NATURAL RESOURCES DEFENSE COUNCIL

July 31, 2014

Lance Wormell
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Antimicrobials Division
Office of Pesticide Programs
U.S. Environmental Protection Agency

Re: Observations on tolerances for hypochlorite to minimize degeneration to perchlorate

Dear Dr. Wormell:

Thank you for agreeing to investigate the degeneration of hypochlorite into perchlorate as part of the Environmental Protection Agency's (EPA) registration review of pesticides containing sodium or calcium hypochlorite pursuant to EPA-HQ-OPP-2012-0004. In light of the potential impacts of perchlorate on fetal and infant brain development, its common presence in hypochlorite, and the extensive use of hypochlorite in food processing, the Natural Resources Defense Council (NRDC) believes it is critical that the agency set tolerances for the two active pesticide ingredients to limit perchlorate residues. These tolerances must consider the combined effect of perchlorate, thiocyanate and nitrate on fetuses and infants and the aggregate exposure to perchlorate not only from hypochlorite but all sources including plastic packaging.

Our preliminary analysis indicates that the guidance from the American Water Works Association and Water Research Foundation is a good starting point for establishing appropriate tolerances. EPA should limit the maximum concentration of hypochlorite in solution, set expiration dates, and require that the pH of the solution be maintained below 12.5 to protect fetuses, infants, and children.

We recognize that perchlorate has been found in ground and surface water as well as drinking water, and is commonly associated with fireworks, rocket propellants, and Chilean fertilizer. For example, in 2008, the Food and Drug Administration (FDA) stated that "[p]erchlorate is used as an oxidizing agent in rocket propellant, is found in other items (e.g., explosives, road flares, fireworks, and car airbags), occurs naturally in some fertilizers, and may be generated under certain climatic conditions."[1]

[1] Murray CW, Egan SK, Kim H, Beru N, and Bolger PM, US Food and Drug Administration's Total Diet Study: Dietary intake of perchlorate and iodine, J Expo Sci Environ Epidemiol. 2008 Nov;18(6):571-80. doi: 10.1038/sj.jes.7500648.

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While these sources may be locally or in some cases regionally significant, it is not clear that they adequately explain the widespread perchlorate contamination of food found by FDA in its national Total Diet Study (also known as the Market Basket Survey) from July 2003 to July 2006 where the agency reported finding perchlorate in almost three-fourths of the 280 types of food products sampled from grocery stores and fast-food restaurants.[2] Some of the highest levels were reported in plain, toasted English muffins at 72 parts per billion (ppb) and boiled shrimp at 158 ppb collected in October 2005 from Fargo, ND, Rockport, IL, and Cincinnati, OH.[3]

The commonly recognized sources also may not adequately explain why perchlorate is found in drinking water at levels over 4 ppb in 371 public water supply systems. These levels prompted the EPA in 2011 to make a regulatory determination that a Maximum Contaminant Level (MCL) is needed for perchlorate because the chemical "may have an adverse effect on the health of persons; perchlorate is known to occur or there is a substantial likelihood that perchlorate will occur in public water systems with a frequency and at levels of public health concern; and in the sole judgment of the Administrator, regulation of perchlorate in drinking water systems presents a meaningful opportunity for health risk reduction for persons served by public water systems."[4]

While EPA and others have long established that environmental contamination from perchlorate manufacture and mishandling is the source of water contamination at many sites, NRDC believes that degradation of hypochlorite into perchlorate is a likely explanation for a significant amount of the widespread contamination of drinking water and food because of its extensive use in both as a registered pesticide. As EPA noted in the hypochlorite docket, sodium and calcium hypochlorite are used to treat drinking water. Its food-related uses include:

- disinfectant for food surfaces;
- sanitizer for food surfaces;
- control of microorganisms for eggs for human consumptions; and
- wash or lye peeling of fruits and vegetables.[5]

The study commissioned by the American Water Works Association (AWWA) and the Water Research Foundation (WRF)[6] provides formulas to estimate levels of perchlorate in hypochlorite, makes suggestions to limit the degradation reaction, and gives ample evidence that:

1) perchlorate is frequently present in hypochlorite solutions with the research showing levels between 7.3 ppb and 3,500 ppm; and
2) the primary factors controlling degradation to perchlorate are: hypochlorite concentration; holding time; ionic strength, and temperature.[7]

As you conduct your investigation, we want to bring to your attention to the following issues in particular.

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[2] FDA, Survey Data on Perchlorate in Food – 2005/2006 Total Diet Study Results, 2008. See http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077615.htm.
[3] *Ibid.*
[4] 76 *Federal Register* 7762 (February 11, 2011).
[5] EPA, Na & Ca Hypochlorite Summary Document Registration Review: Initial Docket, 2012, Docket ID EPA-HQ-OPP-2012-0004-0002. See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0004-0002.
[6] Standford BJ, Pisarenko AN, Synder SA, and Gordon G, Perchlorate, bromate and chlorate in hypochlorite solutions: Guidelines for utilities, Journal of American Water Works Association, 2011, 103:6.
[7] *Ibid.*

1. **Nitrate, thiocyanate, and perchlorate have common mechanism of toxicity**

As you evaluate the cumulative effects of perchlorate on infants and children pursuant to 21 U.S.C. § 346a(b)(2)(C)(i)(III) and to pregnant women and their fetuses pursuant to 21 U.S.C. § 346a(b)(2)(D)(v), please also consider the impacts of exposure to thiocyanate from food and tobacco smoke and nitrate from food and drinking water. 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.[8,9] This same symporter is found elsewhere in the body, most notably in the mammary gland in production of breast milk.[10]

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.[11] 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 CDC study also serves as an excellent reminder of the impacts of hypochlorite. The study had to adjust down the measured levels of perchlorate in the urine squeezed from cloth diapers by 1.24 ppb. The researchers made this adjustment based on the amount of perchlorate leaching into distilled water from sampled unused cloth diapers, presumably as a residue from the use of hypochlorite bleach when the diapers were laundered. They did not find thiocyanate or nitrate in these nine cloth diapers used as a control.[12]

[8] 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.
[9] EPA Science Advisor Board, SAB advice on approaches to derive a maximum contaminant level goal for perchlorate, 2013, EPA-SAB-13-004, p. 31.
[10] 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.
[11] 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.
[12] *Ibid.*

2. Contamination of breast milk may be most critical exposure to infants

Like in an adult, this perchlorate fed to the infant would interfere with iodine absorption that is essential to produce thyroid hormones necessary for the infant's brain development. However, perchlorate in the mother may inhibit the sodium/iodine symporter in her mammary gland much as it does in her thyroid.[13] Therefore, breast milk may contain lower levels of iodine, which may magnify the impact of the infant's exposure to perchlorate. Presumably, thiocyanate and nitrate would also affect both the thyroid and the mammary glands' symporters as well.

Even excluding the impact of low iodine levels, given the small size of the infants, these exposures may be well in excess of the Reference Dose (RfD) of 0.7 µg/kg-bw/day developed by the National Research Council (NRC) panel in 2005.[14] Note that EPA's Science Advisory Board concluded that the NRC panel did not use the most sensitive and appropriate endpoint in setting this level.[15] The proper RfD is likely much lower.

Six studies measured the amount of perchlorate in breast milk from a total of 278 women. Table 2 summarizes the results for each of the studies.

Note that one article concluded that "Although environmental perchlorate and thiocyanate are ubiquitous, these results do not support the concern that maternal and infant environmental perchlorate and thiocyanate exposures affect infant thyroid function."[16] However, we believe the logic is flawed because the maternal and infant samples were all taken within the same hour. Because perchlorate levels in breast milk vary significantly over time[17] and thyroid hormone production takes time to adjust to perchlorate and iodine levels, it was incorrect to assume that the samples in the breast milk would directly and immediately correlate to the infant's thyroid hormone levels. EPA's SAB noted that "Variability incorporates both daily variation in urine excretion and variation in exposure due to a variable diet. A thorough review and synthesis of the literature examining how well a single spot urinary measure of these compounds reflects long term exposure patterns is advised." [18]

[13] Tonacchera M, Pinchera A, Dimida A, Ferrarini E, Agretti P, Vitti P, and Gibbs, J., Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter, *Thyroid*, 2004, *14*(12), 1012-1019.
[14] National Research Council, Health implications of perchlorate ingestion, 2005.
[15] EPA SAB 2013. They recommended EPA use hypothyroxinemia and not hypothyroidism as the most appropriate sensitive endpoint.
[16] Leung 2012.
[17] Dasgupta 2008 and Kirk 2007
[18] EPA SAB 2013, p. 63.

Table 2. Summary of articles describing tests for perchlorate in breast milk

Article	No. women	No. samples	Mean (µg/L)	Median (µg/L)	Min (µg/L)	Max (µg/L)	Location	Sample Dates
Kirk 2005[19]	36	36	**10.5**	3.2	0.6	92	18 states	2003
Pearce 2007[20]	49	49	**33**	9.1	1.3	411	Boston, MA	2002-2006
Kirk 2007[21]	10	147	**5.8**	4.0	0.5	40	TX, CO, FL, MO, NM, NC*	2005-2006**
Dasgupta 2008[22]	13	457	**9.3**	7.3	0.01	48	Arlington, TX**	2007**
Borjan 2011[23]	106	276	**6.8**	4.4	0.3	99.5	New Brunswick, NJ	2007-2008
Leung 2012[24]	64	64		4.4	0.5	29.5	Boston, MA	2008-2011
Totals	278	1029			0.01	411		

* Half from Texas panhandle with one from other states
** Inferred from article but information not clearly reported.

3. Aggregate exposure needs to include exposure from FDA-approved uses in plastic and rubber.

As you estimate the aggregate exposure to infants and children pursuant to 21 U.S.C. § 346a(b)(2)(C)(ii) and to pregnant women and their fetuses pursuant to 21 U.S.C. § 346a(b)(2)(D)(vi), please ensure that you include the contribution of perchlorate from two food additives approved by FDA. We know of two approved uses in food contact substances:

- In 1962, FDA approved its use in sealing gaskets in food containers in processing and packaging at levels up to 1 percent by weight.[25]
- In 2005, FDA approved at levels up to 4 percent by weight in packaging for dry food products to serve as an antistatic agent.[26]

[19] Kirk AB, Martinelango PK, Tian K, Dutta A, Smith EE, and Dasgupta PK, Perchlorate and iodide in dairy and breast milk. *Environmental Science & Technology, 2005, 39*(7), 2011-2017.
[20] Pearce EN, Leung AM, Blount BC, Bazrafshan HR, He X, Pino S, Valentin-Blasini L, and Braverman LE, Breast Milk Iodine and Perclorate Concentrations in Lactating Boston-Area Women, *The Journal of Clinical Endocrinology and Metabolism*, 2007, 92(5):1673-1677.
[21] Kirk, AB, Dyke JV, Martin CF, and Dasgupta PK, Temporal patterns in perchlorate, thiocyanate, and iodide excretion in human milk. *Environmental Health Perspectives*, 2007, 115(2), 182.
[22] Dasgupta PK, Kirk AB, Dyke JV, and Ohira SI, Intake of Iodine and Perchlorate and Excretion in Human Milk. *Environmental Science and Technology*, 2008, 42; 8116-8121.
[23] Borjan M, Marcella S, Blount B, Greenburg M, Zhang J, Murphy E, Valentin-Blasini L, and Robson M, Perchlorate exposure in lactating women in an urban community in New Jersey. *Science of the Total Environment*, 2011, 409; 460-464.
[24] Leung AM, Braverman LW, He X, Schuller KE, Roussilhes A, Jahreis KA, and Pearce EN, Environmental perchlorate and thiocyanate exposures and infant serum thyroid function. *Thyroid*, 2012, 22(9), 938-943.
[25] 27 *Federal Register* 7092 (July 26, 1962). The approval is currently at 21 CFR §177.1210.

We do not know the estimated exposure from the 1962 approval. After reviewing FDA's response to our Freedom of Information Act request regarding the 2005 approval, we found serious flaws in FDA's analysis including an 83-fold math error and a mistake in reporting the decision on its webpage that allows manufacturers to use 3.3 times greater levels in the plastic packaging than FDA actually approved.[27]

In addition, the analysis was based on an assumption that chemicals in dry food packaging migrate into the food at 'negligible' levels rather than on actual migration tests. In 2011, FDA acknowledged this assumption may be flawed. Finally, the agency's methodology assumed exposure only in the final product sold to the consumer. However, the product is marketed for bulk raw material storage and transport used in food production. As a result, the opportunities for migration into food are at least several hundred times greater than FDA assumed. On July 31, 2014, NRDC and others submitted a food additive petition to reverse this approval and prohibit the use of perchlorate in packaging.

Note that this approval was made in November 2005. Therefore, given time for the product to penetrate the market, it is unlikely that it is reflected in the samples taken by FDA in its TDS study because those samples were taken from before July 2006.[28]

4. Concerns with FDA's model for perchlorate exposure

In 2013, FDA published a model for perchlorate exposure in the third trimester of pregnancy.[29] When we learned that EPA's Office of Ground Water and Drinking Water (OGWDW) were planning to use the model to determine an RfD for perchlorate, NRDC examined the model closely. We found that the model has potential but needed significant revisions to include the first two trimesters when a fetus' thyroid is not fully functional and during breastfeeding.

We summarized these concerns in a letter to OGWDW on February 28, 2014.[30] On March 24, EPA confirmed that it would consider these concerns as it worked with FDA to revise the model. On May 28, 2014, we forwarded to OGWDW additional concerns that were raised by graduate students in Dr. Robin Whyatt's class at Columbia University.[31]

Because infant exposure to perchlorate in breast milk is already expected to exceed the NRC RfD of 0.7 µg/kg-bw/day and EPA's SAB has already indicated that the current RfD is not based

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[26] FDA, Threshold of Regulation Exemptions, 2013. See 05-006 at http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/ThresholdRegulationExemptions/default.htm.
[27] NRDC Food Additive Petition submitted to FDA on July 31, 2014.
[28] FDA, Survey Data on Perchlorate in Food – 2005/2006 Total Diet Study Results, 2008. See http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077615.htm.
[29] 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.
[30] Neltner and Maffini letter to Grevatt, February 28, 2014.
[31] Neltner email to Burneson, May 28, 2014.

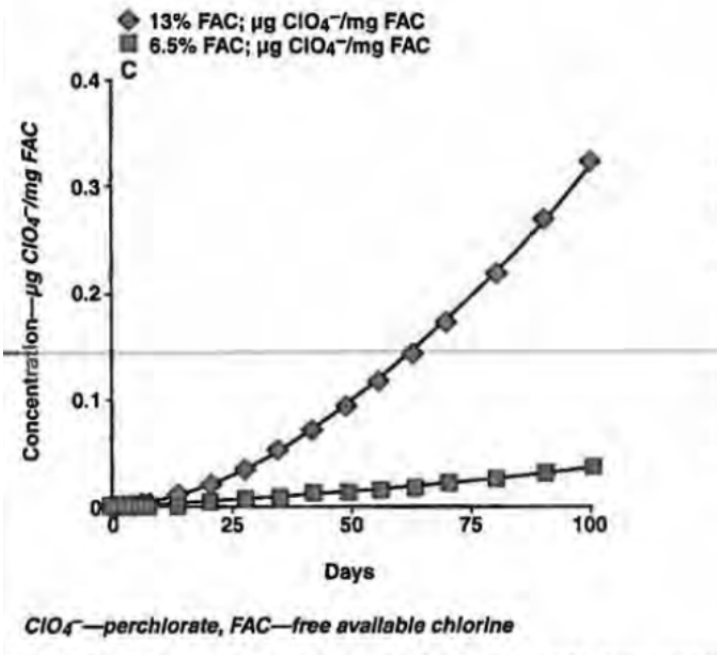
on the most sensitive indicator, we believe that EPA should not wait on the completion of the revised model to move forward on hypochlorite tolerances. That model may take several years to be completed. Rather, EPA should act now to establish appropriate tolerances for sodium and calcium hypochlorite that are protective of public health including sensitive life stages. The AWWA/WRF report and guidance should serve as a helpful starting point for these tolerances.[32]

NRDC's recommended tolerance

NRDC believes the Administrator should determine pursuant to 21 U.S.C. §346a(a)(3) that perchlorate is a degradation product of hypochlorite and that it is likely to pose a potential health risk from dietary exposure in food and water that is of a different type than and of a greater significance than the risk posed by dietary exposure to hypochlorite.

Regarding setting a maximum hypochlorite concentration, we reprint below a portion of Figure 2 from AWWA/WRF report showing the relationship between hypochlorite concentration and perchlorate formation in bulk hypochlorite. It shows that cutting the hypochlorite concentration from 13% to 6.5% free available chlorine reduces the perchlorate concentration after 100 days dramatically. The levels of perchlorate at 6.5% hypochlorite may still be too high: EPA will need to make sure that its standard is protective of public health for all populations, including sensitive life stages.

Figure 1. Relationship between hypochlorite concentration and perchlorate formation in bulk



Regarding residence times, the AWWA/WRF report recommends using fresh hypochlorite solutions, stating that "[o]ver time, bleach will naturally decompose to produce oxygen, chlorate, and perchlorate. Shorter storage times help minimize the formation of these contaminants in the hypochlorite solution. In addition, a fresh bleach solution contains a higher concentration of hypochlorite, thus reducing the amount of solution required to obtain the target chlorine residual. Again, higher hypochlorite concentration in fresh bleach will correspond to lower concentrations of contaminants dosed."[33]

We agree with this reasoning and suggest that the hypochlorite pesticide products have an expiration date to minimize perchlorate levels. While the study only looked at 100 days, we

[32] Standford 2011.
[33] *Ibid.*

recommend that EPA set an expiration date to ensure that all populations are protected, including fetuses and infants.

Regarding pH, the AWWA/WRF report recommends that the pH of the stored hypochlorite solutions be controlled at pH 11-13 as a surrogate for high ionic strength, even after dilution. The report states that "[s]torage of concentrated hypochlorite solutions at pH values < 11 is not recommended because of the rapid decomposition of hypochlorite/hypochlorous acid and the consequent formation of chlorate even though this reduces the amount of perchlorate formed. When the pH is > 13, perchlorate formation is enhanced because of the ionic strength effect."[34]

We recognize that EPA has avoided setting expiration dates for pesticides because the product would become a "solid waste" when discarded and might be classified as a regulated hazardous waste. Since the discarded hypochlorite solution is not "listed" as hazardous waste by EPA, it would only be a regulated hazardous waste based on its potential characteristics. The only hazardous waste characteristic that hypochlorite solutions would likely trigger is when the pH is 12.5 or greater.[35] If EPA took steps to ensure that the pH was below 12.5, the solution would not have to be handled as a hazardous waste.[36]

In conclusion, NRDC believes it is critical that the agency move quickly and diligently to set appropriate health-protective tolerances for sodium and calcium hypochlorite, considering the formation of perchlorate and other contaminants.

If you have questions or comments, please contact Tom Neltner at tneltner@nrdc.org or 202-513-6252. If I am not available, please contact Jennifer Sass at jsass@nrdc.org or 202-289-2362.

Sincerely,

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Senior Attorney

Maricel Maffini, Ph.D.
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[34] *Ibid.*
[35] 40 CFR § 261.22.
[36] *Ibid.*