

# Regulatory rationality and the role of cumulative risk: A case study of perchlorates and related compounds

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## Abstract

This paper examines a range of issues related to the rationality of regulatory risk assessment and risk management in cases of cumulative risk, using perchlorates as the example where this rationality is currently in need of better development. It employs cumulative and aggregate risk methodologies, in tandem with Monte Carlo probabilistic risk assessment, to reinterpret primary health effects data to develop estimates of Perchlorate Equivalent Concentration (PEC) values for three compounds (perchlorate, nitrates and thiocyanates) that act on Iodide Uptake Inhibition (IUI) via the (Sodium-Iodide Symporter) (NIS) mechanism of action.

The results here provide a significantly different set of implications for risk, regulation and risk mitigation of perchlorates when compared against the traditional assessment approach of interpreting the data of the Greer et al (2002) study. The current analysis using cumulative and aggregate risk to interpret those same data suggest the regulatory limit for the action of perchlorates only would be above 300 µg/L in sharp contrast to any of the values below 20 µg/L being proposed in either the US or EU, with the Tolerable Daily Intake (TDI) of the European Food Safety Authority (EFSA) increasing by a factor of approximately 5 to 17 when expressed in units of PEC depending on the assumptions applied. Application of cumulative and aggregate risk methodologies lead to the following primary conclusions and associated recommendations:

- If there is an effect of perchlorates exposures at concentrations below several hundred µg/L, it is small compared to the effect of nitrates and thiocyanates that also act on IUI through the NIS mechanism of action. Therefore regulatory actions should focus firstly on nitrates and thiocyanates exposures.
- If the focus is on nitrates, the current analysis suggests limits on intake of nitrates are already adequately protective in both water and food, even if IUI effects are included in addition to 'blue baby syndrome' or other potential adverse effects.
- Failure to account for cumulative risk in interpreting the primary study used in examining perchlorates risks (Greer et al 2002) can lead to large overstatements of the risks from nitrates in food and water. This logical inconsistency – in which regulatory limits on perchlorates in water appear at first glance to require large reductions in regulatory limits on nitrates - arises from the (incorrect) assumption that effects in the Greer et al (2002) study can be assigned to the incremental exposure to perchlorates alone in that study.
- When a PEC approach is used to reinterpret the Greer et al (2002) data, there is no need to further reduce exposure limits on nitrates in either water or food beyond those based on the current ADI.
- Application of full Monte Carlo analysis indicates that risks to individuals at the 95th percentile of the distribution of exposures are overstated by approximately 50% when the traditional approach to regulatory risk assessment is used, in which only the 95th percentile values for each exposure parameter are employed in estimates of intake from food and water. Ensuring a consistent level of 'margin of safety' to protect the more vulnerable individuals across different sources of risk is therefore better approached through full probabilistic/Monte Carlo methods, which allow regulators to understand and quantify the percentage of the population protected by any given proposed regulatory limit on concentrations in the environment.
- The Monte Carlo analysis suggests that allocation of risk management resources ought to be directed at identifying geographic 'hot spots' (primarily due to food) and instituting controls on pollutants in those locations.
- It is time for cumulative risk to be placed at the centre of regulatory risk assessment, supplemented by Monte Carlo analysis. The science is now suited to the task and failure to do so results in violations of several of the core criteria of the precautionary principle.

The analysis suggests regulatory limits on the three IUI compounds would be between 375 and 1,046 µg(PEC)/L depending on the varying parameter values and options of analysis described in the paper, with a Tolerable Daily Intake (TDI) of between 25 and 30 µg/kg-day.

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## 1. Introduction

The science of human health risk assessment has advanced rapidly in the past decade. For example, the NEXGEN program in the United States is exploring how these advances might be used in both enhancing and restructuring the approach taken to risk assessment for environmental contaminants (Cote et al 2013; Crawford-Brown 2013). The methodologies have evolved under different names, but generally are placed into two groups: those focused on application of methodologies of proteomics, genomics and other biochemical and microbiological tools (EFSA 2014a), and those focused on advances in regulatory risk frameworks related to cumulative and aggregate risk assessment (Sexton 2012; Crawford-Brown and Crawford-Brown 2012; Ragas et al 2011; USEPA 2003) or variants of multiple agent risk assessment (Meek et al 2011; EFSA 2013; Evans et al 2015a and 2015b).

The present paper focuses on this latter group of advances and their implications for regulatory risk assessment and allocation of resources for protection of public health. Cumulative risk here means the collective action of different risk agents (such as chemicals) on the human body, in which the observed adverse effects (such as endocrine disruption) in a population are due to the simultaneous presence of several compounds rather than any one compound in isolation. Aggregate risk here means the collective action of the same risk agent through different routes of exposure (for example inhalation or ingestion).

There are already a few instances in which cumulative risk methodologies have been applied in regulatory decisions and procedures. Regulation of radioactivity in the environment has for decades been based on the concept of cellular dose. Regardless of the source of the radiation, the practice has been to use dose additivity in calculating risks from exposures to different sources of radiation, summing the dose equivalent from these sources and then using a generic risk coefficient (probability of cancer per unit dose equivalent) applied to this summed dose (ICRP 2007). A similar approach has been taken for dioxin and dioxin-like compounds, in which multiple compounds are assigned a Toxicity Equivalence Factor (TEF) and exposures summed to develop a toxicity equivalent exposure to which a common risk coefficient is applied based on the primary dioxin compound 2,3,7,8-tetrachlorodibenzo-p-dioxin (EPA 2010). Recently, cumulative risk assessment was employed by the EFSA Panel on Contaminants in the Food Chain (CONTAM) by setting a group tolerable daily intake (TDI) value for parent and modified forms of mycotoxins and conducting a dietary risk assessment using their relative contribution to food and livestock feed (EFSA 2014b, 2016). In all of these cases, the assumption is that adverse effects in populations are caused by the cumulative (equivalent) exposure or dose, rather than the action of any one compound in a mixture.

In the traditional approach to risk assessment, epidemiological, toxicological or human volunteer studies are conducted for a single compound. Any elevation of effects (above background rates) noted are assumed to be associated with the incremental exposures (additional to background) of the compound, following control for confounding by known risk factors such as age, smoking and prior health status. The assumption is that this control for confounding – if it includes compounds that act by the same mechanism or mode of action – removes the need to further include cumulative risk in the next and final step: establishing safe levels of exposure to the compound of primary interest.

The issue of the potential complications from cumulative risk within this traditional approach has been dealt with (at least in the US) through the concept of a hazard quotient (HQ) for each compound based on a Reference Dose (RfD; Acceptable/Tolerable Daily Intake in the EU) and application of uncertainty and modifying factors (although modifying factors are used primarily in the US to account for interspecies dosimetry differences). This RfD arises from the assumptions above in which increased incidence of effect in a study population is assigned to the incremental exposure to the compound of interest. This is then followed by summing the hazard quotients for individual compounds that act by a common mechanism of action to produce a hazard index (HI). This approach however suffers from two problems:

- Since HQ values include different uncertainty factors for the compounds to be included in a cumulative risk assessment, their summation leads to incommensurability since the HQs reflect both the original health effects data and a policy judgment on the treatment of uncertainty and inter-subject variability. This policy judgment differs between compounds. Especially problematic is the fact that those compounds with the least reliable data have the greatest uncertainty factors applied, meaning they are subject to more stringent regulatory limits than compounds for which the data are better developed and hence the risk better defined.
- The HI value does not reflect any attempt to return to the primary data and re-interpret it in light of the contributions of the different compounds to the effects formerly attributed to an individual compound. This is a natural consequence of assuming that a study based on elevated or excess risk in a population is due to the sole compound under study (following treatment for confounding), rather than the cumulative action of the multiple compounds that act through this same mechanism of action. A calculation of HI therefore includes the assumption that the compounds in cumulative risk act additively and independently, both in natural exposure situations and in the underlying epidemiological and clinical studies.

The issue of cumulative risk becomes especially important when examining the effects of compounds that act on biological or physiological systems characterised by homeostatic mechanisms. An example is exposure to compounds such as perchlorates, nitrates and thiocyanates that all act on the thyroid and its downstream hormones via competitive inhibition of iodide uptake (IUI) through the NIS (Sodium-Iodide Symporter) mechanism. In these instances, the system is under homeostatic control, with that functioning of the thyroid resulting from the background exposures to whatever mixtures of these compounds are in the food, water and air of the individual (epidemiological or clinical) studies. The additional amount of the compound administered during the study perturbs this state of homeostasis, although that perturbation is quickly corrected so long as the perturbation is not sufficiently large to overwhelm the homeostatic system. However, even in this case, the movement outside the ability of the homeostatic system to correct for perturbations is caused by the cumulative action of the three NIS compounds, and not that of the administered compound alone.

Cumulative risk assessment then requires returning to the original studies and re-interpreting the results through consideration of all of the compounds acting, and developing an 'equivalency' risk coefficient similar to that mentioned earlier for radiation or dioxin-like compounds. In the case of perchlorate, this is performed through development of a Perchlorate Equivalent Concentration or PEC (see Bruce et al 2013 for a discussion of the concept of PEC; specific numerical values are developed later in the current paper). Following the argument above, the effects noted in the

epidemiology, toxicology or clinical studies used as the primary basis for regulatory risk assessment would be interpreted through the simultaneous actions of the compounds resulting in the exposures expressed as total PEC. In the case of perchlorate, that study is by Greer et al (2002), the study used to date as the primary basis for perchlorates regulatory risk assessment in the US and EU.

This re-interpretation of original data based on the methodology of cumulative risk is not yet the norm in regulatory risk assessment. As mentioned, under current regulatory risk science, the original data are interpreted solely through the action of the single compound administered (for example perchlorate) to develop an allowed or tolerated concentration. Then if other compounds (such as nitrates or thiocyanates) are present that act by the same mechanism of action, the allowed or tolerated concentration of the original compound (here, perchlorate) is reduced via an HI calculation to reflect the fact that there are simultaneous environmental exposures to these compounds that result in an increase in the PEC.

This regulatory approach makes some sense in the case of aggregate risk, although even there problems may arise. To see this consider the case where the analyst interprets original data such as Greer et al (2002) as by attributing any elevation of effect as resulting from incremental exposure to a compound (such as perchlorate) through a single route of exposure. In traditional regulatory assessment, a Relative Source Contribution (RSC) is then applied to account for the presence of other routes of exposure. The result can be a very low regulatory limit on the original compound and route, such as the case of regulatory limits of below 10 µg/L under consideration for perchlorates in water when an RSC of 0.2 or less is applied in the US (the RSC is not part of the methodology in the EU). Again, this situation arises because the original data are interpreted in the traditional way described above, rather than as an instance of adverse effects being caused by aggregate risk.

When applied to cases of cumulative risk from exposure to other compounds with the same mechanism or mode of action, the conservatism introduced into the risk assessment by the traditional methodology is even more profound because any adverse effect noted in the epidemiological or clinical study is attributed to the action of the single compound under consideration, despite that effect arising from the action of all of the compounds in the cumulative risk framework. The traditional methodology leads to further unnecessary and unreasonable levels of conservatism in regulatory limits. As will be shown in the present paper, it also leads to both mis-allocation of resources to protect public health and to inconsistency (often of a very large magnitude) of protectiveness across compounds and exposure routes. The solution to this problem is to return to the original data (the data of Greer et al 2002 in the case of perchlorate, or the data on 'blue baby syndrome' (methemoglobinemia in infants) as will be considered later for exposures to nitrates) and re-interpret them through the lens of cumulative and aggregate risk.

There is however a policy challenge in application of at least cumulative risk (aggregate risk does not carry this same challenge, or at least not to the same degree as cumulative risk). Cumulative risk carries the possibility that regulation of any one compound in the environment might be conditional upon exposures to other compounds. It therefore carries the possibility that a regulatory limit on one compound such as perchlorates in water might vary geographically or across subpopulations due to differences in exposures to the other compounds acting through the same mechanism of action. This in turn raises issues of equity if one assumes that different individuals should have

allowed or tolerated environmental concentrations that are identical. It appears to raise the spectre of unequal treatment of individuals under the law.

This issue disappears when one turns from a principle of equal protection against a given compound, to one based on equal protection against a given level of risk from the simultaneous action of the compounds in the environment (at times called the 'risk cup'). The focus on simultaneous action of environmental compounds, and resulting cumulative risk, was precisely the basis for the environmental justice movement initially.

The present paper examines the issue of cumulative and aggregate risk through the lens of regulatory rationality. The contention is not that currently proposed regulatory limits on perchlorates in water are incorrect even IF one adopts the default assumption that the change in iodine uptake in the Greer et al (2002) study represents the incremental impact of administered perchlorates alone. Rather the contention is that one achieves significantly different and (as will be shown later) more logically consistent solutions to risk management if one fully considers cumulative risk in reinterpreting the original data as arising from the cumulative effect of at least the three compounds considered here.

The choice to examine cumulative risk through the NIS mechanism is based on the fact that measurements of the effect of perchlorates on this mechanism lie at the heart of current regulatory discussions of perchlorates risks. The central contention is that (i) current or emerging regulations on perchlorates can be significantly altered through more scientific cumulative and aggregate methods (in contrast to the mixture of science and policy methods in traditional regulatory risk), (ii) that risk management resources are better allocated to protect public health when this adjustment is made, (iii) that failure to do so has led to significant differences in the degree of protection against risk from different compounds, and (iv) that this failure has led to incoherence in regulatory limits across pathways of exposure.

The following discussion applies to the case of regulatory assessment for any route of exposure. If one considers perchlorates, the US has been concerned primarily with perchlorates in water while the EU has been concerned primarily with perchlorates in food. The same methodological issues arise in either case.

In the analysis, conversion from daily intake rate of a compound (in units of  $\mu\text{g}/\text{kg}\text{-day}$ ) to concentration in water (in units of  $\mu\text{g}/\text{L}$ ) requires an assumption of body mass (kg) and ingestion rate for water (L/day). These values vary depending on gender, age and percentile of the population selected to establish a regulatory limit. Here, a value of 0.04 L/kg-day is used as the default conversion factor, reflecting the upper reasonable value for a 50 kg woman in the early stages of pregnancy. By contrast, regulatory limits in the US are often set on the basis of 0.03 L/kg-day (a 70 kg male ingesting 2 L/day), and in the EU on the basis of 0.033 (a 60 kg woman ingesting 2 L/day). There is no scientifically correct default value to use, so all results related to allowed concentrations in this paper show the use of the first value (50 kg), followed in parentheses and italics by the values using the 60 kg and 70 kg assumptions.

## 2. Precaution and sound science

Environmental regulation relies in part on the Precautionary Principle aimed at addressing problems related to decisions under significant uncertainty and/or where the science is evolving quickly (Deville and Harding, 1997; O’Riordan and Cameron, 1996; Sand, 2000; Sandin, 1999; Stewart, 2002). Following calls to apply the principle in environmental regulations, the European Union produced the 2000 European Commission Communication on the Precautionary Principle (European Commission, 2000; Rogers, 2001; Wiener and Rogers, 2002). It noted that “The precautionary principle applies where scientific evidence is insufficient, inconclusive or uncertain and preliminary scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen by the EU”.

The EC 2000 Communication also notes that poorly nuanced applications of the principle could have unintended side consequences. This leads them to propose six core criteria that should be satisfied for measures taken rationally in the name of precaution:

1. Proportional to the chosen level of protection. The regulatory action taken – and resources allocated - should match the risks posed and the ‘margin of safety’ sought. In the current paper, this criterion calls for the regulation of compounds and their allocation of risk management resources to be in proportion to their contribution to the overall ‘risk cup’.
2. Non-discriminatory in their application. The principle must be applied in the same way to all actions taken in similar situations of risk. For instances of risk from compounds under cumulative and aggregate risk assessment, focus should be on all compounds acting by similar modes, and all such compounds should be treated equivalently.
3. Consistent with similar measures already taken. In the current paper, this issue will be examined by considering whether proposed regulations on perchlorates are consistent with levels of risk implied in past regulations on nitrates.
4. Based on an examination of the potential benefits and costs of action or lack of action. In the current paper, this criterion is examined through consideration of the most effective allocation of limited regulatory resources across compounds acting by the same mechanism of action.
5. Subject to review, in the light of new scientific data. Actions taken in the name of precaution should be subject to periodic review, and changed as the scientific data allow for more accurate estimates of risk. In the present paper, this refers to re-examination of proposed limits on perchlorates based on advances in the science of cumulative risk assessment.
6. Capable of assigning responsibility for producing the scientific evidence necessary for a more comprehensive risk assessment.

All of these criteria are relevant in the current case, although only the first five inform the analysis. Especially significant are Criterion 5, calling for application of the advances in cumulative and aggregate risk mentioned in Section 1; a combination of Criteria 1 through 4 which call for explicit consideration of available regulatory options for control of multiple compounds acting through the same mechanism of action; and Criterion 3 which will be used in examining the implications of stringent perchlorates regulations for control of risks from nitrates (since that criterion calls for logical and practical consistency across perchlorates and nitrates to the extent that these two are components of a similar mechanism of action).

Taken together, these five criteria provide the basis of the examination of regulatory rationality in instances of cumulative and aggregate risk. See the Acknowledgements at the end of this paper for the implications of the sixth criterion. These criteria in turn provide a partial basis for an assessment of 'sound science' and 'weight of evidence' determinations in regulatory assessment.

### **3. Re-analysis using advances in assigning threshold IUI**

Two previous papers (Crawford-Brown 2015a, 2015b) assessed the implications of alternative approaches to treatment of cumulative risk with respect to regulation of perchlorates and to allocation of regulatory and public health resources across perchlorates, nitrates and thiocyanates. Those analyses were based on a variety of candidate approaches to the application of cumulative and aggregate risk to reinterpret the original study of Greer et al (2002), the study that forms the basis for regulatory risk assessment of perchlorates in the US and EU. Both papers used the concept of Perchlorates Equivalent Concentration (PEC) to place the three compounds onto an equivalent basis proportional to their ability to reach the target organ (thyroid) and induce iodide uptake inhibition through the NIS mechanism. The ratios of effective dose per unit ingested mass (the basis of current regulatory limits) applied were 1:0.5:240 for perchlorates, thiocyanates and nitrates, respectively, on the basis of equivalent mass (rather than molar) serum concentration corrected for circulation half-lives of each compound in serum (Tonacchera et al 2004; Sanchez et al 2007). These values are 1:8.8:150 if no correction for circulation half-times is applied.

In Crawford-Brown (2015a), the magnitude of Iodide Uptake Inhibition (IUI) required to induce down-stream adverse health effects was taken to be an upper bound of 50% based on the US National Research Council review (NRC, 2005), and a lower bound of 5% based on the recent analysis by the EFSA (2014c) and OEHHA (2015). These two values were used to produce upper and lower bound estimates on allowed concentrations. However, these bounds were primarily the result of expert judgment and, in the case of the value of 5%, a decision to introduce a significant level of precaution or margin of safety for pregnant women, fetuses, newborns and toddlers, or the mildly to moderately iodine-deficient subpopulation.

In the current paper, an additional analysis is performed using a more recent analysis of the dose-response characteristics for IUI and its relationship to potentially adverse health outcomes, which produces a value of 20% IUI (Weterings et al 2016) for application as a Benchmark Response (BMR) in benchmark dose analysis. This value is especially significant here because it results from a reinterpretation of the Greer et al (2002) data and hence fits appropriately into the line of argument developed in the current paper. Both the risk and risk management implications under this value of 20% are developed here. The value of 5% is also presented so comparisons can be made with risk estimates and risk management implications under that value.

Turning first to the risk calculation and a potential regulatory limit on perchlorates exposures, the calculation of allowed perchlorates concentration in water under the two benchmark levels of IUI (5% and 20%) employ the same methodology as in Crawford-Brown (2015a, 2015b). This includes the following background intakes (RfD in the US or TDI in the EU) of the three compounds in determining the cumulative (PEC) exposures in the Greer et al (2002) study (see details in Crawford-Brown 2015a):

- Perchlorates in water: 0.004 µg/kg-day
- Total goitrogens (acting through the sodium-iodide symporter or NIS mechanism) in water: 0.054 µg(PEC)/kg-day with half-life correction
- Total goitrogens (acting through the NIS mechanism) in food: 22.8 µg(PEC)/kg-day with half-life correction.

The suggested regulatory limit on perchlorates exposure in water using the methodology of Crawford-Brown (2015a) without accounting for cumulative and aggregate exposure and with the 20% IUI value, is 160 µg/L (*192 µg/L for 60 kg; 224 µg/L for 70 kg*) resulting in an Average Daily Rate of Intake or ADRI of 6.3 µg/kg-day. By contrast, the value for 5% is 38 µg/L (*46 µg/L for 60 kg; 53 µg/L for 70 kg*) with an ADRI of 1.5 µg/kg-day. Here, the value of the regulatory limit on concentration refers to that for perchlorates alone. All calculations here and below assume an identical uncertainty factor of 10 applied to the ADRI associated with the indicated IUI percentage.

The regulatory limit on perchlorates exposure in water accounting for cumulative and aggregate exposure in reinterpreting the Greer et al (2002) results, and with the 20% IUI value (again, based on the methodology of Crawford-Brown 2015a), is 747 µg/L (*896 µg/L for 60 kg; 1,046 µg/L for 70 kg*) with an ADRI of 29.9 µg(PEC)/kg-day. By contrast, the value for 5% IUI is 635 µg/L (*762 µg/L for 60 kg; 890 µg/L for 70 kg*) with an ADRI of 25.4 µg(PEC)/kg-day. Again, the value of the regulatory limit on concentration refers to that for perchlorates alone, and therefore the calculation of risk from water alone does not use aggregate exposures. All of these calculations apply an uncertainty factor of 10 to the incremental perchlorates exposures in the Greer et al (2002) study. The influence of a different set of assumptions for treating uncertainty is considered in the Conclusions section of the current paper.

Note the increase by a factor of 4.7 in potential regulatory limit on perchlorates in water with reinterpretation of the Greer et al (2002) data under cumulative risk, using the 20% IUI value (a factor of 16.7 increase for the case of 5% IUI).

#### **4. Rationality of resource allocation for risk management**

Turning next to the issue of risk management, a previous paper (Crawford-Brown 2015b) used Monte Carlo analysis to estimate the percentage of individuals with a Relative Risk (essentially a Hazard Index) above 1, and the contribution of each of the three indicated compounds to this percentage (of individuals with a Relative Risk of 1 or more). The need to include Monte Carlo analysis in addition to cumulative risk assessment has been recognised in the scientific assessment of risk from IUI compounds, with the USEPA Science Advisory Board stating the need for advances in these two topical areas (SAB 2013). In that assessment of the state of the science and the gaps in knowledge required for risk assessment, they take particular note of advances needed in the ability “...to perform [probabilistic risk assessment via a] Monte Carlo analysis [of the exposure data] to address variability in the human population”, as well as “...The contributions to NIS inhibition from other NIS inhibitors (e.g., thiocyanate, nitrate)”. The current analysis utilizing both cumulative risk and Monte Carlo methodology contributes to filling those gaps.

The original analysis (Crawford-Brown 2015b) considered exposures to the three compounds in US food and water, in keeping with the fact that background exposures to all three compounds in the Greer et al (2002) study were those of the US population. Values of both concentration and intake rate (called the Exposure Factor in the US) were assigned lognormal distributions, as is the case for many environmental and biological parameters (Singh et al. 1997). A lognormal distribution is described by a median value in the population (the value for which 50% of the population is above and below this value) and a geometric standard deviation (GSD), which is the equivalent of a standard deviation in a normal or Gaussian distribution. All distributions are characterized by a GSD of 1.5 and truncated in the current paper at 3 GSDs from the median both because this is common risk assessment practice for probabilistic analyses and to make comparisons possible with the paper by Crawford-Brown (2015b) on US exposures.

The analysis of cumulative risk in the exposed population is extended here to the EU population using both the 5% and 20% IUI values. Distributions for perchlorates concentration were obtained primarily from recent data and analyses developed by the EFSA (2014c), based on a sample of slightly over 9200 food items. The total sample size was 11,675, but 2,467 samples were considered 'suspect' by the EFSA either because they were improperly randomised or had values outside an expected range – being much higher than expected and indicating the possibility of sample contamination or improper conduct of the measurement protocol. The sample of 9,200 was used, and is continued in the current study.

Results are summarized in Table 1. Values are provided for scenarios of correlated intakes and uncorrelated intakes. Correlated intakes are ones where an individual is exposed to the same concentration in a given medium on every day of exposure. Uncorrelated intakes are ones where the concentration varies for the individual day-to-day. These two approaches yield different results (uncorrelated exposures 'average out' daily variability) and so are included here to check for the sensitivity of findings to these assumptions.

As in Crawford-Brown (2015b) the probabilistic (Monte Carlo) methodology used here proceeds in the following steps:

1. The primary environmental media through which exposures occur are established; here they are water plus each food and drink category (dominated by fruits and vegetables, and by milk).
2. The risk agents for which exposure data exist are established (perchlorates, nitrates and thiocyanates); other goitrogens with same mechanism of action exist such as bromide and chlorate, but adequate exposure data are not yet available, although data are being collected currently.
3. Inter-subject variability in the values of concentration  $C$  for each of the three risk agents in water and different food categories is established as a lognormal probability density function (PDF) with median, GSD and level of truncation as described in previous paragraphs. These values of  $C$  use the PEC concept mentioned previously.
4. Inter-subject variability in the values of exposure factor (daily rate of intake of a medium such as food or water per unit body mass)  $EF$  for each environmental medium is established as a lognormal probability density function (PDF) with median, GSD and level of truncation. The distribution is taken from the EFSA Concise European Food Consumption Database (accessed at [www.efsa.europa.eu/en/datex/datexfoodcdb](http://www.efsa.europa.eu/en/datex/datexfoodcdb)). Values of  $C$  and  $EF$  for perchlorates are taken from Appendix B of EFSA (2014c) and the value of  $EF$  is assumed to

apply uniformly to the compounds ingested. They are selected to produce the same ratio of the 95<sup>th</sup> percentile to the central tendency value for ADRI contained in the EFSA report (i.e. they are selected so the GSD squared is equal to this ratio), so the underlying distributional characteristics are identical. The same values of intake rates for food, water and drink categories are assumed for all three compounds considered. Values of C for nitrates are taken from the database provided by CONTAM through [www.efsa.europa.eu/en/efsajournal/pub/689](http://www.efsa.europa.eu/en/efsajournal/pub/689)). Data on thiocyanates in food is largely restricted to the potassium form in the EU ([www.efsa.europa.eu/en/efsajournal/pub/2922](http://www.efsa.europa.eu/en/efsajournal/pub/2922)), and is much less developed than for nitrates. Therefore, the value of C for thiocyanates was taken from Crawford-Brown (2015a; 2015b) based on the more extensive US data; it is justified by the consistency of thiocyanates concentrations across western nations within a single category of crop, in contrast to nitrates which can vary widely.

5. For intakes via drinking water, the values of C for nitrates do not follow a single lognormal distribution function due to the presence of both surface and ground water in the supply, with different medians and GSDs, and the presence or absence of industrial (largely agricultural) activities that influence the values of C. These two separate distributions are obtained from the summaries in EU Implementation of Nitrates Directive reports (accessed through [ec.europa.eu/environment/water/water-nitrates/index\\_en.html](http://ec.europa.eu/environment/water/water-nitrates/index_en.html)), which show that 3% of surface water and 15% of groundwater supplies exceed the EU limit on nitrates in water of 50,000 µg NO<sub>3</sub>/L.
6. A random value is drawn from each of the two distributions (C and EF) for each of the three risk agents (perchlorates, nitrates and thiocyanates) and multiplied to obtain the three values of the ADRI required (one each for perchlorates, nitrates and thiocyanates, expressed in PEC units).
7. These three ADRI values are summed to obtain the total (PEC) value of the ADRI across all routes of exposure and compounds.
8. The process is repeated over 50,000 samples. The sampling size was determined by sequentially increasing the number of runs until stability at the upper 95% estimate of the inter-subject variability distribution was obtained (i.e. the estimate of the 95th percentile value changed by less than 1%).
9. The resulting 50,000 values are summarised as a new probability density function for the ADRI (expressed in PEC) in the exposed population, which is also approximately lognormal due to the dominance of one compound (nitrates) in the summed ADRI.
10. A TDI value is selected as the basis for cumulative and aggregate risk assessment and management. The sum of the ADRI values (PEC) for each individual are divided by this TDI to produce the risk ratio RR. The inter-subject variability distribution of these RR values is then used to calculate the percentage of the population with an RR value above 1.

These steps are repeated for each of several representative ages to characterise the age dependence of the risk results, and for each of the two cases of 'completely correlated' and 'completely uncorrelated' exposures. The ages selected correspond to those used by the EFSA (EFSA 2011; 2014): infants (up to and including 11 months), toddlers (from 12 up to and including 35 months of age), young children (from 36 months up to and including 9 years of age), adolescents (from 10 up to and including 17 years of age), adults (from 18 up to and including 64 years of age), elderly (from 65 up to and including 74 years of age) and very elderly (from 75 years of age and older). In addition, a separate category of pregnant woman is included since this represents a potentially sensitive subpopulation (although values for EF were selected from Crawford-Brown (2015b) as these are not separated out in the EFSA database). The methodology is therefore identical to that of Crawford-Brown (2015b) under approach 4b in that paper, with adjustments for

the differences in values of C and EF for the EU population although with the same GSD. See Table 4 of that paper for comparisons.

Results are presented in Table 1 for the 5% and 20% values of IUI. Both food and water intakes are combined in that table. The values at 5% IUI allow comparison with the EFSA assessment if that assessment had been based on the current cumulative risk approach, while the values at 20% allow for examination of the same public health metric (percentage of population with RR greater than 1) when the most recent estimate of the Benchmark Dose of Weterings et al (2016) is used. Taken together, the two sets of results provide a basis for a sensitivity analysis of the influence of assumed IUI BMD on risk management decisions.

Percentage of population with RR > 1 due to the single goitrogen indicated, food+water combined							
%IUI	Age group	Correlated			Uncorrelated		
		Perchlorate	Nitrates	Thiocyanates	Perchlorate	Nitrates	Thiocyanates
5%	Infants	<0.3	12.1	22.1	<0.3	8.7	19.9
	Toddlers	<0.3	13.3	30.2	<0.3	9.5	27.2
	Young children	<0.3	15.9	31.4	<0.3	11.4	28.3
	Adolescents	<0.3	12.1	21.3	<0.3	8.7	19.2
	Adults	<0.3	11.8	22.6	<0.3	8.5	20.3
	Elderly	<0.3	11.7	20.1	<0.3	8.4	18.1
	Very elderly	<0.3	12.2	20.1	<0.3	8.8	18.1
	Pregnant women	<0.3	21.1	24.3	<0.3	15.2	21.9
	20%	Infants	<0.3	9.1	16.6	<0.3	6.5
Toddlers		<0.3	9.9	22.7	<0.3	7.2	20.4
Young children		<0.3	11.9	23.6	<0.3	8.6	21.2
Adolescents		<0.3	9.1	16.0	<0.3	6.5	14.4
Adults		<0.3	8.9	17.0	<0.3	6.4	15.3
Elderly		<0.3	8.8	15.1	<0.3	6.3	13.6
Very elderly		<0.3	9.2	15.1	<0.3	6.6	13.6
Pregnant women		<0.3	15.8	18.2	<0.3	11.4	16.4

**Table 1.** Percentage of the exposed population with a Relative Risk (RR) greater than 1 due to the single compound considered, using cumulative and aggregate risk in interpreting the Greer et al (2002) data (using food + water intakes). Values are shown for different age groups and for the two levels of IUI BMD considered here. The two candidate values of the percentage IUI are 5% and 20%. A value of <0.3% indicates the effects of truncation of the distributions, which does not allow resolution of results below this percentage.

Note the strong dominance of nitrates and thiocyanates in producing exposures that yield RR values greater than 1. This pattern is retained across the age groups and whether intakes are correlated or uncorrelated. Note also that the assumption of uncorrelated intakes produces percentages (with RR greater than 1) that are smaller, since the uncorrelated intakes ‘average out’ for an individual’s values of C over the course of several weeks.

If only water intakes are considered, the values of RR are shown in Table 2. The same procedure as in Table 1 is used, with the exception of removing intakes via food. The percentages from ‘food only’ intakes are approximately the differences of results in the two tables.

Percentage of population with RR > 1 due to the single goitrogen indicated, water only

%IUI	Age group	Correlated			Uncorrelated		
		Perchlorate	Nitrates	Thiocyanates	Perchlorate	Nitrates	Thiocyanates
5%	Infants	<0.3	1.3	<0.3	<0.3	1.0	<0.3
	Toddlers	<0.3	1.5	<0.3	<0.3	1.1	<0.3
	Young children	<0.3	1.7	<0.3	<0.3	1.3	<0.3
	Adolescents	<0.3	1.3	<0.3	<0.3	1.0	<0.3
	Adults	<0.3	1.3	<0.3	<0.3	0.9	<0.3
	Elderly	<0.3	1.3	<0.3	<0.3	0.9	<0.3
	Very elderly	<0.3	1.3	<0.3	<0.3	1.0	<0.3
	Pregnant women	<0.3	2.3	<0.3	<0.3	1.7	<0.3
20%	Infants	<0.3	1.0	<0.3	<0.3	0.7	<0.3
	Toddlers	<0.3	1.1	<0.3	<0.3	0.8	<0.3
	Young children	<0.3	1.3	<0.3	<0.3	0.9	<0.3
	Adolescents	<0.3	1.0	<0.3	<0.3	0.7	<0.3
	Adults	<0.3	1.0	<0.3	<0.3	0.7	<0.3
	Elderly	<0.3	1.0	<0.3	<0.3	0.7	<0.3
	Very elderly	<0.3	1.0	<0.3	<0.3	0.7	<0.3
	Pregnant women	<0.3	1.7	<0.3	<0.3	1.3	<0.3

**Table 2.** Percentage of the exposed population with a Relative Risk (RR) greater than 1 due to the single compound considered, using cumulative and aggregate risk in interpreting the Greer et al (2002) data (using water intakes only). Values are shown for different age groups and for the two levels of IUI BMD considered here. The two candidate values of the percentage IUI are 5% and 20%. A value of <0.3% indicates the effects of truncation of the distributions, which does not allow resolution of results below this percentage.

From Table 1, if the focus is on risk management (rather than simply compound-specific risk assessment), the analysis using cumulative risk demonstrates the need to focus firstly on exposure to thiocyanates and then on nitrates, with a particular focus on subpopulations with iodine deficiencies (for example, through iodine supplements being provided to such subpopulations). However, concentrations of thiocyanates in food and water are less under control by human activities than nitrates, and so regulation of their sources (which are much more diffuse) is significantly more difficult. This leads in the next section to an assessment of the implications of Table 1 for risk management of exposure to nitrates.

## 5. Implications for regulatory coherence for nitrates

Consider now the case of regulatory limits on intakes of nitrates in food or water. At first glance, the analyses of Sections 3 and 4 might appear to suggest a need for greater control on nitrates before stringent controls are placed on perchlorates. This might in turn suggest that current risk management efforts on nitrates are inadequate to protect human health with respect to effects mediated through the IUI mechanism. The analysis below suggests this is not the case, but only appears so if one does not use a cumulative risk methodology to reinterpret the data of Greer et al (2002) in making the comparison of risks across the three compounds.

What are the implications for nitrates of regulatory limits on exposure to perchlorates, if following the precautionary principle the same levels of risk (with respect to NIS and IUI) are allowed? Beginning with some of the more restrictive regulatory limits on perchlorates exposures based on analysis of the Greer et al (2002) data without consideration of cumulative exposures, values of between 15 µg/L (USEPA Health Reference Level) down to 1 µg/L (California Office of Environmental Health Hazard and Assessment) have been proposed, with the EFSA (European Food Safety Authority) CONTAM Panel establishing a tolerable daily intake for perchlorates of 0.3 µg/kg body weight per day, equivalent to 7.5 µg/L with a body weight of 50 kg and intake rate of 2 L/day (9 µg/L

for 60 kg; 10.5 µg/L for 70 kg), so midway between the USEPA and OEHHA values. All three of these values are based on the inhibition of thyroid iodide uptake (IUI) in healthy adults, and on regulatory risk assessments of the Greer et al (2002) data without consideration of cumulative risk.

Regulatory limits on exposure to nitrates are set traditionally on methaemoglobinemia in infants rather than on IUI. However, nitrates are one of the primary compounds to be included in cumulative risk for perchlorates since they also are candidates to produce adverse health impacts through their influence on IUI via the NIS mechanism. Therefore, if the precautionary principle is to be applied consistently across compounds with similar mechanism of action, it is necessary to consider the implications of perchlorates exposure limits on nitrates acting through the IUI mechanism of action if the two compounds are to be regulated at the same level of public health protection against IUI effects.

Imagine for the moment that any of these three proposed values is adopted for exposures to perchlorates in water. As mentioned in Section 3, the PEC conversion factor for nitrates (effective dose per unit ingested mass following correction for serum half-life) is 240 when considering IUI effects. If the same level of risk through IUI is allowed for nitrates as for perchlorates (a requirement of the precautionary principle criteria mentioned in Section 2), the tolerable daily dose for nitrates as developed by the EFSA methodology would be  $0.3 \times 240 = 72$  µg/kg-day. This corresponds to a water concentration of 1,800 µg/L for nitrates using the same adult body mass and water intake rate as for perchlorates (2,160 µg/L for 60 kg; 2,520 µg/L for 70 kg). However, the MCL for nitrates in water (measured as nitrogen) set by the USEPA is 10 mg N/L (see the standard at [www.epa.gov/sites/production/files/2016-06/documents/npwdr\\_complete\\_table.pdf](http://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf)) or 10,000 µg N/L (the equivalent value for NO<sub>3</sub> is 44,000 µg/L). The value established by the EU is 50 mg NO<sub>3</sub>/L or 50,000 µg NO<sub>3</sub>/L. Therefore, the revised regulatory limit for nitrates in water as based on consistent application of IUI risk assessment for both perchlorates and nitrates would appear at first glance to be a factor of  $44,000/1800 = 24$  below the current US MCL for nitrates (20 for 60 kg; 17 for 70 kg), or 27 below to the EU value (both are based on methaemoglobinemia in infants). If true, this would mean the water from the large majority of wells in both the US and EU is producing unacceptable levels of risks from nitrates just taking into account IUI related effects.

There appears on the surface to be a logical contradiction here in that regulatory limits on nitrates seem to be much less protective than perchlorates if IUI effects are considered in water, in violation of the consistency criterion of the precautionary principle. It also appears that the current nitrates exposure limit would need to be reduced by a factor of between 24 (US) and 27 (EU) in water. However, that contradiction arises from the lack of consideration of cumulative risk in reinterpreting the data of Greer et al (2002) for the IUI effects. If the cumulative risk results from Section 3 are instead used as the basis for perchlorates exposure limits, with PEC exposures calculated, there is complete coherence between the perchlorates and nitrates limits on exposure. The equivalent Acceptable Daily Intake for nitrates that would be calculated using the reinterpreted Greer et al (2002) data from Section 3 of the current paper is between 25.4 and 29.9 µg/kg-day (PEC) depending on the IUI value (5% or 20%) required for potentially adverse effects. Using a PEC conversion factor of 240 for nitrates, the equivalent allowed intake rates of nitrates correspond to  $25.4 \times 240 = 6,096$  µg/kg-day (5% IUI), which is a concentration of 152,000 µg/L (182,400 µg/L for 60 kg; 212,800 µg/L for 70 kg) or  $29.9 \times 240 = 7,176$  µg/kg-day (20% IUI), which is a concentration of 179,000 µg NO<sub>3</sub>/L (214,800 µg NO<sub>3</sub>/L for 60 kg; 250,600 µg NO<sub>3</sub>/L for 70 kg). The inconsistency is resolved as the

proposed intake rates for perchlorates and nitrates levels to achieve health protection are both protective, with corresponding allowable concentrations above the 44,000  $\mu\text{g NO}_3 / \text{L}$  (US) and 50,000  $\mu\text{g NO}_3 / \text{L}$  (EU) values cited previously. The fact that any adjustment upwards in allowed concentration based on the current analysis might not be applied is because the actual nitrates exposure limit is not based on IUI.

The problem appears to continue for food exposures. The Acceptable Daily Intake for nitrates in food for the EU is 3.7 mg/kg-day or 3,700  $\mu\text{g/kg-day}$  (see the value at [www.efsa.europa.eu/sites/default/files/scientific\\_output/files/main\\_documents/689.pdf](http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/689.pdf)). Again, this is not based on IUI. Using the analysis in the previous paragraph, the EU ADI for nitrates is a factor of almost 2 lower than that suggested by use of IUI effects under calculations based on cumulative risk. Current nitrates limits in food are therefore protective of health even when IUI effects are included, although again this protectiveness (and compliance with the requirements of the precautionary principle) is evident only when the Greer et al (2002) data are reinterpreted under cumulative risk.

The conclusion of this analysis is that both nitrates and perchlorates can be accommodated under the regulatory limits developed here through reinterpretation of the Greer et al (2002) data, with both being placed onto a shared level of health protection.

## **6. Intersubject variability and fraction of population protected**

The EFSA analysis of perchlorates risks use only the median and 95<sup>th</sup> percentile values of the exposure parameters. The exposure parameters used in Table 1 here uses a distribution with the same median and 95<sup>th</sup> percentile values as in the EFSA analysis so differences in results will be isolated in the application of cumulative risk and Monte Carlo methodologies rather than in choice of characteristics of the distributions.

The EFSA approach of using either a median or 95<sup>th</sup> percentile for parameters is well suited to some forms of regulatory analysis in which one wants to estimate the intake rate (and hence the Relative Risk as defined in section 4) for an individual likely to be the most highly exposed in the population. However, when that approach to precaution or conservatism is used in cumulative risk assessment, two problems emerge:

- The calculation produces a 'hypothetical' individual which is a composite of exposure parameters from the underlying distributions, all selected to be near the upper end of the individual parameter distributions.
- The regulator cannot specify the percentage of the population protected (only that the percentage is 'high' – above 95%). This is not adequate for performing risk-cost-benefit calculations as required by the fourth criterion of the precautionary principle.

The result of both of these limitations in the treatment of inter-subject variability is that a regulator does not know what specific percentage of the population has a Relative Risk above 1 (other than that this percentage – whatever it is – is very unlikely to be exceeded in an actual population). This arises firstly because the median and 95<sup>th</sup> percentiles used in the EFSA analysis correspond to

percentiles of the individual exposure parameter distributions and not to the distribution of values of Relative Risk. It arises secondly because the resulting distribution is not of any particular parametric form. This in turn prevents a cost-benefit calculation for cases of managing cumulative exposures, since the non-linear relationship between exposure and effect means the median and 95<sup>th</sup> percentiles are insufficient to specify the full distribution required in cost-benefit analysis, since the relationship between median and mean is not analytically clear.

To test the implications of this difference between the two approaches to treatment of intersubject variability (the EFSA default approach that uses only the median and 95<sup>th</sup> percentile and the full Monte Carlo probabilistic analysis used here), a comparison has been made of the median and 95<sup>th</sup> percentile of the full distributions of values of RR in the exposed population in Table 1 and the value calculated using the median and 95<sup>th</sup> percentiles of the exposure parameter values as employed by the EFSA. Results are provided in Table 2. In addition to application of Monte Carlo analysis, all values use the cumulative and aggregate risk assessment methodology employed in previous sections. The intent here is therefore to test the effect of using fully probabilistic analysis rather than ‘upper bound’ values for all parameters.

%IUI	Age group	Median	95th
5%	Infants	1.1	1.3
	Toddlers	1.3	1.5
	Young children	1.3	1.5
	Adolescents	0.9	1.4
	Adults	0.9	1.5
	Elderly	1.2	1.5
	Very elderly	1.2	1.5
	Pregnant women	1.2	1.5
20%	Infants	1.2	1.4
	Toddlers	1.2	1.4
	Young children	1.3	1.4
	Adolescents	1.0	1.6
	Adults	0.9	1.3
	Elderly	1.1	1.5
	Very elderly	1.3	1.5
	Pregnant women	0.9	1.5

**Table 2.** Summary of the ratio of the median value of cumulative Relative Risk using the EFSA methodology over the median value from the Monte Carlo analysis (food+water combined), and the same ratio for the 95<sup>th</sup> percentiles. The methodology is the same as that in Table 1.

Table 2 suggests two features of the use of the EFSA (and the same for the USEPA) approach, which uses ‘upper bound’ (usually 95%) values for parameters in calculating exposures:

- Compared to full Monte Carlo analysis, the default EFSA and USEPA methodology for treating inter-subject variability of risk achieves approximately the correct answers for median values of the Relative Risk in a population when the cumulative and aggregate risk methodology of earlier sections is applied. This is primarily because the current Monte Carlo analysis here uses a distribution for C and EF which is the median of that employed by the EFSA.

- The default (non-Monte Carlo) approach however overstates the Relative Risk for individuals who are at the upper end of the distribution of values in the population, doing so by factors of between 1.3 and 1.6. Since risks to individuals at the upper percentiles of the distribution across the exposed population are usually used in regulatory decisions, this analysis suggests the default methodology will overstate the risk to the upper end individual by approximately 50%.

## 7. Conclusions

The results here provide a significantly different set of implications for risk, regulation and risk mitigation of perchlorates when compared against the traditional assessment approach of interpreting the data of the Greer et al (2002) study. These differences are due to application of cumulative/aggregate risk in interpreting those data, and to use of fully probabilistic Monte Carlo analysis in considering relative contributions of the three compounds to effectiveness of risk mitigation efforts.

As noted in earlier sections, proposed exposure limits for perchlorates in water under the traditional approach have been in the range between 1 and 20 µg/L when the Greer et al (2002) data are interpreted as being due solely to the administered intake of perchlorates in water. By contrast, the current analysis using cumulative and aggregate risk to reinterpret those same data suggest the regulatory limit for the action of perchlorates in water alone would be closer to 600 µg/L (635 µg/L for 5% IUI and 747 µg/L for 20% IUI) using the default 50 kg body weight here (*762 µg/L for 60 kg and 890 µg/L for 70 kg if 5% IUI is used; 896 µg/L for 60 kg and 1,046 µg/L for 70 kg if 20% IUI is used*). They further suggest that the risk of IUI effects mediated by the NIS mechanism of action is dominated strongly by thiocyanates and nitrates, and through food rather than water exposure routes. Both findings have the implication that the Tolerable Daily Intake (TDI) currently under consideration by the EU (EFSA) should be expressed as PEC rather than perchlorates alone, using the methods of cumulative and aggregate risk to reinterpret the data of Greer et al (2002). If this is done, the TDI would increase by a factor of approximately 20.

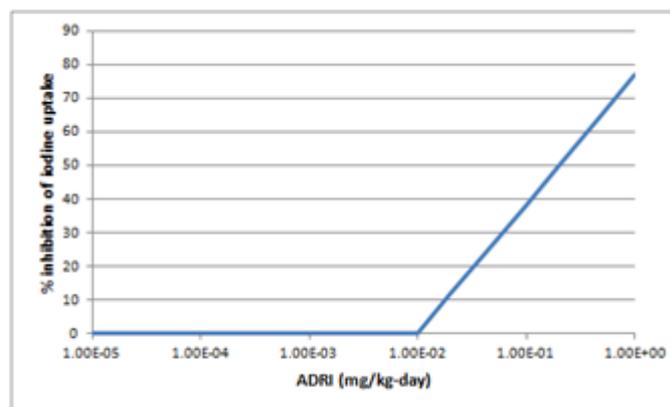
The same results of the present analysis resolve a looming issue of inconsistency in risk levels for allowed concentrations of nitrates allowed in food and water if the IUI effects are included in risk assessments in the absence of reinterpretation of the Greer et al (2002) study under cumulative and aggregate risk. In that absence, existing regulatory limits on exposures to nitrates would appear to be non-protective of public health due to nitrates' IUI effects. Application of cumulative and aggregate risk methodologies as detailed here resolve this problem as well as making the risks approximately equal across the IUI compounds considered here. This removes both a logical inconsistency and a violation of the criteria of the precautionary principle.

From Table 2, note the low percentages of individuals with values of RR greater than 1 in the case of 'water only' intakes. This arises in the present analysis due to small pockets of high levels of exposure (values of C) rather than primarily due to subpopulations with high values of EF. The implication is that allocation of risk management resources ought to be directed at identifying these geographic 'hot spots' (water supplies) and instituting controls on pollutant loading into the source waters, as well as focusing on iodine-deficient subpopulations, perhaps with iodine supplementation.

Note that this is a different approach to risk management than the approach traditionally followed, since one moves directly to consideration of risk management strategies rather than passing through a stage of establishing exposure limits for each individual compound. However, limits on exposure are still established, although in the form of PEC in a mixture rather than exposure to the separate compounds in the mixture of NIS-IUI compounds. As mentioned previously, such an approach has been common practice in radionuclides and dioxin-like compounds, so is not a complete revision of the traditional regulatory procedure.

A question remains concerning how uncertainty factors are to be introduced into the reinterpretation of the Greer et al (2002) results. All of the results in earlier sections applied an uncertainty factor of 10 to the incremental effect of perchlorates on IUI, but not to the background intakes. The reasoning was that the background exposures in the Greer et al (2002) study population had already been accommodated in the homeostatic response prior to the administered perchlorate, so no uncertainty factor was needed for reducing these. Those background exposures already were protective, which is why the exposure-response curves in the Greer et al (2002) study becomes horizontal as one moves down towards environmental (background) levels of exposure to the administered perchlorate.

There is however a different way to interpret the Greer et al (2002) data with respect to cumulative and aggregate risk. The x-axis of the exposure-response curve developed from that study displays the value of ADRI for perchlorates administered exposure. Suppose one argues that any given level of IUI on the y-axis of the curve is caused not by the sole action of the administered perchlorate, but rather by the combined action of the three compounds, including the background exposures. This combined exposure, including the administered perchlorate, could then be used to create a new x-axis, where ADRI now refers to the PEC exposure to all three compounds. If a threshold value of IUI is adopted, a value of ADRI(PEC) can then be identified from the new exposure-response curve. The uncertainty factor might then be applied to this threshold expressed as ADRI(PEC).



**Figure 1.** The Greer et al (2020) data on exposure (ADRI) versus IUI. This figure uses the original (perchlorates) units of exposure. These are then adjusted for background exposures to produce ADRI(PEC) using the background values of earlier sections of this paper.

What would be the effect of taking this approach to application of the uncertainty factor? To explore this, the EFSA recommended uncertainty factor of 4 is applied to this new ADRI(PEC) threshold or TDI. In this case, the regulatory limit for the three compounds reduces from the previous value of 747  $\mu\text{g(PEC)/L}$  (896  $\mu\text{g(PEC)/L}$  for 60 kg; 1,046  $\mu\text{g(PEC)/L}$  for 70 kg) down to 563  $\mu\text{g(PEC)/L}$  (676

$\mu\text{g(PEC)/L}$  for 60 kg; 788  $\mu\text{g(PEC)/L}$  for 70 kg) for 20% IUI. The regulatory limit for the three compounds combined reduces from the previous value of 635  $\mu\text{g(PEC)/L}$  (762  $\mu\text{g(PEC)/L}$  for 60 kg; 889  $\mu\text{g(PEC)/L}$  for 70 kg) down to 375  $\mu\text{g(PEC)/L}$  (450  $\mu\text{g(PEC)/L}$  for 60 kg; 525  $\mu\text{g(PEC)/L}$  for 70 kg) for 5% IUI. While the first option is the preferred interpretation scientifically (due to the action of the homeostatic mechanism as described above), this revised approach to uncertainty factors still produces the same results with respect to all of the conclusions of the previous sections, including the conclusion that nitrates exposure limits are already protective even when IUI effects are considered.

Primary conclusions and associated recommendations from the results of the cumulative risk analyses in Sections 1-6 are:

1. If there is an effect of perchlorates exposures at concentrations below several hundred  $\mu\text{g/L}$ , it is small compared to the effect of nitrates and thiocyanates that also act on IUI through the NIS mechanism of action. Therefore regulatory actions should focus firstly on nitrates and thiocyanates exposures.
2. If the focus is on nitrates, the current analysis suggests limits on intake of nitrates are already adequately protective in both water and food, even if IUI effects are included.
3. Failure to account for cumulative risk in interpreting the primary study used in examining perchlorates risks (Greer et al 2002) can lead to large overstatements of the risks from nitrates in food and water. This logical inconsistency – in which regulatory limits on perchlorates in water appear at first glance to require large reductions in regulatory limits on nitrates - arises from the (incorrect) assumption that effects in the Greer et al (2002) study can be assigned to the incremental exposure to perchlorates alone in that study.
4. When a PEC approach is used to reinterpret the Greer et al (2002) data, there is no need to further reduce exposure limits on nitrates in either water or food beyond those based on the current ADI.
5. Application of full Monte Carlo analysis indicates that risks to individuals at the 95<sup>th</sup> percentile of the distribution of exposures are overstated by approximately 50% when the traditional approach to regulatory risk assessment is used, in which only the 95<sup>th</sup> percentile values for each exposure parameter are employed in estimates of intake from food and water. Ensuring a consistent level of ‘margin of safety’ to protect the more vulnerable individuals across different sources of risk is therefore better approached through full probabilistic/Monte Carlo methods, which allow regulators to understand and quantify the percentage of the population protected by any given proposed regulatory limit on concentrations in the environment.

It is time for cumulative risk to be placed at the centre of regulatory risk assessment, supplemented by Monte Carlo analysis. Failure to do so results in violations of several of the core criteria of the precautionary principle.

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