

To: the EPA Office of Inspection General.

From: Herwig Opdebeeck, MSc

**RE: Use and application of a cumulative risk assessment approach to characterizing the public health risk from a low TIU during pregnancy and lactation**

**Dear Deputy Inspector General,**

**I am a Master in Science and a scientific consultant.**

**Attached you will find comments that indirectly are related to the use and application of a cumulative risk assessment approach to characterizing the public health risk from a low TIU during pregnancy and lactation.**

**Regards,**

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Should a cumulative risk assessment, including nitrate and thiocyanate and lack of iodine be used for perchlorate risk assessment?

### Acronyms

DW: Drinking Water

NAS: National Academy of Science

RfD: NAS Reference dose for perchlorate= 0.0007 mg/kg-day

RSC: Relative Source Contribution

G-RSC: goitrogen RSC expressed in PEC

PEC: Perchlorate Equivalent Concentration of TGL.

TGL: Total Goitrogen Load expressed in PEC: [Perchlorate] + [nitrate/150] + [thiocyanate/15]

UF: Uncertainty Factor

The purpose of these comments is to give a reply to the above question and at the same time raise 2 critical issues not addressed in this OIG analysis:

1. Which drinking water Relative Source Contribution(RSC) that should be used i.e. <1 or =1 or > 1, in order to derive a drinking water(DW) Maximum Contaminant Level (MCL) from the Reference Dose(RfD), with inclusion of the Total Goitrogen Load (TGL) into the RSC and its consequences. It should be kept in mind that the perchlorate RfD, contrary to most other contaminant RfDs, was based on a human dose response trial and therefore the RSC is at least =1.

2. Drawing the attention on the fact that the iodine insufficient female U.S. population has a TGL about half of that of the iodine sufficient female and general U.S population which implies that they are least susceptible to iodine uptake inhibition, if they would have been iodine sufficient.

The answer on the above question is therefore a 2 step answer:

#### 1. Step 1 of the answer

If the question would mean: “*Should a cumulative risk assessment be used to derive an MCL from the NAS RfD by applying not only a perchlorate RSC but also a PEC (Perchlorate Equivalent Concentration) RSC*” then the answer is yes.

##### 1.1. Introduction

The perchlorate NAS (National Academy of Sciences) RfD (Reference Dose) of 0.0007 mg/kg-day is based on the Greer 2002 dose response clinical study.

NAS 2005 did not suggest whether to apply a RSC (Relative Source Contribution) and also did not suggest whether to include nitrate, thiocyanate and the lack of iodine to arrive at a perchlorate MCL for DW. It did not consider this to be part of its mandate.

Also EPA's OIG did not go this last step.

That is unfortunate since the last step to derive a MCL from an RfD is made by applying the RSC.

## 1.2. Determination of the perchlorate RSC and goitrogen RSC

### 1.2.1. Should the RSC be smaller, equal or larger than 1?

Before defining how much in absolute value the RSC should be, the question should be first posed whether the RSC should be <1 or = 1 or even > 1.

#### First some background

-Mostly in toxicological risk assessments and consequently in determining RfDs and MCLs contaminant adverse effect levels are used as benchmark.

For this reason most trials are done on rats or other animals and the results extrapolated to humans.

The Greer 2002 trial had as benchmark a No Observable Effect Level (NOEL), which is a non adverse effect level.

So the trial could be done and has been done on humans.

This is rather exceptional.

- Most of the rat trials are such that intake of the contaminant other than the doses are avoided as much as possible (thru food and drinking water).

When MCLs for humans are derived from those animal trials the DW RSC is normally <1 since a food and DW contaminant background can be expected for the humans.

The Greer trial on humans does not imply such a lateral adjustment and the RSC is either =1 or >1.

#### RSC=1 or RSC>1?

RSC =1: when the RfD is derived from a dose response trial without food and without DW background

There are no other sources besides the doses administered. Therefore the dose administered is directly translated into MCL according to the formula:  $NOEL/UF = RfD$  and  $MCL = RfD \times 70kg/2l$ .

RSC > 1: when the RfD is derived from a dose response trial with food and/or with DW background.

### 1.2.2. RSC for perchlorate taking only perchlorate background into account

If in the Greer trial the participants would have had neither food nor DW perchlorate background the MCL would have been:

$MCL = (RfD \times BW/DWL) \times RSC = (0.7ug/kg\text{-}day) \times 70kg/2 \times 1 = 0.7 \times 35 \times 1 = 24.5 \text{ ug/l} = 24.5 \text{ ppb}$ .

Yet the Greer participants had food and DW perchlorate background.

Therefore the RSC is >1.

Still this perchlorate background in food and DW was very low (see tables 1-3, col.8 on page 5)

Therefore a RSC =1 can be used in first instance.

Example: for nitrate and fluoride US-EPA and CAL-EPA did not apply a MCL <1 but a MCL=1

1.2.3. RSC taking into account the total goitrogen background (TGB)

The Greer participants also had a perchlorate equivalent background in food and DW from thiocyanate and nitrate.

Those food and DW goitrogen loads however are significant, about 100 times the perchlorate background, expressed in PEC (the perchlorate background represents 1% of the total goitrogen load, see following table and tables 1-3, col.5,7,9 and 10, page 5).

Total population (without outliers iodine > 2000 µg)												
	T4	TSH	Nitrate µg	Nitrate (PEC)	SCN µg	SCN (PEC)	ClO4 µg	TGL (in (PEC))	ClO4/TG%	Iodine µg	I/ClO4	I/TGL
	5.4	4.9	59857	399	2507	167	5.1	571	0.9	240	47	0.42
	6.6	1.6	63321	422	2876	192	4.8	619	0.8	229	48	0.37
	7.2	1.6	58824	392	2526	168	5.4	566	1.0	247	46	0.44
	7.7	1.6	61427	410	2308	154	5.5	569	1.0	219	40	0.38
	8.3	1.6	58675	391	2349	157	6.0	554	1.1	245	41	0.44
	8.8	1.8	60640	404	2414	161	5.4	571	1.0	217	40	0.38
	9.6	1.6	62425	416	2098	140	5.2	561	0.9	233	45	0.42
	11.6	1.6	53173	354	2063	138	4.9	497	1.0	207	42	0.42
Mean	8.2	2.1	59793	399	2393	160	5.3	563	0.9	230	43	0.41
1	2	3	4	5	6	7	8	9	10	11	12	13

Col. 5 shows an average nitrate PEC of 400 ppb, col.7 an average SCN PEC of 160 ppb and col. 8 an average of 5 ppb perchlorate resulting in a 1% perchlorate contribution in the total goitrogen load (col. 10).

Now the average urinary perchlorate level in the US is 5.3.ug/l(see above table , col.8) This roughly corresponds with an oral perchlorate dose of 0.075ug/kg-day(Blount et al.). Therefore, since the average perchlorate intake represents less than 1 % of the total goitrogen intake, the total equivalent perchlorate uptake is about 7.5 ug /kg-day. Therefore the total oral goitrogen load of the Greer participants is 7 +7.5 ug /kg-day= 14.5ug/kg-day so the RSC is 14.5 /7= 2.1

This can be explained as following:

$$MCL = (RfD \times BW/DWL) \times RSC = ( BW/DWL \times NOEL/10) \times RSC = 35/10 \times NOEL \times RSC$$

The Greer NOEL of 0.7ug/kg-day is not an absolute NOEL but a lower dose-only NOEL.. The absolute NOEL is the perchlorate dose NOEL + the background perchlorate level + the background equivalent perchlorate level (see fig. 1 page 4).

Since the background perchlorate level is insignificant, the perchlorate dose NOEL + perchlorate background equivalent NOEL= 7 + 7.5= 14.5ug/kg-day = effective NOEL = Total NOEL = T-NOEL.

$$\text{So } T\text{-NOEL} = 2.1 \times \text{NOEL} \text{ and } \text{NOEL} = T\text{-NOEL}/2.1$$

Thus the MCL for perchlorate is 35/10x T-NOEL x RSC

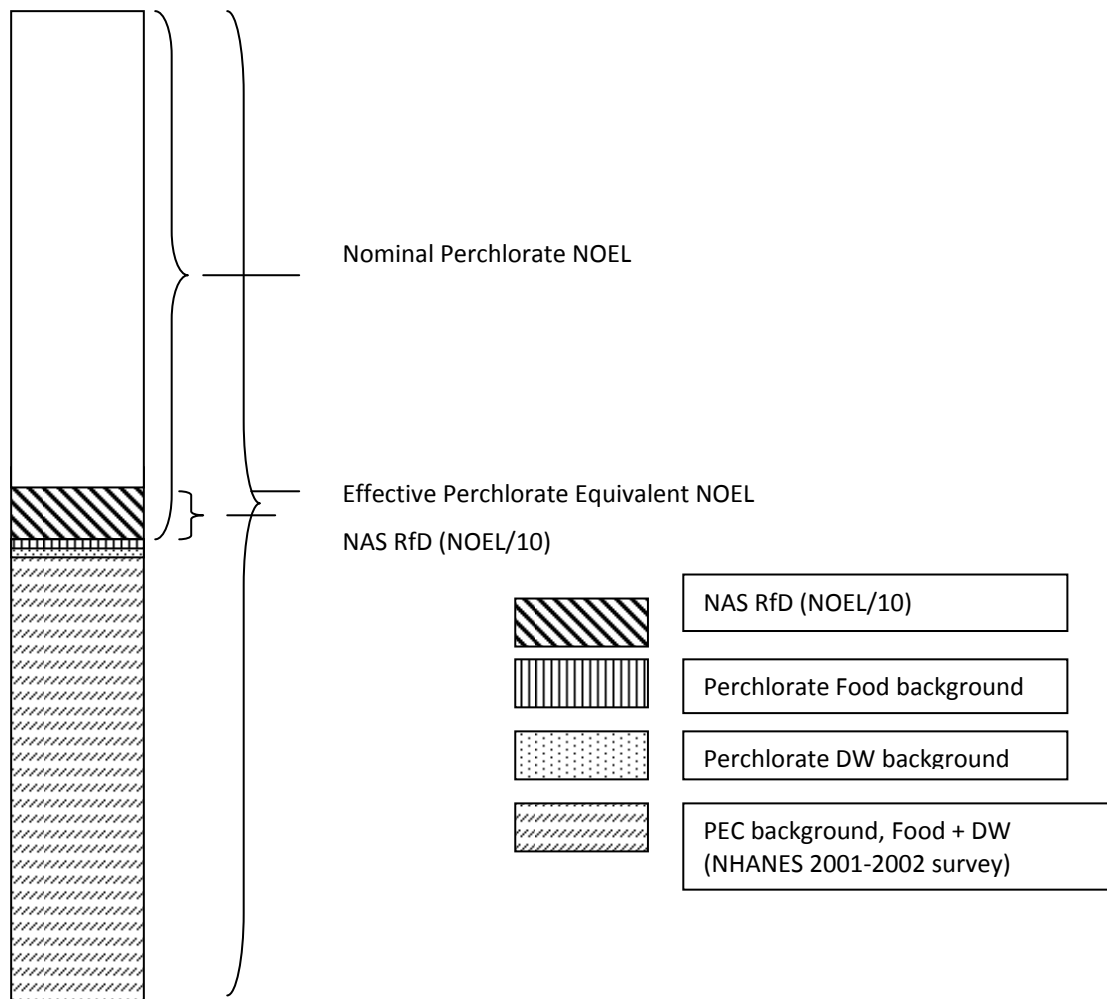
The RSC linked to T-NOEL =1 since there are no other sources neither form perchlorate nor from other goitrogens.

Thus the MCL for perchlorate = 35/10x 14.5 = 35/10 x NOEL x 2.1 which shows that the RSC=2.1.

Thus to correct for the contribution of the other goitrogens or in other words to allow for the higher effective T-NOEL, the RSC of the dose perchlorate should be  $14.5/7=2.1$   
 It follows that the MCL for perchlorate alone =  $35/10 \times \text{NOEL} \times 2.1 = 35/10 \times 7 \times 2.1 = 51$  ppb

All this is illustrated in the following fig.1:

Fig. 1: Greer 2002 NOEL, NAS RfD, Perchlorate and PEC background



Nevertheless, for example, the Office of Policy and Planning, New Jersey Department of Environmental Protection (NJDEP) applied a RSC of 0.20 and consequently arrived at a proposed MCL of 5 ppb ( $\text{MCL} = 0.0007 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2 = 0.0047 \text{ mg/L}$  or 5 ug/L) instead of more than 24.5ppb, see:

[http://www.nj.gov/dep/watersupply/perchlorate\\_mcl\\_10\\_7\\_05.pdf](http://www.nj.gov/dep/watersupply/perchlorate_mcl_10_7_05.pdf)

Note: The perchlorate, nitrate and thiocyanate food and DW background of the Greer participants are assumed to be representative for those of the general U.S. population. If this

were not so then the perchlorate NOEL and RfD would not be so either and therefore could not be used as the basis for deriving a MCL either.

1.3. What would be the additional consequences if a RSC <1 would be applied instead?

If, by error, nevertheless a perchlorate RSC <1 would have been applied(as shown in the example above), a goitrogen adjusted RSC <1 should then logically be applied as well .That RSC however would then end up being << 1 because of its dominant share and therefore the DW MCL for perchlorate would become extremely stringent, well below 1 ppb and well below the natural background even though its contribution is insignificant. That would certainly not be “a meaningful opportunity for health risk reduction” since the lower the contribution of perchlorate in DW compared to food and to the other goitrogens the more stringent the DW MCL would have to be, so stringent that it would become meaningless.

This confirms via another way that applying a perchlorate RSC < 1 is erroneous.

Step 2 of the answer

If the question would additionally mean: “Should a risk assessment including lack of iodine be used to decide how iodine uptake inhibition by goitrogens should be combated?” then the answer is yes as well.

This is indeed amply and convincingly demonstrated in the OIG analysis based principally on the Tonacchera work and confirmed by other evidence.

What was not mentioned in the OIG analysis was that the U.S. iodine insufficient female population, besides an inadequate iodine containing diet, seems to have a generally unbalanced diet characterised by a low consumption of vegetables.

We refer again to the NHANES 2001-2002 data on perchlorate (ClO4), nitrate (NO3) and thiocyanate (SCN).

NHANES 2001-2002 : RELATIONSHIP IODINE WITH ClO4 AND TGP												
TGPL = Total Goitrogen Load = [ClO4]/1 + [NO3]/150 + [SCN]/15												
<b>TABLE 1</b>												
1	2	3	4	5	6	7	8	9	10	11	12	13
<i>Women &lt;100ug/l (without outliers iodine &gt; 2000 µg)</i>												
T4	TSH	Nitrate µg	Nitrate (PEC)	SCN µg	SCN (PEC)	ClO4 µg	TGL (in (PEC))	ClO4/TG %	Iodine µg	I/ClO4	I/TGL	
5.9	1.6	33655	224	1994	133	3.7	361	1.0	61	16	0.17	
6.9	1.7	35353	236	1654	110	4.9	351	1.4	62	13	0.18	
7.5	1.4	33047	220	1597	106	2.8	330	0.9	59	21	0.18	
7.9	1.4	31715	211	1447	96	2.7	311	0.9	59	22	0.19	
8.5	1.6	24077	161	882	59	2.3	222	1.0	53	23	0.24	
9.1	1.7	31355	209	1035	69	2.1	280	0.7	61	29	0.22	
9.8	1.3	43926	293	1607	107	2.5	402	0.6	56	22	0.14	
11.8	1.5	27509	183	1689	113	1.9	298	0.7	51	26	0.17	
Mean	8.4	1.5	32579	217	1488	99	2.9	319	0.9	58	22	0.19
<b>TABLE 2</b>												
<i>Women &gt;100ug/l (without outliers iodine &gt; 2000 µg)</i>												
T4	TSH	Nitrate µg	Nitrate (PEC)	SCN µg	SCN (PEC)	ClO4 µg	TGL (in (PEC))	ClO4/TG %	Iodine µg	I/ClO4	I/TGL	
5.6	2.0	67915	453	2379	159	6.5	618	1.1	305	76	0.71	
6.8	1.4	66304	442	2511	167	5.6	615	0.9	341	99	0.96	
7.4	1.6	56527	377	2107	140	4.9	522	0.9	250	65	0.78	
8.1	1.6	76281	509	2636	176	5.3	690	0.8	250	64	0.60	
8.6	1.6	70570	470	2699	180	5.4	656	0.8	266	71	0.68	
9.2	1.5	68955	460	2311	154	6.3	620	1.0	284	77	0.74	
10.0	1.5	61800	412	2102	140	6.4	559	1.2	267	58	0.77	
11.8	1.6	63503	423	1939	129	6.1	559	1.1	268	78	0.96	
Mean	8.4	1.6	66482	443	2336	156	5.8	605	1.0	279	74	0.78
<b>TABLE 3</b>												
<i>Total population (without outliers iodine &gt; 2000 µg)</i>												
T4	TSH	Nitrate µg	Nitrate (PEC)	SCN µg	SCN (PEC)	ClO4 µg	TGL (in (PEC))	ClO4/TG %	Iodine µg	I/ClO4	I/TGL	
5.4	4.9	59857	399	2507	167	5.1	571	0.9	240	47	0.42	
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Mean	8.2	2.1	59793	399	2393	160	5.3	563	0.9	230	43	0.41
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The first table is for women with <100 ug/l urinary iodine (women<100), the second for women with >100 ug/l urinary iodine (women>100), the third for the total population. (The 3 tables do not include individuals with >2000 ug/l urinary iodine).

From these tables the following observations can be made:

-Women with iodine levels < 100 have a total goitrogen load(TGL) expressed in PEC that is about 50% lower than women > 100 and than the overall population (columns 9 ).

-Split into the constituents, their perchlorate, nitrate and thiocyanate levels, over the entire T4 spectrum (Col. 2 ), are about 50%, 50% and 40% lower respectively (columns 5, 7 and 8).

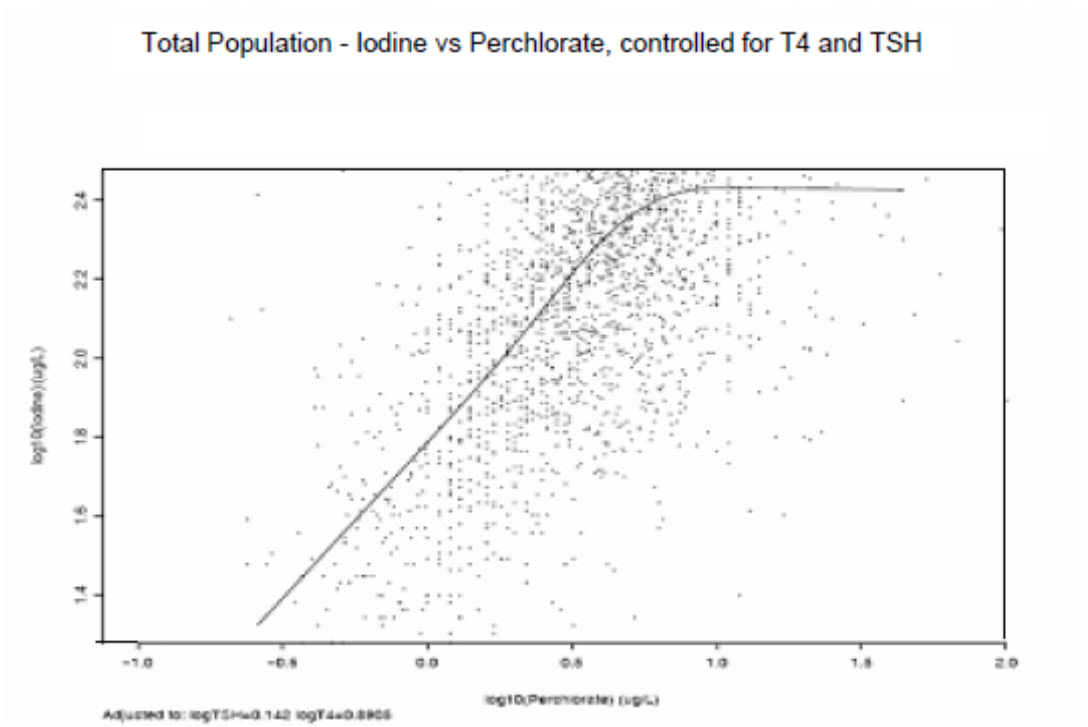
**- This means that women with insufficient iodine levels happen to be those that would be least susceptible to iodine uptake inhibition, if they would have been iodine sufficient.**

-As indicated also in the OIG study, perchlorate for all population groups represent less than 1% of the total goitrogen load expressed in PEC (columns 10).

- It confirms what OIG suggests: lowering the perchlorate intake by any rate (30, 60 or 100%) would indeed not diminish NIS iodine uptake inhibition, also not for iodine-insufficient (<100) women since the NIS iodine uptake inhibition potential caused by TGL which is more than 100 times larger, is already 50 % lower than for iodine sufficient women (>100). So besides the fact that, as OIG showed, eliminating all perchlorate even the background level would still leave 99% of PEC untouched, this remaining 99% is only half that of that of iodine sufficient women.

-Nevertheless women < 100 have a ratio of iodine to PEC equal to about 1/5 for every T4 percentile while women > 100 have about a ratio equal to 1/2 over the whole T4 spectrum (columns 13) which means that, even though the goitrogen load for iodine-insufficient women is only about half that for iodine sufficient women, their iodine inhibition potential is 2.5 times higher.

-For perchlorate this is explained by the fact that perchlorate, at low levels, is strongly related to iodine: see next figure:



Source: Gail Charnley, Perchlorate: Overview of Risks and Regulation, Food and Chemical Toxicology, 2008

This relationship suggests that low levels of perchlorate are naturally linked to iodine (both are formed in the atmosphere and both are found in naturally nitrate -rich soils in the US S-W deserts).

So women with low natural background levels of perchlorate have low natural background levels of iodine. For higher background levels of perchlorate the link with iodine ceases to exist.

So women with higher levels of iodine not only tend to have higher levels of natural perchlorate but additionally some from other (point) sources.

-For the other 2 goitrogens this suggests that those iodine-insufficient women also consume significantly less vegetables than the iodine-sufficient population. This could then also explain the higher non- natural levels of perchlorate from vegetables irrigated with synthetic perchlorate containing water such as the Colorado River. Nevertheless those synthetic perchlorate levels are themselves still insignificant compared to the total goitrogen load.

-All this strengthens the argument made by OIG that in the US population the potential iodine uptake inhibition does not lay with goitrogens and even less with perchlorate but clearly with a lack of iodine.

### Conclusion

1. Should a cumulative risk assessment be used to derive an MCL from the NAS RfD by applying not only a perchlorate RSC but also a PEC (Perchlorate Equivalent Concentration) RSC?

The answer is yes.

1. Contrary to what is usual, the clinical trial on which the NOEL and the RfD for perchlorate is based is a trial on humans and not a trial on animals.

2. This implies that the RSC is either =1 or >1; this depends on the background contamination.

3 The background contamination of perchlorate is insignificant therefore in first instance the RSC would be =1.

4. However, in the case of perchlorate, to derive a MCL from the RfD a RSC taking into account the entire goitrogen load (TGL) i.e. the perchlorate equivalent concentration(PEC), should be applied.

5. This TGL was found to be significant and therefore the RSC is >1 and consequently this would cause the MCL to be larger than 24.5 ppb.

6. An RSC of 2.1 was calculated and therefore the MCL found was 51 ppb applying the same UF=10.

*2. Should a risk assessment including lack of iodine be used to decide how iodine uptake inhibition by goitrogens should be combated?*

The answer is yes

1. Since iodine insufficient women in the US have a total goitrogen load about half of that of iodine sufficient women confirms once more that the problem is iodine insufficiency.

2. In the US, low iodide nutritional status seems to be linked to a diet poor in vegetables. Or in other words people with a healthy diet sufficiently rich in vegetables tend to have a higher goitrogen load compensated by largely sufficient iodine. Health conscious people tend to ingest more goitrogens more than compensated by iodine intake (probably through food such as fish and other seafood or through iodine supplements).

3. Higher goitrogen load and a healthy diet seem, together with adequate iodine levels, to go hand in hand.

4. As a final conclusion, only a holistic approach decreases goitrogen related health risk: a healthy diet and a sufficient intake of iodine. Focusing on perchlorate is a useless distraction.

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