate and the development of a robust RfD depends upon the use of all scientific data, both human and animal. The EWG report did not bring to light the wealth of available laboratory animal or human data for perchlorate, much of which has been developed over the past four years. Because the regulatory process of establishing an RfD depends on scientific data, it is relevant to briefly review what we have learned about perchlorate in recent years.

Human Studies

Occupational Studies:

Occupational studies typically involve higher exposures than would normally occur from ambient environmental exposures and provide a glimpse into effects that may be associated at the high end of the exposure range. Gibbs et al. (1998) evaluated the employees of an ammonium perchlorate production facility in Nevada for airborne perchlorate exposure. Based on exposure measurements, workers were exposed to an average of about 2.5 mg perchlorate per day over an average work period of 8.3 years, a level which the authors report is up to 10 times the cumulative dose that would result from ingestion of perchlorate-containing water from Lake Mead or the Colorado River. No exposure-related effects were noted on thyroid profiles or thyroid function, nor were effects found on the bone marrow, kidney, or liver function.

Lamm et al. (1999) studied occupational exposure to perchlorate at a perchlorate manufacturing plant to assess effects on thyroid function. Exposure was assessed by measurement of ambient air concentrations of perchlorate and systemic absorption was assessed by measurement of urinary perchlorate excretion. Worker exposures (mean absorbed dosages) ranged from 1-34 mg perchlorate per day. For reference purpose, the current Draft RfD for perchlorate is equivalent to human oral exposure of 0.063 mg/day, well below the estimated occupational exposure in this study. No differences in thyroid function parameters (e.g., hormone levels) were found among the four groups of workers (divided by exposure level) and thyroid abnormalities were not reported.

Human Adult Volunteers

Lawrence et al. (2000) evaluated the effect of short-term low-dose exposure on certain aspects of thyroid function to address concerns about potential effects of chronic low-level perchlorate ingestion in drinking water. Healthy male volunteers (n=9) ingested 10 mg in 1 L (approximately 300 times the estimated maximum amount of perchlorate consumed from affected water supplies containing 4-18 ppb) daily for 14 days. The authors found that perchlorate decreased iodide uptake, but did not affect circulating thyroid hormone concentrations.

In a follow-up study by the same authors (Lawrence et al., 2001), eight healthy male volunteers were given a lower dose of perchlorate (3 mg in 1 L) and while this level did not affect thyroid hormone or TSH concentration (similar to the previous study), it had a small, but insignificant, effect on iodide uptake, suggesting that this level is approximating or is very close to the no-effect level for iodide uptake. These low daily doses (3 mg or 3000 µg) are well above potential environmental daily exposure (e.g., 36 µg).

Greer et al. (2001) administered perchlorate in drinking water at various concentrations to 37 male and female volunteers for 15 days in order to determine the dose-response for inhibition of thyroid radioiodine uptake. In addition, thyroid hormones were measured throughout the study. The authors reported the no-effect level for inhibition of radioiodine uptake to be 0.0065 mg/kg/day (determined by regression analysis), an amount that would be consumed if drinking water supplies contained perchlorate at 0.23 mg/L (230 ppb). The authors also reported that only at the high dose level was there any effect on serum hormones.

Additional human studies have been performed at the request of the EPA and the data has been turned over to EPA for use in the risk assessment and regulation of perchlorate in water.

Newborns and Young Children

Crump et al. (2000) conducted a study of newborns (n=9784) and school-age children (n=162) from Chile (a region known for significant levels of perchlorate) to determine the effect of perchlorate in drinking water on thyroid function. This study looked at individuals in three cities in northern Chile with differing water concentrations of perchlorate, one ranging from 100 to 120 µg/L, one with 5-7 µg/L and one with

non-detectable levels (< 4 µg/L). Among schoolchildren, no differences were observed in TSH levels or goiter prevalence. Among newborns there were no differences in thyroid hormones from the three cities that were attributable to perchlorate exposures. The authors concluded that perchlorate in drinking water at concentrations as high as 100-120 µg/L does not suppress thyroid function in newborns or school-age children.

Brechner et al. (2000) studied populations with proximity to the Colorado River and with exposure to perchlorate-containing water from the river and compared TSH levels to individuals with no known perchlorate exposure. The authors report that TSH levels were significantly higher in newborns whose drinking water supply contained 6 ppb perchlorate, than in newborns whose water supply perchlorate levels was undetectable. This study has caused some debate because of methodological issues.

Lamm and Doemland (1999) evaluated data from the neonatal screening programs of the state health departments in both California and Nevada for any increased incidence of congenital hypothyroidism in seven counties within these two states. Perchlorate was known to exist in the drinking water supplies of these counties ranging from 5-16 ppb. Within the 7 counties nearly 700,000 newborns were screened, and in total, 249 cases were identified, while 243 cases were expected. These data do not show an increase in the incidence of congenital hypothyroidism associated with the reported perchlorate levels in drinking water.

Li et al. (2001) evaluated a Medicaid database from Nevada to determine whether an increase in the prevalence of any thyroid disease was associated with perchlorate levels ranging from 4-24 ppb in the water supply. Concentrations in this range may be expected to result in exposure dosages in the tens of micrograms per day. The prevalence of persons being evaluated for thyroid diseases and for thyroid cancer among the Medicaid-eligible population was calculated for a two year period spanning 1997 and 1998. In comparison to residents in other counties in Nevada with no known presence of perchlorate in drinking water, there was no evidence of an increased rate of thyroid disease associated with perchlorate exposure. The authors found no evidence that perchlorate-containing drinking water at the given level increased the prevalence of acquired hypothyroidism or of any other thyroid condition.

Li et al. (2000) compared thyroxine (T4) levels for days 1-4 of life of newborns from the city of Las Vegas, NV, which has up to 15 ppb perchlorate in its drinking water, to those from Reno NV, which has no detectable perchlorate. Temporal differences in the mean T4 level were reported in both cities but were unrelated to perchlorate exposure and the authors reported no observable T4 differences in the two cities related to perchlorate in drinking water.

Li et al. (2000) also compared TSH levels for the same study population and with the same two cities and reported no differences in TSH level related to perchlorate in water at levels up to 15 ppb.

In addition to the human studies that have sought to characterize the effects of perchlorate in drinking water on thyroid function, congenital disease, or thyroid hormone levels, there are other studies with human volunteers aimed at characterizing the metabolism of perchlorate in the body, so that a PBPK model for humans can be validated (Greer et al., Brabant et al., Braverman et al. from TERA, 2001). While these studies sought to characterize the effects of short-term perchlorate exposure, there was a need to evaluate the effects of long-term low-level exposure and, for this, a study conducted at Boston University Medical Center is currently underway that will study subjects taking one of three doses of perchlorate (or placebo) daily for six months, after which time effects on thyroid hormone level and function will be evaluated.

Animal Studies

The EPA Draft RfD document comprehensively discusses each study that was conducted prior to 1998 and readers are referred to that document for a more complete review (EPA, 1998). In addition, extensive external peer review of these studies, from study design to interpretation of results, is available (RTI, 1999). For our purpose, it is important to note the relevant aspects of each study for risk assessment purposes and to give the reader some idea of the level of research that has contributed to the development of perchlorate's toxicological profile and the draft RfD.

90-Day Study in Rats

In order to expand our knowledge of perchlorate’s toxicological action, Siglin et al. (1998) conducted a study in rats to determine whether per-

chlorate affects organs other than the thyroid, to determine whether effects are present following longer-term exposures at low doses (e.g., most similar to any human exposure), and whether effects of perchlorate are reversible. Results of this study showed that increased thyroid weight and thyroid follicular cell hyperplasia were observed at several points during the study, but only at the highest dose level (10 mg/kg/day) which is equivalent to 350,000 ppb in drinking water. These changes were reversible after the 30-day recovery period. Changes in thyroid hormones were observed at all dose levels. No other target organs were identified. For reference purposes, perchlorate concentrations in water supplies have generally been less than 100 ppb (EPA, 1998).

Neurobehavioral Developmental Study in Rats

Potential neurobehavioral effects of perchlorate were evaluated by York et al. (1998) using generally accepted protocols. Specifically, the study was designed to determine whether exposure to perchlorate *in utero* and through mother's milk affects either the brain or behavior of developing and newborn pups. Ammonium perchlorate at doses as high as 10 mg/kg/day (e.g., corresponding to 350,000 ppb in drinking water) did not cause any neurobehavioral effects in the offspring when administered to mothers during gestation and nursing. Learning and memory were not impaired in the rat pups at any time or at any exposure level. In mothers, levels of thyroid hormones were altered at all exposure levels, while in pups altered thyroid hormones were observed only at the highest dose level (10 mg/kg/day).

Developmental Toxicity Study in Rabbits

In order to expand our knowledge on potential developmental toxicity in a second animal species, Poirier et al. (1998) evaluated perchlorate's effects on developmental endpoints (e.g., birth defects) in rabbits. There were no differences between treated and untreated animals in mortality, clinical observations, litter measurements, and, importantly, fetal malformations. In mothers, there were some changes in hormone levels (T4) at the two highest dose levels (30 and 100 mg/kg/day) and some increase in thyroid cell size at the mid and higher dose levels (10, 30, and 100 mg/kg-day).

Two-Generation Reproductive Study in Rats.

Dourson et al. (1998) conducted a standard two-generation reproductive study in rats to address the questions – does exposure to perchlorate as an adult affect reproductive performance in either males or females and does exposure to perchlorate in utero affect the ability of future generations to reproduce? For both parental generation and in the first-born generation, there were no differences in reproductive parameters or function that would indicate an effect from perchlorate. However, as with previous studies, there were indications that perchlorate, particularly at the high dose level (i.e., 30 mg/kg/day) affected thyroid weight, once again confirming that this is the target organ.

Immunotoxicity Study in Mice

A study in mice (Keil et. al., 2000) was conducted to determine if exposure to perchlorate in drinking water affects the immune system. There were some varying effects of unknown biological significance at all dose levels (0.1, 1, 3, and 30 mg/kg-day). The authors concluded that the LOAEL for effects on the immunological system was 0.1 mg/kg-day (the lowest tested) while the NOEL for effects on thyroid hormone (T4) levels and thyroid histopathology was 0.1 m/kg-day. The effects on thyroid hormone levels were reversible.

Genetic Toxicity Studies

Perchlorate was tested in a bacterial assay to address the question of whether perchlorate causes mutations in bacteria or mammalian cells and whether oral exposure causes chromosome breaks in mice. Results showed that perchlorate was not mutagenic in any of the assays conducted and did not cause chromosome damage in mice (TERA, 2001).

Additional Investigative Studies

Following the completion of these studies and the external peer review, which concluded that 32 ppb in water was likely to be a conservative RfD, several additional studies were carried out (RTI, 1999). These were conducted in response to the RTI peer review group's recommendation for additional studies that would address remaining questions over toxicological, mechanistic, exposure, and dose-response characteristics for perchlorate. The results from these studies have been completed and submitted to the EPA; since this information is part of the EPA deliberative process, it is as yet not publicly available. However, the

framework and purpose of these studies are described below.

- A study was conducted to collect data on thyroid hormones, thyroid histopathology and brain morphometry from mothers and pups at key developmental stages of gestation and early postnatal growth, time periods during which brain development is affected by hormone changes (TERA, 2001).

- A human study was conducted for purposes of evaluating dose-response for perchlorate effects on thyroid function. Human subjects were to be exposed to a range of perchlorate doses in order to determine the specific dose at which there is no effect on iodide uptake and to determine at which dose no effects on thyroid hormones are observed (TERA, 2001).

- Additional studies were performed to clarify potential perchlorate effects on immunotoxicity and to determine if effects occur on motor activity since this is believed to be a sensitive indicator of thyroid effects on the developing brain (TERA, 2001).

- Several pharmacokinetic studies were conducted in rats and humans in order to develop a mathematical description of the kinetics of perchlorate, iodide, and thyroid hormones in animals and humans. These studies are particularly important for extrapolation of animal data to humans and to determine interspecies differences in the handling and effects of perchlorate (TERA, 2001).

Collectively, the animal and human database for perchlorate is well developed and will be useful to the EPA as it establishes a final RfD for perchlorate. And, while the previous descriptions of the animal and human studies are perhaps more technical than desired, what we consistently see in both types of studies is similar. That is, perchlorate either has no effect on the measured endpoint of concern or exerts effects at dose levels that are well above environmental levels.

In a more formal analysis of this last point, Soldin et al. (2001) recently reviewed the perchlorate clinical pharmacology and human health literature for perchlorate in order to determine perchlorate exposure levels at which thyroid hormone levels may be reduced or TSH levels increased. The authors report that the weight of scientific evidence shows that the perchlorate exposure level at which these effects occur are likely to be

in the 35-100 mg/day range, concentrations that are hundreds of times greater than any known human daily environmental exposure. Volunteer studies designed to determine the exposure level at which perchlorate begins to affect iodide uptake in humans show this level to be approximately 1 mg/day or 1000 µg/day, again, significantly higher than anticipated daily exposure (e.g., 30 µg/day) from drinking water (Soldin et al., 2001). The key point is that, collectively, the human epidemiological data support the lack of any effect on thyroid hormones or neurodevelopment at existing drinking water levels of perchlorate.

Chapter IV. The Commitment to Sound Science: Should the Public Be Concerned?

Where the Process Stands Today

Since mid-1999, the EPA (Office of Research and Development, or ORD) has been operating under an interim assessment guidance for perchlorate as outlined in a memo to all regional administrators (EPA, 1999). Essentially, the ORD guidance advises that EPA risk assessors and risk managers continue to use the standing provisional RfD range of 0.0001 to 0.0005 mg/kg/day for perchlorate-related assessment activities.

In terms of moving closer to the establishment of a final RfD, the EPA continues to collect information from those investigators that have conducted much of the research described in this report, both animal laboratory studies and human clinical studies. There are additional mechanistic and pharmacokinetic data that have been developed that are expected to be considered in the derivation of the RfD. The current schedule calls for the EPA to release its proposed RfD on January 15, 2002, with external peer review to follow in early March 2002. At the state level, the California Office of Environmental Health Hazard Assessment (OEHHA) is currently in the process of establishing a public health goal (PHG) for perchlorate in drinking water.

Identifying an Appropriate Study and Effect for RfD Development

EPA's draft RfD for perchlorate is based on a rat neurodevelopment study, using thyroid follicular-cell morphology changes at the lowest dose tested (0.1 mg/kg/day) as the critical effect. These changes were observed in rat pups (neonates) five days of age. Given the advances in our knowledge of perchlorate toxicity over the past several years, it is uncertain whether the EPA will retain this particular study and endpoint as the basis for its RfD or select another study and effect. That leads one to speculate as to what will be the critical effect (e.g., that effect upon which the RfD is based), what species or animal model will be selected, and what will be the underlying uncertainty factor associated with the RfD.

In developing the RfD, the EPA is likely to concentrate on the following:

- Hazard identification and data array analysis—In this step the EPA will organize the data by study type and purpose to determine available studies for RfD derivation.

- Designation of effect levels—In this step, the EPA will determine those critical levels at which effects were seen and, if possible, identify levels at which no effects were observed.

- Selection of a critical effect—This is an important step in that the EPA will need to identify what they perceive to be the most sensitive effect on the thyroid and the one that, if protected against, will protect against all other potential adverse effects.

- Dosimetric adjustment—If the critical study is an animal study, there will be some adjustment or extrapolation from animals to humans in terms of what a similar dose is for humans.

- Application of Uncertainty Factors—In the final step, the EPA will determine which uncertainty factors need to be applied (e.g., animal to human extrapolation, acute to chronic adjustment) and the size of each factor (range=1-10).

- Characterization of uncertainty—The EPA will describe in qualitative terms whether it has low, medium, or high confidence in the

overall RfD derived.

It is not the intent of this report to speculate on the critical study or endpoint of concern nor is it the purpose to go through a risk assessment process for perchlorate. However, as a result of our increased knowledge about perchlorate toxicity, there are several studies and findings that may be helpful in defining the RfD.

Given what we know about thyroid homeostasis and function and perchlorate's inhibition of iodine uptake, it appears that the developing fetus or pregnant mothers are the most sensitive individuals in terms of perchlorate's potential effects. The Argus-conducted neuropathology study (TERA, 2001), seeks to further refine this sensitivity by characterizing perchlorate-induced thyroid effects and alteration of hormone levels. The study is designed to evaluate thyroid histopathology and brain morphometry from both mothers and pups at multiple time points during gestation and lactation.

On the human level, the study by Greer et al. (2001) was conducted to identify the dose of perchlorate that would not cause inhibition of iodide uptake by the thyroid gland. Iodine uptake inhibition is a known precursor to other perchlorate effects and in this case, we have a human study (no need for extrapolation from animals) that has identified a no-effect level (again, a powerful finding for risk assessment) for this upstream or precursor event that is not itself considered adverse. The combination of these factors can be helpful in the risk assessment and definition of an RfD for perchlorate. First, the Greer et al. (2001) study was conducted in humans using both males and females. Second, the endpoint is one that advances the practice of risk assessment in that we are not just using the most sensitive adverse effect observed, but using a precursor event – a step that takes advantage of the science that has been developed. Third, there is inherent conservatism built into selection of this effect as it is not considered adverse per se, but rather precedes any thyroid toxicity. Because the relationship between iodine uptake inhibition and thyroid hormone changes is not precisely known, in this case, the use of a precursor event is prudent and conservative. Fourth, the study identified a no-effect level, which reduces uncertainty about effects in humans at the low end of the dose response curve. While pregnant females and developing fetuses were not a part of the study, some of the PBPK models and data that have been collected could be used to estimate a critical effect level for these sensitive humans.

Why Increases in the RfD Should Not be Alarming

Much of the EWG concern over regulatory policy for perchlorate is predicated on the fact that the provisional RfD for perchlorate has increased in recent years and that it may increase even further when the final EPA RfD is determined. EWG promulgates the perception that, by increasing the permissible exposure level, the safety standards for perchlorate are being eased or relaxed. Any increase in the RfD for perchlorate is the result of our ability to use new scientific information to reduce the uncertainty in former risk estimates for perchlorate. This process is encouraged and supported by the regulatory agencies, as it aids their ability to establish data-based exposure limits.

If the final RfD value is higher than in previous iterations of the provisional RfD, which it may well be, American consumers should not assume that this is a "less safe" value. Rather, this RfD results from intensive research on the toxicity of perchlorate. The end result has been to increase our knowledge of perchlorate, knowledge that has replaced uncertainty. On a practical level, many areas of uncertainty have now been delineated that heretofore were addressed by increasing the degree of uncertainty. Currently the EPA has a collective uncertainty factor of 100 for perchlorate; because of technological progress, the total uncertainty factor should soon be reduced to some lower value. While policy can always influence the determination of what constitutes a safe level, we now have sufficient science on perchlorate for the EPA to reduce, to an extent, its reliance on uncertainty factors as a primary means of protecting humans.

Using a Weight of Scientific Evidence Approach

The public should take comfort in knowing that the EPA's RfD for perchlorate, although based on one study and one endpoint of concern, is backed up by a considerable wealth of scientific information and data which increase our confidence in the safety of what the EPA defines as the RfD. Much of that information comes from additional animal studies that have evaluated different aspects of perchlorate toxicity, studies that have defined no-effect levels for most effects associated with toxicity, and studies that have refined our knowledge of perchlorate effects within the body.

In addition to the wealth of animal knowledge, we have a considerable

amount of human data that support the view that current environmental levels of perchlorate are well below those levels that have been associated with effects on thyroid hormones and/or thyroid function. Both occupational and clinical studies have been conducted to determine if and how various levels affect human health, what dose or airborne concentrations are required to elicit measurable effects, and, importantly, what no-effect levels are. In summary, we have a sound database for perchlorate, which increases the confidence and support for the RfD that is established.

The Scientific Process at Work—Why the Public Benefits

What we have witnessed over the course of the past decade regarding perchlorate should be reassuring to both scientific researchers and the general public. Minute amounts of previously undetectable perchlorate in some water sources should not be portrayed as a public health crisis. Progress in technological capability has led us to learn about the exact quantity of perchlorate in water. Similarly, it has been an advancement in toxicological science and a commitment to the scientific process that has led us to learn a significant amount about how perchlorate works, at what levels it exerts effects, and critically, at what levels it does not exert effects. It is because of the advancement in our scientific knowledge that RfD, one that is associated with a minimal amount of uncertainty, will be established.

The scientific process has proceeded over the last 10 years for perchlorate through a unique and collaborative effort between public and private sectors. What has been perhaps most surprising is the speed with which we have gleaned this incredible amount of scientific information. It is highly unusual to have complex and time-consuming laboratory experiments planned, implemented, completed, and published within the time frame that has occurred for perchlorate. It is difficult to understand how a process as transparent and objective could be criticized on any level, and it is anticipated that what emanates as a final RfD will be scientifically supported as well as any other regulated chemical in commerce today. While science can be slow and frustrating at times, if allowed to develop as it has for perchlorate, ultimately the benefits to society, in the form of scientifically sound safe exposure levels, are well worth the effort.

A considerable amount of data has been garnered about perchlorate, data that encompass both animal testing and human studies.

Collectively the data continue to show that the thyroid is by far the most sensitive target organ for perchlorate, and other toxicities that do not stem from perchlorate's action on the thyroid are not evident. The collective studies also demonstrate that effects are seen primarily at high doses of perchlorate relative to environmental exposures and that concentrations in drinking water should not pose a risk to humans. While it is not known what the final RfD for perchlorate will be, the scientific data and knowledge that has been generated will enable the EPA to establish a safe exposure level that will identify the most sensitive individual and protective endpoint known, yet also use the knowledge that has been generated to reduce any remaining uncertainty in the value to a minimum.

Glossary

Anion—An atom or radical with a negative charge.

Dose-response—The relationship between the amount of an agent applied or administered and the corresponding response of the target organ or tissue.

EWG—Environmental Working Group, a Washington D.C.-based activist environmental organization.

Histopathology—A branch of science that addresses the functional and structural manifestations of disease, particularly at the tissue level through microscopic analysis.

Hyperplasia—Excessive proliferation of normal cells or increase in cell number.

Hyperthyroidism—Excessive activity of the thyroid gland.

Hypertrophy—Enlargement of an organ, tissue, or cells as a result of an increase in cell size.

Hypothalamic-pituitary axis—The functional and biochemical interrelation between the hypothalamus, and pituitary and other endocrine glands, most often construed to include the thyroid and adrenal glands.

Hypothyroidism—Deficiency of thyroid activity.

Interspecies variability—The range of variation in response within a particular species.

Iodine—A nonmetallic element essential in human physiology and nutrition.

Mechanistic—In referring to mechanism of action, the means by which a biologically active material (e.g., chemicals, drugs) interacts with the cell or cellular components to elicit a response.

mg/kg/bw/day—This term is used in toxicology, including safety evaluations, and occasionally in pharmacology to describe the amount of chemical to which someone is exposed; weight of chemical per kilogram of body weight.

Neonate—A newborn; generally including the first four weeks of life.

Oxidizing agent—A chemical that is capable of donating electrons; when it occurs with another chemical, it is known as an oxidation-reduction (redox) reaction.

PBPK—Physiologically-based pharmacokinetics – Pharmacokinetics is the study of the time course of the absorption, distribution, metabolism, and excretion of drugs or chemicals in the body through the measurement of concentrations of metabolites in organs, tissues, or other biological matrices. PBPK differs from classical models in that real tissue, organs and body regions are used and as such are more realistic.

Perchlorate—The subject of this report, perchlorate is a contaminant in ground and surface waters whose occurrence results from the dissolution of ammonium, potassium, magnesium, or sodium perchlorate salts.

PPB—Parts per billion—quantitative expression often used to describe the concentration of a substance in air, water, or soil. Equivalent to micrograms per liter (µg/L) or micrograms per kilogram (mg/kg).

PPM—Parts per million. Equivalent to milligrams per liter (mg/L) or milligrams per kilogram (mg/kg).

PSG—Perchlorate Study Group, an interindustry group of company representatives who focus is the development of toxicological studies for enhanced understanding of perchlorate's toxicity and mechanism of action.

Pup—In this document, pup refers to a newborn rat.

RfD—Reference Dose – An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. The RfD is generally used in EPA's noncancer health assessments.

Toxicodynamics—The relationship between toxicant dose and effect or response, with specific emphasis on the mechanism of action. Toxicodynamics deals with the study of physiological, biochemical, and molecular effects of toxicants.

Toxicokinetics—The study of the absorption, distribution, and elimination of toxic compounds in the living organism, with emphasis on the route by which these processes occur.

TSH—Thyroid-stimulating hormone which is produced in the pituitary gland.

T3—Triiodothyronine, one of the thyroid hormones

T4—Thyroxine, one of the thyroid hormones

Uncertainty factor (UF)—One of several, generally 10-fold factors, used in operationally deriving the RfD and RfC from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, i.e., interhuman or intraspecies variability; (2) the uncertainty in extrapolating animal data to humans, i.e., interspecies variability; (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure, i.e., extrapolating from subchronic to chronic exposure; (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation from animal data when the data base is incomplete.

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