The provision of a scientifically defensible basis for perchlorate and goitrogen exposure limits

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Abstract

This Working Paper first considers the rationality of regulatory decisions on environmental exposures characterised by cumulative and aggregate risk pathways. This leads to development of a methodology for aggregate and cumulative risk assessment for compounds acting through the same mode of action, and uses that methodology to consider the exemplar case of alternative scientific strategies for determining potential regulatory limits on exposures to waterborne perchlorate in the presence of other goitrogens. Focus is primarily on intakes through water, although the implications of exposure to goitrogens through food are mentioned because the report is concerned with application of both aggregate and cumulative risk assessment in the practice of protecting public health against environmental exposures.

The four approaches considered here yield the following estimates of the safe levels of perchlorate in water (when perchlorate in water is the sole intake of goitrogens) or total goitrogens (PEC; where there are multiple goitrogens present in the water but again where water is the sole route of exposure):

- Approach 1: 18 µg/L
- Approach 2: 400 µg/L
- Approach 3: 338 µg/L (without serum half-life correction) or 572 µg/L (with serum half-life correction)
- Approach 4: 737 µg/L (without serum half-life correction) or 973 µg/L (with serum half-life correction)

Where water is not the sole route of exposure and perchlorate is not the sole goitrogen, the results of Approaches 3 and 4 can be applied to mixtures of goitrogens that produce these values as PECs. Results of the analysis suggest that compound-by-compound regulatory limits may be better dealt with through a change to risk-based management strategies that are built around the concept of a risk cup for susceptible subpopulations.

Keywords: Cumulative risk; Aggregate risk; Goitrogens; Perchlorate; Regulatory rationality
1. Regulatory rationality

Regulatory decisions must eventually consider how to treat cases of intakes of contaminants when people are exposed through multiple pathways and to a mixture of these contaminants. The question arises because the first step in establishing a safe level of exposure to a contaminant has historically been to consider it as a single contaminant (e.g. perchlorate) in a single medium (e.g. water), and then to ask: What is the highest level of exposure to that contaminant in that medium that would, by itself, produce an acceptable level of risk? This then raises a question of whether the public is being protected against unacceptable levels of health risk if an individual is exposed to multiple contaminants through multiple routes: the problem of aggregate and cumulative risk.

In the earliest regulations, it was recognized that regulatory limits have built-in margins of safety, introduced in the form of uncertainty factors, upper confidence bounds on risk coefficients, maximally plausible scenarios of exposure, etc. The assumption was that an individual might be exposed to several contaminants via several pathways, but that the overall risk (called the ‘risk cup’\(^1\)) would still be acceptable due to the presence of the margins of safety.

With the environmental justice movement in the US\(^2\), it was recognized that there were some populations - especially poorer minorities - who were exposed at times to dozens of contaminants, each at levels deemed safe individually, but which together would cause the risk cup to ‘overflow’. The first treatment of this issue was to consider aggregate risk, in which an individual is exposed to the same contaminant through multiple routes (water, food, etc). The concept of Relative Source Contribution (RSC) was introduced, which attempted to quantify the percentage of exposure through any single route, and to adjust the regulatory limit on that single route accordingly. If a safe level of exposure was 10 mg/kg-day in a single medium (such as water) when exposure is only through that medium, and if that medium contributed only 50% of the total exposure by all pathways combined, the regulatory limit in the single medium was adjusted downwards to 0.5 x 10 = 5 mg/kg-day to allow for ‘space’ in the risk cup for the other pathways of exposure.

An important point to note here is that treatment of the concept of a risk cup through application of RSCs, changed the regulatory question from one of “What total level of exposure to the contaminant by all routes would be acceptable in a real population?” to one of “What level of exposure to the contaminant - through each individual route - would be acceptable if an individual were exposed to each route at its maximally allowed limit?”.

In other words, a hypothetical individual was envisioned who might be exposed to the contaminant in water, food, etc at the maximally allowed limit in each of these environmental media simultaneously. Under these conditions, application of the RSC is a valid interpretation of the concept of a risk cup under aggregate (although not cumulative) exposure.

The challenge faced by regulators under these conditions is that there was an understandable desire to have limits on exposure that applied nationally and would be protective of public health even at the extremes where a single individual is exposed at the regulatory limit in each of several

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environmental media. Otherwise, limits on exposure in any one medium (such as water) might need to differ in different geographic regions and for different individuals due to differences in the contributions of other exposure routes to the total risk cup. While the science made it clear that this would indeed be the case – that allowed local exposures through water for example might need to vary depending on local exposures through food – the policy community did not want different regulatory limits in different geographic areas and for different individuals. To do so would appear – at least on the surface – to raise many of the issues that were found in environmental justice of apparently unequal treatments under the law.

The problem became more acute in the 1980s with the introduction of cumulative risk assessment, driven again by concerns for environmental justice but also by increasing understanding of the biological and biochemical bases for modes of action. Even with application of RSCs, an individual could be exposed to multiple contaminants (by the same route or otherwise), each at its regulatory limit. The total risk cup could in these cases begin to ‘overflow’ and the cumulative risk rise above that deemed acceptable.

It was recognized that the approach of using RSCs as a way of dealing with the risk cup was infeasible for cumulative risk because there were too many combinations of contaminants to which individuals in a population might be exposed. This would lead to regulatory limits on each contaminant and each exposure route that would vary from individual to individual depending on geographic location, diet, etc. To deal with this, the regulatory community first introduced the concept of Hazard Index (HI), equal to the sum of the Hazard Quotients (HQ) across all applicable contaminants with the same mode of action. The HQ is the ratio of the actual ADRI (average daily rate of intake) for an individual, expressed in units of the Reference Dose (RfD, in for example mg/kg-day) divided by the RfD itself. (Note: The RfD is a regulatory term in the US. In the EU, the RfD is replaced by the Tolerable Daily Intake or TDI, and in the WHO by the Provisional Maximal Tolerable Daily Intake or PMTDI; in this paper, RfD is used but the analysis applies also to TDI and PMTDI).

An HQ of 1 occurs when an individual is exposed at exactly the regulatory limit RfD; an HQ of less than 1 occurs when an individual is exposed at below the RfD; and an HQ of greater than 1 occurs when an individual is exposed at above the RfD. The regulatory reasoning was that individuals should not have a total exposure by all routes and to all contaminants with the same mode of action that produced an HI above 1.

Even this advance did not fully address the issue of a risk cup under cumulative risk, because it was applied only to contaminants with the same mode of action. So long as it was assumed that the regulatory limits on exposures were sufficient to prevent any risk (probability) of adverse effect, this issue was not a problem because individuals were fully protected against each individual category of contaminants (a category consisting of contaminants with the same mode of action), each of which were as a consequence producing zero risk. So the sum of these risks over all possible categories of contaminants would also be zero. The strongest initial application of this methodology was in superfund site remediation programmes in the US.

However, this approach was based on the assumption of distinct exposure thresholds for adverse effect, below which the risk was zero; the exception was for carcinogens, where probabilities of cancer or premature death were summed across all carcinogens rather than using the HQ and HI concepts. Advances in the science of risk assessment made it clear in the 1990s that this assumption
of a distinct threshold was a regulatory construct – and a holdout from the very early days of industrial hygiene – but that it was not scientifically correct for most contaminants. An apparent threshold in exposure was an artifact of epidemiological and clinical studies in which sequential reduction in the level of exposure eventually reached a point where the statistical noise of measurements made it impossible to discern any excess probability of effect even if that probability was truly non-zero. Note that this is equivalent to the concept of No Observed Effects Level (NOEL) or No Observed Adverse Effects Level (NOAEL) in regulatory assessments, where the emphasis is on ‘observed’ rather than ‘actual’ existence of effects. This in turn resulted in a programme to harmonise carcinogen and non-carcinogen risk assessment using stochastic models of exposure-response; that programme is still under development due to its scientific complexity and the fact that it would re-write the procedures for establishing regulatory limits on non-carcinogens.

Upon recognising these issues, the scientific community in the policy world began to move towards the only procedure that would fully treat aggregate and cumulative risk under a risk cup: probabilistic risk assessment. In this methodology, probability density functions (PDFs) are established for exposures of individuals to each contaminant by each route of exposure, correlations between exposure routes and contaminants are established (so the individual PDFs are correlated), and Monte Carlo (or similar) procedures are used to calculate the PDF of total risk across individuals in a population. For example, this final PDF would describe the fraction of individuals in a distinct population who would have a risk below X, below Y, etc. If the measure of risk were the HI, the final PDF would show the fraction of individuals with an HI below 0.1, below 1, below 2, etc. Rather than simply applying regulatory limits on exposure to each contaminant through each route, probabilistic risk assessment allows the regulatory community to identify the fraction of people exposed to unacceptably large risks (an overflowing risk cup) in a specific, real, population; to identify why they are at such high levels of risk; and to target risk reduction resources most effectively at reducing this risk. Note that the focus here is not on a hypothetical individual exposed to all contaminants and all routes at the maximally allowed limits for each separate contaminant and route, but rather on the actual exposures of real individuals in the population so limited regulatory resources can have the greatest effect on reducing the risks in the vulnerable populations (those individuals at the upper end of the total risk PDF mentioned above).

However, if the policy decision is that this more scientifically sound approach to risk assessment and risk management is not desired (for whatever reason might be offered), regulators must turn back to how regulatory limits are established currently. Here the lesson from perchlorate is exemplary. The reasoning behind treating aggregate and cumulative risk through application of an RSC (which technically only treats aggregate risk) has been for perchlorate:

1. The Greer et al\textsuperscript{3} study suggests a NOEL for perchlorate of X mg/kg-day
2. This NOEL is associated purely with exposures to perchlorate through water
3. Uncertainty in whether this will be protective of health in all individuals requires application of one or more uncertainty factors, which reduces the NOEL to an RfD of X/UF = Y mg/kg-day; this provides a margin of safety for perchlorate alone
4. If the three premises above are correct, the allowable limit on perchlorate in water is Z mg/L

Individuals exposed at this limit \( Z \) will have their risk cup for at least perchlorate filled

However, they are not exposed only through water; they also are exposed through food

Assume a fraction \( F \) of the total perchlorate exposure is through water

The value of \( Y \) should therefore be reduced to \( Z \times F = C \, \text{mg/L} \)

The remainder of the RfD is allocated to food

This reasoning appears to be sound given the aim of not overflowing the risk cup for individuals exposed simultaneously at the regulatory limits for both water and food. However, the reasoning of steps 3 through 9 depends entirely on the validity of assumption 2 (“This NOEL is associated purely with exposures to perchlorate through water”), as well as the acceptability of the underlined part of the previous sentence as the basis for allocating regulatory and public health resources.

Assumption 2, however, is not correct for studies of contaminant exposures where aggregate and cumulative risk are present in the background exposures to individuals in the study population. If an RSC is to be applied, the original study (here, Greer et al) must be re-examined for the influence of aggregate and cumulative exposures in the study population. To do otherwise and still apply an RSC is to double count the influence of aggregate and cumulative exposures, since these exposures are already reflected in the baseline iodine uptake inhibition used in establishing the NOEL from the study.

Given the issues raised above, it is time for the regulatory community to move towards the most scientifically advanced approach to aggregate and cumulative risk, which is probabilistic risk assessment under the concept of a risk cup. Exposures to perchlorate and goitrogens more generally are illustrative of this issue, and provide a timely example because the inconsistencies that arise in risks associated with regulatory limits on these compounds are emerging. Absent this movement to fully probabilistic risk assessment, the exposure-response studies underlying establishment of a NOEL and RfD must be re-examined to replace assumption 2 above by procedures consistent with scientific recognition of aggregate and cumulative risk. To do otherwise is to produce regulatory limits on exposure that are not harmonized across contaminants and routes, and hence cannot be properly related quantitatively to calculations of the risk cup for populations.

This paper considers different interpretations of the underlying data on perchlorate and goitrogens in the case of the Greer et al study using the concepts of aggregate and cumulative risk, leading to a range of different estimates of the safe level of exposure to perchlorate in water; ‘safe’ here means reasonable confidence that the exposure limit avoids an unacceptably large level of risk in a substantial fraction of the population. This is formulated in the following aim for establishing a regulatory limit such as the RfD: the Reference Dose (RfD) will provide protection against unacceptable levels of risk in a reasonable percentage of the population, and do so with reasonable confidence (including the precautionary principle\(^4\,^5\)).

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2. The methodology of protecting public health through regulatory limits on exposure

The current process of regulatory analysis for risk-based decisions is approximately as follows; some differences exist between the frameworks in different nations, but these differences do not affect the conclusions drawn in this paper, and in any event are being reduced through harmonization of at least US and EU environmental regulatory risk assessment practices. The case of whole organism studies are available, as that is the case most relevant to the perchlorate studies to date, specifically the study by Greer et al which has formed the basis of regulatory risk assessments.

The traditional default steps of regulatory assessment (meaning the steps that are employed when detailed biomathematical models/understanding of exposure, biokinetics, dosimetry and pharmacodynamics are not available or at least are not being employed) are:

1. A compound (such as perchlorate) is determined through Hazard Identification to be of potential regulatory interest, and its relevant human health effects – and mode of action- identified.
2. A population or subpopulation is identified as being the sensitive subpopulation for this compound for regulatory purposes.
3. Either controlled dose or cross-sectional studies of environmental levels of exposure are conducted, with statistical significance of elevation of effect at each level of exposure assessed.
4. Administered or environmental doses are converted to Average Daily Rate of Intake (ADRI) through use of an intake rate of the associated environmental medium (e.g. litres of water consumed per day) and a body weight, usually specified for the sensitive subpopulation.
5. From 3 and 4, a No Observed Adverse Effects Level (NOAEL) if available, or a Lowest Observed Adverse Effects Level (or LOAEL if a NOAEL cannot be found) is established in units of ADRI, representing the highest administered value of ADRI that produces no statistically significant elevation relative to a background of non-exposure (if a NOAEL is available) or the lowest administered value of ADRI that produces a statistically significant elevation relative to a background of non-exposure (the LOAEL).
6. Where there is incomplete information on the effects, where the population studied is not the sensitive subpopulation, where the species studied is not humans, where there are other methodological deficiencies that might mask induced effects due to noise in the measurement, and/or where a LOAEL but not a NOAEL is established, one or more uncertainty factors are specified to produce a margin of safety (consistent with the precautionary principle).
7. From 5 and 6, a Reference Dose (RfD) or related regulatory construct is developed on which to base recommended or required limits on exposure; this is equal to the NOAEL or LOAEL divided by the uncertainty factors.
8. For a given environmental medium (such as water or food separately), a calculation is performed of the equivalent concentration of the compound in the medium that would yield the RfD if that were the only route of exposure. (Note: It is not claimed here that this condition is in fact met in any exposure-response study, but rather that it is an implicit assumption in using the exposure-response data if background exposures are not explicitly accounted for).
9. Where the exposure of regulatory interest is not the only route of exposure, the equivalent concentration from 8 is multiplied by a Relative Source Contribution, equal to the fraction of total intake by all routes that is contributed by the environmental medium of interest. This reduces the allowable limit on exposure below that from a single pathway, although the US EPA recommends that this procedure not be applied where the RSC is less than 10%-20% (the lower value is applied inconsistently; see the discussion in Howd et al6.) The same Howd et al reference notes correctly that regulation of perchlorate should reflect the additional goitrogen exposures such as from nitrate, and that “Development of aggregate, cumulative risk assessment methods will incorporate the RSC concepts into all risk assessment programs” (meaning that aggregate and cumulative risk assessments make the RSCs explicit within calculations rather than requiring application of a separate RSC value).

10. Finally, where there is a need to allocate regulatory resources most effectively (which does not here mean solely ‘cost-efficiently’) and where there are multiple routes of exposure, a decision is taken as to the route of exposure contributing most significantly to population risk, with attention then focused on that route. However, this principle is often missed in practice where there is non-scientific pressure to act on a single exposure pathway.

This 10 step process is intended to provide a measure of ‘reasonable’ confidence that the exposed population is being protected against environmental risks, taking into account uncertainty, inter-subject variability, and consideration of aggregate risk, and to ensure that public resources are directed towards the compounds and routes of exposure that are the largest contributors to that risk. In the italicized policy framework given at the end of Section 1, the use of a NOAEL corresponds to protection against unreasonable levels of risk; application of uncertainty factors corresponds to the concept of reasonable confidence; and use of a sensitive subpopulation corresponds to the principle of protection of a reasonable percentage of the population.

The aggregate and cumulative risk natures of perchlorate exposure in the available exposure-response studies violate especially step 5 in the above. In addition, as mentioned later, the Greer et al study at best produces a NOEL, not a NOAEL. As a result, the NOAEL (or more correctly, the NOEL) from studies such as that of Greer et al is not the value of the ADRI at which perchlorate acting alone produces no statistically significant elevation in an adverse effect, but rather the value at which perchlorate in combination with exposures to other goitrogens produces no statistically significant elevation in a measurable effect.

In public health protection through environmental regulation, there are additionally concerns for both aggregate exposure (multiple routes of exposure to the same compound) and cumulative exposure (multiple compounds that share the same mode of action) in specific contexts such as a geographic region or the risks to a given individual. Outside the realm of establishing uniform, national regulatory limits on exposures, this situation of aggregate and cumulative risk has traditionally been dealt with through development of Hazard Quotients (or similar regulatory construct), equal to the ratio of actual exposure at a specific geographic location (ADRIactual) over the RFD for each compound acting through this mode of action, and then summing these HQ values to yield a Hazard Index (HI), further restricting the HI to 1.

For example, if there are two compounds (Compounds 1 and 2) present in a geographic area and to which the inhabitants are exposed simultaneously, their individual ADRI\text{actual} or ADRI\text{a} values will be shown as ADRI_{a,1} and ADRI_{a,2}. Their respective RFD values will be RFD_{1} and RFD_{2}. Their HQ values are then HQ_{1} = ADRI_{a,1} / RFD_{1} and HQ_{2} = ADRI_{a,2} / RFD_{2}. The HI value is then:

1. \[ HI = HQ_{1} + HQ_{2} = \frac{ADRI_{a,1}}{RFD_{1}} + \frac{ADRI_{a,2}}{RFD_{2}} \]

Assuming the two compounds act by the same mode of action (technically a requirement for applying the concept of HI), the equation above reduces to:

2. \[ HI = \frac{(ADRI_{a,1} + ADRI_{a,2})}{RFD} \]

where there is now no subscript on RFD since the RFD value is the same for all compounds acting through this shared mode of action, assuming ADRI has been calculated for each compound using a Toxicity Equivalency Factor or TEF. In perchlorate risk assessment, the TEF is called the Perchlorate Equivalent Concentration or PEC. Note that in this case (which will be the case for perchlorate considered in Section 3), the same protection of public health is achieved using the concepts of additivity of dose or additivity of effect. For the purposes of Section 3, dose additivity is considered. While additivity has not been fully explored for goitrogens, it has been shown to hold for Thyroid Disrupting Chemicals more broadly\textsuperscript{7} and so is a reasonable assumption here.

Note also from Equation 2 that protection of public health in the case of aggregate and cumulative risk inherently involves the use of the sum of exposures to the class of compounds exerting their effect through the same mode of action. A key consideration of this issue in the discussion of Section 3, is that this same summation of exposures must be carried through the analysis of all primary data used to calculate the Rfd (often requiring re-analysis of those data), to avoid double counting of the contribution of these compounds to the NOAEL (NOEL) or LOAEL (LOEL) from step 5.

3. Application to perchlorate and goitrogens

The debate over regulation of perchlorate has focused on the treatment of several of the steps above. Specifically, concerns raised in regulatory debates in the US revolve around the following issues:

- The underlying clinical study by Greer et al used iodine uptake inhibition as the measure of effect. Iodine uptake inhibition, however, is not an adverse effect in and of itself; it is a precursor to an adverse effect (changes in hormonal levels leading in turn to development and metabolic alterations). This allows establishment of a No Observed Effects Level (NOEL) but not a NOAEL. Since the NOAEL will always be higher than the NOEL (and the RfD similarly elevated), some of the precaution introduced in step 6 is already present in this case. From this point forward, the comments refer to the NOEL rather than the NOAEL.

- Perchlorate is a member of the class of goitrogens with the same mode of action (the competitive inhibitory effect on iodine uptake into the thyroid by the sodium-iodine symporter), which includes a wide range of compounds such as nitrates, perchlorates, chlorates, bromides and thiocyanates. Hence the issue of potential double counting of exposures raised at the end of Section 2 pertains. (Note: There is a wide range of goitrogens that could be included here, but data on the three selected are the most complete. And, in any event, inclusion of these additional goitrogens such as chlorates and bromides in this study would also change interpretation of the PEC values for the Greer et al data and hence produce counterbalancing influences on the regulatory implications for perchlorate and PECs)

- The Greer et al study uses a bolus dose regime for the study subjects. Application of such results to the case of environmental exposures at much lower levels (outside a few geographic hotspots such as Superfund sites, including military munitions depots, firework sites, etc) assumes that the CxT (concentration x time) concept is correct. This concept states that the same level (probability and/or severity) of effect is produced if an individual ingests 1 μg/L for 1000 days, or 1000 μg/L for 1 day, since both produce the same total intake and hence the same Average Daily Rate of Intake (ADRI). While the CxT approach has been used as a regulatory default assumption because it means the assessor does not need to consider the fluctuations in daily rates of intake over time (just the average value of the concentration and the length of time that value applies), this ignores the significant body of scientific evidence concerning an important dose rate effect. For the example given above, the 1000 μg/L for 1 day case would produce a large spike in serum concentration, while the 1 μg/L for 1000 days case would produce a much lower, but more extended, serum concentration. In experimental measurements of the dose rate effect, the same total amount of a pollutant consumed during a shorter period of time enhances the health effect of the compound relative to that same total amount spread out over a longer period of time (see for example Weller et al). This issue is significant here because the study subjects in the Greer et al study were administered perchlorate concentrations of at least 180 ppb, which is a factor of 18 (180 ppb divided by a typical maximum concentration of 10 ppb in water.

8 Diseases of the Thyroid. 2003. edited by Dr. Lewis E. Braverman, second edition, chapter 15, A. Engel and S. Lamm.
outside hotspots) to 1800 (180 ppb divided by a typical average concentration of 0.1 ppb in water outside hotspots) higher than environmental levels found in the large majority of water systems in the US and EU as described later. Hence the dose-rate in the Greer et al study is much higher than that generally found in environmental exposures. Such dose-rate effects are especially important in homeostatic systems such as the thyroid and iodine uptake, since homeostasis can be maintained only within fixed limits of perturbations. Applying intakes of perchlorate at dose rates much higher than those found in environmental exposures (as in bolus experiments) can exceed a tipping point for the homeostatic mechanism, especially in sensitive subpopulations of interest in regulation, inhibiting iodine uptake at total doses of perchlorate that would not produce such a tipping point if the same total dose were distributed across a longer time interval in the manner of environmental exposures. Again, this means the Greer et al study already includes a margin of safety or precaution due to the high dose rates of the administered doses.

- The individuals in the Greer et al study were exposed to all of these goitrogens simultaneously through their diet because there was no control on these additional goitrogens and routes of exposure ('control' in this case referring to the meaning in epidemiological studies where the influence of sources of risk apart from the compound and exposure route of interest are accounted for explicitly in the conduct and interpretation of the study); hence the NOEL and then the RfD as developed using only the administered doses in the Greer et al study significantly understate the magnitude of the exposures to goitrogens leading to this NOEL or RfD. A more scientifically correct statement about the NOEL from the Greer et al study is that there is no statistically significant elevation of the effect examined (iodine uptake inhibition) from the combined action of the goitrogens present. Stated differently, this NOEL is caused by the sum of the ADRI values for the different goitrogens present in the Greer et al study population, as shown in the numerator of Equation 2. Critically for the current discussion, the Greer et al study does not allow establishment of the HQ value for exposure to perchlorate alone in any real population that might be considered in decisions on public health protection, but rather to the HI value for the class of goitrogens.

- If a Relative Source Contribution (RSC) value is then applied to the RfD (or related regulatory construct), this is ‘double counting’ the treatment of aggregate and cumulative risk. The double counting exists because the Greer et al study already reflects exposure by all pathways to all goitrogens with the same mode of action (the latter point arising from the lack of control on exposure to other goitrogens in the primary data). Application of a further RSC in regulatory decisions is inappropriate because there are no other contributing sources (pathways and other goitrogens) that are not already included in the sum of the ADRI values on which the NOEL is based.

- Reduction of iodine uptake into the thyroid produces the ‘downstream’ (adverse) effects only at significant levels of decrease, estimated by the US National Research Council in their 2005 report\textsuperscript{10} to be above 70%; again, this indicates that use of inhibition of iodine uptake to the thyroid as a basis for a NOEL, and then treating it as if it were a NOAEL, already includes a margin of safety. Regardless of the magnitude of inhibition required (the NRC study being

\textsuperscript{10} National Research Council. 2005. Health Implications of Perchlorate Exposure, Washington DC.
only one judgment of the inhibition required; FAO/WHO/JEFCA set the value at 50\%^{11}, the NOEL and hence RfD based on the Greer et al study still contains a margin of safety since the value of inhibition required to produce downstream adverse effects cannot be 0 or less (0 being the value of inhibition associated with the NOEL in that study).

- Control of perchlorate in either water or food should be seen within the context of cumulative risk assessment, and a decision taken as to whether control of perchlorate is either the most effective (in the sense of protecting public health) or cost effective (in the sense of wisest expenditure of regulatory resources) means of protecting the public against the cumulative and aggregate risks from goitrogens in specific circumstances. Perchlorate is found at levels that will exceed the NOEL only in a few subpopulations. Basing broader regulatory limits on calculations from small subpopulations is to mis-direct resources intended to protect the public health, since it will cause regulatory expenditures even in cases where perchlorate exposure is a very small percentage of total goitrogen exposure.

What then is the path forward to establishing regulatory limits on perchlorate in food and/or water? Insight can be gained from the National Research Council report\textsuperscript{10}. That study produced a NOEL (not considered a NOAEL because the biochemical changes measured were not consider adverse in and of themselves) of 0.007 mg/kg-day based on the Greer et al study. The NRC further recommended a total uncertainty factor of 10 for intraspecies extrapolation (the data were from humans, although not from pregnant women and/or their fetuses, who might represent the sensitive subpopulation), resulting in a suggested RfD of:

\[
RfD = \frac{0.007}{10} = 0.0007 \text{ mg/kg-day} \text{ or } 0.7 \mu g/kg-day
\]

This RfD value would, for the case where populations are exposed solely to perchlorate as the goitrogen, yield a lower bound on the regulatory limit (Reference Concentration or RFC in US EPA regulatory terminology) of 18 µg/L, assuming 2 L/day consumption of water by a woman weighing 50 kg. This calculation uses the upper bound estimate of the ratio of water intake rate per unit body weight as distributed across the exposed population of pregnant women (the assumed sensitive subpopulation), again to provide an additional margin of safety or precaution. The value is 24.5 µg/L if 70 kg body weight is used instead. The value of 18 µg/L is retained in the following discussion.

Since the Greer et al population was exposed to perchlorate in food and water, it would be inappropriate to apply a further RSC in establishing a regulatory limit based on consideration of aggregate exposure. To do so would (as mentioned previously) ‘double count’ the aggregate exposure effects.

However, the above discussion fails to consider the issue of cumulative exposure to goitrogens in interpreting the Greer et al study. Four alternative approaches to establishing exposure limits on perchlorate are discussed in Section 4, each reflecting the concerns for aggregate and cumulative risk underlying the previous 10 steps, but having different policy and scientific bases. For each of these, a description is given of the approach and an assessment provided of the strengths and weaknesses. Approach 1 is the closest to the current regulatory procedure, but with the least basis in the current state-of-the-science understanding of aggregate and cumulative risk for compounds.

with a common mode of action. Approaches 3 and 4 are the most deeply rooted in the current state-of-the-science, reflecting consideration of aggregate and cumulative risk considerations in interpretation of the Greer et al results.
4. Four approaches to regulatory control of risks from perchlorate and goitrogens

The following discussion is rooted in Equation 2, noting that the Hazard Index or HI, taken in regulatory risk assessment and risk management as the indicator of acceptable levels of public health protection, requires first summing the ADRI values for food and for water and for perchlorate and the non-perchlorate goitrogens. Expanding Equation 2 to be more explicit:

\[
\text{HI} = \frac{\text{ADRI}_{f,p} + \text{ADRI}_{f,np} + \text{ADRI}_{w,p} + \text{ADRI}_{w,np}}{\text{RfD}}
\]

where \(\text{ADRI}_{f,p}\) is the ADRI of perchlorate (p) from food (f); \(\text{ADRI}_{f,np}\) is the ADRI of non-perchlorate goitrogens (np) from food (f); \(\text{ADRI}_{w,p}\) is the ADRI of perchlorate (p) from water (w); and \(\text{ADRI}_{w,np}\) is the ADRI of non-perchlorate goitrogens (np) from water. The value of RfD is identical for the four components, albeit calculated differently for the four approaches summarised below. This requires calculating the ADRI values using Perchlorate Equivalent Concentration (PEC) rather than the direct mass concentration in the environmental media.

For those PEC values, the summary of results by Tonacchera et al\(^\text{12}\) is used based on four studies (cited in their paper), in which they find ratios of perchlorate:thiocyanate:nitrate of 1:20:240, 1:10:300, 1:20:400 and 1:20:500 for the different studies, each of which is based on circulating serum molar concentration (see also the discussion in Charnley\(^\text{13}\) and in de Groef et al\(^\text{14}\)). Converting to effectiveness of inhibition per unit serum concentration, they recommend ratios of 1:8.8:150. This means a direct mass concentration of 1 unit of perchlorate is equivalent to 8.8 units of thiocyanate and 150 units of nitrate on the basis of equivalent serum concentration, and when circulation half-lives in serum are included yields ratios of 1:0.5:240 on the basis of ingested quantity (the unit of interest here). A full pharmacokinetic model would include the dynamics of absorption from the GI tract into the bloodstream, reflecting also the influences of the food matrix containing the goitrogen. As this component of the modelling analysis is not available, the two values for PEC calculations above (1:8.8:150 and 1:0.5:240) are used here as upper and lower bounding estimates for the calculations that follow.

Note that in dealing with cumulative and aggregate risk, HI values or a measure of total risk in the risk cup are the metrics of health protectiveness, not regulatory allowed concentrations of individual compounds in individual media. This approach to health protection recognizes that the health protective concentration of any particular compound in any particular medium is not a universally applicable value, but depends on the cumulative and aggregate risk context in which exposure to the compound/medium occurs when compounds have the same mode of action.

The problem with application of RSC values, especially quite low ones, is that this draws regulatory resources precisely to those compounds and routes of exposure that have the smallest RSC (all other things being equal), since it is these compounds/media that will have the smallest Maximum Contaminant Level (MCL) or equivalent concept. This in turn draws regulatory attention (and


resources) towards those compounds and routes contributing least significantly to the overall risk cup. Equation 2 (or 2revised) avoids this problem because neither the ADRIs (numerator) nor the RfD (denominator) contain RSC values.

However, this approach to risk reduction either (i) leads to Approaches 3 and 4 below, which leaves open the question of how to set explicit regulatory limits on exposure to a single compound in a single medium, or (ii) leads to regulatory limits in Approaches 1 to 2 for each individual goitrogen/pathway.

For typical background estimates of the various components to Equation 2revised, the results are as follows based on a central tendency US diet (the choice to use a US diet is because the Greer et al study population is represented by this diet, and hence it is this diet that is relevant in calculating non-perchlorate and non-water exposures).

- For perchlorate in water, the ADRI is 0.004 µg/kg-day\textsuperscript{15}
- For perchlorate in food, the ADRI is 0.1 µg/kg-day\textsuperscript{16}
- For nitrate in water, the ADRI is 0.075 (11.3/150) µg/kg-day\textsuperscript{14} without half-life correction, and 0.05 (11.3/240) µg/kg-day with half-life correction
- For nitrate in food, the ADRI is 6.82 (1023/150) µg/kg-day based on the data in the Supplement developed from the 1994-1998 CSFII data of the USDA published in 2010 without half-life correction, and 4.2 (1023/240) with half-life correction
- For endogenous (END) nitrate production, the estimate is 45% of total nitrate exposure (END + NONEND) is via this component, and therefore the endogenous contribution would be (0.075+6.82)*0.82 = 5.65 µg/kg-day\textsuperscript{17} without half-life correction, and (0.075+4.2)*0.82 = 3.5 µg/kg-day with half-life correction; in this calculation, the equality 0.45 = END / (END+NONEND) is solved, so END = (0.45/0.55) x NONEND = 0.82 x NONEND
- For thiocyanate in food (again using the Supplement), the ADRI is 0.86 (7.5/8.8) µg/kg-day without half-life correction, and 15 (7.5/0.5) µg/kg-day with half-life correction. Intakes from water are negligible. The NHANES urinary data suggest this to be an underestimate of thiocyanate exposure in the bloodstream (both due to thiocyanate precursors in food products and the production of endogenous thiocyanate), but the necessary pharmacodynamic models are not available to make the conversion back from urinary excretion to blood serum, which would be required to make the comparison with the Greer et al results on perchlorate.

Note on allowed concentrations in food:
In this paper, attention is on establishing an allowed concentration for perchlorate and total goitrogens in water. Allowed concentrations of goitrogens in foodstuffs should be established in a similar way and with the help of the in the European Food Safety Authority (EFSA) PRIMo model (see www.efsa.europa.eu/en/mrls/mrlteam.htm)

\textsuperscript{17} NRC. 1995. Nitrate and Nitrite in Drinking Water, Subcommittee on Nitrate and Nitrite in Drinking Water, National Academy Press, Washington, DC , p. 38.
Again, the values above are in units of PEC. To summarise, background ADRI values (in PEC units) corresponding to the components of Equation 2 revised are:

- Perchlorate in water: 0.004 µg/kg-day
- Total goitrogens in water: 0.075 + 0.004 = 0.079 µg/kg-day without half-life correction, and 0.05 + 0.004 = 0.054 µg/kg-day with half-life correction
- Total goitrogens in food: 0.1 + 6.82 + 5.65 + 0.86 = 13.42 µg/kg-day without half-life correction, and 0.1 + 4.2 + 3.5 + 15 = 22.8 µg/kg-day with half-life correction; this includes endogenous nitrate intake

4.1. Approach 1:

The approach here is to use the Greer et al study in the procedure typically followed in regulatory risk assessment in establishing exposure limits by a single pathway to a single contaminant. The NOEL is then 0.007 mg/kg-day. The RfD is 0.007/10 = 0.0007 mg/kg-day or 0.7 µg/kg-day, with the Uncertainty Factor of 10 accounting for intraspecies variability to reflect a concern for pregnant women and their fetuses, but with no need for further uncertainty factors since this RfD is already protective of health due to the use of a precursor to adverse effect rather than using an adverse effect itself. No RSC value should be applied both because it falls below the 10%-20% guideline (for example, using average values for water and non-water, this fraction is 0.004/0.1004 = 0.038 = 3.8%) considered by the US EPA as justifiable, and because non-water exposures including exposures from indoor dust with an exposure contribution similar to that of water are already present in the Greer et al study. The latter point is scientific recognition of the methodology of the study, where the study design measured the incremental influence of waterborne perchlorate exposures above and beyond the influence of the other pathways and goitrogens.

**Resulting Allowed Concentrations for perchlorate in water:** 18 µg/L in water for a water intake rate of 2 L/day (the regulatory default) and a body weight of 50 kg. This uses the equation Concentration (µg/L water) = 0.7 (µg/kg-day) x 50 (kg) / 2 (L water/day) = 18 µg/L.

**Resulting Allowed Concentrations for goitrogens (PEC) in water:** Approach 1 does not consider total goitrogens in water because it considers only the incremental exposure to perchlorate. The same concentration of 18 µg/L can, however, be used for the sum of all goitrogens (PEC) in water so long as this intake refers to the increment above the background exposures to goitrogens.

**Strength:** The approach conforms most closely to conventional regulatory practices.

**Weakness:** The approach ignores the presence of the other goitrogens in the diets of people in the Greer et al study, and therefore does not reflect full scientific understanding of aggregate and cumulative risk. It also does not reflect dose rate effects (which would be expected to further increase the NOEL and hence the RfD if the experiments had been conducted with lower levels of dose rate typical of environmental conditions). It also produces results for background levels of goitrogens that are not consistent with background levels of iodine uptake inhibition; i.e. it suggests

that total goitrogen exposures should be producing much greater levels of iodine uptake inhibition than are found in the Greer et al baseline results.

4.2. Approach 2: The approach here is to use the Greer et al study to produce an exposure-response relationship for iodine uptake inhibition, coupled to the current best scientific estimate of the percentage inhibition necessary to produce a down-stream adverse effect (50% or 70% as described previously). This is equivalent to Equations 1A-1D in the Greer et al paper (see page 931 of that paper). These equations are valid only for the region of doses in the study (0.007 mg/kg-day and above).

\[ \text{Equation 1A} \]
\[ (RU_{8})_{E2} = (-0.374) \log_{10}D + (0.209) \]

\[ \text{Equation 1B} \]
\[ (RU_{24})_{E2} = (-0.373) \log_{10}D + (0.202) \]

\[ \text{Equation 1C} \]
\[ (RU_{8})_{E14} = (-0.337) \log_{10}D + (0.229) \]

\[ \text{Equation 1D} \]
\[ (RU_{24})_{E14} = (-0.359) \log_{10}D + (0.213) \]

where D is the excess intake of perchlorate during the experiment (i.e. not the total intake of perchlorate or of other goitrogens included in aggregate and cumulative exposure) in units of ADRI (mg/kg-day); RU8 is the reduction in iodine uptake at 8 hours; RU24 is the reduction in iodine uptake at 24 hours; and E2 and E14 are the two sets of cases.

For Approaches 2, 3 and 4, Figure 1 shows the estimated dose-response function for iodine uptake at 24 hours following exposure to perchlorate (in the Greer et al study) or other goitrogens with the same mechanism and mode of action. If used for goitrogens other than perchlorate, the value of ADRI on the x-axis must reflect the PEC of that goitrogen relative to perchlorate (hence perchlorate has a TEF or PEC value of 1). Note the background uptake of 15% existing at no incremental dose (to goitrogens) above background during the experiments, as determined from the Baseline Visit values.

Figure 1. Estimated exposure(ADRI)-response relationship for iodine uptake inhibition by the thyroid after administration of goitrogen (perchlorate) in the Greer et al study. The response here is % uptake in 24 hours; as mentioned, the response is considered here to provide a basis for a NOEL rather than NOAEL, but this distinction has no practical implications for the analysis.
Figure 2 is similar to Figure 1 except the response is % inhibition relative to the Baseline Value of uptake percentage. Again, the administered dose (ADRI) is the increment above the background levels of intake of goitrogens.

![Figure 2](image)

**Figure 2.** Estimated exposure (ADRI)-response relationship for iodine uptake by the thyroid after administration of goitrogen (perchlorate) in the Greer et al study. The response here is % inhibition in iodine uptake.

For both Figures 1 and 2, the change in response is zero at doses below approximately 0.01 mg/kg-day, indicating that homeostatic mechanisms are fully operational at these low doses.

Using the Equations for E2 and E14 and averaging over the two sets of cases, the value of ADRI corresponding to a 50% decline in iodine uptake relative to the Baseline Visit value is 0.16 mg/kg-day (160 µg/kg-day). With a 10 fold uncertainty factor applied to the increment of dose above background (which has the effect of moving the curve of Figure 2 to the left), the resulting RfD for a 50% decline required to induce the specified levels of iodine uptake inhibition is 0.016 mg/kg-day (or 16 µg/kg-day). Note that the resulting RfC is a factor of 23 (16/0.7) above that from Approach 1, respectively.

Note that in this Approach, the measured effect (iodine uptake inhibition) remains a precursor to adverse effects rather than an adverse effect itself, but the level of inhibition is high enough to correlate well with the eventual down-stream production of adverse effects.

**Resulting Allowed Concentrations for perchlorate in water (50% decline in iodine uptake required):** 400 µg/L for a water intake rate of 2 L/day (the regulatory default) and a body weight of 50 kg using the same calculation as in Approach 1 but with the higher RfD. This uses the equation Concentration (µg/L water) = 16 (µg/kg-day) x 50 (kg) / 2 (L water/day) = 400 µg/L.

**Resulting Allowed Concentrations for goitrogens (PEC) in water:** The same concentration of 400 µg/L can be used for the sum of all goitrogens (PEC) in water so long as this intake refers to the increment above the background exposures to goitrogens.

**Strength:** The approach harmonises perchlorate regulatory risk assessment with other non-probabilistic risk estimation procedures in which full dose-response curves are developed and a response judged adverse is selected as the level of unacceptable risk. It also produces results for
background levels of goitrogens in food that are consistent with background levels of iodine uptake inhibition (in contrast to Approach 1).

**Weakness:** The approach ignores the presence of the other goitrogens in the diets of people in the Greer et al study, and therefore does not reflect full scientific understanding of aggregate and cumulative risk. The approach requires specifying the percentage iodine uptake inhibition required to produce a clinically adverse effect. In addition, the approach does not reflect dose rate effects (which would be expected to further increased the NOEL and hence RfD if the experiments had been conducted with lower levels of dose rate typical of environmental conditions).

**4.3. Approach 3:** The approach here is to use the Greer et al NOEL (0.007 mg/kg-day), but recognise the contribution of the other goitrogens to the total goitrogen intake in that study. In other words, the NOEL from that study is not a NOEL associated solely with perchlorate intakes during the study, but a NOEL reflecting the combined effect of all compounds with the same mode of action present in the diet of the study subjects. The approach is to determine the actual intake rate of perchlorate and other goitrogens from all routes of exposure for the Greer et al population, with application of a PEC factor to each of the goitrogens (similar to the case of dioxin and dioxin-like compounds already applied by US EPA and WHO), as was specified in Equation 2. The x-axis on the exposure-response relationship is adjusted accordingly. This new graph would then be used to establish the NOEL reflecting cumulative and aggregate risk.

Charnley reviewed both the exposure and effects data through 2008. She concludes: “Based on data from 27 foods, the US FDA has made a preliminary estimate of average daily perchlorate intake in the US of 0.053 µg/kg/day, similar to that estimated on the basis of urinary perchlorate measurements, 0.066 µg/kg/day.” Intakes of perchlorate through the diet in the Greer et al population is evidently significantly smaller than the perchlorate consumed at the NOEL (7 µg/kg-day). As shown below, however, this preliminary estimate is significantly lower than what one obtains when more complete data (provided below) are considered.

In addition, the concern for goitrogens is not dominated by perchlorate. Of direct interest here is the daily intake rate of other goitrogens such as those listed at the beginning of Section 3 above. The calculations here are based on the results of Tonacchera et al using PEC ratios of 1:15:240 or 1:8.8:150 for ClO$_4^-$:SCN$^-$:NO$_3^-$ on the molar- and weight-based ratios respectively. Again, these ratios are 1:0.5:240 on the basis of ingested quantity when half-life correction is applied.

As shown at the beginning of Section 3 of the current paper, total background ADRI (using PEC) for goitrogens perchlorates, nitrates and thiocyanates is approximately 0.004 + 0.075 + 13.42 = 13.5 µg/kg-day, or 0.004 + 0.05 + 22.8 = 22.9 µg/kg-day if half-life corrections are included. This in turn suggests (even if only these two additional goitrogens are considered) that the NOEL of 0.007 mg/kg-day is...

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day from the Greer et al study is associated with a total goitrogen intake rate of 13.5 µg/kg-day (without half-life) or 22.9 µg/kg-day (with half-life).

**Resulting Allowed Concentrations for perchlorate in water:** 338 µg/L (without half-life) or 572 µg/L (with half-life) for a water intake rate of 2 L/day (the regulatory default) and a body weight of 50 kg using the same calculation as in Approach 1 but with the higher RfD. This uses the equation Concentration (µg/L water) = 13.5 (µg/kg-day) x 50 (kg) / 2 (L/day) = 338 µg/L (without half-life), or 22.9 (µg/kg-day) x 50 (kg) / 2 (L/day) = 572 µg/L (with half-life). This calculation presumes perchlorate is the sole contributor to the ‘risk cup’ from goitrogens.

**Resulting Allowed Concentrations for goitrogens (PEC) in water:** The same concentration of 338 µg/L (without half-life) or 572 µg/L (with half-life) can be used for the sum of all goitrogens (PEC) in water so long as this intake refers to the increment above the background exposures to goitrogens.

**Strength:** The approach explicitly accounts for the background exposures to goitrogens in the diet. This places the analysis more fully into the framework of cumulative and aggregate risk, and reflects the influence of homeostatic mechanisms in maintaining iodine uptake into the thyroid.

**Weakness:** The approach requires the assumption that the various goitrogens do not act competitively or antagonistically with each other, although there is no evidence that such antagonism applies, and in any event the scientific judgment as stated earlier is that both dose and effect additivity hold across a range of compounds.

**4.4. Approach 4:** The approach here is to use the Greer et al study to produce an exposure-response relationship for iodine uptake inhibition, coupled to the current best scientific estimate of the percentage inhibition necessary to produce a down-stream adverse effect. However, the approach takes on an aspect of Approach 3, which is inclusion of total background goitrogen exposure in the study population. Hence, it combines approaches 2 and 3. Again, Approach 4 uses Equations 4-7.

From Figure 2, a 50% inhibition is associated with an ADRI of 16 µg/kg-day (administered intake from water in the Greer et al study) + 13.5 µg/kg-day (background) = 29.5 µg/kg-day (without half-life), or 16 µg/kg-day (administered intake from water in the Greer et al study) + 22.9 µg/kg-day (background) = 38.9 µg/kg-day (with half-life).

Note that in this Approach as in Approach 2, the measured effect (iodine uptake inhibition) remains a precursor to adverse effects rather than an adverse effect itself, but the level of inhibition is high enough to correlate well with the eventual down-stream production of adverse effects.

**Resulting Allowed Concentrations for perchlorate in water (50% decline in iodine uptake required):** 737 µg/L for a water intake rate of 2 L/day (the regulatory default) and a body weight of 50 kg using the same calculation as in Approach 1 but with the higher RfD. This uses the equation Concentration (µg/L water) = 29.5 (µg/kg-day) x 50 (kg) / 2 (L water/day) = 737 µg/L, or 38.9 (µg/kg-day) x 50 (kg) / 2 (L/day) = 973 µg/L (with half-life). This calculation presumes perchlorate is the sole contributor to the ‘risk cup’ from goitrogens.
Resulting Allowed Concentrations for goitrogens (PEC) in water: The same concentration of 737 µg/L (without half-life) or 973 µg/L (with half-life) can be used for the sum of all goitrogens (PEC) in water so long as this intake refers to the increment above the background exposures to goitrogens.

Strength: The approach harmonises perchlorate regulatory risk assessment with other non-probabilistic risk estimation procedures in which full dose-response curves are developed and a response judged adverse is selected as the level of unacceptable risk. It also produces results for background levels of goitrogens in food that are consistent with background levels of iodine uptake inhibition (in contrast to Approach 1). It also includes the presence of the other goitrogens in the diets of people in the Greer et al study.

Weakness: The approach requires specifying the percentage iodine uptake inhibition required to produce a clinically adverse effect. In addition, the approach does not reflect dose rate effects (which would be expected to further increase the NOEL and hence RfD if the experiments had been conducted with lower levels of dose rate typical of environmental conditions).
5. Summary remarks

The analyses of Section 4 suggest that regulatory limits on perchlorate exposures in water are protective of public health at somewhere between 18 µg/L and 973 µg/L, with the value dependent on the approach taken to regulatory risk assessment and whether half-life corrections are included for clearance of the goitrogens from serum following ingestion. The four approaches considered here yield the following estimates of the safe levels in water of perchlorate (when perchlorate in water is the sole intake of goitrogens) or total goitrogens (PEC; where there are multiple goitrogens present in the water but again where water is the sole route of exposure):

- Approach 1: 18 µg/L
- Approach 2: 400 µg/L
- Approach 3: 338 µg/L (without half-life) or 572 µg/L (with half-life)
- Approach 4: 737 µg/L (without half-life) or 973 µg/L (with half-life)

Approaches 2 through 4 combine current regulatory approaches to risk assessment for compounds that exhibit threshold behaviour of adverse effects, and approaches 3 and 4 apply principles of cumulative and aggregate risk in the interpretation of the Greer et al. study.
Supplement: Estimates of concentrations of nitrates and thiocyanates in food products for the average (central tendency) US diet as cited in the text.

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<th>Food Description</th>
<th>Average US Consumption, Adults 25+ (g/d)*</th>
<th>Average Nitrate Concentration (µg/g)*</th>
<th>Nitrate Intake Rate (µg/d)</th>
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<tr>
<td>Carrot, fresh, peeled, boiled</td>
<td>3.25</td>
<td>1.6312</td>
<td>5.3</td>
</tr>
<tr>
<td>Cauliflower, fresh/frozen, boiled</td>
<td>1.42</td>
<td>89.1432</td>
<td>126.6</td>
</tr>
<tr>
<td>Celery, raw</td>
<td>1.48</td>
<td>0.4692</td>
<td>0.7</td>
</tr>
<tr>
<td>Cole-slaw, mayonnaise-type, from grocery/deli</td>
<td>4.84</td>
<td>16.4011</td>
<td>79.4</td>
</tr>
<tr>
<td>Collards, fresh/frozen, boiled</td>
<td>2.16</td>
<td>1.194</td>
<td>2.6</td>
</tr>
<tr>
<td>Cucumber, peeled, raw</td>
<td>3.84</td>
<td>4.6999</td>
<td>18.0</td>
</tr>
<tr>
<td>Lettuce, iceberg, raw</td>
<td>15.82</td>
<td>3.9206</td>
<td>62.0</td>
</tr>
<tr>
<td>Lettuce, leaf, raw</td>
<td>1.72</td>
<td>3.9206</td>
<td>6.7</td>
</tr>
<tr>
<td>Onion, mature, raw</td>
<td>4.36</td>
<td>0.7843</td>
<td>3.4</td>
</tr>
<tr>
<td>Spinach, fresh/frozen, boiled</td>
<td>2.26</td>
<td>2.5488</td>
<td>5.8</td>
</tr>
<tr>
<td>Tomato, raw</td>
<td>15.35</td>
<td>0.8219</td>
<td>12.6</td>
</tr>
<tr>
<td>Turnip, fresh/frozen, boiled</td>
<td>0.39</td>
<td>13.28</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Total Intake (μg/d)</strong></td>
<td></td>
<td></td>
<td><strong>528.8</strong></td>
</tr>
<tr>
<td><strong>Total Intake (μg/kg-d)</strong></td>
<td></td>
<td></td>
<td><strong>7.55</strong></td>
</tr>
</tbody>
</table>

a 1994-96 CSFII (USDA, 2010)  
b Sanchez et al. 2007, Otea Serrano et al. 1988, Chandra et al. 2004