NATURAL RESOURCES DEFENSE COUNCIL
BREAST CANCER FUND
CENTER FOR ENVIRONMENTAL HEALTH
CENTER FOR FOOD SAFETY
CENTER FOR SCIENCE IN THE PUBLIC INTEREST
CHILDREN'S ENVIRONMENTAL HEALTH NETWORK
CLEAN WATER ACTION
ENVIRONMENTAL WORKING GROUP
IMPROVING KIDS' ENVIRONMENT

October 15, 2014

Dr. Dennis Keefe
Director of the Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: Food additive petition seeking food additive regulation prohibiting the use of perchlorate as a conductivity enhancer in the manufacturer of antistatic agents in contact with dry food and as additive to sealing gaskets for food containers.

Dear Dr. Keefe:

The Natural Resources Defense Council (NRDC), Center for Food Safety, Breast Cancer Fund, Center for Environmental Health, Environmental Working Group, Improving Kids' Environment, Clean Water Action, Center for Science in the Public Interest and Children's Environmental Health Network submit this food additive petition[1], pursuant to section 409(b)(l) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and 21 CFR § 171.130, requesting that the Food and Drug Administration (FDA):

1. Revoke its 2005 approval of "threshold of regulation" (TOR) No. 2005-006 allowing as much as 1.2% sodium perchlorate monohydrate in dry food packaging;[2]
2. Promulgate a new 21 CFR § 189.301 prohibiting the use of perchlorate as a conductivity enhancer in the manufacture of antistatic agents to be used in food contact articles; and
3. Remove potassium perchlorate as an allowed additive in sealing gaskets for food containers in existing 21 CFR § 177.1210.

[1] Draft petition was submitted to FDA on May 18, 2014. FDA assigned it Pre-Notification Consultation (PNC) No. 001447. This petition also addresses concerns raises by FDA in response to a petition filed on July 31, 2014. On August 22, 2014, FDA determined that the petition was not suitable for filing.
[2] See http://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=TOR&id=2005-006.

The actions we are requesting are necessary because of the well-recognized toxicity of perchlorate, its widespread presence in food and in the bodies of virtually all Americans, and the likelihood that the dietary exposure may cause permanent damage to a fetus' or infant's brain by irreversibly altering its development. The risk is especially significant if a pregnant and nursing woman consumes insufficient iodine.

Perchlorate interferes with the thyroid gland's ability to uptake iodine which is fundamental to make hormones.[3] These thyroid hormones are essential for brain development in infants and in fetuses, especially in the first two trimesters when the fetus' thyroid is not fully functioning and the fetus depends entirely on the pregnant woman for thyroid hormones. Therefore, pregnant women and infants exposed to perchlorate may not absorb sufficient iodine to produce adequate levels of thyroid hormones. Even transient exposures to perchlorate may result in permanent deficits in a child's cognitive ability.[4]

Unfortunately, without regard to perchlorate, most pregnant women and nursing mothers do not consume sufficient iodine.[5,6] The World Health Organization (WHO) defines the adequacy of iodine intake based on the concentration of iodine in urine and sets a level of less than 150 µg/L as inadequate for pregnant women.[7] Based on the National Health and Nutrition Examination Survey (NHANES) results for 2007 to 2010, almost 56% of pregnant women have inadequate iodine intake. [8] For women in their first trimester, the median iodine intake was 129 µg/L with levels increasing in later trimesters. Therefore, the risk of harm from perchlorate is particularly high for the 26.3% of pregnant women with urinary iodine concentrations less than 100 µg/L and even worse for the 15.7% of pregnant women whose levels are below 50 µg/L – one-third of the level deemed inadequate by WHO.[9]

We analyzed the documentation supporting FDA's 2005 decision regarding TOR No. 2005-006 to allow perchlorate in dry food packaging that the agency provided to us in response to NRDC's Freedom of Information Act (FOIA) Request No. 2014-1324 on April 7, 2014.[10] The information makes clear that the agency's decision was improperly made at the time. The company's application contained a mathematical error that underestimated the perchlorate exposure by 83 times. When FDA posted its decision on its website, the agency made an additional mistake that allowed levels 3.3 times higher than the level stated in Ciba's submission. Even without these errors, the analysis was based on long-standing assumptions about the migration of chemicals

[3] EPA Science Advisory Board, SAB advice on approaches to derive a maximum contaminant level goal for perchlorate, 2013, EPA-SAB-13-004.
[4] *Ibid.*
[5] Caldwell KL, Pan Y, Mortensen ME, Makhmdov A, Merrill L, and Moye J, Iodine status in pregnant women in the United States: National Children's Study and National Health and Nutrition Examination Survey, *Thyroid*, 2013, doi: 10.1089/thy.2013.0012.
[6] Note that approximate 70% of salt consumed in the U.S comes from salt consumed from processed and restaurant foods which generally do not use iodized salt. Sixty percent of iodine in the U.S. diet comes from dairy products because of iodine added to cattle feed or from an iodine-based disinfectant used in milking. See Caldwell 2013.
[7] World Health Organization, Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers, 2008.
[8] Caldwell 2013.
[9] *Ibid.*
[10] See Appendix 3.

from packaging into dry food that the agency conceded in 2011 were flawed. In addition, while the approval considered only exposure from final product packaging delivered to consumers, it was so broadly written that it can be – and is – used to allow perchlorate in bulk packaging of any dry food ingredient used in food manufacturing. Finally, FDA issued its approval without considering the agency's own testing showing widespread presence of perchlorate in the food supply.

Our analysis below indicates that the uses allowed by FDA are not safe[11] because there is no longer a reasonable certainty that the perchlorate is not harmful under the intended conditions of use considering: 1) the probable consumption of perchlorate; 2) the cumulative effect of perchlorate after taking into account pharmacologically-related substances, such as thiocyanate and nitrate, in the diet; and 3) additional safety factors necessary to protect the developing brain of fetuses and infants from irreversible harm.

PART I: Request to Revoke TOR No. 2005-006

We request that FDA revoke TOR No. 2005-006 pursuant to 21 CFR § 170.39(g). We justify our request in five sections as follows:

I.A. Summary of FDA's approval of perchlorate in packaging under TOR No. 2005-006
I.B. Flaws in Ciba's exemption request
I.C. FDA's unjustified expansion of request to apply to packaging for all dry foods
I.D. Significant new information after FDA approved the use.
I.E. Disproportionate impact on children's health

We have based our analysis of FDA's response to NRDC's Freedom of Information Act (FOIA) Request No. 2014-1324 on April 7, 2014. NRDC requested documentation related to Ciba Specialty Chemicals Corporation's (Ciba) TOR No. 2005-006. We included the agency's response for reference in Appendix 3. Ciba was purchased by BASF in 2010.[12]

I.A. Summary of FDA's approval of perchlorate in packaging under TOR No. 2005-006

Ciba submitted its request for a threshold of regulation (TOR) exemption pursuant 21 CFR § 170.39 on June 17, 2005.[13] It was the subject of a Pre-Notification Consultation No. 381.

Ciba's submission asked for sodium perchlorate monohydrate (perchlorate) to be formulated with other chemicals whose names were redacted in the FOIA response. The FOIA document did state that Ciba's trade name for the product was Irgastat P18.[14] The perchlorate would have a maximum concentration of 4% by weight in the formulation of Irgastat P18. The mixture would be blended into packaging so the finished article would contain 1.2% perchlorate. Ciba said its

[11] 21 CFR § 170.3(i).
[12] http://en.wikipedia.org/wiki/Ciba_Specialty_Chemicals.
[13] Ciba submission, Memo from Ciba's Neal Earhart to FDA's Vivian Gilliam received on June 22, 2005. See Appendix 3.
[14] Ciba submission, Section 6 – Safety Narrative, page 6. See Appendix 3.

use would be identical to its Food Contact Substance Notification No. 406 which FDA did not object to on July 12, 2004.[15]

The perchlorate formulation would serve "as an antistatic agent for use in polymers in contact with dry foods with surface containing no free fat or oil compliant with 21 CFR § 176.170(c), Table 1, Food Type VIII, such as cereals, flour, macaroni, and sugar."[16] Perchlorate would serve as a conductivity enhancer.

Ciba's submission claimed that the estimated dietary concentration of perchlorate in the diet would be 0.030 parts per billion (ppb) or 0.030 micrograms per kilogram of food (µg/kg). The estimate was calculated by multiplying together the following three variables:

1. 1.2% which is the maximum level of perchlorate in the packaging;
2. 50 ppb using the assumption of "virtually nil" migration of perchlorate from packaging into dry foods per FDA's guidance; and
3. 5% which is the consumption factor FDA recommends in its guidance for the particular type of polymer used in the dry food packaging sold to consumers.[17]

Consistent with FDA's guidance, Ciba calculated the estimated daily intake (EDI) by multiplying the 0.030 ppb dietary concentration by the 3 kg of food a person is assumed to eat per day. This calculation yielded an EDI of 0.09 µg perchlorate/person/day. This level is below the 1.50 µg/person/day threshold of regulation FDA established for additives at 21 CFR § 170.39. Because the EDI was below this threshold, Ciba's submission only needed to show there was no evidence that perchlorate was associated with cancer or other health and safety effects.[18]

Ciba concluded the perchlorate "presents negligible health risks" because the EDI for a 70 kilogram person would be 0.00000129 mg/kg-body weight/day.[19] Based on this result, Ciba determined that its calculated EDI was 542 times smaller than the 0.0007 mg/kg-bw/day reference dose adopted by the U.S. Environmental Protection Agency (EPA) in its Integrated Risk Information System (IRIS) report issued February 18, 2005.[20] Ciba did not consider any sources of perchlorate in the diet other than its product.

FDA's committee handling threshold of regulation exemption submissions reviewed Ciba's document and concluded the product was eligible for the exemption. However, it unilaterally expanded the scope of the request beyond Irgastat P18 to allow sodium perchlorate monohydrate to be used as a conductivity enhancer in the manufacture of any duly authorized antistatic agents for use in contact with dry foods.[21]

[15] See http://www.accessdata.fda.gov/scripts/fdcc/?set=FCN&id=406.
[16] Ciba submission, Section 3 – Conditions of Use, page 3. See Appendix 3.
[17] Ciba submission, Section 5 – Estimated Daily Intake, page 5. See Appendix 3.
[18] Ciba submission, Section 6 – Safety Narrative, page 6. See Appendix 3.
[19] 0.00009 milligrams per person per day divided by 70kg body weight = 0.00000129 milligrams/kg body weight/day
[20] Ciba submission, Section 6 – Safety Narrative, page 6. See Appendix 3.
[21] Memorandum of Conference, FDA Threshold of Regulation Committee, Sept., 15, 2005, page 3.

On November 4, 2005, Mitchell Cheeseman, Director of FDA's Division of Food Contact Notification sent a letter to Ciba approving the exemption request after observing that the firm had "provided worst-case extraction data, safety data, and a categorical exclusion under 21 CFR § 25.32(i) and (j) in support of your request."[22] He concluded

> "that Ciba Specialty Chemical Corporation's intended use of sodium perchlorate monohydrate as a conductivity enhancer in regulated or otherwise authorized antistatic agents at a maximum concentration of 4 percent by weight, which would correlate to 1.2 percent by weight in the finished article for use in contact with dry foods qualifies for an exemption under 21 CFR § 170.39 from the requirement of being the subject of a food additive listing regulation."[23]

FDA announced its decision by posting a notice on its website. As of May 16, 2014, the notice is reprinted in Figure 1.

Figure 1: Reprint of FDA's webpage for its approval of sodium perchlorate[24]

TOR No. 2005-006

Threshold of Regulation Exemptions are generally applicable and are effective for the food contact substance (FCS) for the listed intended use regardless of manufacturer or supplier.

Food Contact Substance:	Sodium perchlorate monohydrate (CAS Reg. No. 7791-07-3)
Use Limitations*:	As a conductivity enhancer in the manufacture of antistati agents at a maximum concentration of 4 percent by weigh in the finished article for use in contact with dry foods.
Requestor:	Ciba Specialty Chemical Corp.

I.B. Flaws in Ciba's exemption request

Ciba's exemption request contained three serious flaws: 1) failure to consider existing FDA approval of perchlorate in food contact articles; 2) failure to consider widespread contamination of the food supply with perchlorate; and 3) mistaken exposure calculation resulting in a dietary concentration estimate 83 times lower than FDA's guidance would allow. FDA appears not to have noticed these flaws.

[22] FDA, Letter to Ciba Specialty Chemicals Corporation regarding Sodium Monohydrate Perchlorate, TOR No. 251, 2005. See Appendix 3.
[23] FDA Letter from Mitchell Cheeseman to Neal Earhart of Ciba Specialty Chemicals Corporation, Nov. 4, 2005. See Appendix 3.
[24] FDA, Threshold of Regulation (TOR) Exemptions, TOR No. 2005-006. Accessed May 16, 2014. See http://www.accessdata.fda.gov/scripts/fdcc/?set=TOR&id=2005-006. Note that the first paragraph in the notice was not included on the webpage on November 6, 2013.

I.B.1. Failure to consider potassium perchlorate exposure allowed as an additive to food contact articles by FDA since 1962

Ciba's exemption request stated that "Sodium perchlorate monohydrate is not FDA regulated." This statement is misleading. A search for "perchlorate" in FDA's "List of Indirect Additives Used in Food Contact Substances"[25] shows that potassium perchlorate is allowed to be used for closures with sealing gaskets for food containers by 21 CFR § 177.1210.

This regulation allows gaskets used to seal food containers to contain up to 1% potassium perchlorate (expressed as percentage by weight of closure-sealing gasket composition). FDA issued this rule on July 20, 1962 in response to a food additive petition filed by Anchor Hocking Glass, W.R. Grace and Company and Chemical Products Corporation. Its decision was effective on July 26, 1962 when it was published in the *Federal Register*.[26]

Ciba's omission is significant because 21 U.S.C. § 348(c)(5) requires FDA to consider "(A) the probable consumption of the additive and of any substance formed in or on food because of the use of the additive" and "(B) the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet." FDA incorporated these requirements into its definition of safe or safety at 21 CFR § 170.2(i).

While potassium perchlorate and sodium perchlorate monohydrate are different chemicals, they are both salts of perchlorate and would serve a similar function and pose similar health risks. They are chemically-related because in solution the sodium or potassium would disassociate from the perchlorate which would be absorbed and circulate in the body as such. They are also pharmacologically related because they both adversely affect the function of the thyroid gland acting in a similar fashion.

Since Ciba did not consider the exposure from this use of perchlorate, its EDI calculation was flawed. Had this exposure been considered, the proposed use may not have been eligible for the Threshold of Regulation Exemption pursuant to 21 CFR § 170.39.

I.B.2. Failure to consider widespread contamination of food supply with perchlorate

Ciba did not consider the presence of perchlorate as a contaminant in the food supply in its cumulative exposure estimate. At the time the petition was submitted in 2005, there was widespread concern of perchlorate contamination in drinking water.

In response to the concerns, on December 23, 2003, FDA issued a high priority assignment to collect and analyze lettuce and bottled water for perchlorate.[27] Fourteen months later and four months before Ciba submitted its TOR request, the agency expanded the assignment to include

[25] http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?filter=perchlorate&sortColumn=&rpt=iaListing.
[26] 27 *Federal Register* 7092 (July 26, 1962).
[27] FDA, Collection and Analysis of Food for Perchlorate – High Priority – DFP#04-11, 2003. See http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077780.htm.

broccoli, oranges, orange juice, apples, apple juice, spinach, carrots, cantaloupe, tomatoes, grapes, cornmeal, and oatmeal.[28] This expansion was a clear indication that FDA had found perchlorate in its initial sampling.

As FDA later expanded its testing to include all types of food products, the agency found perchlorate in most samples in all food types and all regions of the country. See section I.D.4 for more information on the sampling results.

Ciba's safety narrative only considered the human exposure to sodium perchlorate resulting from the proposed use of Irgastat P18. This is contrary to 21 U.S.C. § 348(c)(5) and 21 CFR § 170.2(i) because it does not consider the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet.

I.B.3. Mistaken exposure calculation resulted in estimate exposure that is 83 times lower than FDA's guidance would allow

FDA's guidance recommends the following equation to calculate the dietary concentration (DC) of a food contact substance:

DC = Migration (M) X Consumption Factor (CF)

For food contact substances in contact with dry food, FDA's guidance assumes that the chemical migrates at levels not higher than 50 ppb – a level described as "virtually nil" migration. This 50 ppb migration would result in dry food contamination of 50 µg of perchlorate per kilogram of food (µg/kg).

According to FDA, the consumption factor represents the agency's estimate of "the fraction of the daily diet expected to contact specific packaging materials."[29] For this particular product, the consumption factor was 0.05.

Therefore, the dietary concentration for perchlorate would be:

DC = 0.05 (representing the CF) x 50 µg perchlorate per kilogram of food (representing the migration) = 2.5 µg perchlorate/kg food

The agency then recommends that the estimated daily intake (EDI) is calculated as the product between the DC and the estimated 3 kilograms of food a person consumes per day. This calculation would be:

EDI = DC X 3 kg food

[28] FDA, Collection and Analysis of Food for Perchlorate – High Priority – DFP#05-09, 2005. See http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077709.htm.

[29] FDA, Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations," 2002. See Section E.1.A. http://www.fda.gov/Food/GuidanceRegulation/ucm081818.htm. FDA revised the document in 2007 but the revisions did not alter this aspect of the guidance.

EDI = 2.5 µg perchlorate/kg food X 3 kg food/person/day
EDI = 7.5 µg perchlorate/person/day

In calculating the DC, Ciba varied from FDA's guidance without explanation. In addition to the migration and consumption factor, Ciba inserted the amount of perchlorate in the formulation (4%) and the amount of formulation in the packaging (30%) into the above equation as can be seen in Figure 2 which is an extract of the relevant section from Ciba's submission.

This mistake in the DC estimation led to improperly calculating the EDI. As a result, the calculated EDI of 0.090 µg perchlorate/person/day was 83 times smaller than the EDI of 7.5 µg perchlorate/person/day calculated according to FDA's guidance.

Had Ciba properly calculated the EDI, it would not have been eligible for the threshold of regulation exemption requested because the EDI would have been 5 times larger than the 1.5 µg perchlorate/person/day threshold established in 21 CFR § 170.39.

Figure 2: Extract from "Section 5 – Estimated Daily Intake" (page 5) of Ciba's exemption request

The dietary concentration (DC) of sodium perchlorate monohydrate in [redacted] can be calculated as:

DC = [(0.05CF[1]) x (4% sodium perchlorate in the [redacted] formulation) x (30% maximum use level of the [redacted] formulation) x (50ppb, dry foods "virtually nil" migration) = **0.030 ppb**

Based on this DC, the estimated daily intake (EDI) can be calculated as

EDI = 0.030ppb x 3 kg food/person = **0.090 µg/person/day**

[1] CF = Consumption Factor

I.C. FDA's unjustified expansion of request to apply to packaging for all dry foods

FDA posted on its website a notice of its decision to approve TOR No. 2005-006. See Figure 1 on page 5 for a reprint of FDA's webpage.

Like all TOR exemptions, any supplier or manufacturer, even Ciba's competitors, may rely on this notice and sell packaging and food products consistent with the approval. FDA's website makes this point clear in the first paragraph of Figure 1.

However, in addition to not identifying and correcting the flaws in Ciba's DC and EDI calculations, FDA's public notification of its decision went further than the scope of Ciba's request in six critical ways described below. This conclusion is drawn from our analysis of the agency's response to our FOIA request since FDA does not make publicly available additional information beyond what is posted on its website.

I.C.1. Expanded to all antistatic agents

Despite the narrow request, FDA intentionally and without justification approved the use of perchlorate in any antistatic agent not just Irgastat P18 or that type of plastic. It was not limited to the specific type of plastic used in Ciba's product.

I.C.2. Expanded to all types of dry-food packaging and not just polymers

FDA's letter to Ciba limited the approval to "use in polymers in contact with dry foods."[30] However, the notice on the agency's website does not include such a limitation. Since FDA does not make the approval letter publicly available, manufacturers and suppliers other than Ciba would be unaware of this limitation. Consequently, Ciba's competitors are implicitly authorized to use perchlorate in paper, metal coating, or glass.

I.C.3. Expanded to all dry-food including infant formula and other food for children younger than 2 years old

FDA's guidance for calculating the EDI is based on what an adult eats. For instance, it uses 3 kg of food consumed a day and uses consumption factors based on a wide variety of food products. Therefore, the guidance and Ciba's request are implicitly limited to adults consuming a diverse diet.

The guidance could grossly underestimate exposure of an infant relying on powdered formula as the sole source of nutrition – as is common for infants younger than six months of age. If the formula packaging used the perchlorate as an antistatic agent to allow the powder to flow more fully and freely from the container, then the infant would have much greater exposure to perchlorate. Also, infants and children consume more food per body weight than adults, adding to a higher exposure.[31]

I.C.4. Expanded to include bulk packaging for raw materials

FDA's consumption factors are based on packaging for consumer products. Its guidance states the factors represent "the fraction of the daily diet expected to contact specific packaging materials."[32] It goes on to state that the "values were derived using information on the types of food consumed" and by implication not the ingredients used as raw materials in food production.[33]

In an October 5, 2011 speech at a seminar organized by an industry-sponsored law firm, FDA's Michael Adams, a supervisory chemist in the food contact notifications division at the time, described the sources of information FDA uses to estimate consumption factors and discussed potential changes to its guidance. The next day, Food Chemical News summarized his speech as follows:

[30] FDA Letter from Mitchell Cheeseman to Neal Earhart of Ciba Specialty Chemicals Corporation, Nov. 4, 2005. See Appendix 3.
[31] EPA, Children Are Not Little Adults! Accessed at http://www2.epa.gov/children/children-are-not-little-adults on July 27, 2014.
[32] FDA, Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations," 2002. See Section E.1.A. http://www.fda.gov/Food/GuidanceRegulation/ucm081818.htm. FDA revised the document in 2007 but the revisions did not alter this aspect of the guidance.
[33] *Ibid*.

"Additionally, the agency has signed new contracts with data mining companies Food Essentials, Mintel Corp. and Gladson Corp. to determine consumption factors for various polymers." They mainly do packaging surveys around the world," he reported. "We can get photos of packages from all over the world. We can find out what the package is made of. Our package analysis can feed into a database. If we set it up right, we'll be able to update it regularly." Food Chemical News, October 6, 2011.

As far as we can discern, these three data mining companies are evaluating only final products sold to consumers.

However, FDA's approval of TOR No. 2005-006 referred only to "finished article" (Figure 3, Use limitations). In this context, "finished article" applies to packaging for raw materials throughout the supply chain and not solely food products sold to the consumer. This issue is significant since food manufacturers typically prefer to store and transport materials as dry powders or solids rather than as liquids to reduce costs and to allow longer storage without spoilage.

Therefore, consistent with FDA's broad public statement, whenever a dry food ingredient came in contact with the Irgastat P18, perchlorate would be likely to migrate into it. Even if FDA's assumption of 50 ppb migration levels from the packaging were correct, perchlorate could be entering any food through the manufacturing process and not just from the final packaging of dry food sold to the consumer.

As evidence that these exposures from multiple sources must be cumulatively assessed, consider the following two resources:

1. In 2004, the U.S. Patent Office issued patent US2004/0004804 A1 for "a mechanism for use in a Flexible Intermediate Bulk Container (FIBC), which enables the immediate neutralization of the electrostatic charges generated during filling, emptying or transporting of the FIBC. **FIBCs are used to carry bulk solid powders**, such as **sugar, flour, starch** and chemical substances." The patent application states that "[t]hese fibers for neutralizing the electrostatic charges preferably include permanent antistatic additives such as **IRGASTAT P18** or IRGASTAT P22 manufactured by **Ciba Geigy**® at a ratio of %6-%20 preferably." *Emphasis added.* The IRGASTAT P18 is the same product that FDA approved to contain perchlorate as a conductivity enhancer pursuant to TOR No. 2005-006 a year later.
2. In 2013, BASF, which bought Ciba in 2010, published a brochure specifically targeted for food manufacturers called "Solutions for Food Packaging".[34] It states that "**Irgastat® P18 FCA features:** • Anti-dust protection – the use of a permanent anti-static agent reduces the electrostatic charge on film surfaces, avoiding dust deposit and preserving the original appearance of the package. The product is approved and used for **bulk and industrial food and non-food contact packaging**." *Emphasis added.* We found the

[34] BASF, Solutions for Food Packaging, 2013. See http://chinaplas.basf.com/sites/default/files/brochure/Solutions%20for%20Food%20Packaging_English_2013_lo.pdf.

document at a BASF website – chinaplas.basf.com – that focused on the China plastics market.

I.C.5. Expanded to allow perchlorate in repeated use packaging

The bulk packaging described above may be reused. While FDA's guidance has special procedures to consider migration from repeated use packaging, Ciba did not rely on those sections.[35] However, FDA's approval did not contain any limitation to single use packaging.

I.C.6. Expanded to levels of up to 4% in antistatic agents

FDA's letter to Ciba limited the approval to "1.2 percent by weight in the finished article for use in contact with dry foods."[36] However, the notice on its website only limits the perchlorate levels to 4% in the finished article (Figure 1, Use limitations). As a result, food in packaging from a Ciba competitor who is unaware of this limitation could have exposures that are 3.3 times greater than Ciba's products thus further increasing the health risk for consumers.

I.D. Significant new information after FDA approved the use.

If FDA receives significant new information that raises questions about the dietary concentration or the safety of a substance that the agency has exempted from regulation, 21 CFR § 170.39(g) authorizes the agency to reevaluate the substance. If FDA tentatively concludes that the information that is available about the substance no longer supports an exemption for the use of the food-contact material from the food additive regulations, the agency should notify any persons that requested an exemption for the substance of its tentative decision. The requestors will be given an opportunity to show why the use of the substance should not be regulated under the food additive provisions of the act. If the requestors fail to adequately respond to the new evidence, the agency will notify them that further use of the substance in question for the particular use will require a food additive regulation. Because other manufacturers and suppliers may rely on the notice, FDA will notify them by means of a *Federal Register* notice of its decision to revoke an exemption issued for a specific use of a substance in a food contact article.

In our review of the scientific literature and other sources of information since the agency's approval of the exemption in 2005, we identified four types of significant new information that would warrant a reevaluation of the decision. First, additional research shows that the endpoint used in the decision was not the most appropriate or sensitive one to protect fetuses and infants from permanent brain damage. Second, it is now known that nitrates and thiocyanates are pharmacologically-related to perchlorate and, therefore, must be considered in any safety evaluation of perchlorate as an additive. Third, in 2011, FDA acknowledged that the 50 ppb

[35] FDA, Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations," 2002. See Appendix II Section 4. http://www.fda.gov/Food/GuidanceRegulation/ucm081818.htm.

[36] FDA Letter from Mitchell Cheeseman to Neal Earhart of Ciba Specialty Chemicals Corporation, Nov. 4, 2005. See Appendix 3.

migration to dry-food default assumption ("virtually nil" migration) may be flawed based on research evidence from Europe. Fourth, FDA has demonstrated that there is widespread contamination of the food supply with perchlorate that must be considered.

I.D.1. Additional research identified a more sensitive and appropriate endpoint to assess perchlorate risk in pregnant women, fetuses and to infants.

Ciba's submission uses EPA's IRIS document issued a few months earlier to conclude that their estimated perchlorate migration from Irgastat P18 (using the flawed assumption of 50 ppb as discussed below) was more than two orders of magnitude lower than the IRIS reference dose of 0.7 micrograms/kg body weight/day and, therefore, did not pose a health risk. The same year, a National Research Council (NRC) report confirmed that reference dose.

In 2013, EPA's Science Advisory Board (SAB) considered the latest science regarding perchlorate. The SAB disagreed with NRC's reference dose because it does not provide sufficient protection to susceptible populations. The SAB questioned NRC's use of hypothyroidism in pregnant women as the most sensitive indicator of perchlorate health effects. Instead, it recommended that the safe level be based on "maternal hypothyroxinemia (without hypothyroidism)."[37] Hypothyroxinemia is a low level of thyroxine or T4 hormone without elevated thyroid-stimulating hormone (TSH).

SAB stated that hypothyroxinemia is a more sensitive indicator of the adverse effects on a fetus' or infant's brain development and based its recommendation on its conclusion that

> "Although adverse neurodevelopmental effects of perchlorate in infants and children have not been reported in the literature, the risk of adverse effects can be reasonably inferred from perchlorate's mode of action and the known role of thyroid hormone on human brain development." [38]

We agree with the SAB's conclusion that hypothyroxinemia is a more sensitive indicator of perchlorate health effects. Its conclusion warrants deference because it was developed through a robust and transparent process that involved public comment, public meetings and peer review. The SAB also recommended that the EPA expand the available physiologically-based pharmacokinetic/pharmacodynamics model to explicitly incorporate predictions of thyroid hormone insufficiencies and sensitive life stages to develop a maximum contaminant level goal.

Recently published research published in the Journal of Clinical Endocrinology and Metabolism reinforces the strength of SAB's conclusions. The authors undertook a retrospective analysis of 487 mother-child pairs in mothers who were hypothyroid/hypothyroxinemic during pregnancy. They found that children of women with perchlorate levels in the highest 10% in the first

[37] EPA Science Advisory Board, SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate, 2013. See page 10
[38] *Ibid* at page 2 of the cover letter.

trimester had increased odds of being in the lowest 10% IQ at 3 years of age.[39] The greater negative impact was in verbal performance with odds ratio of 3.14 (95%CI 1.42, 6.9) and p value of 0.005. This study supports the SAB recommendation of using hypothyroxinemia as a more sensitive indicator of the adverse effects of perchlorate exposure brain development.

Regarding a no-observe-adverse-effect level (NOAEL) for this new endpoint, we have not identified one that was developed taking into consideration the most sensitive endpoint and life stages as recommended by the SAB and that we support. Two articles regarding models for a NOAEL or Reference Dose have been published, one led by FDA's National Center for Toxicological Research and the other one led by EPA's scientists; however, both are incomplete.

Using a model originally developed by AEgis Technologies Group for the Air Force, FDA published a model of perchlorate's impact on pregnant women and fetuses in the third trimester of pregnancy.[40] The model considers both maternal endpoints: hypothyroidism and hypothyroxinemia and various iodine intake levels. It calculated that a daily intake of 4.2 µg perchlorate/kg body weight was necessary to reduce free T4 serum levels to a hypothyroxinemic state in women with a low iodine intake of 75 µg/day.

Although a good attempt to tackle a difficult problem, the model has several shortcomings including only considering pre-term women and fetuses, not considering NHANES biomonitoring data and using assumptions without supporting rationale, and not considering the nitrate and thiocyanate in the pharmacologically-related substances in the diet. See Appendix 4 for a detailed description of the model's deficiencies we submitted to EPA on February 2014. FDA and EPA have been collaborating to expand the model to represent all three trimesters as well as for a formula-fed or breast-fed infant. The model has not yet been published or made available for peer review.

In 2014, EPA's scientists published their analysis of the available models using a six-step framework for PBPK model evaluation.[41] The authors did not consider the SAB recommendation of hypothyroxinemia as the most sensitive endpoint to protect the most vulnerable populations. However, they still found that the models have several limitations including 1) not considering the effect of thiocyanate and nitrate on iodide uptake inhibition and the flux of dietary iodine, and 2) being insufficiently protective of newborns. It is worth noting that the models reviewed by EPA had additional limitations including not considering first and second trimester or women with iodine deficiency.

[39] Taylor PN, Okosieme OE, Murphy R, Hales C, Chiusano E, Maina A, Joomun M, Bestwick JP, Smyth P, Paradice E, Channon S, Braveman LE, Dayan CM, Lazarus JH, Pearce EN. Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring; Data from the Controlled Antenatal Thyroid Study. J Clin Endocrinol Metab. 2014. Jul 24:jc20141901.

[40] Lumen A, Mattie DR, and Fisher JW, Evaluation of Perturbations in Serum Thyroid Hormones During Human Pregnancy Due to Dietary Iodide and Perchlorate Exposure Using a Biologically Based Dose-Response Model, *Toxicological Sciences*, 2013, 133(2), 320–341.

[41] McLanaham ED, White P, Flowers L, Schlosser PM. The use of PBPK models to inform human health risk assessment: Case study on perchlorate and radioiodide human life stages models. Risk Analysis 2014. 34(2):356-366

This information is significant because it raises questions about the safe level of exposure to perchlorate relied on by Ciba when the agency approved TOR No. 2005-006.

I.D.2. Since 2005, research shows that nitrates and thiocyanates are pharmacologically-related to perchlorate

When FDA approved TOR No. 2005-006, it did not consider the contribution of chemicals that were pharmacologically but not structurally-related to perchlorate such as thiocyanate and nitrates. Research since 2005 has made clear that these chemicals have a common mechanism of toxicity with perchlorate: all three disrupt the sodium/iodide symporter and interfere with the thyroid's uptake of iodine and its ability to make hormones essential to fetal and infant brain development.[42,43] This same symporter is found elsewhere in the body, most notably in the mammary gland in production of breast milk.[44]

The amount needed to disrupt the symporter mechanism likely varies for each of the three chemicals. However, the levels of the other chemicals in the body are also likely to be greater than perchlorate.

One particularly useful study on the issue was published by researchers at the Centers for Disease Control and Prevention (CDC) and their colleagues.[45] They measured levels of all three chemicals (perchlorate, thiocyanate and nitrate) in the urine of more than 200 infants younger than one year old in Philadelphia and correlated the levels with the infant's nutrition source. Table 1 summarizes the findings.

Table 1. Comparison of levels of three contaminants in urine based on the nutrition source for infants younger than one year old.

Nutrition source for infant	Perchlorate	Nitrate	Thiocyanate
Breast milk (n = 92)	4.97 ppb	18,350 ppb	189 ppb
Cow milk-based formula (n = 51)	2.89 ppb	29,330 ppb	151 ppb
Soy-based formula (n = 63)	1.07 ppb	32,070 ppb	70 ppb
Adapted from Table 1 of Valentin-Blasini, 2011.			

The information is significant because the 21 U.S.C. § 348(c)(5)(B) and 21 CFR § 170.2(i) requires FDA to consider "the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet."

[42] Steinmaus C, Miller MD, Cushing L, Blount BC, Smith AH, Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the National Health and Nutrition Examination Survey 2007-08, Environ Res. 2013 May;123:17-24. doi: 10.1016/j.envres.2013.01.005.
[43] EPA SAB 2013.
[44] Dasgupta PK, Kirk AB, Dyke JV, Ohira S, Intake of Iodine and Perchlorate and Excretion in Human Milk, *Environ. Sci. Technol.* 2008**,** *42*, 8115–8121.
[45] Valentin-Blasini L, Blount BC, Otero-Santos S, Cao Y, Bernbaum JC, and Rogan WJ, Perchlorate exposure and dose estimates in infants, Environ. Sci. Technol. 2011, 45, 4127–4132, dx.doi.org/10.1021/es103160j.

Another recent study[46] evaluated the potential associations between urinary perchlorate, nitrate and thiocyanate and serum free T4 (the hormone associated with hypothyroxinemia) in individuals with low urinary iodine levels in two NHANES cycles: 2001-2002 and 2007-2008. Low iodine levels were defined as those less than 100 µg/L. The authors found that in a meta-analysis, urinary perchlorate, nitrate, and thiocyanate were significant predictors of serum free T4 in non-pregnant women. They concluded that "risk assessment for perchlorate exposure should consider co-exposure to nitrate and thiocyanate."

Given the widespread use of these chemicals, particularly nitrates,[47] in food or food packaging, this new information must be taken into account when evaluating their cumulative effect on the thyroid in pregnant women and children. This, together with new epidemiological data that children exposed to perchlorate during the first trimester of gestation have impaired neurodevelopment, constitute new scientific evidence that should lead FDA to reconsider TOR No. 2005-006.

I.D.3. In 2011, FDA acknowledged that 50 ppb migration assumption may be flawed

Ciba based its request on FDA's *Guidance for Industry – Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances* issued in 2002.[48] For dry food with surfaces containing no free fat or oil, the guidance states that:

> "Dry foods with the surface containing no free fat or oil typically exhibit little to no migration, although some studies have shown migration of certain adjuvants into dry foods (*e.g.*, volatile or low molecular weight adjuvants in contact with porous or powdered foods). If the FCS is intended for use *only* with dry foods with surface containing no free fat or oil, **a migration of 50 ppb may be assumed**. This migration level can then be multiplied by the appropriate food-type distribution factor and consumption factor to obtain an estimated dietary concentration. If the intended use for the FCS includes other food types (*e.g.*, acidic, aqueous, or fatty foods), in addition to dry foods with surface containing no free fat or oil, then the migration studies conducted for those food types will subsume any migration for a dry food with surface containing no free fat or oil. If you desire to conduct migration studies for dry foods containing no free fat or oil, consult with FDA for recommended migration protocols."[49] *Emphasis added.*

FDA has acknowledged that the long-standing 50 ppb assumption needs to be reconsidered based on European Union studies showing substantial migration of chemicals into dry food. In

[46] Suh M, Abraham L, Hixon JG, Proctor DM. The effects of perchlorate, nitrate, and thiocyanate on free thyroxine for potentially sensitive subpopulations of the 2001-2002 and 2007-2008 National Health and Nutrition Examination Surveys. J Expo Sci Environ Epidemiol. 2013. Published ahead of print on Oct 23. Doi: 10.1038/jes.2013.67

[47] Nitrates are allowed by 21 C.F.R. §§ 172.160, 172.170, 172.175, 173.310, 175.105, 176.180, 176.320, 181.33, 181.34.

[48] FDA, Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations," 2002. See Appendix II Section 13. http://www.fda.gov/Food/GuidanceRegulation/ucm081818.htm. It was revised in 2007 but the changes do not affect the recommendations relied upon by Ciba.

[49] *Ibid.*

an October 5, 2011 speech at a seminar organized by an industry-sponsored law firm, FDA's Michael Adams, a supervisory chemist in the food contact notifications division at the time, described these concerns. The next day, Food Chemical News summarized his speech as follows:

> "Much of the data used in FDA [food contact] recommendations is showing its age," Adams said. "New analytical techniques, new products and new markets must be accommodated."
>
> "Maybe we need to look at the science behind our assumptions," Adams said, acknowledging that many of the agency's recommendations, such as chemical residue levels "of no consequence," rely on data from the 1970s and 1980s. "How do we handle these numbers?" he asked.
>
> Adams noted that FDA doesn't require migration tests for packaging adhesives. Instead, the agency uses a default assumption of 50 parts per billion that he said apparently "came out of the ether. For some adhesives, 50 ppb might be okay, but with 'hot melts' and rubber adhesives, migration may be very high."
>
> Adams noted that FDA's standing assumption has been that there is no migration of polymers from packaging into dry food. Exposure is based on a default dietary concentration of 50 parts per billion. However, evidence from EU lab studies shows substantial migration into dry food, more than 50 ppb in some cases."
>
> "We're contemplating a change to require migration studies for dry foods," he said. "We'll put out some guidance when we put it all together."
>
> Noting that FDA has recently received some grants for its research, Adams concluded, "Hopefully, we'll be able to bring our science into the 21st century."[50]

We believe the 50 ppb migration assumption is particularly flawed for a chemical like perchlorate whose function in the package is to chemically-interact with the dry food by neutralizing the static charge. Unlike others, packaging made with perchlorate-laden Irgastat P18 is not intended to simply be an inert barrier.

To our knowledge, FDA has not updated its guidance despite these statements.

I.D.4. Information on widespread contamination

As noted earlier, Ciba's submission did not consider the possibility that perchlorate was already widely present in the food and drinking water supply despite FDA's public steps to investigate the issue.

In 2008, FDA published the results of its investigation into perchlorate contamination of the food supply.[51] It found that 625 of the 1065 (59%) samples it tested had detectable levels of

[50] Food Chemical News, October 6, 2011.

perchlorate and 211 of the 285 (74%) food types had at least one sample containing measurable levels of perchlorate. Children between six months and 6 years old had the greatest average exposures ranging from 0.25 to 0.39 micrograms per kilograms of body weight per day (µg/kg-bw/day). Compared to the 2005 Reference Dose (RfD) used by Ciba of 0.7 µg/kg-bw/day based on the less sensitive endpoint of hypothyroidism, the average young child would be exposed to about half of the acceptable daily intake.

While in its 2008 publication of perchlorate contamination FDA did not estimate the 90th percentile of exposure, typically, the 90th percentile is twice the mean. FDA's guidance for estimating the EDI recommends using the more protective 90th percentile value, not just the average. If the 90th percentile was used, some children may already be exposed above the 2005 RfD (which may not be sufficiently protective of fetuses and infants during their critical stages of brain development).

If the more sensitive endpoint of hypothyroxinemia were considered as EPA's SAB now recommends, many more children would be at risk of permanent harm to their brain from even transient exposure to perchlorate.

Samples of infant milk formula collected from October 2004 to July 2005, before FDA made a decision on Ciba's application had levels as high as 3.6 µg perchlorate/kg infant formula with all regions having levels in milk-based formula greater than 1.2 µg/kg.[52]

Because the FDA perchlorate dietary contamination results are from samples taken from October 2004 to July 2006, they most likely do not reflect the contribution from Ciba's product since FDA approved it in November 2005 because it would take time for the manufacturer of Irgastat P18 and its competitors to make significant new inroads into this market.

FDA's survey published in 2008 represents significant new information that warrants a reassessment of its approval in 2005 of TOR No. 2005-006.

I.E. Disproportionate impact on children's health

EPA, EPA's Science Advisory Board, and FDA's evaluations of perchlorate in recent years make clear that infants are likely to be disproportionately impacted by perchlorate because their brains are undergoing development in the womb and in their younger years. Therefore, FDA has an obligation under Executive Order 13045 regarding protection of children from environmental health risks and safety risk[53] to ensure its policies, programs, activities and standards specifically address these risks. The order expressly applies to food and drink.

[51] Murray, Egan, Kim, Beru, and Bolger, US Food and Drug Administration's Total Diet Study: Dietary intake of perchlorate and nitrate, *Journal of Exposure Science and Environmental Epidemiology* (2008) 18, 571–580.
[52] *Ibid*.
[53] See http://yosemite.epa.gov/ochp/ochpweb.nsf/content/whatwe_executiv.htm.

Because perchlorate is associated with potentially irreversible harm to pre-natal and post-natal brain development, we believe that FDA should use additional safety factors designed to protect children beyond the default of 100-fold recommended by the agency at 21 CFR § 170.22.

PART II: Request to Prohibit Use of Perchlorate as Conductivity Enhancer

We understand that FDA would publish a *Federal Register* notice announcing its revocation of TOR No. 2005-006 should it accept Part I of this petition. However, in light of the magnitude of the errors and the significance of the potential risk to pre-natal and post-natal brain development, we believe that notice is insufficient to alert industry to the change. Many companies have relied on the nine-year old decision and may miss the notice. Therefore, we request that FDA promulgate a new 21 CFR § 189.301 prohibiting the use of perchlorate as a conductivity enhancer in the manufacture of antistatic agents to be applied to food contact articles. We propose language for that new section in Appendix 2.

PART III: Request to Remove Perchlorate as Additive to Sealing Gaskets

Existing 21 CFR § 177.1210 allows more than 75 chemicals to be added to sealing gaskets for food containers. Potassium perchlorate is one of them with gaskets allowed to contain up to 1% potassium perchlorate (expressed as percentage by weight of closure-sealing gasket composition). FDA issued this rule on July 20, 1962 in response to a food additive petition filed by Anchor Hocking Glass, W.R. Grace and Company and Chemical Products Corporation. Its decision was effective on July 26, 1962 when it was published in the *Federal Register.*[54]

While potassium perchlorate and sodium perchlorate monohydrate are different chemicals, they are both salts of perchlorate, serve a similar function, and pose similar health risks. They are chemically-related because in solution the sodium or potassium would disassociate from the perchlorate which would be absorbed and circulate in the body as such. Pursuant to U.S.C. § 348(c)(5), and pharmacologically related because they affect the same sodium iodine symporter in the thyroid gland. Therefore, FDA must consider potassium perchlorate when evaluating perchlorate exposures.

We do not know how common perchlorate is used in these gaskets and what the cumulative exposure is from their use. Presumably the 1962 food additive petition contained an estimate because the agency could not have approved it without considering "the probable consumption of the additive and of any substances formed in or on food because of the use of the additive" as required by 21 U.S.C. § 348(c)(A). Since the agency has that information in its possession, there is no need for us to submit a Freedom of Information Act request and submit it back to the agency once we get it.

[54] 27 *Federal Register* 7092 (July 26, 1962).

Whatever exposure estimate FDA used to approve it in 1962, we believe the use is unnecessary in light of the existing perchlorate exposures and the significance of the potential risk to pre-natal and post-natal brain development. Therefore, we request that FDA delete the potassium perchlorate listing in Table 1 of 21 CFR § 177.1210.

Conclusion

Based on all the new evidence we just introduced, we ask that FDA:

1. Revoke its 2005 approval of "threshold of regulation" (TOR) No. 2005-006 allowing as much as 1.2% sodium perchlorate monohydrate in dry food packaging;[55]
2. Promulgate a new 21 CFR § 189.301 prohibiting the use of perchlorate as a conductivity enhancer in the manufacture of antistatic agents to be used in food contact articles; and
3. Remove potassium perchlorate as an allowed additive in sealing gaskets for food containers in existing 21 CFR § 177.1210.

See Appendix 1 for additional details on the petition and Appendix 2 for the specific changes we seek in the regulation. Appendix 3 provides the agency's response to NRDC's FOIA request.

Please note that this letter and all appendices and references constitute our complete petition. Please note that this is NOT a citizens petition. We have enclosed three copies per 21 CFR § 171.1.

If you have questions or comments, please contact Erik D. Olson at eolson@nrdc.org or 202-289-2415.

Sincerely,

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[55] See http://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=TOR&id=2005-006.

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Appendices

1. Responses to Elements Required by 21 CFR § 171.1
2. Requested New 21 CFR § 189.301
3. FDA Response to NRDC FOIA Request No. 2014-1324, April 7, 2014
4. NRDC Comments to EPA regarding FDA model for perchlorate

Appendix 1
Responses to Elements Required by 21 CFR § 171.1

Per 21 CFR § 171.1, we provide responses to the requested elements of a food additive petition with one element per page.

Name and Pertinent Information Concerning Food Additive
The identity of the food additive is as follows:

Name	Chemical Formula	Formula Weight	CAS No.
Perchlorate	ClO_4^-	99.451	14797-73-0
Sodium Perchlorate	$NaClO_4^-$	122.44	7601-89-0
Sodium Perchlorate Monohydrate	$NaClO_4 \cdot H_2O$	140.46	7791-07-3
Potassium Perchlorate	$KClO_4^-$	138.55	7778-74-7
Ammonium Perchlorate	$NH_4ClO_4^-$	117.49	7790-98-9
Perchloric Acid	$HClO_4^-$	100.46	7601-90-3

Directions, Recommendations, and Suggestions Regarding Proposed Use

We are asking FDA to prohibit the use of any form of perchlorate to enhance the conductivity of any antistatic agent in contact with food and to remove potassium perchlorate as an allowed additive to sealing gaskets for food containers. Since there is no use being proposed, we do not have any directions, recommendations or suggestions regarding proposed uses.

Data establishing that food additive will have intended physical or other technical effect. We are asking FDA to prohibit the use of any form of perchlorate to enhance the conductivity of any antistatic agent in contact with food and to remove potassium perchlorate as an allowed additive to sealing gaskets for food containers. As a result, there should be no intended physical or technical effect from the absence of perchlorate as a food additive.

Description of practicable methods to determine the amount of the food additive in the food
We are asking FDA to prohibit the addition of any form of perchlorate to enhance the conductivity of any antistatic agent in contact with food and to remove potassium perchlorate as an allowed additive to sealing gaskets for food containers. As a result, there should be no detectable amount of the food additive in the food.

Full reports of investigations made with respect to the safety of the food additive
Our cover letter identified the key investigations. Specifically, we reference 11 recent comprehensive evaluations of perchlorate:

1. EPA Science Advisory Board, SAB advice on approaches to derive a maximum contaminant level goal for perchlorate, 2013, EPA-SAB-13-004. See http://yosemite.epa.gov/sab/sabproduct.nsf/0/86E44EE7F27EEC1A85257B7B0060F364/$File/EPA-SAB-13-004-unsigned2.pdf.
2. EPA, Life Stage Considerations and Interpretation of Recent Epidemiological Evidence to Develop a Maximum Contaminant Level Goal for Perchlorate, 2012. See http://yosemite.epa.gov/sab/SABPRODUCT.NSF/PeopleSearch/D3BB75D4297CA4698525794300522ACE/$File/Final+Perchlorate+White+Paper+05.29.12.pdf.
3. Murray, Egan, Kim, Beru, and Bolger, US Food and Drug Administration's Total Diet Study: Dietary intake of perchlorate and nitrate, *Journal of Exposure Science and Environmental Epidemiology* (2008) 18, 571–580.
4. Caldwell KL, Pan Y, Mortensen ME, Makhmdov A, Merrill L, and Moye J, Iodine status in pregnant women in the United States: National Children's Study and National Health and Nutrition Examination Survey, *Thyroid,* 2013, doi: 10.1089/thy.2013.0012.
5. World Health Organization, Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers, 2008.
6. Lumen A, Mattie DR, and Fisher JW, Evaluation of Perturbations in Serum Thyroid Hormones During Human Pregnancy Due to Dietary Iodide and Perchlorate Exposure Using a Biologically Based Dose-Response Model, *Toxicological Sciences,* 2013, 133(2), 320–341.
7. Steinmaus C, Miller MD, Cushing L, Blount BC, Smith AH, Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the National Health and Nutrition Examination Survey 2007-08, Environ Res. 2013 May;123:17-24. doi: 10.1016/j.envres.2013.01.005.
8. Dasgupta PK, Kirk AB, Dyke JV, Ohira S, Intake of Iodine and Perchlorate and Excretion in Human Milk, *Environ. Sci. Technol.* 2008**,** *42,* 8115–8121.
9. Valentin-Blasini L, Blount BC, Otero-Santos S, Cao Y, Bernbaum JC, and Rogan WJ, Perchlorate exposure and dose estimates in infants, Environ. Sci. Technol. 2011, 45, 4127–4132, dx.doi.org/10.1021/es103160j.
10. McLanahan, White, Flowers, and Schlosser, The Use of PBPK Models to Inform Human Health Risk Assessment: Case Study on Perchlorate and Radioiodide Human Lifestage Models, *Risk Analysis,* 0272-4332/13/0100-0001, 2013.
11. Aycock, Heinemann, Lanier-Christensen, and Larr, Dietary Risk Assessment of Perchlorate, Case Studies in Risk Assessment and Environmental Policy, Columbia University Mailman School of Public Health, 2014

The following evaluates five key studies published since EPA's SAB that are relevant to ingestion of perchlorate.

Study #1: Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring; Data from the Controlled Antenatal Thyroid Study. Taylor PN , Okosieme OE, Murphy R, Hales C, Chiusano E, Maina A, Joomun M, Bestwick JP, Smyth P, Paradice R, Channon S, Braverman LE, Dayan CM, Lazarus JH, Pearce EN., J Clin Endocrinol Metab. 2014 Jul 24:jc20141901. [Epub ahead of print]

Abstract

Objective: Thyroid dysfunction is associated with impaired cognitive development. Perchlorate decreases thyroidal iodine uptake, potentially reducing thyroid hormone production. It is unclear whether perchlorate exposure in early life affects neurodevelopment.

Design: Historical cohort analysis. Patients: During 2002-2006, 21,846 women at gestational age <16 weeks recruited from antenatal clinics in Cardiff, UK and Turin, Italy were enrolled in the Controlled Antenatal Thyroid Screening Study (CATS). We undertook a retrospective analysis of 487 mother-child pairs in mothers who were hypothyroid/hypothyroxinemic during pregnancy and analyzed whether first trimester maternal perchlorate levels in the highest 10% of the study population were associated with increased odds of offspring IQ being in the lowest 10% at age 3 years.

Main Outcome Measures: Maternal urinary perchlorate, offspring IQ. Results: Urine perchlorate was detectable in all women (median 2.58μg/liter); iodine levels were low (median 72μg/liter). Maternal perchlorate levels in the highest 10% of the population increased the odds of offspring IQ being in the lowest 10% OR=3.14 (95%CI 1.38, 7.13) p=0.006 with a greater negative impact observed on verbal OR=3.14 (95%CI 1.42, 6.90) p=0.005 than performance IQ. Maternal levothyroxine therapy did not reduce the negative impact of perchlorate on offspring IQ.

Conclusions: This is the first study using individual-level patient data to study maternal perchlorate exposure and offspring neurodevelopment and suggests that high-end maternal perchlorate levels in hypothyroid/hypothyroxinemic pregnant women have an adverse effect on offspring cognitive development, not affected by maternal levothyroxine therapy. These results require replication in additional studies, including in the euthyroid population.

Petitioners' analysis: The purpose of this study was to assess whether perchlorate exposure in early life affects neurodevelopment. A group of 487 mother-child pairs were analyzed where the mothers were hypothyroid/hypothyroxinemic during the first trimester of pregnancy. Levels of perchlorate in maternal urine were measured; IQ tests were performed in children at age 3 years. The study showed that all women had measurable levels of perchlorate in urine. However, children of women with perchlorate levels in the highest 10% in the first trimester had statistically significant increased odds of being in the lowest 10% IQ. The greater negative impact was in verbal performance. It is clear from the data that perchlorate exposure in pregnant women with low thyroid hormone is associated with impaired neurodevelopment in their children.

Study #2: The effects of perchlorate, nitrate, and thiocyanate on free thyroxine for potentially sensitive subpopulations of the 2001-2002 and 2007-2008 National Health and Nutrition Examination Surveys. Suh M , Abraham L, Hixon JG, Proctor DM., J Expo Sci Environ Epidemiol. 2013 Oct 23. doi: 10.1038/jes.2013.67. [Epub ahead of print]

Abstract
Among women with urinary iodine concentration <100 μg/l in the 2001-2002 National Health and Nutrition Examination Survey (NHANES), urinary perchlorate was associated with significant changes in thyroid stimulating hormone and total thyroxine (T4). Although perchlorate, nitrate, and thiocyanate all potentially act to inhibit iodide uptake, free T4 was not found to be associated with exposure to these chemicals in the same data. Fetuses of pregnant mothers with iodine deficiency are thought to be a sensitive subpopulation for perchlorate exposure, but the potential associations between free T4 and exposure to these chemicals among pregnant mothers in NHANES 2001-2002 and 2007-2008 have not been specifically evaluated to date. This study investigates the potential associations between urinary perchlorate, nitrate, and thiocyanate and serum free T4 in individuals with low urinary iodine levels and pregnant women. Multivariate regression models of free T4 were conducted and included urinary perchlorate, nitrate, thiocyanate, and covariates known to have an impact on the thyroid (anti-thyroid peroxidase (TPO) antibodies, age, race/ethnicity, body mass index, and hours of fasting). Meta-analyses were also conducted on non-pregnant and on pregnant women from the two survey cycles. Urinary nitrate was associated with serum free T4 in non-pregnant women of NHANES 2001-2002 who had urinary iodine ≥100 μg/l. In the meta-analysis, urinary perchlorate, nitrate, and thiocyanate were significant predictors of serum free T4 in non-pregnant women. No association was found in men and pregnant women. TPO antibodies were significant predictors of free T4 among non-pregnant women only when the models included urinary perchlorate, nitrate, or thiocyanate. Risk assessment for perchlorate exposure should consider co-exposure to nitrate and thiocyanate.

Petitioners' analysis: The purpose of this study was to investigate potential associations between urinary perchlorate, nitrate and thiocyanate and serum free T4 (thyroxine) in individuals with low urinary levels of iodine and pregnant women. The study used biomonitoring data from two cycles of NHANES. In a meta-analysis, all three chemicals were significant predictors of serum free T4 in non-pregnant women; the lack of significant association in pregnant women is likely due to a smaller sample size. This study is important because it highlights the need to perform cumulative risk assessment for pharmacologically-related chemicals.

Study #3: Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the National Health and Nutrition Examination Survey 2007-08. Steinmaus C , Miller MD, Cushing L, Blount BC, Smith AH., Environ Res. 2013 May;123:17-24. doi: 10.1016/j.envres.2013.01.005. Epub 2013 Mar 7.

Abstract
Perchlorate, thiocyanate, and low iodine intake can all decrease iodide intake into the thyroid gland. This can reduce thyroid hormone production since iodide is a key component of thyroid hormone. Previous research has suggested that each of these factors alone may decrease thyroid hormone levels, but effect sizes are small. We hypothesized that people who have all three factors at the same time have substantially lower thyroid hormone levels than people who do not, and the effect of this combined exposure is substantially larger than the effects seen in analyses focused on only one factor at a time. Using data from the 2007-2008 National Health and Nutrition Examination Survey, subjects were categorized into exposure groups based on their urinary perchlorate, iodine, and thiocyanate concentrations, and mean serum thyroxine concentrations were compared between groups. Subjects with high perchlorate (n=1939) had thyroxine concentrations that were 5.0% lower (mean difference=0.40 μg/dl, 95% confidence interval=0.14-0.65) than subjects with low perchlorate (n=2084). The individual effects of iodine and thiocyanate were even smaller. Subjects with high perchlorate, high thiocyanate, and low iodine combined (n=62) had thyroxine concentrations 12.9% lower (mean difference=1.07 μg/dl, 95% confidence interval=0.55-1.59) than subjects with low perchlorate, low thiocyanate, and adequate iodine (n=376). Potential confounders had little impact on results. Overall, these results suggest that concomitant exposure to perchlorate, thiocyanate, and low iodine markedly reduces thyroxine production. This highlights the potential importance of examining the combined effects of multiple agents when evaluating the toxicity of thyroid-disrupting agents.

Petitioners' analysis: This study looked at whether people who have perchlorate, thiocyanate and low iodide levels in their urine at the same time will have substantially lower thyroid hormone levels compared to those who don't, and their combined effect is larger than the effect of an individual factor alone. The authors used NHANES biomonitoring data. Individuals with high perchlorate, high thiocyanate and low iodine combined had 13% reduction in thyroid hormone compared to those with low perchlorate, low thiocyanate and adequate iodine. The individual effect of perchlorate was 5% and greater than both thicyanate and iodine. This study clearly shows that the potential adverse effect is greater when all the factors associated with thyroid hormone production are combined than when assessed individually.

Study #4: The Use of PBPK Models to Inform Human Health Risk Assessment: Case Study on Perchlorate and Radioiodide Human Lifestage Models. Eva D. McLanahan, Paul White, Lynn Flowers, and Paul M. Schlosser, *Risk Analysis, Vol. 34, No. 2, 2014* DOI: 10.1111/risa.12101

Abstract
Physiologically-based pharmacokinetic (PBPK) models are often submitted to or selected by agencies, such as the U.S. Environmental Protection Agency (U.S. EPA) and Agency for Toxic Substances and Disease Registry, for consideration for application in human health risk assessment (HHRA). Recently, U.S. EPA evaluated the human PBPK models for perchlorate and radioiodide for their ability to estimate the relative sensitivity of perchlorate inhibition on thyroidal radioiodide uptake for various population groups and lifestages. The most well-defined mode of action of the environmental contaminant, perchlorate, is competitive inhibition of thyroidal iodide uptake by the sodium-iodide symporter (NIS). In this analysis, a six-step framework for PBPK model evaluation was followed, and with a few modifications, the models were determined to be suitable for use in HHRA to evaluate relative sensitivity among human lifestages. Relative sensitivity to perchlorate was determined by comparing the PBPK model predicted percent inhibition of thyroidal radioactive iodide uptake (RAIU) by perchlorate for different lifestages. A limited sensitivity analysis indicated that model parameters describing urinary excretion of perchlorate and iodide were particularly important in prediction of RAIU inhibition; therefore, a range of biologically plausible values available in the peer-reviewed literature was evaluated. Using the updated PBPK models, the greatest sensitivity to RAIU inhibition was predicted to be the near-term fetus (gestation week 40) compared to the average adult and other lifestages; however, when exposure factors were taken into account, newborns were found to be populations that need further evaluation and consideration in a risk assessment for perchlorate.

Petitioners' analysis: In this study, the authors applied a six-step framework for PBPK model evaluation to inform human health risk assessment on perchlorate exposures using the uptake of radionuclear iodine as an endpoint. The authors concluded that the two published models were suitable for use in human health risk assessment. Although the greatest sensitivity to uptake inhibition was found in the near-term fetus, newborns were found to be further evaluated in a risk assessment for perchlorate.

Study #5: Evaluation of Perturbations in Serum Thyroid Hormones During Human Pregnancy Due to Dietary Iodide and Perchlorate Exposure Using a Biologically Based Dose-Response Model, Annie Lumen, David R. Mattie, and Jeffrey W. Fisher, Toxicological Sciences 133(2), 320‑341 2013, doi:10.1093/toxsci/kft078

A biologically based dose-response model (BBDR) for the hypothalamic pituitary thyroid (HPT) axis was developed in the near-term pregnant mother and fetus. This model was calibrated to predict serum levels of iodide, total thyroxine (T4), free thyroxine (fT4), and total triiodothyronine (T3) in the mother and fetus for a range of dietary iodide intake. The model was extended to describe perchlorate, an environmental and food contaminant, that competes with the sodium iodide symporter protein for thyroidal uptake of iodide. Using this mode-of-action framework, simulations were performed to

determine the daily ingestion rates of perchlorate that would be associated with hypothyroxinemia or onset of hypothyroidism for varying iodide intake. Model simulations suggested that a maternal iodide intake of 75 to 250 µg/day and an environmentally relevant exposure of perchlorate (~0.1 µg/ kg/day) did not result in hypothyroxinemia or hypothyroidism. For a daily iodide-sufficient intake of 200 µg/day, the dose of perchlorate required to reduce maternal fT4 levels to a hypothyroxinemic state was estimated at 32.2 µg/kg/day. As iodide intake was lowered to 75 µg/day, the model simulated daily perchlorate dose required to cause hypothyroxinemia was reduced by eightfold. Similarly, the perchlorate intake rates associated with the onset of subclinical hypothyroidism ranged from 54.8 to 21.5 µg/kg/day for daily iodide intake of 250‑75 µg/day. This BBDR-HPT axis model for pregnancy provides an example of a novel public health assessment tool that may be expanded to address other endocrine-active chemicals found in food and the environment.

Petitioners' analysis: This study describes the development of a biologically based dose-response model for the hypothalamic pituitary thyroid axis in the near-term pregnant mother and fetus. The model calculated the daily intake of perchlorate that would be associated with hypothyroxinemia or hypothyroidism (measured as maternal free T4 levels) for varying iodide intake. Simulations showed that in a low iodine intake scenario much lower levels of perchlorate were needed to cause hypothyroxinemia. Although a good step forward, this model has a number of shortcomings that are explained in detail in Appendix 4.

Proposed tolerances for the food additive

We are asking FDA to prohibit the use of any form of perchlorate to enhance the conductivity of any antistatic agent in contact with food and to remove potassium perchlorate as an allowed additive to sealing gaskets for food containers. As a result, no tolerance is needed.

Regarding a no-observe-adverse-effect level (NOAEL) for this new endpoint, we have not identified one that was developed taking into consideration the most sensitive endpoint and life stages as recommended by the SAB and that we support. Two articles regarding models for a NOAEL or Reference Dose have been published, one led by FDA's National Center for Toxicological Research and the other one led by EPA's scientists; however, both are incomplete.

Using a model originally developed by AEgis Technologies Group for the Air Force, FDA published a model of perchlorate's impact on pregnant women and fetuses in the third trimester of pregnancy.[56] The model considers both maternal endpoints: hypothyroidism and hypothyroxinemia and various iodine intake levels. It calculated that a daily intake of 4.2 µg perchlorate/kg body weight was necessary to reduce free T4 serum levels to a hypothyroxinemic state in women with a low iodine intake of 75 µg/day.

Although a good attempt to tackle a difficult problem, the model has several shortcomings including only considering pre-term women and fetuses, not considering NHANES biomonitoring data and using assumptions without supporting rationale, and not considering the nitrate and thiocyanate in the pharmacologically-related substances in the diet. See Appendix 4 for a detailed description of the model's deficiencies we submitted to EPA on February 2014. FDA and EPA have been collaborating to expand the model to represent all three trimesters as well as for a formula-fed or breast-fed infant. The model has not yet been published or made available for peer review.

In 2014, EPA's scientists published their analysis of the available models using a six-step framework for PBPK model evaluation.[57] The authors did not consider the SAB recommendation of hypothyroxinemia as the most sensitive endpoint to protect the most vulnerable populations. However, they still found that the models have several limitations including 1) not considering the effect of thiocyanate and nitrate on iodide uptake inhibition and the flux of dietary iodine, and 2) being insufficiently protective of newborns. It is worth noting that the models reviewed by EPA had additional limitations including not considering first and second trimester or women with iodine deficiency.

[56] Lumen A, Mattie DR, and Fisher JW, Evaluation of Perturbations in Serum Thyroid Hormones During Human Pregnancy Due to Dietary Iodide and Perchlorate Exposure Using a Biologically Based Dose-Response Model, *Toxicological Sciences*, 2013, 133(2), 320–341.

[57] McLanaham ED, White P, Flowers L, Schlosser PM. The use of PBPK models to inform human health risk assessment: Case study on perchlorate and radioiodide human life stages models. Risk Analysis 2014. 34(2):356-366

Full information on each proposed change to the original regulation
See Appendix 2 for the specific changes requested to 21 CFR §189.301. Text in strikethrough font is to be deleted.

We also ask that FDA delete the potassium perchlorate listing in Table 1 of 21 CFR § 177.1210.

Environmental impact statement

This food additive petition is categorically excluded from the need to prepare an Environmental Assessment under 21 CFR 25.32(m) for actions to prohibit or otherwise restrict or reduce the use of a substance in food, food packaging, or cosmetics. The proposed action complies with the categorical exclusion criteria. No extraordinary circumstances exist which would require the submission of an Environmental Assessment or Environmental Impact Statement.

Appendix 2
Request New 21 CFR § 189.301

The Natural Resources Defense Council (NRDC) petitions the Food and Drug Administration (FDA) to adopt a new section 189.301 to 21 CFR Part 189 that would ban the addition of perchlorate in antistatic agents. The new section would read as follows:

New section 21 CFR **§**189.301 would read as follows:

> TITLE 21--FOOD AND DRUGS
> CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
> SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION
> PART 189 -- SUBSTANCES PROHIBITED FROM USE IN HUMAN FOOD
> Subpart D--Substances Prohibited From Indirect Addition to Human Food Through Food-Contact Surfaces
>
> Sec. 189.301 Perchlorate.
> (a) Perchlorate is an ion with the molecular formula, $ClO4^-$ commonly manufactured in solid form with sodium, potassium or ammonium or in liquid form as perchloric acid. It has been used in gaskets to seal containers or as an antistatic agent in packaging for dry food. It is also produced as a contaminant from degradation of hypochlorite solutions used to make sanitizing solutions.
>
> (b) Food contact articles containing perchlorate as a food contact substance in antistatic agents are deemed to be adulterated in violation of the act.

APPENDIX 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

April 7, 2014

Tom Nelter
Natural Resources Defense Council
1152 15th Street,
Suite 300
Washington, DC 20005

Re: FOI Request No. 2014-1324

Dear Mr. Nelter:

This is in response to your request of February 10, 2014, requesting records regarding Threshold of Regulation Submission No. 05-006 regarding sodium perchlorate monohydrate. Your request was forwarded to the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition.

__X__ Enclosed are the records you requested.

__X__ Certain material has been deleted from the records furnished to you because a preliminary review of the records indicated that the deleted information is not required to be publicly disclosed and that disclosure is not appropriate. FDA has taken this approach to facilitate the process of responding to you. If you dispute FDA's preliminary determination with respect to these records and would like FDA to reconsider any particular deletion, please let us know in writing at the following address: Food and Drug Administration, Division of Freedom of Information, HFI-35, 5600 Fishers Lane, Rockville, MD 20857 within 30 days from the date of this letter. If we do not receive a response in that time period, we will consider the matter closed with respect to these records. If you do request further consideration and if the agency then formally denies your request for any or all of the previously-withheld information, you will have the right to appeal that decision. Any letter of denial will explain how to make this appeal.

The following charges for this request to date may be included in a monthly invoice:

Reproduction $ 0.00 Search $0.00 Review $46.00 Other $1.00 (CD) Total $47.00

THE ABOVE TOTAL MAY NOT REFLECT THE FINAL CHARGES FOR THIS REQUEST. **PLEASE DO NOT SEND PAYMENT** UNTIL YOU RECEIVE AN INVOICE FOR THE TOTAL MONTHLY FEE.

Sincerely Yours,

Sharon R. Dodson
Program Analyst
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

Enclosure

TOR #251

IS

Ciba Specialty Chemicals Corporation
Ciba® Expert Services
Neal J. Earhart, Ph.D.
Sr. Compliance Applications Specialist
540 White Plains Road, PO Box 2005
Tarrytown, NY 10591-9005
E-mail: neal.earhart@cibasc.com
Tel: 914-785-4518 Fax: 914-785-4147

Ciba

2005-3767

June 17, 2005

Vivian Gilliam
Office of Food Additive Safety, HFS-275
Center for Food Safety & Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Subject: Prenotification Consultation #381

Dear Ms. Gilliam:

Ciba Specialty Chemicals Corporation is submitting the enclosed Threshold of Regulation (TOR) document for an exemption from the food additive regulations under 21 CFR 170.39 for Sodium Perchlorate Monohydrate, CASRN 7719-07-3, to be used as a "conductivity enhancer" in (b) (4) a commercially available permanent antistatic agent.

The request for exemption of regulation is based on the dietary concentration (DC) of sodium perchlorate monohydrate, at the maximum proposed use level of (b) (4) ® (b) (4) of 30% in the finished article, to be calculated as 0.030 ppb, with a resulting estimated daily intake (EDI) of 0.09µg/p/d. The dietary concentration is less than 0.5 ppb and therefore qualifies for a Threshold of Regulation submission.

This TOR is the subject of Prenotification Consultation #381.

Should you have any questions, please do not hesitate to contact the undersigned at (914) 785-4518, or e-mail at neal.earhart@cibasc.com.

(b) (6)

Neal J. Earhart, Ph.D.
Sr. Compliance Applications Specialist
Ciba® Expert Services

Anna
Mike
Alejako

000001

Comprehensive Summary

Comprehensive Summary

Ciba Specialty Chemicals Corporation commercially markets (b) (4) a permanent antistatic agent. (b) (4) is formulated blend of the following:

CAS Number	Component	% by weight
(b) (4)		
7791-07-3	Sodium perchlorate monohydrate	4

(b) (4)
(b) (4)
. Sodium perchlorate monohydrate is not FDA regulated.

(b) (4)

The maximum concentration of sodium perchlorate monohydrate to be used in the (b) (4) formulation would be 4% (wt.), which would correlate to 1.2% (wt) in the finished article.

Sodium Perchlorate Monohydrate is a commodity inorganic chemical produced by various manufacturers worldwide such as:

Manufacturer *	Chemical Description	Purity
ABCR	Sodium Perchlorate Monohydrate p.a.	99%
Calibrechem	Sodium Perchlorate Monohydrate	98.5%
Lancaster	Sodium Perchlorate Monohydrate 98%	98%
Loba chemie	Sodium Perchlorate Monohydrate granules	98%

Table of Contents

* Representative technical data sheets from the above manufacturers are included in Section 8 of this submission. Purity of sodium perchlorate monohydrate ranges between 98% - 99%.

The primary chemical process used in the commercial manufacturing of sodium perchlorate monohydrate involves electrochemical oxidation of lower valence chlorine-containing compounds, mainly sodium chlorate.

Ciba Specialty Chemicals will be purchasing sodium perchlorate monohydrate from a variety of manufacturers based on volume pricing.

(b) (4) is incorporated into the polymer during processing and develops a conductive network within the polymer matrix. This conductive network dissipates any acquired static charge. Sodium perchlorate monohydrate is used in the (b) (4) formulation as a "conductivity enhancer."

The proposed use of (b) (4) is identical to the FDA regulated product (b) (4) (FCN 000406), as an antistatic agent for use in polymers in contact with dry foods with surface containing no free fat or oil compliant with 21 CFR 176.170 (c), Table 1, Food type VIII, such as cereals, flour, macaroni, and sugar.

Per the FDA's Guidance for Industry - *Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations, Final Guidance, April 2002, Appendix II, Section 13*, migration testing is not required and for non-fatty dry foods a "virtually nil" migration (50ppb) may be assumed.

Based on the maximum use level and the minimum consumption factor (CF) of 0.05 for all exposure estimates, the dietary concentration (DC) for sodium perchlorate monohydrate can be calculated as 0.030 ppb, with a resulting estimated daily intake (EDI) of 0.09μg/p/d.

Ciba Specialty Chemicals believes that sodium perchlorate monohydrate, as a component of the (b) (4) formulation to be used as an antistatic agent in polymers in contact with dry foods with surface containing no free fat or oil, would be exempt from regulation by the agency, due to the very low dietary concentration that will not be detected by an analytical technique and a negligible risk to human heath in the proposed end-use application.

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Sections 1-7

Section 1 – Chemical Composition

Sodium Perchlorate Monohydrate a commodity inorganic chemical produced by various manufacturers worldwide such as:

Manufacturer *	Chemical Description	Purity
ABCR	Sodium Perchlorate Monohydrate p.a.	99%
Calibrechem	Sodium Perchlorate Monohydrate	98.5%
Lancaster	Sodium Perchlorate Monohydrate 98%	98%
Loba chemie	Sodium Perchlorate Monohydrate granules	98%

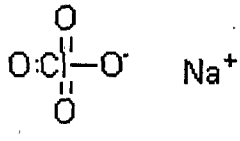
* Representative technical data sheets from the above manufacturers are included in this submission. Purity of sodium perchlorate monohydrate ranges between 98% - 99%.

See Section 8 – Attachment #1 – Representative Manufacturers' Data Sheets for Sodium Perchlorate Monohydrate

Chemical Name:
Sodium Perchlorate Monohydrate

CAS Reg. No.:
7791-07-3

Structure:



Molecular Formula::
$NaClO_4 \cdot H_2O$

Molecular Weight:
140.45 g/mol

Density:
2.02 g/ml

Melting Point:
130 °C

Section 2 – Intended Technical Effect

The Food Contact Substance (FCS) Sodium Perchlorate Monohydrate is added during the manufacture of (b) (4), a commercially available permanent antistatic agent. The FCS functions as a "conductivity enhancer" in the (b) (4)® (b) (4) formulation.

Section 3 – Conditions of Use

Sodium Perchlorate Monohydrate will be used in (b) (4) at a maximum level of 4% by weight, which corresponds to 1.2% by weight of the finished article. (b) (4) will be used in polymers at concentrations of up to 30 % by weight of the polymer in contact with dry foods with surface containing no free fat or oil compliant with 21 CFR 176.170 (c), Table 1, Food type VIII, such as cereals, flour, macaroni, and sugar, and under temperature conditions of use E through G. The proposed use of (b) (4) is identical to the FDA regulated use for product (b) (4) (FCN 000406)

Section 4 – Basis of Request for Exemption

This threshold of regulation request is based on the fact that given the maximum use level of (b) (4) [redacted] and using a minimum consumption factor (CF) of 0.05 for all exposure estimates, the dietary concentration (DC) for sodium perchlorate monohydrate can be calculated as 0.030 ppb. The dietary concentration is less than 0.5 ppb and therefore qualifies for a Threshold of Regulation submission.

Section 5 – Estimated Daily Intake

Per the FDA's Guidance for Industry - *Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations, Final Guidance, April 2002, Appendix II, Section 13*, migration testing is not required and for non-fatty dry foods a "virtually nil" migration (50ppb) may be assumed.

The dietary concentration (DC) of sodium perchlorate monohydrate in (b) (4) (b) can be calculated as:

DC = [(0.05CF[1]) x (4% sodium perchlorate in the (b) (4) formulation) x (30% maximum use level of the (b) (4) formulation) x (50ppb, dry foods "virtually nil" migration) = **0.030 ppb**

Based on this DC, the estimated daily intake (EDI) can be calculated as

EDI = 0.030ppb x 3 kg food/person = **0.090 µg/person/day**

[1] CF = Consumption Factor

Section 6 – Safety Narrative

The estimated dietary concentration (DC) of sodium perchlorate in [redacted] is 30 parts per trillion (30 nanograms per kg of food). Based on this DC, the following human dose is calculated:

30 ng/kg (ppt in food) x 3 kg food/person = **90** ng/person/day

90 ng/person/day ÷70 kg bw = 1.29 ng/kg/day
= 0.00129 µg/kg/day
= **0.00000129** mg/kg/day

EPA (IRIS) has recently published (2/18/2005) an Oral RfD for Perchlorate and perchlorate salts (including sodium perchlorate). The RfD is based on a study with human subjects.[1, 2] The RfD (lifetime safe oral exposure level) is 0.0007 mg/kg/day.

The dietary exposure for sodium perchlorate here determined for this use of Irgastat P18 is much less than the RfD:

RfD ÷DC = **0.0007** mg/kg/day ÷ **0.00000129** mg/kg/day = 542

We conclude, therefore, that the human exposure to sodium perchlorate resulting from the proposed use of [redacted] presents negligible health risks.

---

[1] Greer, M.A., Goodman, G., Pleuss, R.C., Greer, S.E. 2002. Health effect assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodide uptake in humans. Environ. Health Perspect. 110:927-937.

Greer et al. (2002) studied 21 healthy women and 16 healthy men (mean age 38 years, range 18-57 years) who were given potassium perchlorate in doses of 0.007, 0.02, 0.1 and 0.5 mg perchlorate/kg body weight per day for 14 days. The dose was administered in 400 ml of water with instructions that 100 ml be consumed four times each day. Thyroid uptake of radioiodide was measured at 8 and 24 hours after radioiodide administration: at baseline, on days 2 and 14 of perchlorate administration, and 15 days after cessation of dosing. The human subjects research ethics of the study were approved by the Oregon Health & Science University Institutional Review Board (IRB). On day 14 of administration, the mean 24-hour radioiodide uptake was 98.2% of the baseline value in the seven subjects given 0.007 mg/kg/day, a non-statistically significant decrease of 1.8% (standard error of the mean 8.3%). The day-14 24-hour radioiodide uptake value was 83.6% of the baseline value (16.4% decrease; n=10) in the subjects given 0.02 mg/kg/day, 55.3% of the baseline value (44.7% decrease; n=10) in those given 0.1 mg/kg/day, and 32.9% of the baseline value (67.1% decrease; n=10) in those given 0.5 mg/kg/day.

The effects of perchlorate in these healthy adult humans did not change over time, as indicated by very similar results for thyroid radioiodide uptake measurements on day 2 of perchlorate administration compared to day 14 in the three higher dose groups (uptake was not measured on day 2 in the lowest dose group). The 8-hour thyroid radioiodide uptake values 15 days after exposure were very similar to the baseline values, indicating rapid disappearance of inhibition on cessation of dosing. The results were similar in the women and men. The statistical no observed effect level (NOEL) for perchlorate-induced inhibition of thyroid iodide uptake was 0.007 mg/kg/day. An Uncertainty Factor of 10 was applied to the NOEL to obtain the RfD value.

[2] NRC. 2005. Health Implications of Perchlorate Ingestion. National Research Council of the National Academies. National Academies Press, Washington, D.C.

Section 7 – Environmental Assessment

A - CLAIM OF CATEGORICAL EXCLUSION

1. Cite the specific section of the CFR under which the categorical exclusion is claimed 21 CFR 25.32 (i) and (j)

Class of Action	Description
(i)	Approval of a food additive petition or GRAS affirmation petition, the granting of a request for exemption from regulation as a food additive under Sec. 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is present in finished food-packaging material at not greater than 5 percent-by-weight and is expected to remain with finished food-packaging material through use by consumers or when the substance is a component of a coating of a finished food-packaging material.
(j)	Approval of a food additive petition or GRAS affirmation petition, the granting of a request for exemption from regulation as a food additive under Sec. 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is to be used as a component of a food-contact surface of permanent or semipermanent equipment or of another food-contact article intended for repeated use.

2. Does your proposed food-contact use comply with the categorical exclusion criteria?

Yes

3. To the best of your knowledge are there any extraordinary circumstances that would require your submission of an EA

No

Attachment 1

Representative Manufacturers' Data Sheets for
Sodium Perchlorate Monohydrate

Manufacturers Listed in Order:

1 – ABCR

2 – Calibrechem

3 – Lancaster

4 - Loba chemie

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deutsch english >> HOME

Search Criteria

Search Help [?] Search

Name:

Productno.:

Formular:

CAS:

Name:	SODIUM PERCHLORATE MONOHYDRATE, 99%, WHITE POWDER
Productno.:	S93-1170
Formular:	$NACLO_4H_2O$
CAS:	[7791-07-3]
Formular weight:	122,44
Density:	2,02
Melting point:	130°C
R:	9-22
S:	13-22-27
UN:	1502
EINECS:	231-511-9

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ABCR

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R.B. Chemicals & Agro Industries Pvt. Limited
A Calibre Group Company mail@calibrechem.com

Sodium Perchlorate Monohydrate

Product Data Sheet

(Perchloric Acid, Sodium Salt - Hydrated)
$NaClO_4.H_2O$ **M.W. 140.46**

SPM-02-R3
Effective 1/04/04

Appearance : White deliquescent crystals

Specifications :

Sodium Perchlorate (as $NaClO_4.H_2O$):	98.5%	(Minimum)
(as $NaClO_4$) :	86.0%	(Minimum)
Chlorides (as NaCl) :	0.1%	(Maximum)
Chlorates (as $NaClO_3$) :	0.5%	(Maximum)
Sulphates (as SO_4^{--}) :	0.05%	(Maximum)
Free Moisture (as H_20) :	1.5%	(Maximum)

Physical Properties :

Melting Point	: 482 °C	
Boiling Point	: -	
Decomposition	: Starts losing water of hydration above 130 °C; decomposition starts at 482 °C.	
Solubility	: Very soluble in water	
Particle Density	: 2.02	grams/cc
Bulk Density	: About 1.3	grams/cc

Packing - Domestic : 25 Kg net laminated HDPE woven bags with separate inner LDPE bag.

- Exports : 25 Kg nett certified UN performance standard HDPE bags with LDPE inner bags.

Storage & Handling : Store in cool dry place away from direct sunlight and heat. Keep away from organic and readily oxidizable materials. In case of spillage, flush with *plenty* of water.

Uses : In manufacture of PVC stabilizers and explosives.
In chemical synthesis.
In perchloric acid and other perchlorates production.

Shipping Information :

CAS No.	: 7791-07-3
EINECS Nr.	: 231 – 511 - 9
UN No.	: 1502 Packing Group: II
IMDG Code: Proper Shipping Name	: Sodium Perchlorate Hydrate
Hazard Class	: 5.1 Oxidizing Substance
EmS No.	: 5.1-06
MFAG Table No.	: 745
Label	: Oxidizer 5.1
Subsidiary Risk Label	: None

Committed to Better Chemistry

000018

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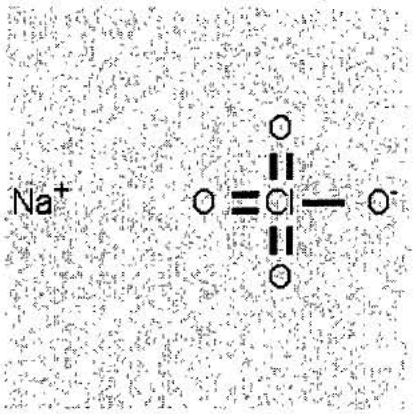
Product Details

Catalogue Number:	**14315**
Name:	**Sodium perchlorate monohydrate**
Structure:	
(To enlarge the structure double-click the structure and then resize the window)	
Pack sizes:	100g, 500g
Grade:	98
Melting Point:	
Molecular Formula:	ClNaO4.H2O
Molecular Weight:	140.46
CAS number:	7791-07-3
EINECS number:	231-511-9
UN number:	1502
Air Freight Status:	P
Hazard Storage:	OXIDISING HARMFUL HYGROSCOPIC
Safety Phrases:	S:13-22-27
Risk Phrases:	R:9-22
RTECS:	SC9850000
TSCA:	Y
Merck:	13,8726

5954
SODIUM NITRITE GR 500 gm
$NaNO_2$ M.W. 69.00 10 x 500 gm
Minimum assay 98.0% 50 kg
Maximum Limits of Impurities:
Insoluble matter 0.003%
Chloride (Cl) 0.005%
Sulphate (SO_4) 0.005%
Arsenic (As) 0.00004%
Calcium (Ca) 0.002%
Copper (Cu) 0.0005%
Iron (Fe) 0.001%
Lead (Pb) 0.0005%
Magnesium (Mg) 0.002%
Potassium (K) 0.001%

SODIUM NITROSO PENTACYANO FERRATE (III)
(See Sodium Nitro prusside LR/GR)

5956
SODIUM NITROPRUSSIDE 100 gm
EXTRA PURE 10 x 100 gm
$Na_2[Fe(CN)_5NO].2H_2O$ M.W. 297.95 500 gm
Minimum assay 98% 10 x 500 gm
Maximum Limits of Impurities:
Ferricyanide 0.02%
Ferrocyanide 0.1%
Sulphate (SO_4) 0.05%

5958
SODIUM NITROPRUSSIDE GR 100 gm
(Reagent for the detection of many organic 10 x 100 gm
compounds such as acetone aldehyde also 500 gm
of alkali sulphides etc.) 10 x 500 gm
$Na[Fe(CN)_5NO].2H_2O$ M.W. 297.95
Minimum assay 99%
Maximum Limits of Impurities:
Insoluble matter 0.01%
Chloride (Cl) 0.01%
Ferricyanide ($Fe(CN_6)$] 0.01%
Ferrocyanide ($Fe(CN_6)$] 0.02%
Sulphate (SO_4) 0.01%

5958 - D
SODIUM OLEATE pure 1 Kg
(Oleic acid sodium salt)
$C_{18}H_{33}NaO_2$ M.W. 304.50
Minimum Assay (GC) >99.0%
Maximum Limits of Impurities
Assay of fatty acid >82%
Free alkali (as NaOH) <0.5%
Heavy metals (as Pb) <0.005%
Chloride (Cl) <0.2%

5959
tri-SODIUM ORTHOPHOSPHATE 500 gm
(DODECAHYDRATE)EXTRA PURE 50 kg
$Na_3PO_4.12H_2O$ M.W. 380.12
Minimum assay (acidimetric) 98%
Chloride (Cl) 0.1%
Sulphate (SO_4) 0.05%
Sodium hydroxide (Na) 2.0%
Iron (Fe) 0.04%

5960
tri-SODIUM ORTHOPHOSPHATE GR 500 gm
(DODECAHYDRATE) 10 x 500 gm
$Na_3PO_4.12H_2O$ M.W. 380.12 50 kg
Minimum assay 98%
Maximum Limits of Impurities:
Insoluble matter 0.005%
Free alkali (NaOH) 2.0%
Chloride (Cl) 0.001%
Nitrogen compounds (N) 0.001%
Sulphate (SO_4) 0.005%
Calcium (Ca) 0.002%
Copper (Cu) 0.0005%
Iron (Fe) 0.001%
Lead (Pb) 0.0005%
Magnesium (Mg) 0.002%
Potassium (K) 0.005%

5961
SODIUM OXALATE EXTRA PURE 500 gm
$(COONa)_2$ M.W. 134.00 10 x 500 gm
Minimum assay (oxidimetric) 99.5% 50 kg
Chloride (Cl) 0.005%
Sulphate (SO_4) 0.03%
Iron (Fe) 0.005%
Potassium (K) 0.02%

5962
SODIUM OXALATE GR 500 gm
$C_2Na_2O_4$ M.W. 134.00 10 x 500 gm
Assay (manganometric) 99.8% 50 kg
pH 3% water 7.5-8.5
Maximum Limits of Impurities:
Chloride (Cl) 0.002%
Sulphate (SO_4) 0.002%
Total nitrogen (N) 0.001%
Heavy metals (as Pb) 0.001%
Iron (Fe) 0.0005%
Potassium (K) 0.005%
Loss on drying (105°C) 0.01%

5964
SODIUM PERBORATE 1 kg
(TRIHYDRATE) PURE 10 x 1 kg
$NaBO_2.H_2O_2.3H_2O$ M.W. 153.86 25 kg
Minimum assay (by iodometry) 98%
Maximum Limits of Impurities:
Chloride (Cl) 0.1%
Sulphate (SO_4) 0.05%
Heavy metals (as Pb) 0.003%
Iron (Fe) 0.001%

5965
SODIUM PERCHLORATE GR 500 gm
(Monohydrate) 10 x 500 gm
$NaClO_4.H_2O$ M.W. 140.46
Minimum assay (by argentometric) 99%
pH (5% water) 4.5-7
Maximum Limits of Impurities:
Chloride & Chlorate (as Cl) 0.002%
Sulphate (SO_4) 0.002%
Total nitrogen (N) 0.0005%
Iron (Fe) 0.0003%
Heavy metals (as Pb) 0.0005%
Calcium (Ca) 0.002%
Potassium (K) 0.005%

5967
SODIUM (META)PERIODATE 100 gm
EXTRA PURE 10 x 100 gm
$NaIO_4$ M.W. 213.89 500 gm
Assay (iodometric) minimum 98% 10 x 500 gm
Maximum Limits of Impurities:
Bromate, bromide, chlorate
and chloride (as Cl) 0.01%
Sulphate (SO_4) 0.005%
Manganese (Mn) 0.0005%

5968
SODIUM (META)PERIODATE GR 100 gm
(For the colorimetric determination 10 x 100 gm
of tri-glycerides) 500 gm
$NaIO_4$ M.W. 213.89 10 x 500 gm
Minimum assay of $NaIO_4$ 99.8%
Maximum Limits of Impurities:
Chloride chlorate bromide
and bromate (as Cl) 0.01%
Sulphate (SO_4) 0 005%
Manganese (Mn) 0.0001%

5969
SODIUM PEROXIDE for synthesis 500 g
(granular)
Na_2O_2 M.W. 77.98
Minimum Assay (by manganometry) >95%

000020

FD

MEMORANDUM OF CONFERENCE
THRESHOLD OF REGULATION COMMITTEE
Date: September 15, 2005

COMMITTEE MEMBERS

Michael VanDerveer	HFS-275
Adejoke Ogungbesan	HFS-275
Anna Shanklin	HFS-275
Julius Smith	HFS-275

Project 1
CSO:V. Gilliam
CTS #: 2005-3767
TOR # 251

Ciba Specialty Chemicals Corp. - Use of sodium perchlorate monohydrate as a conductivity enhancer in (b) (4), a commercially available permanent antistatic agent.

Ciba Specialty Chemicals Corporation (CSCC) submits this TOR request for an exemption from the need for a food additive listing regulation for the use of sodium perchlorate monohydrate as a conductivity enhancer in (b) (4), a commercially available antistatic agent. The maximum concentration of sodium perchlorate monohydrate (CAS Reg. No. 7791-07-3) proposed for use in (b) (4) formulation is 4 percent by weight, which would correlate to 1.2 percent by weight in the finished article for use in contact with dry foods.

CSCC states that the request for an exemption is based on the dietary concentration (DC) of sodium perchlorate monohydrate, at the maximum proposed use level of (b) (4) of 30% in the finished article, which can be calculated as 0.030 ppb, with a resulting estimated daily intake (EDI) of 0.09 µg/p/d.

Chemistry
CSCC commercially markets (b) (4) as a permanent antistatic agent and is a formulated blend of the following substances:

CAS Number	Component	Wt. %
(b) (4)		
7791-07-3	Sodium perchlorate monohydrate	4

(b) (4) [redacted] Sodium perchlorate monohydrate is not FDA regulated.

(b) (4) [redacted]

The maximum concentration of sodium perchlorate monohydrate to be used in the (b) (4) formulation would be 4% (wt.), which would correlate to 1.2% (wt) in the finished article.

The primary chemical process used in the commercial manufacturing of sodium perchlorate monohydrate involves electrochemical oxidation of lower valence chlorine-containing-compounds, mainly sodium chlorate.

(b) (4) is incorporated into the polymer during processing and develops a conductive network within the polymer matrix. This conductive network dissipates any acquired static charge. Sodium perchlorate monohydrate is used in the (b) (4) formulation as a "conductivity enhancer."

The proposed use of (b) (4) is identical to the FDA regulated product (b) (4) (FCN 000406), as an antistatic agent for use in polymers in contact with dry foods with surface containing no free fat or oil compliant with 21 CFR 176.170 (c), Table 1, Food type VIII, such as cereals, flour, macaroni, and sugar.

Based on the maximum use level and the minimum consumption factor (CF) of 0.05 for all exposure estimates, the dietary concentration (DC) for sodium perchlorate monohydrate can be calculated as 0.030 ppb, with a resulting estimated daily intake (EDI) of 0.09 µg/p/d.

Estimated Daily Intake

The dietary concentration (DC) of sodium perchlorate monohydrate in (b) (4) (b) can be calculated as:

DC = [(0.05 CF) x (4% sodium perchlorate in (b) (4) formulation) x (30% maximum use level of the (b) (4) formulation) x (50 ppb, dry foods "virtually nil" migration) = 0.030 ppb

Based on this DC, the estimated daily intake (EDI) can be calculated as

EDI = 0.030 ppb x 3 kg food/person = 0.09 µg/person/day

Toxicology (Safety Narrative)
As stated above, the estimated DC for sodium perchlorate monohydrate in (b) (4) is 30 parts per trillion (ppt). Based on the fact that the DC of this compound is less that 50 ppt, in addition to lack of carcinogenicity data, toxicology has no safety concerns for the proposed use of this compound at the level of dietary exposure indicated.

Environmental

A claim of categorical exclusion under 21 CFR 25.32 (i) and (j) is included in the submission, including CSCC's statement that there are no extraordinary circumstances that would require the submission of an EA.

Conclusion

The Committee agrees with the requestor's conclusion that this action qualifies for a categorical exclusion from the need to prepare an Environmental Assessment in accordance with 21 CFR 25.32(i) and (j).

Review of the available toxicity data indicates that the proposed use of sodium perchlorate monohydrate does not raise any safety concerns at the above exposure level. Also, the Committee is not aware of any study showing sodium perchlorate monohydrate, itself, to be carcinogenic in humans or in animals.

The Committee notes that the FCS will be used in the manufacture of an antistatic agent, consisting of (b) (4) intended for use in polymers in contact with dry foods. Because the FCS is intended for use in contact with dry foods only, the Committee has no reason to limit use of the FCS to only in the manufacture of (b) (4) as mentioned in the submission. Therefore, the Committee concludes that the FCS may be used as a conductivity enhancer in the manufacture of an antistatic agent that are duly authorized (by regulation, FCN, TOR, etc) for use in contact with dry foods.

Therefore, based on the above findings, the Committee concludes that Ciba Specialty Chemical Corporation should be issued a letter indicating that the use of sodium perchlorate monohydrate as a conductivity enhancer in regulated or otherwise authorized antistatic agents at a maximum concentration of 4 percent by weight, which would correlate to 1.2 percent by weight in the finished article for use in contact with dry foods qualifies for an exemption under 21 CFR 170.39 from the requirement of being the subject of a food additive listing regulation. (TR/05-006)

Julius Smith

Reviewed by:

M.VanDerveer:HFS-275 9-29-05
A.Ogungbesan:HFS-275:9-29-05
A.Shanklin:HFS-275:9:28-05
J.Smith:HFS-275:9-30-05
E.Machuga:HFS-275:10-3-05

FD

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

Sept 23, 2005

Dr. Neal Earhart
Ciba Expert Services
540 White Plains Road
Tarrytown, NY 10591

Dear Dr. Earhart:

This correspondence is in response to your letter, dated June 17, 2005, requesting an exemption from regulation as a food additive the use of sodium perchlorate monohydrate, as a conductivity enhancer in (b) (4), a commercially available antistatic agent for use in polymers in contact with dry foods, under 21 CFR 170.39 ***Threshold of regulation for substances used in food-contact articles***.

We have reviewed your claim of categorical exclusion under 21 CFR 25.32(i) and (j) and have determined that it is incomplete as submitted. A claim of categorical exclusion should include a citation of the CFR section under which the exclusion is warranted, a statement of compliance with the categorical exclusion criteria, and a statement that to the submitter's knowledge that there are no extraordinary circumstances that will require the preparation of an environmental assessment (EA). In your claim you do cite the CFR section under which the categorical exclusion is claimed, however we have noted the following deficiencies:

1) A statement of compliance with the categorical exclusion criteria is not included in your submission.

2) A statement that to your knowledge there are no extraordinary circumstances that will require the preparation of an EA is not included in your submission.

You need to provide the above information in order to completely satisfy the criteria for a categorical exclusion from preparation of an EA.

If you have any questions concerning this matter, please do not hesitate to contact us.

Sincerely,

(b) (6)

Vivian Gilliam.
Consumer Safety Officer
Division of Food Contact Notifications, HFS-275
Office of Food Additive Safety
FDA/Center for Food Safety and Applied Nutrition

Section 7 – Environmental Assessment

A - CLAIM OF CATEGORICAL EXCLUSION

1. Cite the specific section of the CFR under which the categorical exclusion is claimed 21 CFR 25.32 (i) and (j)

Class of Action	Description
(i)	Approval of a food additive petition or GRAS affirmation petition, the granting of a request for exemption from regulation as a food additive under Sec. 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is present in finished food-packaging material at not greater than 5 percent-by-weight and is expected to remain with finished food-packaging material through use by consumers or when the substance is a component of a coating of a finished food-packaging material.
(j)	Approval of a food additive petition or GRAS affirmation petition, the granting of a request for exemption from regulation as a food additive under Sec. 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is to be used as a component of a food-contact surface of permanent or semipermanent equipment or of another food-contact article intended for repeated use.

2. Does your proposed food-contact use comply with the categorical exclusion criteria?

Yes

3. To the best of your knowledge are there any extraordinary circumstances that would require your submission of an EA

No

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

Sept 23, 2005

Dr. Neal Earhart
Ciba Expert Services
540 White Plains Road
Tarrytown, NY 10591

Dear Dr. Earhart:

This correspondence is in response to your letter, dated June 17, 2005, requesting an exemption from regulation as a food additive the use of sodium perchlorate monohydrate, as a conductivity enhancer in (b)(4) a commercially available antistatic agent for use in polymers in contact with dry foods, under 21 CFR 170.39 ***Threshold of regulation for substances used in food-contact articles***.

We have reviewed your claim of categorical exclusion under 21 CFR 25.32(i) and (j) and have determined that it is incomplete as submitted. A claim of categorical exclusion should include a citation of the CFR section under which the exclusion is warranted, a statement of compliance with the categorical exclusion criteria, and a statement that to the submitter's knowledge that there are no extraordinary circumstances that will require the preparation of an environmental assessment (EA). In your claim you do cite the CFR section under which the categorical exclusion is claimed, however we have noted the following deficiencies:

1) A statement of compliance with the categorical exclusion criteria is not included in your submission.

2) A statement that to your knowledge there are no extraordinary circumstances that will require the preparation of an EA is not included in your submission.

You need to provide the above information in order to completely satisfy the criteria for a categorical exclusion from preparation of an EA.

If you have any questions concerning this matter, please do not hesitate to contact us.

Sincerely,

Vivian Gilliam.
Consumer Safety Officer
Division of Food Contact Notifications, HFS-275
Office of Food Additive Safety
FDA/Center for Food Safety and Applied Nutrition

FileName:TOR251DEF
R/D: VGilliam:HFS-275:09/23/05
F/T:HFS-275:VGilliam:sgg:9/23/05

Section 7 – Environmental Assessment

Upon review, it has been determined that Sodium Perchlorate Monohydrate qualifies for a claim of Categorical Exclusion under 21 CFR 25.32 classes of action (i) and (j).

Class of Action	Description
(i)	Approval of a food additive petition or GRAS affirmation petition, the granting of a request for exemption from regulation as a food additive under Sec. 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is present in finished food-packaging material at not greater than 5 percent-by-weight and is expected to remain with finished food-packaging material through use by consumers or when the substance is a component of a coating of a finished food-packaging material.
(j)	Approval of a food additive petition or GRAS affirmation petition, the granting of a request for exemption from regulation as a food additive under Sec. 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is to be used as a component of a food-contact surface of permanent or semipermanent equipment or of another food-contact article intended for repeated use.

Earhart Neal PX US

From: Earhart Neal PX US
Sent: Friday, September 23, 2005 11:46 AM
To: 'Gilliam, Vivian M'
Subject: RE: Formal Response for TOR 251...
Importance: High
Attachments: NaClO4_TOR_EA.doc

Dear Ms. Gilliam,

Attached is the additional Environmental Assessment information as requested by the FDA in support of the Threshold of Regulation Exemption for the use of sodium perchlorate monohydrate, as a conductivity enhancer in (b) (4), a commercially available antistatic agent for use in polymers in contact with dry foods.

The attached page is a replacement page for page 7 of the TOR document.

If you have any questions upon review, please contact me at your convenience.

Best regards,
Neal

Neal J. Earhart, Ph.D.
Regulatory Services
Ciba® Expert Services
540 White Plains Road
Tarrytown, NY 10591
Telephone: (914) 785-4518
Fax: (914) 785-4147
http://www.cibasc.com/index/exs-index.htm

-----Original Message-----
From: Gilliam, Vivian M [mailto:Vivian.Gilliam@cfsan.fda.gov]
Sent: Thursday, September 22, 2005 3:05 PM
To: Earhart Neal PX US
Subject: Formal Response for TOR 251...

September 23, 2005

Neal Earhart
Ciba Expert Services
540 White Plains Road
Tarrytown, NY 10591

000025

Dear Dr. Earhart:

This correspondence is in response to your letter, dated June 17, 2005, requesting an exemption from regulation as a food additive the use of sodium perchlorate monohydrate, as a conductivity enhancer in (b) (4) [redacted], a commercially available antistatic agent for use in polymers in contact with dry foods, under 21 CFR 170.39 ***Threshold of regulation for substances used in food-contact articles.***

We have reviewed your claim of categorical exclusion under 21 CFR 25.32(i) and (j) and have determined that it is incomplete as submitted. A claim of categorical exclusion should include a citation of the CFR section under which the exclusion is warranted, a statement of compliance with the categorical exclusion criteria, and a statement that to the submitter's knowledge that there are no extraordinary circumstances that will require the preparation of an environmental assessment (EA). In your claim you do cite the CFR section under which the categorical exclusion is claimed, however we have noted the following deficiencies:

1) A statement of compliance with the categorical exclusion criteria is not included in your submission.

2) A statement that to your knowledge there are no extraordinary circumstances that will require the preparation of an EA is not included in your submission.

You need to provide the above information in order to completely satisfy the criteria for a categorical exclusion from preparation of an EA.

If you have any questions concerning this matter, please do not hesitate to contact us.

Sincerely,

Vivian Gilliam.
Consumer Safety Officer
Division of Food Contact Notifications, HFS-275
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

FD

Date: September 26, 2005

From: Environmental Review Group (ERG)
Threshold of Regulation Committee, Environmental Review Chemist via ERG
Division of Chemistry Research and Environmental Review (HFS-246)

Subject: TOR 251 (CTS# 2005-3767) – Sodium perchlorate monohydrate as a conductivity enhancer in antistatic agent for use in polymers in contact with dry foods. Ciba Specialty Chemicals

To: Division of Food Contact Notifications (HFS-275)
Threshold of Regulation Committee
Attention: Julius Smith
Through: Annette McCarthy, Ph.D., ERG [redacted]

CC: Division of Food Contact Notifications (HFS-275)
Attention: Vivian Gilliam, Consumer Safety Officer

I have reviewed the claim of categorical exclusion for the above referenced Threshold of Regulation submission and have concluded that categorical exclusion is warranted. The food additive to be exempt from regulation under 21 CFR 170.39 is to be used as a conductivity enhancer in [redacted], a commercially available antistatic agent for use in polymers in contact with dry foods. The claim of categorical exclusion cites the section under which categorical exclusion is warranted, 21 *CFR* 25.32 (i) and (j), states compliance with the categorical exclusion criteria, and states that no extraordinary circumstances exist that would require the submission of an environmental assessment.

Please let me know if there is any change in the identity or use of the food contact substance.

Anna P. Shanklin, Ph.D.

cc:
HFS-246 File: TOR No. 251 (CTS 2005-3767)

HFS-246:APShanklin:aps:09/27/05 H:
FT: APShanklin:aps:09/27/05 p:\EIS Documents\MEMOS\TOR251_E_CatEx.doc

FD

November 4, 2005

TR 2005-006

Neal J. Earhart, Ph.D.
Sr. Compliance Applications Specialist
Ciba Expert Services
Ciba Specialty Chemicals Corporation
540 White Plains Road, PO Box 2005
Tarrytown, NY 10591-9005

Re: Sodium Perchlorate Monohydrate
TOR No 251

Dear Dr. Earhart:

This is in response to your letter of June 17, 2005, and amended on September 23, 2005, requesting an exemption under 21 CFR 170.39 for the safe use of sodium perchlorate monohydrate (CAS Reg. No. 7719-07-3) as a conductivity enhancer in the manufacture of antistatic agents at a maximum concentration of 4 percent by weight, which would correlate to 1.2 percent by weight in the finished article for use in contact with dry foods.

We note that sodium perchlorate monohydrate will be used in the manufacture of an antistatic agent, (b) (4) [redacted] intended for use in polymers in contact with dry foods. You have provided worst-case extraction data, safety data, and a claim of categorical exclusion under 21 CFR 25.32(i) and (j) in support of your request.

We have completed our review of your submission and conclude that the dietary concentration for sodium perchlorate monohydrate resulting from its intended use would be below the threshold of regulatory concern. Also, we are not aware of any study showing this copolymer to be carcinogenic to humans or animals.

Additionally, we have reviewed your claim of categorical exclusion and conclude that this action qualifies for a categorical exclusion from the requirement to submit an environmental assessment pursuant to 21 CFR 25.32(i) and (j).

Therefore, based on the above findings, we conclude that Ciba Specialty Chemical Corporation's intended use of sodium perchlorate monohydrate as a conductivity enhancer in regulated or otherwise authorized antistatic agents at a maximum concentration of 4 percent by weight, which would correlate to 1.2 percent by weight in the finished article for use in contact with dry foods qualifies for an exemption under 21 CFR 170.39 from the requirement of being the subject of a food additive listing regulation.

000032

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFS-276	(b) (6) [redacted]	11/4/05						
HFS-021		11/4/05						

We trust that this letter is responsive to your inquiry. If you have additional questions, please feel free to contact us.

Sincerely yours,

Mitchell A. Cheeseman, Ph.D.
Director
Division of Food Contact Notificatioin, HFS-275
Center for Food Safety and Applied Nutrition

cc: HFS-200
HFS-275(2)
TR 2005-06
E. Machuga (HFS-275) Letter No. 20053767
Named: Earhart
R/D: J.Smith:HFS-275:11-2-05
Init: E.Machuga:HFS-275:11-2-05
F/T: sgg:11/4/2005

APPENDIIX 4

NATURAL RESOURCES DEFENSE COUNCIL

February 28, 2014

By Electronic Delivery

Dr. Peter Grevatt, Director
Office of Ground Water and Drinking Water
USEPA Headquarters
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N. W.
Mail Code: 4601M
Washington, DC 20460

Re: NRDC concerns with FDA's perchlorate biologically based dose-response model

Dear Dr. Grevatt:

As the EPA Office of Ground Water and Drinking Water is working to develop a Maximum Contaminant Level Goal (MCLG) and a national primary drinking water standard for perchlorate, we are very concerned that EPA may be weakening the perchlorate Reference Dose (RfD) to make it less health-protective by relying on a flawed model. Overall, we think the model is a strong starting point, but EPA needs to make the following improvements:

- Expand the model to include the first two trimesters in addition to infants. The current model is based only on the end of the third trimester when the fetus has a functioning thyroid.
- Ensure the model considers iodide levels at the 95th and 99th percentiles of pregnant women, not just the 90th percentile.
- Reevaluate affinity constants for iodide and perchlorate to ensure they are based on a robust data set and are calculated consistently.
- Incorporate thiocyanate and nitrate in the model as recommended by EPA's Science Advisory Board since they also inhibit iodide uptake in a manner similar to perchlorate.
- Justify the selection of 10 pmol/L of maternal free T4 as the threshold for hypothyroxinemia.
- Compare the model results to NHANES monitoring data.

Background

In 2005, EPA adopted a Reference Dose (RfD) of 0.7 µg/kg/day, which is posted on its public IRIS database.[1] It is derived from a No Observed Effect Level (NOEL) of 7 µg/kg/day for the critical effect of radioactive iodide update inhibition in the thyroid, with a 10-fold uncertainty factor for differences between humans. EPA felt that this would protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency.

[1] http://www.epa.gov/iris/subst/1007.htm

Because the principal study was of humans – healthy adults - not laboratory animals, no additional uncertainty factor was used for interspecies differences.[2]

EPA based its IRIS assessment and RfD on the recommendations of the National Research Council (NRC) perchlorate report (2005). The IRIS assessment sums up the NRC approach and recommendations as follows:

> The NRC (2005) reviewed a number of benchmark dose models for the radioiodide uptake inhibition point of departure, as developed by the U.S. EPA (2003), California Environmental Protection Agency (CalEPA 2004) and Crump and Goodman (2003). The NRC (2005) concluded that these analyses used different models, approaches, parameters, response levels, and input data, making the comparison of results difficult. Although the NRC Committee recognized that BMD modeling can be an improvement over the use of the NOAEL or LOAEL as a point of departure, there appeared to be no consensus on the criteria for choosing one BMD approach over another. Because no clear justifications were provided with the individual analyses of the Greer et al. (2002) data that allowed selection of one set of results over another, the NRC Committee concluded that using the NOEL (0.007 mg/kg/day) for iodide inhibition from Greer et al. (2002) as the point of departure provided a reasonable and transparent approach to perchlorate risk assessment.[3]

In 2012, EPA convened its Scientific Advisory Board (SAB) to advise the Office of Water on how to consider sensitive life stages, the physiologically-based pharmacokinetic (PBPK) modeling efforts, available epidemiologic and biomonitoring data, and approaches to integrate these data to derive an MCLG for perchlorate.

In its final 2013 report to EPA the SAB recommended the following:[4]

- EPA should derive a perchlorate MCLG that addresses sensitive life stages through PBPK/pharmacodynamics modeling based on the mode of action. The SAB preferred this approach over using the RfD with specific chemical exposure parameters.
- EPA should expand its models to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure.
- Clinical thyroid literature is relevant to identify the degree of iodide uptake inhibition required for onset of hypothyroxinemia in a pregnant woman.
- In developing the pharmacodynamics aspects of the model, EPA should consider information on potential adverse health effects due to thyroid hormone perturbations, regardless of the cause, to document and support the model.

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[2] Greer, M.A., Goodman, G., Pleus, R.C., Greer, S.E. 2002. Health effect assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodide uptake in humans. Environ. Health Perspect. 110:927-937.

[3] http://www.epa.gov/iris/subst/1007.htm

[4] EPA-SAB-13-004, May, 2013. Available at: http://yosemite.epa.gov/sab%5CSABPRODUCT.NSF/86E44EE7F27EEC1A85257B7B0060F364/$File/EPA-SAB-13-004-unsigned2.pdf

- EPA must consider specific adverse effects on brain development due to inadequate iodide update or low thyroid hormone levels vary at different life stages, but are especially critical during the early formative stages of brain development, when the human brain most needs thyroid hormone.

NRDC's Concerns with the FDA Model

We are concerned that EPA may be considering adoption – in whole or in part – of a perchlorate biologically based dose-response model (BBDR) developed by U.S. Food and Drug Administration (FDA) scientists. The FDA model is published as Lumen A, Mattie DR, Fisher JW. *Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model*. Toxicol Sci. 2013 Jun;133(2):320-41.

According to the FDA model, the intakes of perchlorate required to alter maternal thyroid levels enough to induce hypothyroxinemic conditions are 6-fold greater than the current reference dose, and for hypothyroid conditions are 31-fold greater (Lumen et al, Table 8), making the model predictions much less protective than EPA's current RfD.

We understand that EPA's adaptions of the above FDA model may include consideration of infant exposure from breastfeeding and from bottle feeding. While we agree with this, we also believe that the FDA model should be expanded to cover the first two trimesters and infant exposure. The FDA model is based on pregnant women in weeks 37 to 40 – the late third trimester just before giving birth. By the third trimester, the fetus has a functioning thyroid that is contributing thyroid hormones. However, in the previous two trimesters, the thyroid does not exist or is not functioning. The 2011 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum make clear that the fetus needs greater levels of thyroxin (T4) in the first trimester than in the third.[5] Given this and other differences, the model needs to include the first and second trimesters as well in addition to the planned modeling for the infant.

If EPA relies on the FDA model, then it should be expanded to protect all women. The model uses 75 µg/day as the lowest iodide intake without any explanation. By back-calculating the relationship between daily intake and urinary concentrations from NHANES, it seems that this dose corresponds to only the 90th percentile of pregnant women, leaving 10% of women unaddressed by FDA's model. [6] [7] [8] The potential for irreversible damage to a child's brain

[5] Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011 Oct;21(10):1081-125. doi:10.1089/thy.2011.0087. Epub 2011 Jul 25. PubMed PMID: 21787128; PubMed Central PMCID: PMC3472679.

[6] Blount BC, L Valentin-Blasini, JD Osterloh, JP Mauldin, and JL Pirkle. 2007. Perchlorate exposure of the US population, 2001-2002. J Expo Sci Environ Epidemiol. 17(4):400-7.

[7] Based on NHANES biomonitoring data from 2005 to 2008, 11.5% of pregnant women had urinary iodide concentrations of < 50 µg/L and 5.2% had < 20 µg/L. At 90%, a 75 µg/day uptake corresponds to 67.5 µg/day excretion in urine. Assuming mean daily urine output of 1.5 L per day in the third trimester (Thorp et al 1995), the concentration of perchlorate in the urine would be 45 µg/L, representing approximately 10% of pregnant women.

[8] Thorp, J. M., Jr, Norton, P. A., Wall, L. L., Kuller, J. A., Eucker, B., and Wells, E. (1999). Urinary incontinence in pregnancy and the puerperium: A prospective study. Am. J. Obstet. Gynecol. 181, 266–273.

warrants protecting all pregnant women. The model should include iodide levels for the 95th and 99th percentiles of pregnant women.

Perchlorate binds and inhibits the sodium/iodide symporter (NIS) that is meant to transport iodide into the thyroid gland, where it is used to produce thyroid hormone. Therefore, the affinity of perchlorate and iodide for the NIS – which one binds more strongly and replaces the other – must be accurate in the model. The model uses an affinity constant of 3.15×10^4 nmol/L for iodide in both the mother and fetus, and 1.5×10^3 nmol/L for perchlorate in both the mother and fetus (Lumen et al Table 2). Lumen et al cite three sources[9,10,11] for these affinity constants.

It is unclear how any of these articles could support the derivation of an NIS affinity constant in pregnant mothers and their fetuses. Gluzman et al is a comparison between normal and diseased thyroid tissue from 1983. The constant for iodide in normal human thyroid was given as 3.12×10^{-5} mol/L with a standard deviation of 0.98 relying on only five samples. After adjusting the units to be consistent, the number is similar but not exactly the same as the one used in the model (3.12 in the article v. 3.15 in the model).

Kosugi et al from 1996 uses hamster-derived cell line with no consideration of women, pregnancy, or fetal tissue kinetics. Tonacchera et al from 2004 focused on the expression and cell localization of the NIS in diseased thyroid tissue, and did not provide information regarding NIS uptake kinetics or affinity constants.

EPA should reevaluate affinity constants for iodide and perchlorate to ensure they are based on a robust data set and are calculated consistently. If the Gluzman et al data is used, given the wide standard deviation, the high (4.10×10^{-5} mol/L) and low (2.14×10^{-5} mol/L) levels should be evaluated.

It is interesting to note that Kosugi et al – the hamster cell line study – not only provided an affinity constant for perchlorate, but also estimated the affinity constant of thiocyanate at 1.6×10^2 nmol/L – ten times greater than perchlorate. Because thiocyanate acts like perchlorate on the same target, EPA should incorporate thiocyanate into its MCLG determination. Thiocyanate is naturally present in some foods and is also found in cigarette smoke. FDA also allows ionic forms of thiocyanate to be used as an indirect additive in adhesives; 25 organic thiocyanates are approved by FDA for food uses, primarily as flavors, which would contribute to human dietary exposures that the EPA should consider an MCLG.

The perchlorate model recently published by EPA's Office of Research and Development, (McLanahan et al 2014) notes that nitrate is also known to competitively inhibit iodide uptake by

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[9] Gluzman, B. E., and Niepomniszcze, H. (1983). *Kinetics of the iodide trapping mechanism in normal and pathological human thyroid slices*. Acta Endocrinol. 103, 34–39.

[10] Kosugi, S., Sasaki, N., Hai, N., Sugawa, H., Aoki, N., Shigemasa, C., Mori, T., and Yoshida, A. (1996). *Establishment and characterization of a Chinese hamster ovary cell line, CHO-4J, stably expressing a number of Na+/I- symporters*. Biochem. Biophys. Res. Commun. 227, 94–101.

[11] Tonacchera, M., Viacava, P., Fanelli, G., Agretti, P., De Marco, G., De Servi, M., Di Cosmo, C., Chiovato, L., Pinchera, A., and Vitti, P. (2004). *The sodium-iodide symporter protein is always present at a low expression and confined to the cell membrane in nonfunctioning nonadenomatous nodules of toxic nodular goitre*. Clin. Endocrinol. (Oxf) 61, 40–45.

the thyroid using the same mechanism as perchlorate.[12] Given its extensive use in food, and widespread presence in drinking water, EPA should also include nitrate exposure in its MCLG determination.

The use of <10 pmol/L of maternal free T4 threshold (fT4) in the model is unfounded (see Lumen et al page 329 and Table 8). The model authors reference Moleti et al (2011) as the basis of the 10 picomolar cut-off for fT4 for maternal hypothyroxinemia.[13] However, when we reviewed the reference, it does not provide a specific cut-off value of fT4 for either hypothyroxinemia or hypothyroidism. Table 1 in the Moleti article summarizes criteria used by various researchers but there is no consensus on a particular concentration. Moleti states that the fT4 values depend on the population's iodide intake, the trimester, and the methodology used to measure the hormone. Therefore, it is clear that a single value for the cut-off of fT4 is not appropriate.

In setting a MCLG, EPA also needs to consider the impact of perchlorate on the fetus' thyroid in addition to its existing plans to include infants. The FDA model indicates that perchlorate levels in the fetus serum (19.8 µg/L) are 50% higher than in the mother's serum (12.4 µg/L) (Lumen et al, page 332). The effects of these higher levels on fetal thyroid do not appear to be considered in the model. Although during the first trimester the fetus is reliant on maternal thyroid hormone, in the second and third trimester the fetus can synthesize its own thyroid hormone in limited amounts. Studies have shown that the cognitive development of the fetus is impaired in mothers with even mild disruptions in thyroid hormone levels, prompting the medical community to recommend thyroid hormone replacement therapy for pregnant women who are found to have sub-clinical hypothyroidism (mildly elevated TSH but normal T4).[14] At a minimum, EPA should ensure the fT4 levels in the fetus do not exceed the threshold for maternal fT4.

The FDA model results need to be compared to the NHANES monitoring data. The model is calibrated for high perchlorate exposures based on a longitudinal epidemiological study of 184 pregnant women in three Chilean cities from 2002 to 2004.[15] Other researchers have raised concerns with the conclusions being drawn from this study, particularly because some residents moved from city-to-city. In contrast, NHANES has data on thousands of people, including pregnant woman with information on maternal levels of iodide, perchlorate, thyroid hormones, as

[12] McLanahan ED, White P, Flowers L, Schlosser PM. The Use of PBPK Models to Inform Human Health Risk Assessment: Case Study on Perchlorate and Radioiodide Human Lifestage Models. Risk Anal. 2014 Feb;34(2):356-66.

[13] Moleti M, Trimarchi F, Vermiglio F. Doubts and Concerns about Isolated Maternal Hypothyroxinemia. J Thyroid Res. 2011;2011:463029. doi:10.4061/2011/463029. Epub 2011 Jun 15. PubMed PMID: 21765991; PubMed Central PMCID: PMC3134327.

[14] Cooper, D. 2004. Sub-clinical thyroid disease: consensus or conundrum. Clinical Endocrinology 60 (410-412); Haddow JE, Palomake GE, Allan, WC, Williams JR, Knight GJ, and Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. New England Journal of Medicine 1999: 341: 549-555; Pop VJ, Kuijpens J., van Baar, AL, Verkert, G. et al. 1999. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clinical Endocrinology 50 (149); Surks M., Ortiz E., Daniels G., Sawin C., Col N., Cobin R., Franklyn J. Hershman J., Burman K., Denke M., Gorman C., Cooper R., Weissman N. 2004. Subclinical Thyroid Disease. Subclinical Thyroid Disease. Journal of the American Medical Association 2004: 228-238.

[15] Téllez Téllez R, Michaud Chacón P, Reyes Abarca C, Blount BC, Van Landingham CB, Crump KS, Gibbs JP. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid. 2005 Sep;15(9):963-75. PubMed PMID: 16187904.

well as thiocyanate.[16] Therefore, EPA should use the data from the NHANES survey rather than the flawed Chilean cities study.

Again, we appreciate the opportunity to provide you with these comments and would like to discuss them in more detail as EPA works with FDA to fix the problems we described above in the model.

If you have any questions, please contact me at tneltner@nrdc.org.

Sincerely,

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Senior Attorney

Maricel Maffini
Senior Scientist

cc: Eric Burneson, Acting Director, Standards and Risk Management Division
Mae Wu, Program Attorney, NRDC

[16] Blount BC, L Valentin-Blasini, JD Osterloh, JP Mauldin, and JL Pirkle. 2007. Perchlorate exposure of the US population, 2001-2002. J Expo Sci Environ Epidemiol. 17(4):400-7.