Perchlorate in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Preface

Access to safe drinking-water is essential to health, a basic human right and a component of effective policy for health protection. A major World Health Organization (WHO) function to support access to safe drinking-water is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...", including those related to drinking-water safety and management.

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition was published in 2011, and the first addendum to the fourth edition was published in 2017.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water was prepared. The draft health criteria document was submitted to a number of scientific institutions and selected experts for peer review. The draft document was also released to the public domain for comment. Comments were carefully considered and addressed as appropriate, taking into consideration the processes outlined in the *Policies and Procedures Used in Updating the WHO Guidelines for Drinking-water Quality* (http://apps.who.int/iris/bitstream/10665/70050/1/WHO_HSE_WSH_09.05_eng.pdf) and the *WHO Handbook for Guideline Development* (http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf), and the revised draft was submitted for final evaluation at expert consultations.

During the preparation of background documents and at expert consultations, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Meeting on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO website and in the current edition of the GDWQ.

Acknowledgements

Abbreviations

BMD	benchmark dose
BMD_{50}	benchmark dose for a 50% response
$BMDL_{50}$	lower 95% confidence limit for the benchmark dose for a 50% response
BMR	benchmark response
bw	body weight
CAS	Chemical Abstracts Service
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	median lethal dose
MDL	method detection limit
MRL	method reporting limit
NAS	National Academy of Sciences (USA)
NIS	sodium–iodide symporter
NRC	National Research Council (USA)
PMTDI	provisional maximum tolerable daily intake
POD	point of departure
T_3	triiodothyronine
T_4	thyroxine
TSH	thyroid stimulating hormone
USA	United States of America
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

Contents

1. GENERAL DESCRIPTION

1.1 Identity

Perchlorate is a naturally occurring anion of oxyhalide salts that is frequently detected in the environment (Rajagopalan et al., 2006). The Chemical Abstracts Service (CAS) registry numbers and molecular formulas for common perchlorate salts are given in Table 1.

Table 1. CAS numbers and molecular formulas

Compound	CAS No.	Molecular formula
Perchlorate anion	14797-73-0	ClO_4^-
Ammonium perchlorate	7790-98-9	NH_4ClO_4
Sodium perchlorate	7601-89-0	$NaClO_4$
Potassium perchlorate	7778-74-7	$KClO_4$
Perchloric acid	7601-90-3	$HClO_4$

1.2 Physicochemical properties

The physicochemical properties of common perchlorate salts are given in Table 2.

Table 2. Physicochemical properties

Property	*Ammonium perchlorate*	*Sodium perchlorate*	*Potassium perchlorate*
Boiling point (°C)	N/A	N/A	N/A
Melting point (°C)	130 (decomposes)	472 (decomposes)	400 (decomposes)
Density at −20 °C (g/mL)	1.95	2.02	2.52
Vapour pressure at 25 °C	Very low	Very low	Very low
Water solubility (mg/L)	2.49×10^5 (25 °C)	2.10×10^6 (25 °C)	2.06×10^4 (25 °C)

N/A: not applicable
Source: ATSDR (2008)

1.3 Organoleptic properties

Perchlorate has no known organoleptic properties at the concentrations commonly found in water supplies. However, a bitter and salty taste has been reported for ammonium perchlorate in water at 28–90 mg/L (Vonburg, 1995).

1.4 Major uses and sources in drinking-water

Perchlorate has found a variety of commercial uses; however, its primary uses are as an oxidizer in solid rocket fuels, automotive airbags, fireworks and road flares (Urbansky, 2000). Perchlorate has also been used as a pharmaceutical to treat overactive thyroid disorders (Graves' disease) (Wolff, 1998) and has been detected in certain dietary supplements (Snyder et al., 2006).

Drinking-water contamination can result from environmental releases from perchlorate manufacturing or use (Roefer et al., 2000). Contamination of water can also occur through natural deposits of perchlorate or use of fertilizers containing natural deposits of perchlorate

(Foubister, 2006). Atmospheric deposition of perchlorate also contributes to the ubiquitous presence of perchlorate in water (Rajagopalan et al., 2006).

In some arid regions, deposits containing high concentrations of perchlorate have been discovered, most notably co-occurring with nitrates harvested as fertilizers used commercially since the mid-1840s (Urbansky et al., 2001). These natural deposits are primarily attributed to atmospheric formation and deposition in rainfall (Dasgupta et al., 2005).

Perchlorate also forms in hypochlorite solutions to varying degrees, depending on the hypochlorite concentration, age and storage conditions (Asami, Kosaka & Kunikane, 2009; Stanford et al., 2011). Similarly to chlorate, perchlorate formation increases in hypochlorite solutions stored in warmer temperatures for extended periods of time. In addition to conventional hypochlorite solutions, perchlorate has also been identified in the hypochlorite produced by on-site generators using electrolysis (Snyder, Vanderford & Rexing, 2005).

1.5 Environmental fate

The perchlorate anion is highly stable in water and is capable of being transported long distances in water without significant degradation (Dasgupta et al., 2006). Perchlorate generally is not well retained by soils, with more than 90% of perchlorate remaining in the aqueous phase (Urbansky & Brown, 2003). In certain arid climates, sporadic and insufficient rainwater results in an accumulation of perchlorate in soils (Rajagopalan et al., 2006). Natural attenuation of perchlorate in water is limited. Perchlorate can be decomposed (reduced) by certain anaerobic bacteria; however, nitrates and sulfates can inhibit degradation (Dugan et al., 2009). Some plants can effectively take up perchlorate, providing some attenuation capacity (Yu et al., 2004). Neither photolysis nor vaporization is known or expected to significantly affect perchlorate concentrations in water. Perchlorate is a powerful oxidizer and would not be additionally oxidized during natural processes; however, it may be reduced by anaerobic bacteria or reducing environments.

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Air

Perchlorate is known to form in the atmosphere and is transferred through rainfall (Ericksen, 1983). Concentrations of perchlorate found in rain and snow are discussed in Section 2.2.

2.2 Water

Perchlorate has near ubiquitous occurrence in water in the nanogram per litre range, which is due in part to natural formation in the atmosphere and deposition during rain or snow events (Dasgupta et al., 2005). Using ultra-trace methods, perchlorate has been quantified in groundwater and surface water (Snyder, Vanderford & Rexing, 2005). Perchlorate is also known to occur ubiquitously in seawater (Martinelango, Tian & Dasgupta, 2006).

Rainwater in China was recently reported to contain perchlorate at concentrations between 0.35 and 27.3 µg/L, with a mean concentration of 6.37 µg/L (Qin et al., 2014). Conversely, a study from Harbin, China, showed no detectable levels of perchlorate in rain (method

detection limit [MDL] for snow water = 0.008 µg/L); however, seasonal detection of perchlorate in snow was linked to fireworks displays and ranged from 0.02 to 0.15 µg/L (Ye et al., 2013). In a study of Arctic snow from Nunavut, Canada, a mean perchlorate concentration of 5.5 ± 3.9 ng/L was measured (Furdui & Tomassini, 2009). Seventy per cent of samples of rainwater collected between August 2003 and November 2004 in Texas, United States of America (USA), contained detectable concentrations (MDL = 0.01 µg/L) of perchlorate, ranging from 0.02 to 1.6 µg/L (Dasgupta et al., 2005). In another study from the USA conducted from November 2005 through July 2007, a mean perchlorate concentration of 0.21 ± 0.04 µg/L, with a maximum value of 2.78 µg/L, was found in rainwater after fireworks displays at holiday celebrations (Munster et al., 2009). Thus, rainwater is well documented to contain perchlorate formed in the atmosphere at relatively low levels; however, influences from fireworks can result in elevated levels of perchlorate.

Between 2000 and 2005, the United States Environmental Protection Agency (USEPA) conducted a survey of 3870 public water systems and found that 160 of the systems (4.1%) contained perchlorate at concentrations above the method reporting limit (MRL) of 4 µg/L, and 13 of the systems surveyed had concentrations above 40 µg/L (Brandhuber, Clark & Morley, 2009). Concentrations of perchlorate in drinking-water at 20 locations in England and Wales ranged from <0.020 to 2.073 µg/L, with a mean concentration of 0.747 µg/L (McLaughlin et al., 2011). In the Republic of Korea, 80% of 520 tap water samples were positive for perchlorate, at detectable concentrations ranging from <1 to 6.1 µg/L, with a mean concentration of 0.56 µg/L (Her et al., 2011). Seventy-six per cent of water samples from 13 locations in six states from India contained perchlorate at concentrations above 0.02 µg/L, with a maximum concentration of 6.9 µg/L and a mean concentration of 0.42 µg/L (Kannan et al., 2009). In the Tone River basin in Japan, with known industrial discharges of perchlorate, tap water samples contained 0.06–37 µg/L (Kosaka et al., 2007).

The Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) reviewed data from six countries (Canada, China, India, Japan, Republic of Korea, USA) on the occurrence of perchlorate in water. Analytical data on 35 073 samples of groundwater and drinking-water indicated that the perchlorate concentration in 98% of samples was below the limit of reporting. In drinking-water, perchlorate levels exceeded 20 µg/L in only 1% of the samples (FAO/WHO, 2011).

2.3 Food

Perchlorate is commonly found in foods, likely originating in most cases from natural deposition from rain (Rajagopalan et al., 2006) and use of fertilizers containing perchlorate (Dasgupta et al., 2006). Perchlorate is known to accumulate in some marine plants (Martinelango, Tian & Dasgupta, 2006); the accumulation of perchlorate in aquatic plants used as a source of iodine has led to the contamination of dietary supplements with perchlorate, including those marketed as prenatal supplements (Snyder et al., 2006).

Concentrations of perchlorate in food in Ottawa, Canada, ranged from non-detectable to 536 µg/kg, with highest concentration ranges reported in imported food from Guatemala, Chile and the USA (Wang et al., 2009). In a study of perchlorate in 350 foods and beverages from various countries, all measured in triplicate, the highest levels were as follows: bottled water from Portugal at 5.1 µg/L, produce from Guatemala at 463.5 µg/kg, wine from Portugal at 50.3 µg/L, beer from France at 21.1 µg/L and tap water from the USA at 2.9 µg/L (El Aribi

et al., 2006). In bottled beverages from Japan, over half contained perchlorate (MRL = 0.05 µg/L), with a maximum concentration of 0.92 µg/L (Asami, Kosaka & Yoshida, 2009). In the USA, perchlorate was detected in 10 of 21 bottled waters (MRL = 0.05 µg/L), with a maximum reported concentration of 0.74 µg/L (Snyder, Vanderford & Rexing, 2005).

Based on a recent evaluation of 4731 data points for perchlorate occurrence in foods from six member states of the European Union, leafy vegetables contained the highest concentrations, with an average concentration of approximately 77 µg/kg (EFSA, 2014). In a study of food and water in the Hatay region of Turkey, remarkably similar concentrations of perchlorate in food and water were reported, at approximately 0.4–0.5 µg/kg or µg/L in all matrices tested (Sungur & Sangun, 2011). In an evaluation of 31 dietary supplements, 20 contained detectable levels of perchlorate, with the highest reported concentration of 2400 µg/kg in a vitamin supplement recommended for pregnant mothers (Snyder et al., 2006).

JECFA reviewed analytical data from 1866 samples of food (vegetables, fruits, rice, milk, infant formula, fish and fish products, and beverages, such as juices, beer and wine) from six countries (Canada, China, India, Japan, Republic of Korea, USA), finding perchlorate concentrations in 33% of the samples to be below the limit of reporting. Weighted mean perchlorate concentrations in raw vegetables were in the range 4.8–110 µg/kg; in fruits, the weighted mean concentrations ranged from 0.5 to 28 µg/kg. Other weighted mean perchlorate concentrations were as follows: rice, 1 µg/kg; whole wheat flour, 3.5 µg/kg; milk, 6.8 µg/kg; beer, 1 µg/kg; and wine, 6 µg/kg. The mean perchlorate concentrations in human milk in China and the USA were found to be 19.7 µg/L (range 2.1–136 µg/L) and 9.3 µg/L (range 0.01–411 µg/L), respectively. Based on limited data, the weighted mean perchlorate concentration in infant formula was 10 µg/kg (FAO/WHO, 2011).

2.4 Estimated total exposure and relative contribution of drinking-water

In a study by the United States Food and Drug Administration, perchlorate intake through food was highest in infants (aged 6–11 months) and children (aged 2 years), ranging from 0.26 to 0.39 µg/kg body weight (bw) per day. Baby food contributed 49% of the perchlorate dose in infants, whereas dairy products had the highest contribution (51%) in 2-year-olds and vegetables contributed the most towards dietary exposure to perchlorate in adults, ranging from 26% to 38% (Murray et al., 2008). In a review of occurrence data for drinking-water and food in the USA, one study concluded that for the general population in the USA, the contribution of perchlorate from food relative to water was roughly 4:1, except for children aged 6–11 years, for whom the contribution from food was even greater (Huber et al., 2011).

In the Republic of Korea, in an investigation of 39 types of food, Korean adults were exposed to perchlorate at approximately 0.04 µg/kg bw per day from the diet (Lee, Oh & Oh, 2012). A recent study from Japan demonstrated that the majority of perchlorate exposure arose from food rather than water, with intake from water ranging from 0.1 to 4.4 µg/day and intake from food ranging from 2.5 to 84 µg/day (Asami et al., 2013). Canadian data reviewed by JECFA showed that mean dietary exposure to perchlorate was approximately 0.04 µg/kg bw per day for children aged 1–11 years compared with 0.03 µg/kg bw per day for adults, including women of childbearing age (FAO/WHO, 2011). JECFA also evaluated the data from the USA described in the previous paragraph (Murray et al., 2008).

JECFA estimated that international dietary exposure to perchlorate (using the 13 consumption cluster diets of the Food Contamination Monitoring and Assessment Programme of the Global Environment Monitoring System) was 0.03–0.22 µg/kg bw per day (FAO/WHO, 2011).

For most geographical locations, exposure to perchlorate from food greatly exceeds that from water. However, in the relatively rare cases of industrial or agricultural contamination or unique geographical deposits, exposure to perchlorate from water can exceed that from the diet.

3. TOXICOLOGICAL SUMMARY

The JECFA monograph on perchlorate served as the primary source of information for the toxicological evaluation of perchlorate, and the key sections are summarized or taken directly from that source (FAO/WHO, 2011). The EFSA evaluation of perchlorate, undertaken in 2014, was also evaluated (EFSA, 2014), and it was concluded that the report included no significant additions to the studies evaluated by JEFCA (FAO/WHO, 2011).

3.1 Kinetics and metabolism

Perchlorate is rapidly absorbed in both humans and experimental animals following oral exposure (EFSA, 2014). It has been detected in serum, plasma, urine, breast milk and saliva of humans exposed to the chemical (FAO/WHO, 2011) and exhibits a short half-life of 6.0–9.3 hours (mean 8.1 hours) in human blood serum (Greer et al., 2002). Perchlorate undergoes relatively little, if any, metabolism in humans, with more than 90% of ingested doses excreted in the urine (FAO/WHO, 2011).

3.2 Effects on laboratory animals and in vitro test systems

Detailed reviews of the effects of perchlorate on laboratory animals may be found in NRC (2005), ATSDR (2008), FAO/WHO (2011), ECHA (2014) and EFSA (2014).

3.2.1 Acute toxicity

When a single dose (300 or 2000 mg/kg bw) of ammonium perchlorate was administered to female rats by oral gavage, no deaths occurred, although hypoactivity was noted up to 2 hours post-dosing for all animals dosed at 2000 mg/kg bw (ECHA, 2014).

3.2.2 Short-term studies of toxicity

A dietary concentration of 3.55% (35 500 mg/kg diet, approximately 3621 mg/kg bw per day as perchlorate) was reported as the median lethal dose (LD_{50}) for potassium perchlorate in mice exposed for up to 30 days. The first deaths occurred within 4 days of the start of treatment (Gauss, 1972).

Several short-term (ranging from 7 to 90 days) studies of toxicity have been carried out in which rats were administered ammonium perchlorate in drinking-water (Eskin et al., 1975; Siglin et al., 2000; Khan et al., 2005; McLanahan et al., 2007). Effects on thyroid hormones, thyroid gland weights and histological changes to the thyroid gland were the primary end-points studied. In an 8-week study, the mammary glands of female rats were of normal weight but histologically showed mild atrophy, some atypia of the lobular epithelium and scattered foci of hyperplastic activity (Eskin et al., 1975).

3.2.3 Long-term studies of toxicity and carcinogenicity

Potassium perchlorate and sodium perchlorate have been shown to produce thyroid tumours (papillary and/or follicular adenomas and/or carcinomas) in rats and mice with long-term exposure (1–24 months) to 1–1.2% concentrations in the feed (10 000–12 000 mg/kg) or drinking-water (10 000–12 000 mg/L) (Kessler & Krüskemper, 1966; Gauss, 1972; Florencio Vicente, 1990; Fernandez Rodriguez et al., 1991; Pajer & Kalisnik, 1991; Toro Guillen, 1991). Estimated perchlorate doses in these studies ranged from 928 to 2573 mg/kg bw per day. The cancer effect levels from these studies were around 1000 mg/kg bw per day.

3.2.4 Genotoxicity

No evidence of the genotoxicity of magnesium perchlorate or ammonium perchlorate was observed in a wide array of both in vivo and in vitro genotoxicity tests (Nakamura & Kosaka, 1989; Costa et al., 1996; Zeiger, 1998a,b; San & Clarke, 1999; Siglin et al., 2000).

3.2.5 Reproductive and developmental toxicity

Several studies have been carried out to investigate the reproductive and developmental toxicity of perchlorate in rats, prairie voles, deer mice and rabbits (York et al., 2001a,b, 2003; Thuett et al., 2002a,b; Mahle et al., 2003; Smith et al., 2006; Stoker et al., 2006). The results of these studies indicate effects on some reproductive end-points following exposure to perchlorate, including decreases in the number of litters born, decreases in mean litter size, increases in the percentage of stillborn pups, and reduced ossification of fetal sternebrae and phalanges; however, the changes, where observed, were usually slight. Exposure to perchlorate in utero and via lactation resulted in thyroid findings in fetuses and pups that were similar to those noted in adults.

Several studies in rats have also investigated the relationship between exposure to perchlorate and developmental neurotoxicity, including effects on brain weight and dimensions and on spatial learning (York et al., 2004, 2005; Gilbert & Sui, 2008). However, limitations of the data preclude the determination of an association between exposure to perchlorate and developmental neurotoxicity (EFSA, 2014).

3.3 Effects on humans[1]

Human observations include clinical studies on thyroid function in healthy adult volunteers given perchlorate in drinking-water, clinical studies on thyroid function in workers occupationally exposed to perchlorate for several years, population-based epidemiological studies and ecological studies comparing populations living in areas with differing concentrations of perchlorate in the drinking-water. Some of the ecological studies included pregnant women, newborns and children and, in the case of newborns, benefited from neonatal screening programmes that included measurements of serum thyroid stimulating hormone (TSH) and/or thyroid hormones. In the various studies, outcome measures investigated included one or more of the following: radiolabelled iodide uptake by the thyroid, serum TSH and thyroid hormone concentrations, urinary perchlorate and iodide concentrations, incidence of thyroid diseases, neonatal birth weight, head circumference and length, incidence of congenital hypothyroidism and neurobehavioural measures in children.

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[1] References for this section, except for the critical study, can be found in FAO/WHO (2011).

There are also historical clinical data from past use of perchlorate as a treatment for hyperthyroidism.

There were no reported associations between perchlorate concentrations in drinking-water and the incidence of thyroid diseases, including congenital hypothyroidism and thyroid cancer in the ecological studies. With respect to TSH and thyroid hormones, one study reported a significant association between elevated newborn TSH levels and concentrations of perchlorate in drinking-water. However, it is notable that the concentrations of perchlorate in drinking-water in this study were not as high as in other, negative studies on newborns.

The clinical studies in healthy adult volunteers and workers did not show any significant effects on TSH or thyroid hormone concentrations at exposures of up to 0.5 mg/kg bw per day. From consideration of human clinical studies in healthy subjects and studies of long-term treatment of patients with hyperthyroidism, the National Academy of Sciences (NAS) in the USA has estimated that a sustained exposure to perchlorate of more than 0.4 mg/kg bw per day would probably be necessary in order to trigger hypothyroidism in normal adults. The NAS also commented that in pregnant women, infants, children and people with low iodide intake or pre-existing thyroid dysfunction, the dose of perchlorate required to cause hypothyroidism may be lower. Despite lack of effects on TSH and thyroid hormones, the studies in healthy adult volunteers did show clear, dose-related effects on radiolabelled iodide uptake by the thyroid.

A key issue for human risk assessment is whether a point of departure (POD) for deriving a health-based guidance value (i.e. tolerable daily intake) for perchlorate should be based on the end-point of inhibition of thyroidal uptake of iodide or on end-point(s) with clearer implications for adversity, such as increases in TSH, reductions in circulating thyroid hormone levels and clinical hypothyroidism. Inhibition of iodide uptake by the thyroid is clearly a precursor event in the chain of events that ultimately can lead to adverse effects on thyroid function; by itself, however, it cannot be considered adverse if circulating thyroid hormone levels remain unchanged. The available human data provide support for such a conclusion. For example, for short-term exposure, in a 14-day clinical study by Greer and co-workers (2002) in healthy adults, there was no effect on TSH or thyroid hormones at the highest perchlorate dose tested, 0.5 mg/kg bw per day, despite the observation that the highest dose caused an average 67% inhibition of iodide uptake by the thyroid. For chronic exposure, support is provided by data from the two occupational studies, in which about half the participants in each study had been exposed for more than 5 years. In one study, perchlorate exposure equivalent to about 0.5 mg/kg bw per day (the same as the highest dose in the study by Greer et al. [2002]) was not associated with any change in TSH or thyroid hormones; in the other study, in which uptake of radiolabelled iodide by the thyroid was measured, a 38% reduction in iodide uptake was not associated with any effect on TSH or thyroid hormones. The NAS review also expressed the view that uptake of iodide by the thyroid would need to be inhibited by at least 75% for several months or longer in adults with a normal dietary iodine intake in order to cause declines in thyroid hormone production that would have adverse health effects. A further practical constraint in selecting the end-point is that, with the exception of one study, the human clinical and epidemiological studies on perchlorate did not actually identify any significant association between perchlorate exposure and changes in TSH and thyroid hormones that could be used for the POD.

A second key issue is to what extent a POD derived from studies in healthy adults relates to potentially more vulnerable groups in the population. Given the critical role of thyroid hormones in brain development, it is widely considered that the probability of a permanent adverse effect on neurodevelopment from thyroid disruption, including transient disruption, would be greatest during early life. Consideration needs to be given to the differing thyroid physiology in the fetus and neonate compared with that of children and adults; for example, the amount of thyroid hormone stored in the colloid in late-gestation fetuses and neonates is estimated to be sufficient for less than 1 day only, compared with several months for adults. It is also unclear whether infants consuming breast milk from mothers exposed to perchlorate may have an additional risk if perchlorate were to reduce the passage of iodide into breast milk; at present, there are very few data on this, and what data are available are contradictory.

As perchlorate competitively inhibits iodide uptake by the thyroid, another issue for consideration is whether populations living in parts of the world where the diet is deficient in iodine would be more susceptible to perchlorate than iodine-replete individuals.[1] The data on this aspect are sparse. A further consideration is whether individuals, in particular pregnant women, who already have the condition of hypothyroidism or subclinical hypothyroidism might be additionally affected by low-level perchlorate exposure. The above subgroups of the general population are numerically significant.

JECFA also noted that there can be co-exposure in the diet to other ubiquitous anti-thyroid substances with the same mode of action (i.e. competitive inhibition at the sodium–iodide symporter [NIS]; see Section 3.4), such as nitrate or thiocyanate, or with differing modes of action, such as organochlorines.

Given the mode of action of perchlorate (see Section 3.4), the key vulnerable groups are likely to be pregnant women, fetuses, newborns, young infants, those with hypothyroidism and possibly those with iodine-deficient diets. As there are no good quantitative data relating perchlorate dietary exposure to changes in thyroidal iodide uptake, TSH or thyroid hormones in these key groups that are comparable with the quantitative data obtained in the study by Greer and co-workers (2002), these represent significant data gaps and are the major sources of uncertainty in any population-wide risk assessment. The uncertainties discussed above need to be weighed alongside the fact that the POD for the risk assessment can be based on inhibition of iodide uptake by the thyroid, a precursor event that, at least at low to moderate levels of inhibition, appears to be non-adverse.

3.4 Mode of action of critical effect

The health effects of perchlorate salts are due to the perchlorate ion itself. The primary effect of perchlorate is its ability to competitively inhibit uptake of iodide by the thyroid gland. The inhibition is at the level of the NIS, which actively transports iodide and perchlorate from the blood into the thyroid gland. Inhibition of iodide uptake by perchlorate reduces the amount of iodide available for the synthesis of thyroid hormones, resulting in reductions in the concentrations of circulating thyroxine (T_4) and the more biologically active hormone, triiodothyronine (T_3). In a negative feedback loop, reductions in the concentrations of T_4 and T_3 reaching the brain trigger the release of thyrotropin-releasing hormone in the

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[1] WHO has estimated that 54 countries may still be iodine deficient, yet the rates of iodine deficiency continue to decline (http://www.who.int/nutrition/topics/idd/en/#).

hypothalamus, which, in turn, causes the release of thyrotropin, also known as TSH, from the anterior pituitary gland. TSH initiates the events in the thyroid that result in NIS transport of iodide into the thyroid and synthesis of T_3 and T_4. Sustained reduction in iodide uptake by the thyroid may result in hypothyroidism. Hypothyroidism has adverse implications for structural and functional brain development in the fetus, infant and child and for metabolism and the functioning of cardiovascular, gastrointestinal, skeletal, neuromuscular and reproductive systems in adults.

4. PRACTICAL ASPECTS

4.1 Analytical methods and analytical achievability

Numerous methods are available to identify and quantify the perchlorate anion in water; however, the majority utilize ion chromatography for separation and either conductivity or mass spectrometry for detection. The limits of detection for these methods are generally in the micrograms per litre or nanograms per litre range, respectively. USEPA Method 314.0 (USEPA, 1999) utilizes ion chromatography with suppressed conductivity detection and can generally achieve an MRL of approximately 4 µg/L, whereas USEPA Method 331.0 (USEPA, 2005a) using liquid chromatography with mass spectrometry detection achieves MRLs between 20 and 50 ng/L.

4.2 Treatment and control methods and performance

The perchlorate anion is highly stable in water and is difficult to remove using conventional water treatment technologies. The advanced treatment technologies that have been shown to effectively remove perchlorate from water may not be readily available or applicable to low-resource regions. Effective advanced technologies include reverse osmosis and nanofiltration membranes (Yoon et al., 2009), anaerobic biodegradation (Hatzinger, 2005) and ion exchange using strong basic anion exchange or perchlorate-selective ion exchange resins (Gu, Brown & Chiang, 2007; Srinivasan & Sorial, 2009). Anaerobic biodegradation has generally been applied to remediate perchlorate releases at high concentrations (>100 µg/L), whereas advanced treatment processes (e.g. reverse osmosis and ion exchange) have also been applied to lower concentrations. However, other technologies (e.g. electrochemical reduction) and hybrids (e.g. ion exchange coupled with biodegradation) have also been found to be successful (USEPA, 2005b; Ye et al., 2012).

Proper selection, handling and storage of hypochlorite solutions are important to minimize perchlorate formation in hypochlorite solutions. Control measures include obtaining the freshest hypochlorite possible of appropriate quality; diluting the concentrated solutions as soon as they are received; keeping the hypochlorite in a cool, dark storage facility; and controlling its pH in the range of pH 11–13 during storage (Stanford et al., 2011).

5. GUIDELINE VALUE

5.1 Relevance of animal data for human risk assessment

JECFA noted that for substances known to affect the thyroid and having a mode of action involving inhibition of the uptake of iodide, the rat is not a good model for humans. This applies not only to the likelihood of thyroid cancer but also to other perturbations of thyroid

physiology and pathology in response to thyroid toxicants. For this reason, the animal data reviewed by JECFA, which comprised mostly data from rats and were qualitatively supportive of the human data, were not further considered for deriving a health-based guidance value for perchlorate.

5.2 Selection of pivotal study and point of departure

The pivotal study for dose–response analysis was the human clinical study on 16 male and 21 female healthy adult volunteers published by Greer and co-workers in 2002, in which perchlorate was given in drinking-water at a dose of 0.007, 0.02, 0.1 or 0.5 mg/kg bw per day for 14 days. The uptake of iodide into the thyroid was measured at baseline before administration of perchlorate and on days 2 and 14 of administration at both 8 and 24 hours after administration of radiolabelled iodine. These data were used for modelling.

JECFA selected a critical effect size of 50% inhibition of iodide uptake as the benchmark response (BMR). This choice was made because human clinical data from healthy adults following both short-term and chronic exposure to perchlorate have shown that such a level of inhibition is not associated with any changes in TSH or thyroid hormone levels. JECFA noted that a BMR of 50% inhibition was within the observed range of the study.

PROAST software (version 23.2) for analysis of continuous data was used. In the clinical study, each subject served as his or her own control, with baseline values measured 1 day before the start of the 14-day perchlorate exposure period. In the benchmark dose (BMD) analysis, the baseline value for iodide uptake in each subject was set at 100%. Analysis of the post-treatment values for iodide uptake at 8 and 24 hours and the values from exposure days 2 and 14 as covariates showed that these factors did not have any significant impact. Therefore, the two models used for continuous data – the exponential and Hill models – were fitted to all the data combined. Similar values for the benchmark dose for a 50% response (BMD_{50}) and the lower 95% confidence limit on the BMD_{50} ($BMDL_{50}$) were obtained from the two models. The lower of the two $BMDL_{50}$ values (rounded to two significant figures) of 0.11 mg/kg bw per day was used as the POD.

5.3 Derivation of the provisional maximum tolerable daily intake

As perchlorate has a very short half-life and is rapidly cleared from the body, it is considered appropriate to derive a provisional maximum tolerable daily intake (PMTDI). The $BMDL_{50}$ of 0.11 mg/kg bw per day for inhibition of uptake of radiolabelled iodide by the thyroid was chosen as the POD for derivation of a PMTDI. As it is based on human data, there is no need to apply any interspecies uncertainty factor.

JECFA noted that the $BMDL_{50}$ was derived from a study of relatively short duration but that there are efficient homeostatic mechanisms to cope with short-term and long-term inhibition of iodide uptake, up to (at least) 50%, in healthy children and adults. JECFA also noted that there is at least a fourfold margin between the value of the $BMDL_{50}$ and the estimate of more than 0.4 mg/kg bw per day that would probably be necessary as a sustained exposure in order to trigger hypothyroidism in normal adults. JECFA therefore concluded that it was not necessary to apply an uncertainty factor to account for the short duration of the pivotal study.

In considering the size of any necessary uncertainty factor for inter-individual human differences, JECFA took account of the fact that the effect of perchlorate on inhibition of

iodide uptake by the thyroid and on the subsequent synthesis of thyroid hormones in potentially vulnerable groups – such as pregnant women, fetuses, neonates and young infants, those with iodine-deficient diets and those with clinical or subclinical hypothyroidism – may differ from that in healthy adults. JECFA concluded that an uncertainty factor of 10 would be appropriate to cover any differences in the general population, including those in potentially vulnerable subgroups. Applying this 10-fold factor to the $BMDL_{50}$ and rounding to one significant figure, a PMTDI of 0.01 mg/kg bw was established for perchlorate.

5.4 Establishing a guideline value

Using the unrounded PMTDI of 0.011 mg/kg bw, a typical adult body weight of 60 kg, the assumption that drinking-water contributes 20% of the total exposure to perchlorate and a typical consumption of 2 L of water per day, a health-based value of 0.07 mg/L (rounded figure) can be calculated. The allocation factor (floor value) of 20% was determined to be appropriate considering the large number of occurrence studies indicating that perchlorate exposure from food exceeded the exposure from water. As a recent example, in a study from Japan, the actual relative source contribution of perchlorate from water ranged from 0.5% to 22% of the total daily perchlorate intake (Asami et al., 2013).

A guideline value of 0.07 mg/L is therefore established. Analysis of perchlorate at the guideline value is readily achievable. Although perchlorate is not readily removed by conventional treatment technologies, it can be removed to the guideline value by a variety of non-conventional, more advanced processes, such as ion exchange, reverse osmosis, nanofiltration and anaerobic biological processes, which are generally costly to install and relatively more complex to operate.

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