Dow AgroSciences LLC

Response to Request for Public Comments

Sulfuryl Fluoride; Proposed Order Granting

Objections to Tolerances and Denying Request for a Stay

Public Docket Identification Number:

EPA-HQ-OPP-2005-0174-0128

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EXECUTIVE SUMMARY

EPA's Proposed Order regarding sulfuryl fluoride seeks to eliminate from the marketplace ProFume® Gas Fumigant ("ProFume"), a product that with the EPA's active encouragement has become instrumental to the safe and efficient storage and processing of food in America. ProFume keeps rodents, insects and other pests from invading food commodities and contaminating those commodities with their waste and body parts. It is a critical replacement for methyl bromide, an ozone-depleting chemical scheduled for complete phase-out under the Montreal Protocol.

In 2002, EPA awarded Dow AgroSciences an EPA Stratospheric Ozone Protection Award for the development of sulfuryl fluoride as a methyl bromide replacement. In 2007, the Agency again recognized this significant accomplishment when EPA included the development of sulfuryl fluoride in its "Best of the Best" Stratospheric Ozone Protection Awards.

On January 19, 2011 EPA issued a proposed order that, if finalized, would eliminate the food uses of sulfuryl fluoride. The Agency proposes the elimination of ProFume because of concern that certain subpopulation groups are exposed to the chemical fluoride above what EPA has newly calculated as an acceptable level. However, the Agency readily acknowledges that the vast majority of the public's exposure to fluoride comes from drinking water, including fluoride that occurs naturally in water, and other sources that have nothing to do with pesticides, and that ProFume contributes only minimally to fluoride exposure. In fact, the Agency admits that its proposal to take ProFume off the market will have absolutely no impact in reducing overall fluoride exposure to an acceptable level. Thus, EPA's Proposed Order is an admittedly pointless

exercise when it comes to the minimal fluoride exposure that may result from the use of ProFume.

Moreover, as set forth in detail in these Comments, EPA's Proposed Order has been issued without the transparency and valuable contributions of a public hearing where affected stakeholders could be heard, an independent scientific review, the input of other federal agencies, and without the additional process due the registrant, Dow AgroSciences, all as required by law. In addition, the Proposed Order has been issued without consideration by EPA of more reasonable, less onerous, alternatives. More specifically:

- The Agency's Proposed Order violates the terms of the conditional registration issued to Dow AgroSciences for ProFume. The conditional registration put in place a process for determining what action EPA would take as to the 2006 National Research Council's report on fluoride in drinking water. This includes addressing the adequacy of the current Maximum Contaminant Level Goal for fluoride in drinking water before taking any action with respect to tolerances for sulfuryl fluoride's food-related uses. The Proposed Order completely abandons the process promised to and relied upon by Dow AgroSciences.

- EPA failed to use the best available data and apply sound scientific principles in reaching its determination of a new reference dose for fluoride. There are errors in and significant questions left from EPA's science analysis which beg for review and input from the independent Scientific Advisory Panel established by Congress for that very purpose.

- EPA's Proposed Order leaves no doubt that the Agency's current intention is to ultimately remove ProFume's food uses from the market, effectively cancelling Dow AgroSciences' registrations for those uses. Yet the Agency has failed to comply with the Federal Insecticide, Fungicide, and Rodenticide Act by denying Dow AgroSciences and other adversely affected parties a hearing and failing to seek the input of other federal agencies and an independent science review before issuing the Proposed Order.

- EPA has failed to consider reasonable and appropriate alternatives to the termination of the tolerances for the food-related uses of sulfuryl fluoride and cancellation of the underlying ProFume uses. These reasonable alternatives include:

  -- using the Agency's inherent authority to determine that exposure to fluoride from ProFume is so negligible — *de minimis* — as to present no

public health or safety concerns and to authorize continued use of ProFume on that basis;

-- recognizing that all significant fluoride exposures result from non-pesticide sources that are subject to regulation under statutes other than Section 408 of the Federal Food, Drug, and Cosmetic Act — exposures which must be considered but need not be included in EPA's aggregate exposure assessment;

-- complying with the statutory requirement to base tolerance decisions on "reliable information" and "anticipated" exposure levels;

-- adopting a policy that allows the Administrator, under extraordinary circumstances including *de minimis* exposure and risk from the use of a pesticide, and taking into account risk, benefits, and public policy considerations, to make a determination that tolerances that might otherwise not meet the Agency's current aggregate exposure policy are permissible; and,

-- revoking the fluoride tolerances as unenforceable while maintaining tolerances for sulfuryl fluoride that are already in place.

The disruption to the food chain that would result from the Proposed Order is too significant, and the potential contamination of food and other public health impacts too real for the Agency to ignore these reasonable alternatives, especially in the face of minimal exposure to fluoride from the product it contemplates eliminating.

For these and other reasons set forth in these Comments, EPA should not finalize its Proposed Order. Instead, the procedural and substantive concerns raised by the Proposed Order and the Agency's underlying analyses must be carefully reviewed and addressed. EPA should abide by the terms of the conditional registration that it issued to Dow AgroSciences for ProFume, conduct a public hearing, and seek input from other federal agencies and an independent Scientific Advisory Panel with respect to the matters raised in the Proposed Order. And, finally, the Agency should consider the various reasonable alternatives that are available to address concerns associated with fluoride and select a path forward that will best serve the overall public interest while allowing ProFume to continue to protect the food supply and serve as a critical replacement for methyl bromide.

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I. Purpose of Dow AgroSciences Comments

The purpose of this document is to provide comments, on behalf of Dow AgroSciences LLC , in response to the public comment period announced by the U.S. Environmental Protection Agency ("EPA" or "Agency") on January 19, 2011. *Sulfuryl Fluoride; Proposed Order Granting Objections to Tolerances and Denying Request for a Stay*, 76 Fed. Reg. 3422 (January 9, 2011). The public comment period is associated with EPA's proposed resolution of objections and a stay request with regard to sulfuryl fluoride and fluoride tolerances promulgated in 2004 and 2005 under section 408(d) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"). The active ingredient in ProFume® Gas Fumigant is sulfuryl fluoride.

II. Introduction

Dow AgroSciences is a global leader in developing agricultural chemicals and biotechnology products in the food and agriculture industries with experience and expertise in the post-harvest and structural fumigation segments. Among the extensive and diverse mix of products registered and produced by Dow AgroSciences for agriculture are two pesticide products containing sulfuryl fluoride as the active ingredient. Sulfuryl fluoride is a structural and post-harvest fumigant utilized in enclosed environments to eradicate a wide range of harmful rodent, insect and other pests. Vikane® is the brand name of the Dow AgroSciences structural (non-food) use product registered for use in the United States since 1959. ProFume, approved for use in the United States in 2004, was developed by Dow AgroSciences specifically to serve as a direct replacement for methyl bromide (MeBr) in the food processing industry. Methyl bromide is an ozone-depleting substance which was scheduled for complete phaseout by December 31, 2004, under the Montreal Protocol signed by the United States and 182 other countries. The safety, economics and performance of sulfuryl fluoride have permitted many

MeBr users in this industry to adopt this alternative fumigant to facilitate compliance with the important environmental goals of the Montreal Protocol and the U.S. Clean Air Act. The EPA recognized sulfuryl fluoride with its Stratospheric Ozone Protection Award in 2002 and "Best of the Best" Stratospheric Ozone Protection Award in 2007. It heralded the use of sulfuryl fluoride as an alternative to the ozone-depleting methyl bromide and strongly encouraged industry's transition away from methyl bromide to sulfuryl fluoride over the last six years.

A. Uses of ProFume

As a replacement for MeBr, the use of ProFume in the U.S. is associated with post-harvest, structural and enclosure (*e.g.*, chamber) fumigations of food handling and processing facilities. Major use scenarios include grain milling and other food processing operations. There are approximately 300 of these types of facilities in the U.S., *United States Nomination for Critical Use Exemptions from the 2008 Phaseout of Methyl Bromide* (EPA Jan. 24, 2006) (hereafter 2008 MeBr Critical Use Nomination), and it is estimated that, following the complete phaseout of MeBr, up to approximately 40% of these facilities will use ProFume ranging from less than one to up to five times per year. *Human Health Risk Assessment for Sulfuryl Fluoride and Fluoride Anion Addressing the Section 3 Registration of Sulfuryl Fluoride as a Fumigant for Foods and Food Processing Facilities*. PP# 3F6573, at 24 (EPA Jan. 18, 2006) (hereafter *EPA Human Health Risk Assessment*). As required by EPA product labeling restrictions, structures are emptied of food to the extent practical prior to the fumigation. Food impractical to remove or isolate from the fumigation can remain in the facility and be subject to the fumigation inadvertently.

In addition to the uses of ProFume in structures, the product is also used in some circumstances to fumigate food items in enclosures or chambers. Food commodities subject to

direct fumigation (with either MeBr or sulfuryl fluoride) are generally limited to some processed foods, dried fruit, tree nuts and beans. *2008 MeBr Critical Use Nomination*.

B. Regulation of ProFume

In support of pesticide registrations for the use of ProFume, submissions were prepared and submitted to EPA for review in 2000 (Experimental Use Permit), 2001 and 2003. Following comprehensive reviews of health, safety and environmental data by EPA's Office of Pesticide Programs ("OPP"), a conditional registration for ProFume was granted by the Agency on January 26, 2004, under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"), EPA Registration No. 62719-376. The registration was subsequently amended on July 15, 2005. Following a comprehensive review of the best available food safety data, EPA issued pesticide tolerances in support of the ProFume registrations in both 2004 and 2005 under FFDCA Section 408. The tolerances issued by EPA were for both sulfuryl fluoride (parent active ingredient) and the fluoride anion (F-), the primary residue of interest. In addition to the U.S., ProFume is registered for use in sixteen countries as a MeBr replacement in the post-harvest and structural fumigation use patterns. Maximum Residue Limits ("MRLs" – comparable to pesticide tolerances) associated with the uses of ProFume have been established in other countries and by the Codex Alimentarius Commission.

C. Regulatory Profile of Fluoride and Sulfuryl Fluoride

The food-related uses of sulfuryl fluoride are regulated by the EPA's OPP under FIFRA. These uses may initially result in very low, but detectable levels of sulfuryl fluoride in treated commodities or in small quantities of commodities that cannot practically be removed from a food storage or processing facility before the facility is treated for pests. However, these sulfuryl fluoride residues rapidly break down and leave very low residues of the fluoride anion. While

these fluoride residues may be detectable, they are indistinguishable from fluoride that may be present in food from other sources unrelated to the use of sulfuryl fluoride (*e.g.*, food processed with water to which fluoride has been added).

Fluoride has a very unique regulatory profile. Any residues of fluoride in food that result from the use of sulfuryl fluoride are subject to regulation by OPP under FFDCA Section 408. The same is true with respect to any resulting sulfuryl fluoride residues in food. By law, "any pesticide chemical residue in or on a food shall be deemed unsafe" unless a tolerance (or exemption from the requirement of a tolerance) has been established by OPP. FFDCA Section 408(a)(1). In the event that a pesticide chemical residue is found in food that exceeds the tolerance established by OPP, the Food and Drug Administration ("FDA") is responsible for taking appropriate enforcement action.

The use of fluoride itself and the fluoride residues resulting from that use are subject to regulation by three federal agencies – EPA, FDA, and the Centers for Disease Control and Prevention ("CDC") – under at least six federal statutory provisions:

- EPA, Office of Water – Safe Drinking Water Act (drinking water);
- CDC – Public Health Service Act (drinking water);
- FDA – FFDCA Section 409 (bottled water);
- FDA – FFDCA Section 402(a)(1) (naturally-occurring sources in food, *e.g.*, crops irrigated with water with high background levels of fluoride, foods processed with water with high background levels of fluoride);
- FDA – FFDCA Section 406 (residues in food that are not naturally-occurring but are unavoidable, *e.g.*, food processed with water with added fluoride); and
- FDA – FFDCA Section 505 (dental pharmaceutical products).

As these Comments will demonstrate, fluoride's unique regulatory profile creates administrative options which EPA has not considered and which would not require the termination of the sulfuryl fluoride tolerances.

III. EPA's Proposed Order

A. Summary of EPA's Proposed Order and Purported Basis for It

On January 19, 2011, EPA issued a proposed order under the pesticide provisions of the FFDCA that, if finalized, would eliminate the food uses of the pesticide active ingredient sulfuryl fluoride. *Sulfuryl Fluoride; Proposed Order Granting Objections to Tolerances and Denying Request for a Stay* ("Proposed Order"), 76 Fed. Reg. 3422 (January 19, 2011). The Proposed Order was prepared by OPP in response to objections and a stay request submitted with respect to sulfuryl fluoride and fluoride tolerances promulgated in 2004 and 2005 pursuant to FFDCA Section 408(d). The objections and stay request, as well as several threats of litigation against the Agency with respect to the tolerances, were made by the Environmental Working Group, Beyond Pesticides and the Fluoride Action Network ("FAN")(collectively, the "Objectors").[1]

The centerpiece of EPA's Proposed Order is a revised risk assessment for fluoride, discussed below. Proposed Order at 3434. This reassessment included a dose-response analysis and an exposure and relative source contribution analysis. These analyses were conducted under the lead of EPA's Office of Water ("OW"), presumably because the overwhelming source of human exposure to fluoride is through drinking water, which contains fluoride either naturally in distinct geographic areas or through addition of fluoride to prevent dental caries at levels

[1] FAN, for example, is a group opposed to water fluoridation and touts on its website that "[a]fter a vigorous nine-year effort [it] … convinced the U.S. Environmental Protection Agency to phase out ALL sulfuryl fluoride pesticides from the US food supply." *See http://www.fluoridealert.org/about-fan.htm.*

established by OW under the Safe Drinking Water Act. The Office of Water's reassessment ("OW Reassessment"), in turn, was used by OPP in the conduct of a revised aggregate assessment of fluoride exposure and risk under FFDCA Section 408 ("OPP Revised Assessment"). Proposed Order at 3437.

Prior to the Proposed Order, OPP relied on the Maximum Contaminant Level Goal ("MCLG") for fluoride in drinking water that OW had established under the Safe Drinking Water Act in order for OPP to assess the risk of fluoride exposure from sulfuryl fluoride under the FFDCA. Proposed Order at 3429. The fluoride MCLG is 4 mg/L, was established in 1986, and is based on the adverse effect of crippling skeletal fluorosis. *Id*. When EPA registered sulfuryl fluoride in 2004 for use as a direct fumigant of various grains and dried fruits under FIFRA and established corresponding tolerances under FFDCA, it relied on the MCLG in order to establish an acceptable level of exposure – *i.e.*, reference dose ("RfD") – for fluoride. *Id*. "As was the case with the MCLG, EPA determined that dental fluorosis was not an adverse effect and thus was not an appropriate benchmark for evaluating the safety of fluoride under FFDCA." *Id*.

In 2005, EPA registered sulfuryl fluoride under FIFRA for use on additional commodities and also as a structural fumigant for food processing facilities and established corresponding tolerances under FFDCA. Again, EPA relied on the acceptable exposure estimate derived from the MCLG in assessing aggregate risk to fluoride. Proposed Order at 3430.

In March 2006, a committee of the National Research Council ("NRC") issued the latest of a series of reports on fluoride in drinking water. *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*, National Research Council of the National Academies, National

Academies Press (March 22, 2006) ("NRC Report"). As set forth in its report, the NRC committee was convened, at EPA's request, "because the Safe Drinking Water Act requires periodic reassessment of regulations for drinking water contaminants." NRC Report at xi. The NRC committee's task was to review research on fluoride, "focusing primarily on studies generated since the early 1990s" in order to evaluate the adequacy of EPA's MCLG and Secondary Maximum Contaminant Level ("SMCL") for fluoride to protect public health. NRC Report at xi and 2. It does not appear that the NRC committee generated any new data, but instead conducted a review of existing scientific literature. The NRC Report was released on March 22, 2006. EPA completed risk assessments evaluating the appropriateness of sulfuryl fluoride and fluoride tolerances on January 20, 2004 and January 18, 2006. In these risk assessments, EPA relied on several of the studies that were also reviewed by NRC. *Response to Public Comments Concerning the Use of Sulfuryl Fluoride as a Post-Harvest Fumigant* (EPA Jan. 16, 2004). Moreover, it appears that most of the studies reviewed by the NRC committee and relevant to NRC's primary conclusions were critically reviewed by EPA (if available) in the preparation of its risk assessments for ProFume in 2004 and 2006, *i.e.*, little of the data reviewed by the NRC committee was "new" since EPA issued its risk assessments.

The NRC Report concluded, based on the committee's literature review, that EPA's MCLG of 4 mg/L should be lowered because exposure to fluoride at 4 mg/L and higher can result in severe dental fluorosis, which for the first time was considered an "adverse health effect" by a committee of the NRC.[2] The NRC Report did not make any recommendations with

[2] This is completely contrary to the NRC's 1993 report on fluoride, for which the NRC was given nearly the identical charge by EPA. In its 1993 report, the NRC did not recommend a change to the MCLG for drinking water and specifically disclaimed any ability to judge whether dental fluorosis was an adverse health effect. *See* 58 Fed. Reg. 68,826, 66,827 (Dec. 29, 1993)

respect to ProFume or any other sulfuryl fluoride product. The NRC Report did not conclude that the tolerances established by EPA for sulfuryl fluoride and fluoride residues should be re-evaluated, stayed or modified in any way. Indeed, the NRC Report did not conclude that commerce should be interrupted at all with respect to Dow AgroSciences' or any other manufacturers' products containing sulfuryl fluoride or the end-users of those pesticide products.

Subsequent to the NRC Report, OW conducted its reassessment with respect to fluoride. Proposed Order at 3434. As noted earlier, the OW Reassessment is the focal point of the Proposed Order and each of its key findings was adopted by OPP. In conducting its reassessment of fluoride, OW did not undertake a review of the MCLG for fluoride, as recommended by the NRC Report or as promised to Dow AgroSciences in its registration for ProFume (discussed below). Indeed, OW abandoned its prior use of the MCLG to determine the RfD for fluoride and instead relied upon a nearly 70-year-old study as the basis for its revised RfD calculation.[3] Proposed Order at 3434-35, 3438. The OW Reassessment also adopted the NRC Report's conclusion that severe dental fluorosis, previously considered a cosmetic effect, is an adverse health effect due to the pitting it causes in permanent teeth. Proposed Order at 3434, 3437. This represented another reversal of course for the Agency.[4] Accordingly, OW based its new RfD (0.08 mg/kg/day) on the more sensitive endpoint of severe dental fluorosis. Proposed Order at 3435, 3438.

(to be codified at 40 C.F.R. pt. 141); *Health Effects of Ingested Fluorides*, National Research Council of the National Academies, National Academic Press (1993).

[3] H.T. Dean, "The Investigation of Physiological Effects by the Epidemiological Method." (1942) (edited by F.R. Moulton, In *Fluorine and Dental Health*, Washington, D.C., American Association for the Advancement of Science).

[4] *See Natural Resources Defense Council, Inc. v. EPA*, 812 F. 2d 721, 724 (D.C. Cir. 1987) ("The agency … determined that dental fluorosis, although manifested by unattractive staining and pitting, did not appear to cause loss of function or mortal injury to the teeth.… [EPA thus found] the evidence inadequate to conclude that dental fluorosis is an adverse health effect….").

OPP then considered numerous sources (but not all) of exposure to fluoride – toothpaste, drinking water (natural and fluoridated), beverages, soil and sulfuryl fluoride – and determined that the aggregate fluoride exposure to certain groups exceeded the new RfD. Proposed Order at 3441. As a result, OPP determined that it could not "conclude that there is a reasonable certainty of no harm for certain major identifiable groups of consumers from aggregate exposure to fluoride." Proposed Order at 3442. Thus, OPP concluded that it could not make the required finding that the sulfuryl fluoride and fluoride tolerances are "safe" and proposed to grant the objections to the establishment of the sulfuryl fluoride and fluoride tolerances established in 2004 and 2005. *Id*.

In coming to this conclusion, OPP conceded that "the threat that fluoride poses … is due to aggregate exposure to fluoride not the fluoride in food resulting from use of sulfuryl fluoride when viewed in isolation." Proposed Order at 3443. And, most notably, OPP acknowledged that its Proposed Order would have absolutely no impact whatsoever in reducing overall fluoride exposure to an acceptable level:

> Given the aggregate level of fluoride exposure, termination of the use of sulfuryl fluoride would not change the fact that aggregate fluoride levels would still exceed the safe level for highly-exposed subpopulations.

Id.

> Use of sulfuryl fluoride results in a minimal contribution to fluoride exposure. Elimination of sulfuryl fluoride does not solve, or even significantly decrease, the fluoride aggregate exposure problems identified earlier.

Id. at 3446.

Notwithstanding ProFume's inconsequential impact on aggregate fluoride exposure, and apparently believing that it had no other choice, OPP issued its Proposed Order that would terminate the tolerances associated with the food-related uses of ProFume pursuant to a

sequential implementation schedule (*i.e.*, immediately upon the effective date of the order for dried eggs and powdered milk tolerances, ninety days after the order for several additional food uses, and three years after the order for structural fumigation and remaining food uses). *Id*. at 3447-48. Pursuant to the Proposed Order, all tolerances for residues that might result in food because of the use of ProFume would be terminated by the conclusion of the sequential implementation period.

B. Impacts of Proposed Order

- Impact on fumigant companies and distributors:

Over the past six years as methyl bromide has been phasing out, fumigation companies have been actively changing their business to adopt the use of sulfuryl fluoride. These changes included the acquisition of application equipment, monitoring equipment, the modification of their fumigation truck fleet and appropriate training, all at significant cost. These investments were made to meet the demand created by the milling and food processing industries transitioning to ProFume gas fumigant. The Proposed Order will directly lead to significant financial loss by these fumigation companies as they try to again adapt to the needs of the milling and food processing industries. Potential changes could include scaling back their companies through employee reductions as their business operations move away from the mainstay of their business, fumigation. Distributors have made significant capital investments for additional warehousing, vehicles and monitoring equipment. They have expanded their offices and employed additional staff to manage the increased business resulting from the continued adoption of sulfuryl fluoride by the post-harvest, milling and food processing industries. EPA's proposed action will negatively impact these businesses resulting in the loss of their capital investments and the loss of jobs.

- Impact on food handling and processing facilities:

The grain milling and food processing industry can in some cases utilize alternative methods for facility sanitation. However, each of these methods brings to the industry significant problems and additional financial burdens. These include additional down-time resulting in lost production and revenue, additional labor to perform a more aggressive cleaning program (micro cleaning), additional equipment and structural modifications to utilize an alternative, and increased costs of structural and equipment repairs resulting from damage caused by the alternative process. The added costs will place a huge burden on all mills with smaller facilities that do not have sufficient capital to survive the transition.

Moreover, Congress recently passed comprehensive food safety legislation (the FDA Food Safety Modernization Act, or "FSMA") Pub. L. No. 111-353, 124 Stat. 3885 (2010). For the first time, FDA has a legislative mandate to require comprehensive, prevention-based controls across the food supply. FSMA requires food processing, manufacturing, shipping, and other regulated facilities to conduct an analysis of the most likely food safety hazards and to design and implement risk-based controls to prevent them. Section 103 of FSMA creates new requirements for each owner, operator, or agent of a food facility to evaluate the hazards that could affect food manufactured, processed, packed, transported, or held there; to identify and implement preventive controls to significantly minimize, prevent, or eliminate such hazards; and to monitor and maintain records on these controls once they are in place. It further requires facilities to conduct a re-analysis at specified intervals, and to maintain at least two years of records to document and verify their control measures, among other details. EPA failed to consider the additional economic burdens that the industry will face as a consequence of the new mandate coupled with the removal of this critical tool as described in the Proposed Order.

- Impact on post-harvest commodity producers:

Post-harvest commodity producers have no economical alternative to rapid fumigation for commodity disinfestations. This industry will have to radically alter its business operations. The costs to develop the needed infrastructure to accommodate moving to an alternative fumigant such as phosphine would be enormous. Development of infrastructure assumes that significant amounts of land required are available near the current location of these companies. These domestic impacts will also have potential negative impacts on international trade in that a number of the commodities fumigated with sulfuryl fluoride (*e.g.* walnuts and rice) are exported in large quantities. To keep product quality high, post-harvest commodity producers may be required to deal with a greater amount of spoilage in food that must then be destroyed. If forced to utilize non-economical alternatives, these producers will incur additional labor costs.

- Impact on growers and the public:

Removal of ProFume from the box of tools needed to maintain a high level of sanitation in the milling and food processing industries will effectively remove the ability to conduct cost effective general disinfestations. Alternatives have significant limitations which will drive up the cost of maintaining the current general level of facility sanitation. This cost will be pushed down to growers as they will be required to bring to the processing facilities insect free raw agricultural commodities from the field. The on-farm cost of maintaining pest free commodities will be placed directly on the grower. As the processed commodity moves through the chain of commerce toward finished foods on the grocery shelves, the increased cost of maintaining high standards of sanitation will be directly passed to the consumer in the way of increased food prices.

- Impact on methyl bromide replacement:

Petitioners for methyl bromide critical use exemptions will identify the proposed revocation of tolerances for sulfuryl fluoride as a foundation to request additional allocations to again make available methyl bromide for uses for which ProFume is serving as an effective alternative. The U.S. Government agreed under the Montreal Protocol and the Clean Air Act to phase out methyl bromide. This has the potential of undoing the phase-out plan.

- Impact on avoiding exceedence of risk cup or severe dental fluorosis:

There is no impact on avoiding exceedence of the risk cup or severe dental fluorosis by the revocation of the tolerances for use of sulfuryl fluoride. EPA acknowledges that "[u]se of sulfuryl fluoride is responsible for a tiny fraction of aggregate fluoride exposure. For example, for the most highly exposed age groups in the populations examined in the revised risk assessment, fluoride from sulfuryl fluoride accounts for about 2 to 3% of aggregate fluoride exposure. Given the aggregate level of fluoride exposure, termination of the use of sulfuryl fluoride would not change the fact that aggregate fluoride levels would still exceed the safe level for highly-exposed subpopulations." Proposed Order at 3443.

C. Assessment of Alternative Treatments to Sulfuryl Fluoride

The analysis of Ranville and Cook (2011) predicted if food tolerances were removed for sulfuryl fluoride, heat or fumigation with sulfuryl fluoride of facilities emptied of food product would be the two primary methods used to disinfest food processing facilities. Heat repeatedly has been documented to be less effective than fumigation with sulfuryl fluoride for disinfesting food processing facilities due to structural components, food residues, paper products or other contents providing thermal refugia for insects. Even when best practices for heat treatment are

followed, all heated areas may not attain lethal temperatures for the required time. No single, comprehensive calculation tool for planning and evaluating heat treatment for insects exists, unlike the Fumiguide® used for dosage calculations with ProFume gas fumigant (sulfuryl fluoride). Overheating can cause costly damage to the structure, equipment, food and its packaging, and other contents. The heat lability of many items, including construction elements, in food processing facilities may be unknown until damage occurs. Experts agree that additional research is needed to verify rates of temperature increase and duration of lethal temperatures required to ensure mortality of target pests and the effect of these temperature regimes on building components and contents. Therefore, heat treatment requires removing packaging, heat labile materials including raw and finished foods before treatment and replacing them after treatment, intensive cleaning, and preparing heat-sensitive equipment, steps which are not required for fumigation. Heat treatment is more expensive than fumigation with sulfuryl fluoride. Heat treatment also substantially reduces total annual revenue of food processing facilities by decreasing production time due to extra time to prepare the facility and conduct the treatment, compared to fumigation.

The second option, removal of all raw and finished food products prior to fumigation, will add significant and potentially unsustainable cost and liability to fumigation. There are currently numerous pre-fumigation actions taken by food processing facility managers that serve to minimize the raw and processed food products that remain in the facility during fumigation with ProFume. Even after all these steps are taken in preparation for fumigation, in some circumstances finished food product cannot be completely removed from the facility to be fumigated. These situations include when alternative space for storing food is not available, and/or does not provide the necessary security, environmental, or sanitation requirements to

prevent spoilage or cross contamination of food ingredients. Sometimes packaged, processed foods must be fumigated in-situ. An example is when the product shipping or bundling materials become infested and sufficient disinfested pallets and boxes may not available for re-bundling finished goods. Moving the infested pallets and boxes before fumigation will infest the temporary storage area, the destination location if shipped, and the food processing facility when returned after the fumigation.

The analysis of Cook and Ranville (2011) concluded that phosphine would be an economic and effective replacement for ProFume gas fumigant for fumigation of commodities. Their analysis did not take into account many factors that prevent food processors from using phosphine instead of ProFume, including shipping and warehousing logistics, existing infrastructure for fumigation, and lack of space to expand fumigation facilities. In addition, insect resistance to phosphine is documented globally and in the United States. Recent research in the United States has verified high levels of phosphine resistance in stored product insects that would interfere with the applicator's ability to effectively control key stored-product pests using phosphine as currently labeled. Sulfuryl fluoride and phosphine have different modes of action, making ProFume the primary candidate for rotating with phosphine to combat resistance. The unique opportunity to use ProFume to efficiently remediate phosphine resistance in insects infesting grain storage has been initiated in Australia. The EPA's proposed removal of food tolerances for ProFume eliminates the only practical fumigant alternative for managing phosphine resistance in stored product insects in the United States.

If there are no food tolerances for ProFume, the analyses of EPA did not consider the unintended consequences resulting from the likely increased use of contact and residual insecticide treatments, including selection for insecticide resistance and reduced availability of

natural pyrethrins for a broad range of pest control applications. In addition, removal of food tolerances for ProFume eliminates its use to eradicate structural infestations of new exotic, invasive stored product pests to prevent their dissemination and establishment. Sulfuryl fluoride has been used to efficiently, effectively, and readily eliminate structural infestations of introduced pest species, preventing their further dissemination**.**

IV. ProFume Presents Unique Exposure and Relative Risk Issues

A. Contribution of ProFume to Fluoride Exposure is Insignificant

The proposed phase-out of sulfuryl fluoride and fluoride tolerances associated with food-related uses of sulfuryl fluoride will have negligible impact on aggregate fluoride exposures. In fact, aggregate fluoride exposures for those subpopulations currently estimated by EPA to exceed the Agency's new reference dose ("RfD") will still exceed the new RfD after the proposed phase-out of sulfuryl fluoride. Simply stated, the use of sulfuryl fluoride contributes insignificantly to aggregate fluoride exposure, a fact that EPA acknowledges and clearly states. Specifically, the "[u]se of sulfuryl fluoride is responsible for a *tiny* fraction of aggregate fluoride exposure…. Given the aggregate level of fluoride exposure, *termination of the use of sulfuryl fluoride would not change the fact that aggregate fluoride levels would still exceed the safe level for highly-exposed subpopulations.*" Proposed Order at 3443 (emphasis added). Consequently, removing the use of ProFume will not address EPA's public health concerns for aggregate fluoride exposures. (See Appendix II for more in-depth discussion.)

The vast majority of fluoride exposure comes from drinking water followed by food (background levels), beverages, and toothpaste. Fluoride exposure due to residues in food resulting from the use of sulfuryl fluoride is nominal. OPP's risk assessment clearly

demonstrates this, as reported in Table 9 of its assessment. OPP Revised Assessment at 21. This is vividly depicted in Figures 1 - 3 below, which illustrate the contribution to aggregate fluoride exposure from drinking water, food (background levels), beverages, toothpaste, soil, and sulfuryl fluoride for children 6 months to 1 year, 1 to 4 years, and 4 to 7 years, respectively. Figures 1 - 3 depict contributions to total aggregate fluoride exposure for three scenarios, i.e., drinking water is assumed to contain 2.59 mg/L fluoride, drinking water is assumed to contain 1.76 mg/L fluoride, and the results of the EDA's relative source contribution analysis. OPP Revised Assessment at 15 and 21. (See Appendix II for more in-depth discussion.)

Figure 1. Aggregate Fluoride Exposure with Drinking Water at 2.59 mg/L Fluoride

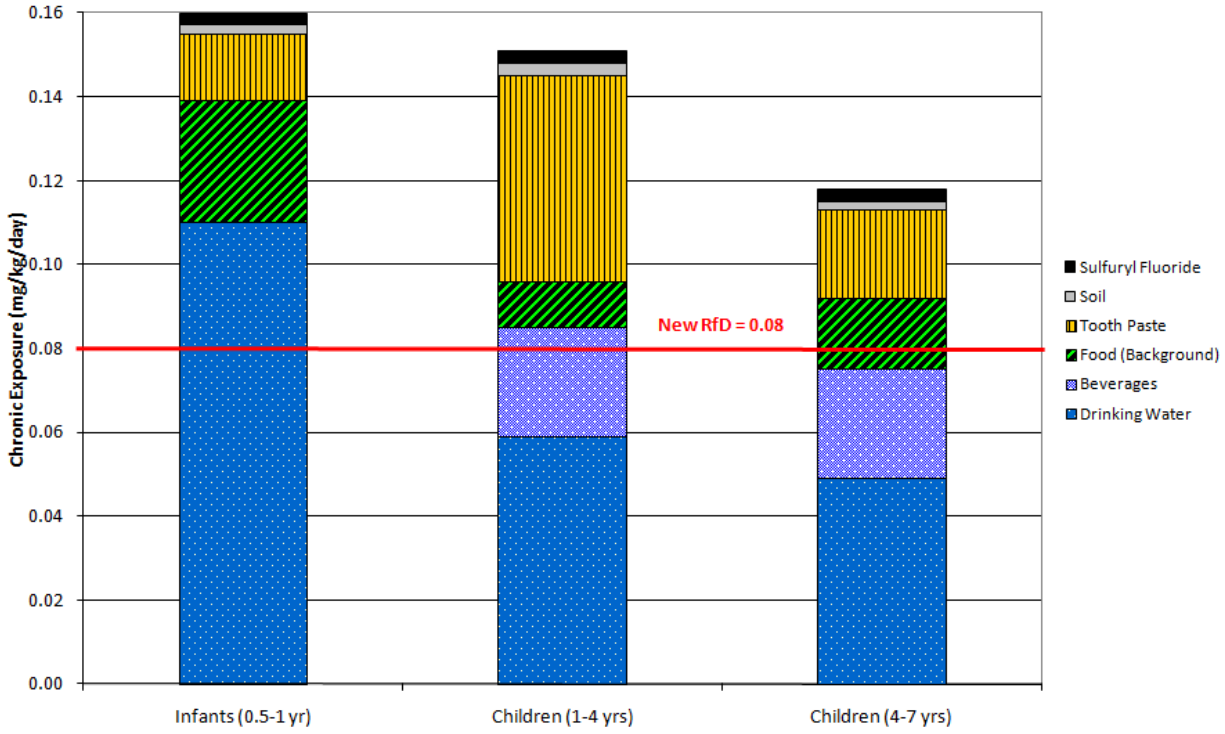


Figure 2. Aggregate Fluoride Exposure with Drinking Water at 1.76 mg/L Fluoride

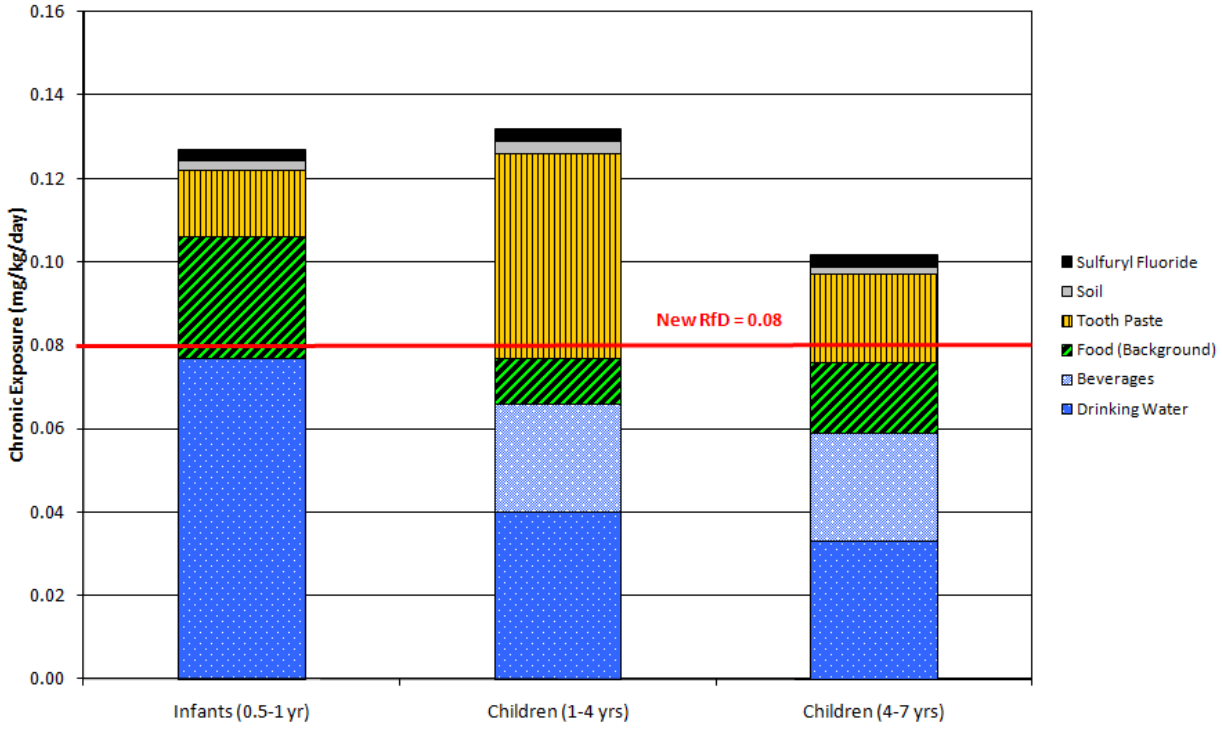
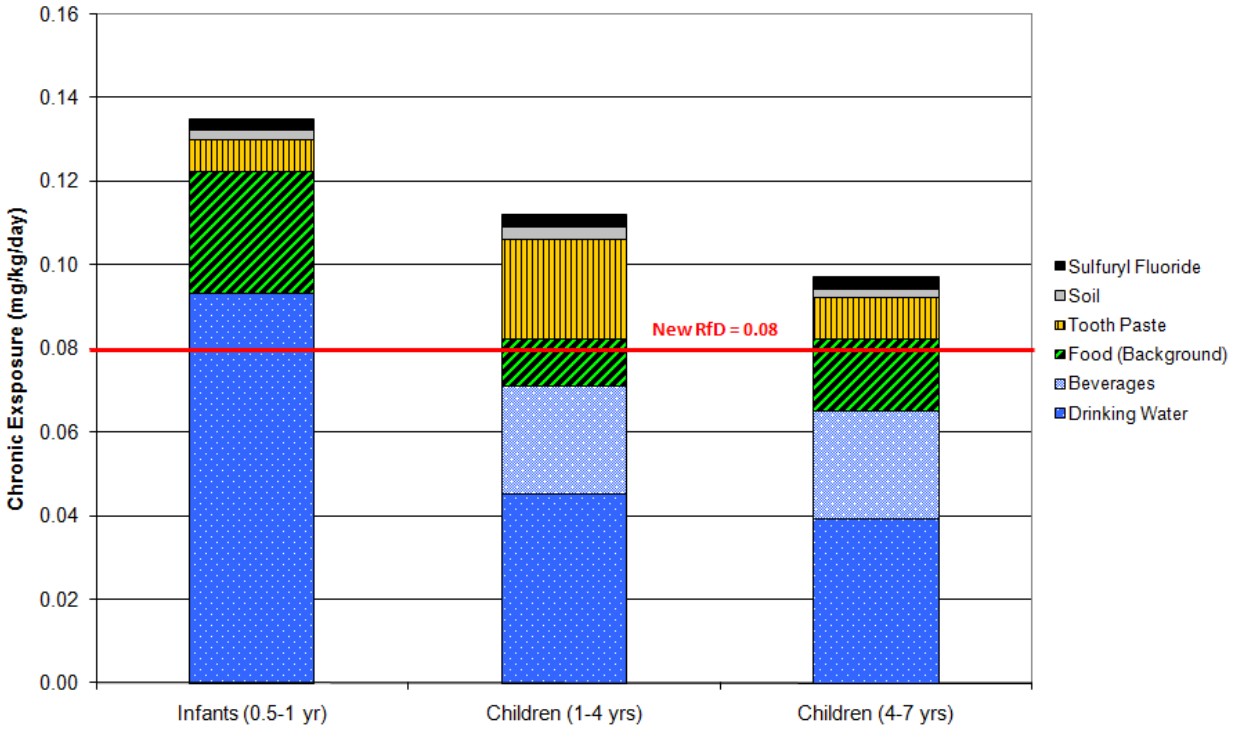


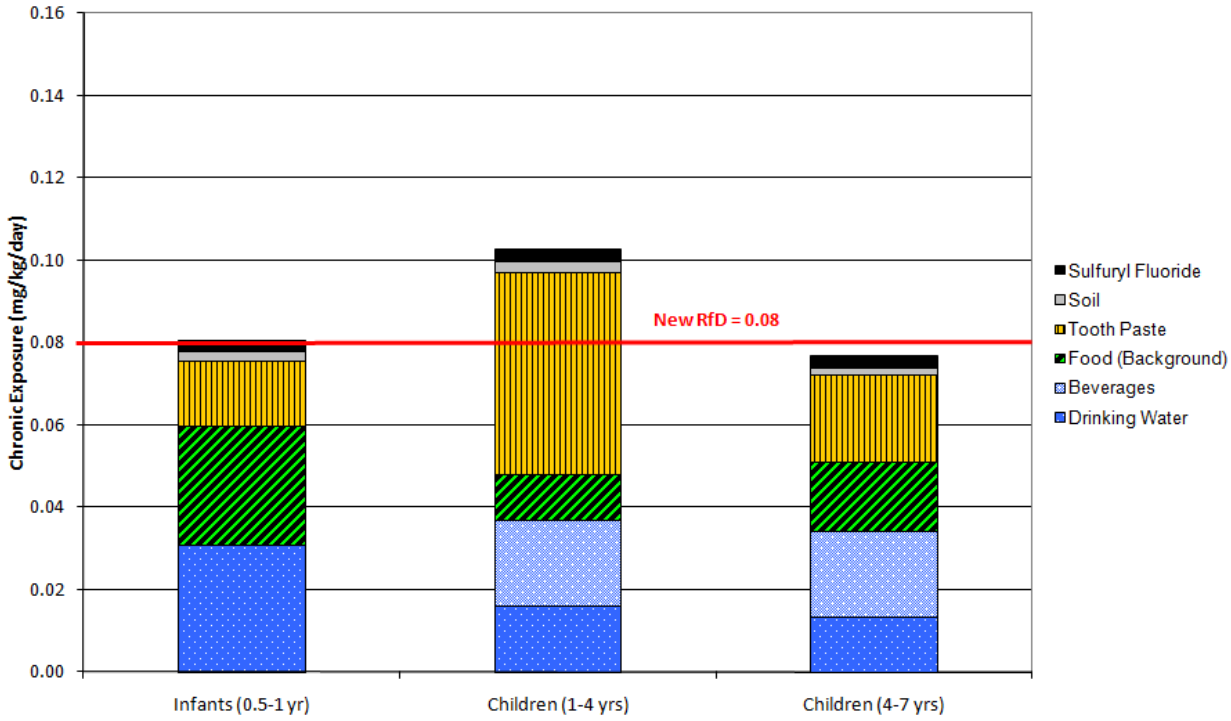
Figure 3. Aggregate Fluoride Exposure from Office of Water Relative Source Contribution Analysis



The driver behind the high levels of aggregate fluoride exposure from drinking water is the high naturally-occurring levels of fluoride in some geographic regions. Therefore, it is imperative that OW re-evaluate the MCL and MCLG under the SDWA. Further, this is the appropriate first step for EPA in assessing aggregate fluoride exposure and the associated public health concerns. An analysis of data on fluoride concentrations in public water systems from the OW and data on the prevalence of dental fluorosis from NHANES (see Appendix II for more in-depth discussion) indicates that fluoride concentration in water is a significant determinant in the occurrence of moderate and severe dental fluorosis. Regions with higher naturally-occurring levels of fluoride have higher prevalence of moderate and severe dental fluorosis.

Additional analyses demonstrate that the revised beneficial level for fluoridation of drinking water (0.7 mg/L) proposed by the Department of Health and Human Services (76 Fed. Reg. 2383-2388) would result in aggregate exposures greater than the new reference dose (RfD) of 0.08 mg/kg/day for some age groups, even when all sulfuryl fluoride tolerances have been terminated. Figure 4 illustrates these findings. (See Appendix II for more in-depth discussion.) Even when assessing fluoride exposure with drinking water at the proposed beneficial level, the vast majority of aggregate fluoride exposure is from drinking water, beverages, food (background levels), and toothpaste. Fluoride from the use of ProFume is still an insignificant part of the overall exposure and is clearly not a driver of the exposure. These results demonstrate yet again that removing the use of ProFume will not address EPA's public health concerns regarding aggregate fluoride exposures.

Figure 4. Aggregate Fluoride Exposure Assuming All Water Sources at the Beneficial Level (0.7 mg/L) for Fluoride



It is clear from EPA's assessments (*i.e.*, OPP Revised Assessment and OW Reassessment) that the leading contributor to fluoride aggregate exposure is high naturally-occurring levels of fluoride in drinking water. Following this primary driver are three secondary drivers, *i.e.*, background levels in food, beverages, and toothpaste. Fluoride exposure from sulfuryl fluoride is nominal and in no way materially impacts the aggregate exposure of, nor risk from, fluoride. Removing the use of sulfuryl fluoride and the nominal resultant exposure does nothing to address the public health issue before EPA. The required action in this case is not against sulfuryl fluoride, but to address the high levels of fluoride in drinking water under the SDWA (42 U.S.C. § 300f *et seq.*) which "was enacted to assure that water supply systems serving the public meet minimum national standards for the *protection of public health*…." Proposed Order at 3427 (emphasis supplied).

B. ProFume Has Unique Benefits

EPA recognizes the unique benefits of ProFume. This is evident through the awards it has bestowed on ProFume as a methyl bromide replacement, and, in this current action, EPA's rejection of the Objector's request for a stay of tolerances resulting from the food-related uses of sulfuryl fluoride, as well as EPA's proposed phase-out plan which stages the termination of key uses.

In 2002, the EPA awarded Dow AgroSciences an EPA Stratospheric Ozone Protection Award for the development of sulfuryl fluoride as a methyl bromide replacement. The Agency recognized this significant accomplishment again in 2007, when EPA included the development of sulfuryl fluoride in its "Best of the Best" Stratospheric Ozone Protection Awards. In addition, EPA promoted the use of ProFume as a methyl bromide replacement with the user community, indicating their support and desire for industry to shift from methyl bromide to sulfuryl fluoride.

Industry responded in kind, relying on this endorsement for making the transition, which was a time- and cost-intensive endeavor.

In EPA's current action against ProFume, the Agency has identified a number of alternatives that it believes are potential replacements for sulfuryl fluoride (*e.g.*, phosphine, heat, fogging, and sanitation). EPA conducted an analysis of the viability and availability of these alternatives, leading it to conclude that options do in fact exist in the absence of sulfuryl fluoride. However, this analysis was based on incomplete and inaccurate information. As discussed above in Section III.B., these alternatives are often ineffective and/or economically impractical. The reality for the user community is that, in the absence of ProFume, they have no viable options, and certainly not in the short term. It is important to note that even if viable and economical alternatives were available, the ability to transition to those alternatives in a period ranging from immediate to 3-years is unreasonable, as it has required 15 years for major users to transition from methyl bromide to sulfuryl fluoride.

The use of sulfuryl fluoride has public health benefits. Specifically, it is used to control insect and rodent infestations, which in turn, combats the contamination of food by insects, rodents and related pests. Such contamination poses a clear threat to public health. The use of sulfuryl fluoride allows the food industry to meet FDA "filth" standards. Removal of sulfuryl fluoride as a tool to control pests in food handling and storage facilities and on certain commodities will entail major disruption in the food processing sector. Removal of sulfuryl fluoride could give rise to increased risk of disease due to lack of alternatives, delay in putting alternatives into place, and the use of alternatives that are less effective and/or more costly. Further delays in the complete phase-out of methyl bromide and increased costs associated with

the expensive transitions to other technology and active ingredients could also result. (See Appendix II for more in-depth discussion.)

The use of sulfuryl fluoride helps keep markets open for American products. Specifically, if American products are not treated with sulfuryl fluoride, then the odds for use of methyl bromide or for contamination which could lead to foodborne illness are increased. Both factors may limit the ability of American growers and food producers to export their products.

The proposed revocation of sulfuryl fluoride tolerances in the U.S. may encourage countries not subject to the Montreal Protocol to revert to the use of methyl bromide. If the producers in these countries cannot export their sulfuryl fluoride treated commodities to the U.S., as would be the case in the absence of the required tolerances, then these producers would seek alternatives. The most viable, effective alternative would be methyl bromide, hence significantly increasing the likelihood that this would be their alternative of choice. As such, on a global basis, the phase-out of sulfuryl fluoride in the U.S. would have far reaching implications for the use of ozone depleting methyl bromide and the potential impact on climate change.

C. Fluoride Has Unique Benefits

EPA, FDA, CDC, the Department of Health and Human Services ("HHS") and the American Dental Association ("ADA") have all consistently recognized the benefits to public health associated with fluoridation of drinking water, specifically the prevention of dental caries. HHS (76 Fed. Reg. 2383-2388) has recently proposed to reduce the recommended level of fluoride in drinking water to 0.7 mg/L, the lower limit of the existing recommended level of 0.7 mg/L to 1.2 mg/L. However, at this proposed level, the resultant aggregate exposures would still be greater than the new reference dose (RfD) of 0.08 mg/kg/day (0.07 mg/kg/day, or 87.5%, of

which comes from drinking water) for fluoride for some age groups, even when all sulfuryl fluoride tolerances have been terminated. Foods and beverages are not uniformly distributed across the U.S., so background fluoride exposures from foods and beverages could vary. Therefore, establishing the recommended level of fluoride in water should take into consideration these variable potential sources of fluoride exposure. Similarly, further consideration regarding the role of fluoridated toothpaste and other sources of exposure may also be warranted. It is clear that there is a beneficial effect from fluoride, and efforts to reach but not exceed this level are complicated given the array of sources of fluoride. Such an effort requires discussion and coordination between the agencies involved. Dow AgroSciences encourages and supports the agencies in their endeavors to engage in this important public health discussion.

Drinking water with high levels of fluoride has been shown to cause severe dental fluorosis. OW Reassessment. As previously discussed, an analysis of data on fluoride concentrations in public water systems from the OW and data on the prevalence of dental fluorosis from NHANES indicates that fluoride concentration in water is a significant determinant in the occurrence of moderate and severe dental fluorosis. The occurrence of moderate and severe dental fluorosis parallels the concentration of fluoride in drinking water. Fluoride levels in artificially fluoridated water do not reach the same levels as those seen in some high naturally fluoridated drinking water. Therefore, drinking water supplies that are artificially fluoridated are less likely than drinking water with high naturally-occurring levels of fluoride to be associated with severe dental fluorosis, even with the current recommended fluoridation level of 0.7 mg/L to 1.2 mg/L.

V. EPA's Proposed Order is Flawed in Multiple Respects

A. EPA Violated the Terms of the Conditional Registration Issued to Dow AgroSciences

The 2004 conditional registration issued by EPA for ProFume contained several conditions, including the following express reference to the then ongoing NRC review of data associated with national drinking water standards for fluoride ("NRC Report"):

> Understand that as part of the Office of Water's Six-Year Review of the existing fluoride MCL and SMCL, a subcommittee of the National Academy of Sciences' National Research Council's (NRC) Committee on Toxicology (COT) is currently reviewing toxicologic, epidemiologic, and clinical data, particularly data published since 1993, and exposure data on orally ingested fluoride from drinking water and other sources (*e.g.*, food, toothpaste, dental rinses). Subsequent to this review, the Office of Water will undertake an analysis to assess the adequacy of the current maximum contaminant level goal (MCLG) and secondary maximum contaminant level (SMCL) for fluoride. If the Office of Water determines that revisions to either the MCLG or the SMCL are required or if the Agency subsequently determines that dental fluorosis is an adverse health effect under the Federal Food, Drug, and Cosmetic Act, the Agency may undertake a re-evaluation of the adequacy of the tolerances established for sulfuryl fluoride and fluoride as a result of this or subsequent registration actions for this product.

See Notice of Conditional Pesticide Registration for ProFume Gas Fumigant at 6 (EPA Jan. 26, 2004) (hereafter "Conditional Registration").

Evident from these conditions of registration is that OPP knew, at the time it issued the Conditional Registration to Dow AgroSciences, that the NRC committee was conducting a fluoride-related data review. Indeed, the NRC committee was conducting its review at EPA's request as part of OWs six-year review of the existing fluoride maximum containment level goal ("MCLG") and secondary maximum contaminant level ("SMCL"). The NRC committee released its report on March 22, 2006.

Also evident from the above-referenced conditions of registration for ProFume is that EPA was fully prepared for the eventual receipt of the NRC Report. As set forth in the Conditional Registration, EPA planned to review the NRC Report after it was completed and, in fact, had established a two-step process by which the Agency would consider the report. The first step in this process, as set forth above, is that "[s]ubsequent to [NRC's] review, the Office of Water will undertake an analysis to assess the adequacy of the current maximum contaminant level goal (MCLG) and secondary maximum contaminant level (SMCL) for fluoride." *Id*. Since the NRC Report has been completed, it is up to the Office of Water to conduct its analysis. However, the last public statement from the Agency with respect to the adequacy of the existing Safe Drinking Water Act levels for fluoride, published in January 2011, said that "[T]he Agency has not yet made a decision about revising the drinking water standard for fluoride. The Agency will review the new risk assessment of fluoride along with other information (*e.g.*, analytical methods and treatment feasibility, occurrence and exposure, etc.) to determine whether it is appropriate to revise the drinking water standard." *Questions and Answers on Fluoride*, U.S. Environmental Protection Agency, Office of Water, EPA 815-F-11-001 (January 2011). Thus, it is unclear when, or if, EPA will comply with the first step of the process that the Agency established in its Conditional Registration for ProFume.

The second part of the process established by EPA for the review of the NRC Report calls for OPP to consider a re-evaluation of the adequacy of the tolerances for sulfuryl fluoride and the fluoride anion if (i) OW, as part of its analysis, concludes that the MCLG or the SMCL for fluoride in drinking water should be revised or (ii) the EPA *subsequently* concludes that dental fluorosis is an adverse health effect under the FFDCA. (emphasis added). The term "subsequently" as it appears in this portion of the Conditional Registration of ProFume is not

entirely clear. However, Dow AgroSciences submits that it means that the Agency's possible consideration of whether dental fluorosis is an adverse health effect was to take place subsequent to OW's analysis of the NRC Report and determination of whether revisions to either the MCLG or the SMCL are required. This interpretation of the chronology of consideration is based on the facts that OW is the logical place to initially consider possible revisions to the drinking water standard and the NRC review was done as part of OW's six-year review. Moreover, "adverse health effect" is not a term defined in either FIFRA or FFDCA. It is, however, an important component of the Safe Drinking Water Act ("SDWA"), which requires the EPA, and more specifically OW, to establish MCLGs and other regulations for drinking water contaminants that "may have an adverse effect on the health of persons." 42 U.S.C. § 300 g-1(b)(1)(A)(i). This connection between adverse effects on health and SDWA makes it all the more appropriate for OW to be the initial evaluator of the NRC Report.

Clear from the foregoing discussion of the Conditional Registration for ProFume is that EPA had a process in place, promised to Dow AgroSciences, for determining what actions would be taken as a result of the NRC Report. That process first required OW's consideration of the NRC Report to determine whether changes were warranted to either the MCLG or the SMCL for fluoride. That process should have preceded (and may well have influenced) the determination of a new RfD for fluoride. Indeed, in the event that OW ultimately does not agree with the data reviewed by the NRC committee or the committee's assessment of that data, and therefore does not agree with the conclusions of the NRC Report, then the current Safe Drinking Water Act exposure levels for fluoride would likely be sustained and most, if not all, of the objections to the tolerances issued for sulfuryl fluoride would become moot. At a minimum, OW's review would

have impacted the determination of a new RfD, and may have even left in place the MCLG as the basis for the RfD.[5]

EPA's abandonment of a process established by the Agency years ago as a condition of registration and relied upon by the registrant and users of sulfuryl fluoride and the scientific community is arbitrary and fundamentally unfair. Moreover, by issuing the Proposed Order – essentially a notice to cancel the registration of ProFume's food uses under FIFRA – without abiding by the terms of the registration that it issued to Dow AgroSciences, EPA is contemplating an action that would violate the due process rights of Dow AgroSciences. *See, e.g., Indus. Safety Equip. Ass'n. v. EPA*, 656 F. Supp. 852, 856 (D.D.C. 1987), *aff'd*, 837 F.2d 1115 (D.C. Cir. 1988) ("It is well settled that an agency license can create a protectible [sic] property interest, such that it cannot be revoked without due process of law."); *see also Reckitt Benckiser, Inc. v. Jackson*, 762 F. Supp. 2d 34, 45 (D.D.C. 2011) ("A FIFRA registration is essentially a license to sell and distribute pesticide products in accordance with the terms of the registration and the statute."). By failing to abide by the terms of the license it issued to Dow AgroSciences, EPA, through its contemplated action, also would violate the Administrative Procedure Act because the proposed action is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); *Reckitt Benckiser*, 762 F. Supp. 2d at 41.

[5] Even if the Agency, after an analysis by OW of the NRC Report, determined that the MCLG for fluoride does need to be lowered, appropriate administrative and procedural steps would be required to first determine the new MCLG. Then and only then, would it be appropriate to reassess the appropriate tolerance levels for sulfuryl fluoride and other fluoride compounds (40 C.F.R. § 180.145) based on a new risk assessment that accounts for a new MCLG.

B. EPA Failed to Use the Best Available Data and Apply Sound Scientific Principles in Reaching its Determination of a New RfD for Fluoride

EPA states in the Proposed Order that the OW Reassessment of fluoride risk was subjected to an external peer review by scientific experts. Specifically, "[b]oth parts [dose-response analysis and exposure and relative source contribution analysis] of the OW risk assessment were subjected to an external peer review by scientific experts." Proposed Order at 3434. No information about the external process has been publicly disclosed, nor does it appear that the review process was open for participation from stakeholders. It is imperative that this review be open and transparent and that stakeholders are provided an opportunity to participate as well as understand the peer review process.

EPA relied on a 70-year-old study (Dean, 1942) for the determination of the new fluoride RfD despite several flaws in the study, as noted in its *Fluoride: Dose-Response Analysis for Non-Cancer Effects* (at 87, 92-93, 104):

- Only white children were included in the survey
- Potential socio-economic and cultural differences between the samples populations were not documented
- Cultural and physiological differences make extrapolation between children in the Dean study and today's children more complicated
- Lack of information on dietary fluoride intake and drinking water intake
- Relatively small numbers of children examined in high-fluoride communities

Furthermore, OW indicated a preference for older studies because determination of fluoride exposure in more contemporary studies is made more difficult due to "the widespread use of fluoride-containing dentifrices and mouth rinses, the use of fluoride supplements in early childhood, and the potential presence of fluoride in processed foods and beverages (a result of the use of fluoridated water in the preparation of these products)." OW Reassessment at 9.

However, neither OW nor OPP included dentifrices (other than toothpaste), mouth rinses or supplements in early childhood as sources of exposure in their risk assessments. If these exposures are sufficient to impact the selection of data for determining the RfD, then they should also be sufficient to be included in the risk assessment. If, on the other hand, they are not sufficient to be included in the risk assessment, then they should not be used as justification for the use of a 70-year old study in the RfD determination. Therefore, data from contemporary studies should be thoroughly reviewed, and their impact on the dose-response models and RfD determination should be considered.

In establishing the new RfD, OW "chose" the value of 0.07 mg/kg/day as the contribution to exposure from drinking water. It is not clear what other values were considered and why they were rejected. Once again greater transparency is needed with respect to the Agency's decision-making process. OW recognized that other sources of fluoride would impact exposures and the dose-response observed in the Dean study and therefore estimated a contribution to fluoride exposure from solid food at the time of the Dean study of 0.01 mg/kg/day. However, contribution from beverages (other than drinking water) was not considered. Using these two sources of exposure, OW calculated the new RfD to be 0.08 mg/kg/day. However, EPA's current assessment indicates fluoride exposures of 0.0054-0.029 mg/kg/day from background levels in food and 0.0075-0.026 mg/kg/day from commercial beverages, with total exposures from these sources to be 0.014-0.042 mg/kg/day, *i.e,* generally exceeding the 0.01 mg/kg/day for background food accounted for in the new RfD by OW. OPP Revised Assessment at 15 (Table 6) and 21 (Table 9). Whereas contemporary fluoridation of water systems would tend to increase potential fluoride concentrations in some commercial beverages (compared to the 1940s), background levels in food arise from fluoride's natural occurrence in the environment and would

therefore not be expected to increase as a result of fluoridation of drinking water. Therefore, it would appear that EPA's contribution of 0.01 mg/kg/day from solid food is an underestimate and should be increased, perhaps as high as 0.03-0.04 mg/kg/day. EPA's failure to adequately account for all fluoride exposures in the populations considered in the Dean study has resulted in a new RfD that may be lower than necessary to protect human health and which therefore makes it increasingly difficult to find a balance between prevention of dental caries and prevention of severe dental fluorosis. It is paramount that fluoride exposures from background levels in food *and* commercial beverages in the 1940s be accurately considered in the determination of the new RfD.

OW and OPP included soil as a source of fluoride in their aggregate exposure assessments; but it does not appear that soil was considered in the determination of the RfD. Although soil exposure is low compared to other sources, EPA's estimates indicate exposures (0.0003 to 0.0029 mg/kg/day) that are not insignificant compared to the 0.01 mg/kg/day contributed by solid food sources that EPA included in calculating the RfD to be 0.08 mg/kg/day. The role of potential soil exposures in setting the RfD should be re-evaluated.

EPA indicates that Benchmark Dose ("BMD") is the preferred approach for deriving a Point of Departure for use in risk assessment, as compared to the historically used approach of using No Observed Adverse Effect Levels ("NOAELs") or Lowest Observed Adverse Effect Levels ("LOAELs"). However, it is paramount that the data used in the BMD approach is of sufficient quality and appropriate for use in the assessment. Without the proper open forum to evaluate and discuss these data, such a determination cannot be made. Furthermore, was it scientifically reasonable and was EPA scientifically justified in changing the basis for the determination of RfD from the MCLG to the Dean study, especially in light of the deficiencies

EPA found in the Dean study? MCLGs are health goals which should be set at levels at which the Administrator can determine "no known or anticipated adverse effects on the health of persons occur and which allows [for] an adequate margin of safety." 42 U.S.C. § 300g-1(b)(4)(A). As such, one is led to question how the RfD can be revised without triggering a re-evaluation of the MCLG.

In determining the new RfD, the adverse health effect was changed from skeletal fluorosis to severe dental fluorosis. EPA's rationale for departing from its previous stance that severe dental fluorosis was not an adverse health effect is a matter which requires evaluation by a review panel and consideration in an open forum. In addition, did the ADA have input into this discussion and change in position? It would be critical to ensure that they are party to such discussions and evaluations.

The foregoing issues demonstrate why peer review of the Proposed Order and the underlying exposure and risk assessments is critical from the EPA's Scientific Advisory Panel ("SAP"). As discussed below, FIFRA demands an independent SAP review of proposed EPA actions that would result in the cancellation of a pesticide registration.

C. EPA Failed to Comply with FIFRA in Issuing the Proposed Order

FIFRA Sections 6 and 25 require the Agency to obtain the comments of (i) the Secretary of Agriculture, (ii) the Secretary of Health and Human Services, and (iii) an independent Scientific Advisory Panel ("SAP") regarding any proposed cancellation of the ProFume food-

related registrations that would result from the actions set forth in the Proposed Order. EPA has thus far failed to meet these obligations and, accordingly, has not complied with FIFRA.[6]

Pursuant to the Proposed Order, all tolerances for residues that might result in food as a result of the use of ProFume would be terminated by the conclusion of the sequential implementation period. In the absence of approved tolerances, a food containing any detectable residue of sulfuryl fluoride or its breakdown products would be considered adulterated under FFDCA Section 402, would be subject to enforcement action by FDA, and could not be legally moved in interstate commerce. Moreover, the termination of tolerances that support the food-related uses of ProFume for the reasons stated in the Proposed Order would require EPA to take action to cancel the underlying FIFRA registered uses and make it a violation of federal law to sell or distribute ProFume for any of those food-related uses. *See, e.g.*, FIFRA Sections 2(bb) and 12(a)(1)(A).

In enacting the Food Quality Protection Act of 1996 ("FQPA"), Congress went to great lengths to harmonize the relevant amendments to the FFDCA and FIFRA. As stated by EPA, "Congress integrated action under the two statutes by requiring that the safety standard under FFDCA be used as a criterion in FIFRA registration actions as to pesticide uses which result in

[6] By way of a letter to the Administrator, Dow AgroSciences requested that EPA comply with these FIFRA requirements. Letter from Stanley H. Abramson and Donald C. McLean to Lisa Perez Jackson, Administrator, U.S. EPA (February 18, 2011) ("February 18 Letter"). The Agency has thus far failed to comply. Dow AgroSciences also requested through its February 18 letter that the Agency conduct the hearing required under FIFRA Section 6(b) once it had secured the aforementioned comments and made them publicly available. EPA denied Dow AgroSciences' request for a hearing. Letter from Stephen A. Owens, Assistant Administrator, U.S. EPA, to Stanley H. Abramson and Donald C. McLean (May 13, 2011) ("EPA's May 13 Letter"). By way of these Comments, Dow AgroSciences renews its request that EPA obtain the input required under FIFRA from the Secretary of Agriculture, Secretary of Health and Human Services and an independent SAP and make these comments publicly available. Dow AgroSciences also reserves all of its rights with respect to EPA's denial of its request for a hearing under FIFRA.

dietary risk from residues in or on food, (7 U.S.C. 136(bb)), and directing EPA to coordinate, to the extent practicable, revocations of tolerances with pesticide cancellations under FIFRA. (21 U.S.C. § 346a(l)(1)).”[7] Proposed Order at 3424. Most importantly, in spite of the numerous amendments made by FQPA to both FIFRA and FFDCA, Congress never so much as suggested that it intended to diminish in any way the rights and protections afforded to adversely affected parties or the obligations imposed upon EPA under FIFRA since 1972.

EPA states in its May 13 Letter denying Dow AgroSciences' request for a hearing under FIFRA that there is no "statutory provision subordinating action under the FFDCA to the FIFRA cancellation process." EPA's May 13 Letter at 4. EPA misses the point. In FQPA, Congress requires *coordination* between FFDCA and FIFRA. FQPA's legislative history makes this clear: "The Committee expects EPA to coordinate and harmonize its actions under FIFRA and the FFDCA in a careful, consistent manner *which is fair to all interested parties*." H.R. Rep. No. 104-669, pt. 2, at 51 (1996) (emphasis added). "Coordination" does not mean interpreting FIFRA into non-existence and doing so is certainly *not* "fair to all interested parties"; yet this is exactly what EPA has done in denying a hearing to Dow AgroSciences and otherwise failing to

[7] The statute actually requires coordination of tolerance actions "[t]o the extent practicable … with any *related necessary* action" under FIFRA. FFDCA Section 408(l)(1) (emphasis supplied). EPA concedes that this coordination provision is relevant to the tolerance withdrawal actions set out in the Proposed Order. Proposed Order at 3424. In that regard, the withdrawal of the sulfuryl fluoride and fluoride tolerances under FFDCA as set out in the Proposed Order is clearly "related" to cancellation of the underlying food-related uses of ProFume under FIFRA that would result from those tolerance actions. Indeed, EPA expressly linked the existence of those tolerances to ProFume's registration in the terms of the ProFume registration itself. In addition, FIFRA Section 6(b) makes clear that compliance with its cancellation procedures is mandatory and therefore "necessary". Finally, no basis has been identified in the Agency's Proposed Order or elsewhere to make compliance with required FIFRA cancellation procedures impracticable. This is especially true in light of the facts that (i) the Proposed Order sets forth a sequential implementation period and (ii) there is no imminent health hazard that would be cured by termination of the tolerances at issue and cancellation of the underlying registered uses.

comply with FIFRA Sections 6 and 25. There can be little doubt that EPA's current intention is to ultimately remove ProFume's food uses from the market, effectively cancelling the registrations for those uses without following the regulatory procedures provided in FIFRA Section 6. EPA is not authorized to do this. See *Reckitt Benckiser, Inc. v. Jackson*, 762 F. Supp. 2d at 42-43. ("Section 6 is the 'cancellation' section within FIFRA. It establishes a detailed, multi-step process that EPA *must* follow when it wants to cancel or suspend a registration…. The process imposes certain obligations on EPA before it may issue a notice of intent to cancel … and it entitles the registrant to notice, a hearing and other procedural protections before EPA can make a final decision on cancellation.") (Citations omitted.)

Because EPA's termination of the tolerances as set forth in the Proposed Order would require the Agency to take action to cancel the registration for all food-related uses of ProFume and force Dow AgroSciences to remove all such uses from its ProFume label rather than have its customers face federal enforcement action, the Proposed Order is, in effect, a notice of intent to cancel Dow AgroSciences' food-use registrations for ProFume. The mere fact that EPA has not issued what it calls a "formal Notice of Intent to Cancel under FIFRA" for ProFume can hardly be used to justify the Agency's failure to follow FIFRA's procedural mandates. EPA's May 13 Letter at 4. Accordingly, EPA must follow the administrative procedures for cancellation of registrations required by FIFRA and accord Dow AgroSciences its due process rights thereunder. The fact that these cancellations would result from the second prong (*i.e.*, unsafe residue) of the FIFRA registration standard rather than the first prong (*i.e.*, unreasonable risk) should have no bearing on the due process rights accorded to Dow AgroSciences and the obligations imposed on the Agency under FIFRA Sections 6 and 25.

Specifically, under FIFRA Section 6(b), before making public its notice to cancel a pesticide registration, EPA is required to "include among those factors to be taken into account the impact of the action proposed in such notice on production and prices of agricultural commodities, retail food prices, and otherwise on the agricultural economy." FIFRA also requires EPA to provide the Secretary of Agriculture with notice of the proposed action that would result in registration cancellation and a copy of the EPA's analysis of the impact on the agricultural economy. EPA is required to publish in the Federal Register any input on the proposed action from the Secretary of Agriculture. *Id.* Similarly, EPA is required to consult with the Secretary of Health and Human Services with respect to the proposed action, and publish the Secretary's comments. *Id.* Moreover, EPA is required to present its case for the proposed action to an independent Scientific Advisory Panel ("SAP") and the SAP's comments and recommendations are to be published in the Federal Register.[8] FIFRA Section 25(d).[9]

Finally, FIFRA Section 6(b) allows a "person adversely affected by" the proposed action that would result in the cancellation of a registration to request a hearing. As the registrant of ProFume, Dow AgroSciences is clearly a person adversely affected by the threatened cancellation of ProFume's food uses and is thus entitled to a hearing pursuant to FIFRA. In order to ensure that a hearing would be efficient, informed and just, EPA should follow the required procedures outlined above with respect to consultation regarding the proposed cancellation of ProFume's food uses with the Secretaries of Agriculture and Health and Human Services and an independent SAP and make public all comments resulting from their review

[8] Pursuant to FIFRA Sections 6 and 25, all of these procedures should have been followed *prior to* issuance of the Proposed Order.

[9] Having sought and failed to obtain its hearing rights under FIFRA, Dow AgroSciences specifically reserves and does not waive any of its rights to challenge EPA's failure to comply with the FIFRA cancellation procedures prior to issuance of the Proposed Order.

before a hearing took place. A hearing should address all of the issues raised in these comments and those of other stakeholders; at a minimum, a hearing is necessary for a full examination of the benefits of ProFume, the impact on stakeholders of its cancellation, and the appropriateness of the sequential tolerance termination schedule set forth in the Proposed Order.[10]

D. EPA Failed to Consider Reasonable and Appropriate Alternatives to the Termination of the Sulfuryl Fluoride Tolerances and Cancellation of the Underlying ProFume Uses

Rather than seek a solution concerning sulfuryl fluoride that makes sense from national public policy and public health perspectives, EPA has chosen to proceed down a path that would eliminate significant public health benefits and potentially increase health risks. There are, however, other administrative and legal options that allow for a different conclusion than those contained in the Proposed Order. As set forth below, these reasonable alternatives include: (i) consistent application of the *de minimis* standard to fluoride tolerance decisions; (ii) recognition that all significant fluoride exposures result from non-pesticide sources that are subject to regulation under statutes other than FFDCA Section 408, which must be considered but need not be included in EPA's aggregate exposure assessment; (iii) compliance with the statutory requirement to base tolerance decisions on "reliable information" and "anticipated" exposure levels; (iv) adoption of a policy by EPA that allows the Administrator, under extraordinary circumstances including *de minimis* exposure and risk from the use of a pesticide, and taking into account risk, benefit, and public policy considerations, to make a determination that tolerances that might otherwise not meet the Agency's current aggregate exposure policy are permissible; and (v) revocation of the fluoride tolerances as unenforceable while maintaining tolerances for sulfuryl fluoride that are already in place.

[10] As discussed earlier, EPA has rejected Dow AgroSciences' request for a hearing pursuant to FIFRA, and that issue is preserved for appeal.

1. EPA Should Apply the *De Minimis* Standard Consistently to Tolerance Decisions Under FFDCA Section 408

EPA has the inherent authority to determine that exposure to a particular chemical is so negligible – *de minimis* – as to present no public health or safety concerns and to approve continued use of the chemical on that basis. There is no dispute that any fluoride exposure that might result from the use of sulfuryl fluoride and any risk that might result from that exposure are *de minimis*. Indeed, as set forth below, sulfuryl fluoride presents a classic legal *de minimis* situation.

In 1996, FQPA amended the pesticide tolerance provisions in FFDCA Section 408 by requiring EPA to use the same safety standard used by FDA since 1958 for food additives, commonly referred to as the "reasonable certainty of no harm" safety standard.[11] *See* 21 C.F.R. § 170.3(i). The FQPA defined "safe" to mean that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." Section 408(b)(2)(A)(ii).

Pursuant to FFDCA Section 408(b)(2)(A)(i), EPA may establish or leave in effect a tolerance for a pesticide chemical residue in or on food only if the Administrator determines that the tolerance is "safe" based on the "reasonable certainty of no harm" standard in Section

[11] Based on the legislative history of the food additive provisions in FFDCA Section 409, the FDA defines the term "safe" to mean that "there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use." 21 C.F.R. § 170.3(i). The definition goes on to provide, again based on the legislative history, that it is "impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance." *Id*. One of the factors to be considered is the "cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet." Pesticide residues in processed foods were covered by Section 409 until they were moved to Section 408 with the enactment of FQPA in 1996.

408(b)(2)(A)(ii). There is nothing in the "reasonable certainty of no harm standard" that limits EPA's ability to recognize "*de minimis*" exposure and risk and to act in the public interest on that basis when making decisions to establish or maintain tolerances for pesticide chemical residues. Sulfuryl fluoride presents just such a situation.

EPA has already recognized that exposure to fluoride from sulfuryl fluoride is *de minimis*, referring to those exposures as "tiny" and minimal":

> Use of sulfuryl fluoride is responsible for a tiny fraction of aggregate fluoride exposure.

Proposed Order at 3443.

> Use of sulfuryl fluoride results in a minimal contribution to fluoride exposure. Elimination of sulfuryl fluoride does not solve, or even significantly decrease, the fluoride aggregate exposure problems identified earlier.

Id. at 3446. And the Agency has concluded that any risk that might result from those tiny exposures is also *de minimis*:

> Given the aggregate level of fluoride exposure, termination of the use of sulfuryl fluoride would not change the fact that aggregate fluoride levels would still exceed the safe level for highly-exposed subpopulations.

Id. at 3443.

Federal courts have long held that regulatory agencies have the authority to avoid the literal application of a statutory provision in *de minimis* situations. In *Monsanto Co. v. Kennedy*, 613 F.2d 947 (D.C. Cir. 1979), the U.S. Court of Appeals for the District of Columbia Circuit reviewed a FDA decision regarding whether a particular chemical – acrylonitrile copolymers used in beverage containers – were food additives and whether, as food additives, they were safe pursuant to the "reasonable certainty of no harm" standard in FFDCA Section 409. With respect

to the safety issue, the Court of Appeals held that the FDA had significant discretion in a *de minimis* situation:

> Thus, the Commissioner may determine based on the evidence before him that the level of migration into food of a particular chemical is so negligible as to present no public health or safety concerns, even to assure a wide margin of safety. This authority derives from the administrative discretion, inherent in the statutory scheme, to deal appropriately with *De minimis* situations…. [The Commissioner's] finding on the safety element will be open to reexamination on remand at the discretion of the Commissioner. He would have latitude to consider whether [the chemical] is generally recognized as safe at concentrations below a certain threshold ….

Id. at 955-956. *See also Ober v. Whitman*, 243 F.3d 1190, 1193, 1198 (9th Cir. 2001) ("The [Clean Air] Act makes no explicit provision for a '*de minimis*' exception …. We hold that EPA has the power to make *de minimis* exemptions to controls under the 1990 amendments to the Clean Air Act."); *Alabama Power Co. v. Costle*, 636 F.2d 323, 360 (D.C. Cir. 1979) ("[C]ategorical exemptions may also be permissible as an exercise of agency power, inherent in most statutory schemes, to overlook circumstances that in context may fairly be considered *de minimis*. It is commonplace, of course, that the law does not concern itself with trifling matters, and this principle has often found application in the administrative context. Courts should be reluctant to apply the literal terms of a statute to mandate pointless expenditures of effort."). (Citations omitted).

FFDCA Section 408 does not define the end points that underlie the EPA's determinations of what is "safe" and certainly does not do so in the context of a non-carcinogen. When setting tolerances, EPA is required by Section 408(b)(2)(D) to consider aggregate exposure and several other elements, "among other relevant factors," which must certainly include the relative contributions of the pesticide chemical residue to overall exposure. As noted above, within the FDA context of a "food additive," the Commissioner has authority to

determine that possible exposures are *de minimis* and therefore meet the definition of "safe." The results should be no different in the EPA context for safety determinations for pesticide tolerances. This is especially true for ProFume since:

- There are significant public health benefits to the continued use of sulfuryl fluoride as noted in these comments and recognized by EPA in its Proposed Order;
- EPA has in essence, as noted above, already introduced the *de minimis* issue with respect to sulfuryl fluoride;
- Sulfuryl fluoride is a non-carcinogen (and, therefore, there is no requirement under FFDCA that it be treated as a non-threshold chemical); and
- There does not appear to be anything prohibiting EPA from making a *de minimis* determination.[12]

OPP has already exercised its discretion to exclude certain fluoride exposures that the Agency determined to be "insignificant" from its aggregate risk assessment:

> Although people are also potentially exposed to fluoride from fluoride in ambient air, fluoride dental treatments, and pharmaceuticals, among other things, OW concluded that these sources of exposure are <u>insignificant compared to other sources of fluoride exposure</u>. Accordingly, OPP is not including such exposures in its aggregate assessment.

Proposed Order at 3440 (emphasis added). This approach is consistent with the *de minimis* precedents cited above and, as to the FDA-regulated uses, the precedent established by EPA and FDA for addressing exposure from other chemicals that have both pesticidal and pharmaceutical uses.

Further analysis suggests rather strongly, however, that while exposure from fluoride dental treatments and pharmaceuticals should be considered *de minimis*, the manner in which

[12] Indeed, in a recent proposal to extend time-limited interim tolerances for the organophosphate insecticide tetrachlorvinphos, the Agency appears to have applied the *de minimis* standard by proposing to maintain several individual tolerances which "make, at most, only a negligible contribution to the overall risks" from organophosphate pesticides. 76 Fed. Reg. 33,184, 33,186 (June 8, 2011).

exposure from ambient air should be treated requires further analysis and independent peer review.

In the EPA's 2004 assessment, OPP estimated air exposures to fluoride of 0.0006 to 0.0020 mg/kg/day. Adjusting by body weights for the various subpopulations, these exposure estimates correspond to 13.3-42 µg/day. In 2006, the NRC Report identified exposures from air of 2-4 µg/day in *rural* areas and 20-40 µg/day in *urban* areas. The NRC Report's urban air estimate of 20-40 µg/day is comparable to OPP's air estimate of 13.3-42 µg/day.

The relative source contribution analysis ("RSC") prepared as part of the OW Reassessment mentions both the 2-4 µg/day rural range and 20-40 µg/day urban range for fluoride exposures via air. But the RSC then omits the urban range in summation when it indicates that the numbers are consistent with older monitoring data and fails to mention that the 2-4 µg/day range is for rural exposure only. RSC at 84, 88. The OPP Revised Assessment, in turn, quotes only the range of 2-4 µg/day and fails to mention that it is for rural populations only. OPP Revised Assessment at 16. This lower range was indicated as the reason why OPP chose not to include fluoride exposures via air in its 2011 aggregate exposure assessment.

The OPP Revised Assessment estimates a range of 0.0011 to 0.0030 mg/kg/day for fluoride exposure resulting from the use of sulfuryl fluoride. This estimate is actually on the same order, and only slightly higher, than OPP's original ambient air estimate from 2004 of 0.0006 to 0.0020 mg/kg/day.[13] Accordingly, OPP was in error when it excluded ambient air as

[13] Compare *U.S. EPA Human Health Risk Assessment for Sulfuryl Fluoride and Fluoride Anion Addressing the Section 3 Registration of Sulfuryl Fluoride as a Fumigant for Foods and Food Processing Facilities* at 26 (January 18, 2006) with *U.S. EPA Sulfuryl Fluoride – Revised Human Health Risk Assessment for Fluoride to Incorporate New Hazard and Exposure Information* at 10 (January 7, 2011)

a source from its revised aggregate exposure assessment but left in exposures attributable to the use of sulfuryl fluoride. Dow AgroSciences submits that both of these sources should be excluded as *de minimis* from the aggregate exposure assessment.[14]

In light of all of these circumstances, it would be entirely appropriate for EPA to use its discretion to determine that exposure to fluoride as a result of the food uses of sulfuryl fluoride is so negligible as to present no public health or safety concerns and to maintain the current tolerances established for food-related uses of sulfuryl fluoride. Indeed, it would be erroneous for the Agency not to make a *de minimis* determination as to sulfuryl fluoride given its insignificant exposure profile, the adverse impacts on public health that would follow its elimination, and the *de minimis* treatment that EPA has afforded sources of similar amounts of fluoride exposure. *See, e.g., Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). (Under the Administrative Procedure Act, "an agency rule would be arbitrary and capricious if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise."). By way of these comments, Dow AgroSciences requests that the Agency make the *de minimis* determination that it is authorized to make with respect to fluoride residues resulting from the use of sulfuryl fluoride.

[14] If EPA were to conclude, following independent peer review, that both sources should be included in the aggregate exposure assessment, then exposure to fluoride resulting from the use of sulfuryl fluoride should still be treated as *de minimis* for purposes of the Section 408 safety finding because it is dwarfed by the exposure from all of the remaining, non-pesticide sources of exposure to fluoride.

2. EPA Should Recognize that All Significant Human Exposure to Fluoride Results from Sources Other Than Sulfuryl Fluoride and is Subject to Regulation under Statutes Other Than FFDCA Section 408

EPA's Proposed Order is based on an aggregate exposure assessment for fluoride residues from many sources, the least of which results from the current and anticipated uses of sulfuryl fluoride. The other sources of human exposure to fluoride included in the Proposed Order include drinking water and beverages, background levels in food, toothpaste and soil and dust.

a. Required elements of an aggregate exposure assessment versus consideration of other relevant factors.

Under Section 408, EPA must consider exposure to fluoride in drinking water and other non-pesticidal sources of fluoride when making its safety determinations under Section 408 for pesticide chemical residues, but need not include those non-pesticidal sources in its Section 408 aggregate exposure assessment. This is particularly the case where other statutory provisions are available to address those exposures.

EPA's safety determination for pesticide chemical residues must include aggregate exposure to the pesticide chemical residue (*i.e.*, by definition, residues in food), including all anticipated dietary exposures (*i.e.*, to the pesticide chemical residue) and all other exposures (*i.e.*, non-dietary, non-occupational exposures to the pesticide chemical residue) for which there is reliable information. FFDCA Section 408(b)(2)(A)(ii). By definition, fluoride naturally present in or added to drinking water is not a "pesticide chemical residue". Under the provisions of the FFDCA, as amended by FQPA, in order for EPA to determine aggregate exposure to a pesticide chemical residue, the exposure must relate solely to either (a) the pesticide chemical itself, or (b) another added substance that is present on or in the commodity or food primarily as a result of

the metabolism or other degradation of the pesticide chemical. FFDCA Section 201(q)(2). There is no statutory mandate to include any other substance, regardless of its similarity to the pesticide chemical residue, in the aggregate exposure assessment for the "pesticide chemical residue."

The need to consider non-pesticidal sources of exposure is found in a separate provision of Section 408 which requires EPA to:

> consider, among other relevant factors ... available information concerning the aggregate exposure levels of consumers (and major identifiable subgroups of consumers) to the pesticide chemical residue and to other related substances, including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other non-occupational sources.

FFDCA Section 408(b)(2)(D)(emphasis supplied).

It is instructive that the statutory reference to "other related substances" is not new. In particular, in setting tolerances under the pre-FQPA version of Section 408, FDA and ultimately EPA were required to consider other ways in which the consumer might be affected "by the same pesticide chemical or by other related substances." *See* 21 U.S.C. 346a(b)(2) (1994), *amended by* FQPA. This language applied to EPA once the Agency was given authority to set pesticide tolerances in 1970. *See* Reorganization Plan No. 3 of 1970, 84 Stat. 2086. Prior to that time, FDA had the responsibility.

In 1954, Congress passed the Pesticide Residues Amendment, Pub. L. No. 518, 68 Stat. 511, which added section 408 to the FFDCA and provided FDA with explicit authority to set levels for pesticide residues in food years before EPA was ever established. In the only apparent example given for "other related substances" in the legislative history of Section 408, the then

FDA Commissioner, Charles W. Crawford, while testifying on the 1954 Act, made reference to the possibility that two insecticides might react together in a way that would adversely affect the consumer. Commissioner Crawford was responding to a question from Representative Mack regarding the extent to which "the combination of two or more of these chemical residues resulting from the eating of the food might produce for some, a highly toxic condition." Hearing Before the Committee on Interstate and Foreign Commerce on H.R. 7125, U.S. House of Representatives, 83rd Congress, 2d Sess. (Mar. 8, 1954), at 39. The Commissioner made specific reference to the then-proposed provision of section 408 (ultimately adopted) that would require FDA to give appropriate consideration "to the other ways in which the consumer may be affected by the same pesticide chemical or by other related substances that are poisonous or deleterious," and interpreted the provision as follows:

> In other words, the Secretary must take into account the overall load of these various toxic substances the consumer is liable to get.
>
> Now, if there should be in the group of things here, <u>which are to be used for insecticidal purposes</u>, two things which might react to each other to produce more toxic conditions that too would have to be taken into consideration and dealt with in the tolerance for those two substances, and the amount that should be restricted to a point so small that the consumer would not be adversely affected by it.

Id. (emphasis added).

Moreover, even if EPA were, *arguendo*, required to include exposure from non-pesticidal sources in its aggregate exposure assessment, it would be incumbent upon the Agency to determine if "aggregate exposure to the pesticide chemical residue" would have any meaningful impact on the end point of concern. Section 408(b)(2)(A)(ii). In the case of sulfuryl fluoride, if aggregate exposure to fluoride residues resulting from the use of sulfuryl fluoride caused the "risk cup" to overflow, then EPA might well conclude that it could not make the requisite safety

finding for the sulfuryl fluoride and associated fluoride tolerances. Here, as the Proposed Order makes abundantly clear, the contribution made by sulfuryl fluoride to overall fluoride exposure is "tiny", "minimal" and of no meaningful impact. Proposed Order at 3443, 3446.

b. Fluoride from drinking water sources.

As previously discussed, the vast majority of exposure to fluoride comes from drinking water. Public water supplies are regulated by EPA under the Safe Drinking Water Act and include water that is artificially fluoridated for public health reasons (i.e., prevention of cavities) and water that is naturally fluoridated. OW has yet to determine whether revisions to either the MCLG or the SMCL for fluoride are required based upon its analysis of the NRC Report.

All naturally occurring sources of fluoride in food (e.g., raw agricultural commodities irrigated with water with high background levels of fluoride and foods processed with water containing high background levels of fluoride) are covered under FFDCA Section 402(a)(1), which provides that a substance that would otherwise render food adulterated but is not an "added substance," will not render the food adulterated (and subject to FDA enforcement action) if the quantity of such "naturally occurring" substance in such food does not "ordinarily render it injurious to health." FFDCA Section 402(a)(1).

Fluoride residues in food that are not naturally occurring, but are unavoidable (i.e., "cannot be avoided by good manufacturing practice"), are subject to regulation under FFDCA Section 406. As an example, FDA is authorized to establish a Section 406 tolerance for fluoride that is sufficient for the protection of the public health. 21 C.F.R. § 109.6. Such a tolerance could cover the unavoidable residue that is likely to result from use of fluoridated water (*i.e.*, food processed with water to which fluoride has been added).

In certain cases, FDA is authorized to establish a Section 406 regulatory limit (or possibly an action level), rather than a tolerance. This would be intended to cover unavoidable fluoride exposures that result from sources other than the pesticidal uses of sulfuryl fluoride. 21 C.F.R. § 109.6. Such a regulatory limit would be based on (i) lack of sufficient information to establish a tolerance under Section 406 and/or (ii) technical changes reasonably possible that may affect the appropriateness of a tolerance (*e.g.*, anticipated remediation of drinking water sources using available technologies in communities with high background levels). The regulatory limit would be set based on the adulteration standard in Section 402(a)(1).

The requirement to conduct aggregate exposure assessments is one of the key elements of the pesticide tolerance process established under Section 408, as amended by the FQPA. The plain language of the FQPA simply confirms the logical conclusion that tolerances should be based on exposures to pesticide chemical residues and, in appropriate instances, related pesticidal substances. It is unnecessarily strained and counterintuitive to set tolerances for pesticides in or on food by looking at the therapeutic use of chemically related substances in humans. These uses would include fluoride added to public water supplies to prevent dental caries and various dental health products and antibiotics regulated by FDA as drugs under FFDCA Section 505. Indeed, an approach by EPA that would aggregate such uses with the use of a pesticide may well be *ultra vires*, and is most certainly unnecessary to achieving the public health objectives set forth by Congress with respect to the regulation of pesticide residues in food.

c. Fluoride from pharmaceutical products.

The EPA has taken a cautious and measured approach with respect to FDA-regulated pharmaceutical products in its FIFRA reregistration decisions for various chemically-related pesticides. Under FFDCA Section 505, FDA reviews human drugs for safety and effectiveness

and may approve a drug notwithstanding the possibility that some users may experience adverse side effects. EPA has taken the position as indicated through previous actions discussed below that, for purposes of the Section 408 aggregate exposure assessment, it is not compelled to treat a pharmaceutical user the same as a non-user, or to assume that combined exposures to pesticide and pharmaceutical residues that lead to a physiological effect in the user constitute "harm" under the meaning of Section 408.

Rather, EPA has determined that the appropriate way to consider the pharmaceutical use of a compound in the Agency's tolerance risk assessment is to examine the impact that the additional non-occupational pesticide exposures would have to a pharmaceutical user exposed to a related (or, in some cases, the same) compound. Where the additional pesticide exposure has no more than a minimal impact on the pharmaceutical user, EPA has determined that it can make a "reasonable certainty of no harm" finding for the pesticide tolerances of that compound under Section 408 of the FFDCA. If, however, the potential impact on the pharmaceutical user as a result of the related exposure from pesticide use is more than minimal, then EPA would not be able to conclude that the pesticide chemical residues were safe, and would need to discuss with FDA appropriate measures to reduce exposure from one or both sources.

EPA confronted the potential relationship between pesticide exposure and drug exposure in the context of the reregistration of two insecticides – lindane and permethrin – that have both pesticidal and pharmaceutical uses. A brief discussion the Agency's position as set forth in the Reregistration Eligibility Decisions ("REDs") for these two pesticide chemicals follows.

In the case of lindane, the Agency acknowledged that, in light of the wording of Section 408(b)(2)(D)(vi), it was "considering whether the statute requires the Agency to include in its safety assessment those exposures resulting from the use of lindane in pharmaceutical products." RED for Lindane, Sept. 25, 2002. While EPA assessed the risks of exposure that might result from lindane's FDA-regulated drug uses, it went to great pains to avoid doing so as part of the FFDCA aggregate exposure assessment. As noted in the RED:

> EPA and FDA have worked together to examine the available data to assess the potential of lindane pharmaceuticals to cause adverse effects, sharing our assessments and commenting on the other agency's assessments. As discussed more fully later in this document, although the information for assessing risks is limited, the exposure and risk assessment indicates that the use of lindane for head lice control does not pose risks of concern. The limited information available on the scabies product, however, suggests that there is some possibility a portion of the patient population using lindane for scabies control may experience adverse effects. FDA has taken steps – including stronger warnings, clearer use directions, and other measures – to limit such potential adverse effects. Based on these additional steps, FDA has concluded that the therapeutic benefits of the lindane pharmaceutical products outweigh the limited potential to cause adverse effects in the patient population. Therefore, FDA regards these products as safe and effective for the purposes for which they were approved.

In a candid discussion of the underlying public policy and legal issues, the lindane RED set forth EPA's thinking as follows:

> The existence of pharmaceutical sources of exposure to lindane raise questions of public policy and statutory interpretation that have not been resolved. These questions include: whether "aggregate exposure" encompasses exposures resulting from the use of lindane in pharmaceutical products; and if so, whether there is any reasonable statutory interpretation that could avoid apparently questionable public policy results. EPA is particularly concerned that the statute be interpreted and applied in a manner that yields results that are protective of public health and consistent with common sense. If sec. 408 were interpreted to cover exposure from pharmaceutical uses, then EPA might never be able to establish new tolerances, or to leave existing tolerances in effect, for a substance that is used both as a pesticide and a pharmaceutical product, if the pharmaceutical product caused adverse effects in humans. This result could occur regardless of the level of risk posed by the exposures permitted under the tolerance(s) and their associated pesticide registrations, and even though the pharmaceutical product has been deemed "safe and effective." In other words, EPA would be concerned about relying on an interpretation of FFDCA sec. 408 that could compel regulatory actions which would have

> no impact on the major source of exposure, and where the source of such exposure is fully regulated and approved under a public health standard.

Id. (emphasis added). In the case of sulfuryl fluoride, the "major source[s] of exposure" are clearly non-pesticidal, i.e., drinking water and toothpaste, and these sources of exposure are "fully regulated and approved under a public health standard." Thus it is difficult to understand why the Agency has abandoned the common sense, public health concerns evidenced in the case of lindane and taken such a dramatically different approach in its aggregate exposure assessment for sulfuryl fluoride.

The RED for permethrin, issued in 2006, suggests a further refinement and solidification of the Agency's position on the relationship between pesticide exposure and drug exposure for purposes of section 408. RED for Permethrin, April 2006, at 27-28. In particular, the RED contains the following statement of position:

> EPA does not believe that, for purposes of the section 408 dietary risk assessment, it is compelled to treat a pharmaceutical patient the same as a non-patient, or to assume that combined exposures to pesticide and pharmaceutical residues that lead to a physiological effect in the patient constitutes "harm" under the meaning of section 408 of the FFDCA.
>
> Rather, EPA believes the appropriate way to consider the pharmaceutical use of permethrin in its risk assessment is to examine the impact that the additional non-occupational pesticide exposures would have to a pharmaceutical patient exposed to a related (or, in some cases, the same) compound. Where the additional pesticide exposure has not more than a minimal impact on the pharmaceutical patient, EPA could make a reasonable certainty of no harm finding for the pesticide tolerances of that compound under section 408 of the FFDCA. If the potential impact on the pharmaceutical user as a result of co-exposure from pesticide use is more than minimal, then EPA and FDA could discuss appropriate measures to reduce exposure from one or both sources. The Agency provided its findings with respect to permethrin to FDA in a letter dated August 10, 2005, which is available on the public docket (EPA-HQ-OPP-2004-0385).

Three additional examples will serve to further illustrate the application of this policy by EPA and FDA with respect to pesticides and their pharmaceutical counterparts.

Oxytetracycline. The EPA provided its findings with respect to the antimicrobial pesticide oxytetracycline to FDA in a letter dated May 24, 2006, which is available in the public docket (EPA-HQ-OPP-2005-0492). The EPA's pesticidal exposure estimates reflect the dietary dose from pesticidal uses of oxytetracycline that a user treated with a pharmaceutical (*i.e.*, antibiotic) oxytetracycline product would receive in a reasonable worst-case scenario. EPA's pesticide exposure assessment has taken into consideration the appropriate population, exposure route, and exposure duration for comparison with exposure to the pharmaceutical use of oxytetracycline. EPA estimates that the pharmaceutical oxytetracycline exposure a user is expected to receive from a typical therapeutic dose (25 mg/kg/day for children) is 50,000 to 200,000 times greater than the estimated dietary exposure from the pesticidal sources of oxytetracycline (0.000121 mg/kg/day to 0.000473 mg/kg/day). Therefore, because the pesticide exposure has no more than a minimal impact on the total dose to a pharmaceutical user, EPA has concluded that there is a reasonable certainty that the potential dietary pesticide exposure will result in no harm to a user being treated therapeutically with oxytetracycline. FDA is aware of EPA's conclusions regarding pesticide exposure in users receiving treatment with a pharmaceutical oxytetracycline drug product and FDA's June 7, 2006 response to EPA is available in the public docket (EPA-HQ-OPP-2005-0492).

Streptomycin. EPA provided its findings with respect to the antimicrobial pesticide streptomycin to FDA in a letter dated May 24, 2006, which is available in the public docket (EPA-HQ-OPP-2005-0493). The EPA's pesticidal exposure estimates reflect the dietary dose from pesticidal uses of streptomycin that a user treated with pharmaceutical (*i.e.*, antibiotic) streptomycin product would receive in a reasonable worst-case scenario. EPA's pesticide exposure assessment has taken into consideration the appropriate population, exposure route, and

exposure duration for comparison with exposure to the pharmaceutical use of streptomycin. EPA estimates that the pharmaceutical streptomycin exposure a user is expected to receive from a typical therapeutic dose (15 mg/kg/day) is 3,000 to 21,000 times greater than the estimated dietary exposure from the pesticidal sources of streptomycin (0.000704 mg/kg/day to 0.004479 mg/kg/day). Therefore, because the pesticide exposure has no more than a minimal impact on the total dose to a pharmaceutical user, EPA has concluded that there is a reasonable certainty that the potential dietary pesticide exposure will result in no harm to a user being treated therapeutically with streptomycin. FDA is aware of EPA's conclusions regarding pesticide exposure in users receiving treatment with a pharmaceutical streptomycin drug product and FDA's June 7, 2006 response to EPA is available in the public docket (EPA-HQ-OPP-2005-0493).

Propiconazole. The fungicide propiconazole shares a common metabolite, 1,2,4-triazole, with several triazole-derivative pharmaceutical compounds. EPA has determined that an appropriate way to consider the metabolite 1,2,4-triazole resulting from pharmaceutical use of triazole-derivative drugs would be to consider the additional contribution that non-occupational pesticide exposure would have to a pharmaceutical patient exposed to the same compound. EPA consulted with FDA on triazole drugs that could metabolize to 1,2,4-triazole and the two agencies concluded that only one compound, anastrozole, a chemotherapy drug used to treat breast cancer, had this metabolic pathway in humans. Because anastrozole is used at very small doses in a limited population of patients, EPA conducted a conservative screening-level assessment to determine whether the combined metabolites from triazole pesticide uses and anastrozole would adversely impact pharmaceutical users. EPA determined that, using upper-bound estimates for metabolites of anastrozole, the combined metabolite exposure is below the Agency's level of concern.

Therefore, EPA concluded that the potential dietary exposure to triazole pesticide residues in food and water will result in no harm to a patient being treated with anastrozole. The May 19, 2006 memo from FDA and the July 18, 2006 EPA document summarizing EPA and FDA discussions on potential free triazole metabolites of traizole derivative drugs are both available in the public docket for propiconazole, EPA-HQ-OPP-2005-0497.

EPA and FDA employed a common sense approach to address the potential risks associated with all sources of exposure to these dual-use chemicals. What is puzzling about EPA's Proposed Order is that, while OPP excluded most pharmaceuticals containing fluoride, including professional dental treatments, and fluoride dietary supplements from its aggregate exposure assessment because those exposures were deemed to be insignificant, the Agency included toothpaste containing fluoride. It is beyond question that FDA regulates toothpaste as a drug under FFDCA Section 505. The Final Monograph covering Anticaries Over-the-Counter ("OTC") Drug Products was published on October 6, 1995. 60 Fed. Reg. 52,474. Throughout the Final Monograph the FDA made findings on the levels of sodium fluoride, sodium monofluorophosphate, and stannous fluoride that could be used as active ingredients in OTC Anticaries Drug Products, and in the process discussed whether certain levels could cause fluorosis. See, *e.g.*, 60 Fed. Reg. 52,478 *et seq*. In addition, the Agency also provided for Warnings for the use of anticaries products for various categories of children which were incorporated into the Final Rule. For example, for paste dosage forms containing 850 to 1150 ppm: "Adults and children 2 years of age and older.… Instruct children under 6 years of age in good brushing and rinsing habits (to minimize swallowing)"; for paste dosage forms containing 1500 ppm: "Adults and children 6 years of age and older.… Children under 6 years of age: Do not use unless directed by a dentist or doctor;" and for rinse dosage forms "Children under 6

years of age: Consult a dentist or doctor." See 21 C.F.R. § 355.50. Accordingly, fluoridated toothpaste should be handled in the same manner as other FDA-regulated drug products have been handled in the EPA actions discussed above.

In summary, there are various administrative options available under federal law for the consideration of non-pesticidal sources of exposure to fluoride. Moreover, if EPA were to make use of some or all of those alternatives, it would allow the Agency to eliminate or dramatically reduce the current Section 408 tolerances for fluoride leaving only those tolerances that are needed to cover residues that result from the food uses of sulfuryl fluoride. A review of the administrative record fails to provide any evidence that EPA ever so much as considered making use of these alternative approaches to fluoride residues.

3. EPA Should Base Tolerance Decisions on Reliable Information and Anticipated Exposure Levels

The safety standard mandated by Congress in 1996 for pesticide chemical residues directs EPA to include in its aggregate exposure assessment for the pesticide chemical residue "all anticipated dietary exposures and all other exposures for which there is reliable information." FFDCA Section 408(b)(2)(A)(ii). As EPA recognized when granting registrations and establishing tolerances for the food-related uses of sulfuryl fluoride, the reevaluation of those tolerances should be coordinated with, and follow an analysis by, OW to assess the adequacy of the current Maximum Contaminant Level Goal for drinking water. In addition, EPA should consider any likely reduction in naturally-occurring fluoride levels in drinking water as a result of remediation. Finally, any decisions made with respect to sulfuryl fluoride must be based on reliable estimates of the amount of exposure anticipated from non-pesticide sources, including a

reevaluation of the estimated exposure from ambient air to include both urban and rural sources, as discussed earlier in these comments.

4. EPA Should Issue An Extraordinary Circumstances Exemption from the Aggregate Exposure Tolerance Policy

These Comments present compelling reasons why EPA can make the statutorily required finding that the existing tolerances for sulfuryl fluoride and fluoride are "safe" as that term is defined under Section 408 of the FFDCA. If, notwithstanding these arguments, the Agency concludes otherwise, this section and the next present alternative approaches that would still allow for continuation of the food-related uses of sulfuryl fluoride.

EPA has the inherent discretion to develop and implement a policy that would allow the EPA Administrator to make tolerance and associated food-use registration decisions that are in the public interest, and are in keeping with the intent of FFDCA Section 408, but which might otherwise not meet the Agency's current approach to aggregate exposure ("risk cup") assessment. Under such a policy, the Administrator could make a determination either to maintain certain tolerances and associated registrations or to establish such tolerances and registrations in the first instance where any pesticide residues that might be found in food would be at negligible (*i.e.*, *de minimis*) levels.

The Agency could issue such a policy which would be specific to the sulfuryl fluoride tolerances or which could be more general in nature. For sulfuryl fluoride, the policy could (i) recognize the *de minimis* contribution of sulfuryl fluoride to fluoride exposure in the U.S.; (ii) recognize that eliminating the use of sulfuryl fluoride would not address any risk concerns (*i.e.*, if sulfuryl fluoride were not in use as a fumigant, there would be no change in the number of children in the U.S. currently exposed to excessive levels of fluoride (based on the EPA's new

RfD)); (iii) recognize sulfuryl fluoride's unique role as an alternative to methyl bromide; (iv) recognize sulfuryl fluoride's public health benefits and avoid increases in food contamination by insect parts and rodent waste; (v) avoid disruption in the amount and availability of certain major food commodities; and (vi) recognize substantial industry reliance on federal endorsement and encouragement of the use of sulfuryl fluoride as a methyl bromide replacement.

In any case, the policy would be limited to extraordinary situations, and the authority to act under the policy could be limited only to the EPA Administrator, and not subject to delegation.

Policy elements could include the following:

- Exposure levels associated with the pesticide uses would have to be clearly negligible or *de minimis* contributors to aggregate exposure. Furthermore, any risks associated with those exposure levels would have to be a negligible or *de minimis* component of the overall risk assessment;

- The situations subject to the policy would be limited to those pesticide uses that provide significant public health or environmental benefits; i.e., the uses would have to be substantially in the public interest;

- The Administrator's actions could be time-limited unless it were determined that no reasonable actions within a reasonable period of time would reduce aggregate risks to acceptable levels. For actions that were time-limited, the actions could not be renewed unless reasonable steps were taken within reasonable periods of time to address risk concerns; and

- In deciding whether to use the policy, the Administrator could commit to developing and vetting a plan to address overall risks in concert with other Federal and State agencies including public health officials, as appropriate.

In summary, the extraordinary policy approach could be considered only in *de minimis* risk situations. While a *de minimis* risk finding is sufficient, in and of itself, to allow sulfuryl

fluoride uses to continue, the use of an extraordinary policy approach could specify additional criteria that would have to be met over and above the basic *de minimis* finding.

5. EPA Should Revoke Fluoride Tolerances Related to the Use of Sulfuryl Fluoride

When EPA established tolerances for sulfuryl fluoride's food-related uses, the Agency also established related tolerances for fluoride levels that result from the use of the fumigant. While these levels theoretically could be above natural background levels, the fluoride from sulfuryl fluoride use is indistinguishable from naturally occurring fluoride. Naturally occurring levels of fluoride vary. Levels of fluoride from sulfuryl fluoride use also vary. In some cases, detectable levels of fluoride may be partly a result of sulfuryl fluoride use, but, in others, detectable levels would be from naturally occurring fluoride only. Thus, the enforceability of the fluoride tolerances for currently approved food uses is questionable. In addition to fluoride levels in excess of established tolerances, it would also be difficult for FDA to pursue adulterated food actions for non-approved food uses, since it would be difficult to determine if the fluoride levels resulted from natural background fluoride or from the illegal use of sulfuryl fluoride.

EPA could consider revoking the fluoride tolerances because of these enforceability issues. Such revocations would also be consistent with the international harmonization provisions of Section 408(b)(4) of the FFDCA, as amended by FQPA. In other countries (*e.g.*, Canada and Japan) there are Maximum Residue Levels ("MRLs") for sulfuryl fluoride, but MRLs for fluoride have not been established.

Eliminating the fluoride tolerances as being unenforceable while maintaining tolerances for sulfuryl fluoride that are already in place would provide an enforceable, regulatory control over the fumigant's use and the resulting fluoride residues resulting from that use.

VI. Conclusion

For the reasons set forth in these Comments, EPA should not finalize its Proposed Order. Instead, the procedural and substantive concerns raised by the Proposed Order and the Agency's underlying analyses must be carefully reviewed and addressed. EPA should abide by the terms of the conditional registration that it issued to Dow AgroSciences for ProFume, conduct a public hearing, and seek input from other federal agencies and an independent Scientific Advisory Panel with respect to the matters raised in the Proposed Order. And, finally, the Agency should consider the various reasonable alternatives that are available under federal law to address concerns associated with fluoride and select a path forward that will best serve the overall public interest while allowing ProFume to continue to protect the food supply and serve as a critical replacement for methyl bromide.

Appendix I - Assessment of Alternative Treatments to Sulfuryl Fluoride (ProFume® gas fumigant)

Assessment of Alternative Treatments to Sulfuryl Fluoride (ProFume® gas fumigant)

Submitted to:
Office of Pesticide Programs
Regulatory Public Docket (7502P)
Environmental Protection Agency
1200 Pennsylvania Avenue, NW.
Washington, DC 20460-0001

RE: Sulfuryl Fluoride - Docket ID No. EPA-HQ-OPP-2005-0174

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Executive Summary

The analysis of Ranville and Cook (2011) predicted if food tolerances were removed for sulfuryl fluoride, heat or fumigation with sulfuryl fluoride of facilities emptied of food product would be the two primary methods used to disinfest food processing facilities. Heat repeatedly has been documented to be less effective than fumigation with sulfuryl fluoride for disinfesting food processing facilities due to structural components, food residues, paper products or other contents providing thermal refugia for insects. Even when best practices for heat treatment are followed, all heated areas may not attain lethal temperatures for the required time. No single, comprehensive calculation tool for planning and evaluating heat treatment for insects exists, unlike the Fumiguide® used for dosage calculations with ProFume® gas fumigant (sulfuryl fluoride). Overheating can cause costly damage to the structure, equipment, food and its packaging, and other contents. The heat lability of many items, including construction elements, in food processing facilities may be unknown until damage occurs. Experts agree that additional research is needed to verify rates of temperature increase and duration of lethal temperatures required to ensure mortality of target pests and the effect of these temperature regimes on building components and contents. Therefore, heat treatment requires removing packaging, heat labile materials including raw and finished foods before treatment and replacing them after treatment, intensive cleaning, and preparing heat-sensitive equipment, steps which are not required for fumigation.[1] Heat treatment is more expensive than fumigation with sulfuryl fluoride. Heat treatment also substantially reduces total annual revenue of food processing facilities by decreasing production time due to extra time to prepare the facility and conduct the treatment, compared to fumigation.

The second option, removal of all raw and finished food products prior to fumigation, will add significant and potentially unsustainable cost and liability to fumigation. There are currently numerous pre-fumigation actions taken by food processing facility managers that serve to minimize the raw and processed food products that remain in the facility during fumigation with ProFume. Even after all these steps are taken in preparation for fumigation, in some circumstances finished food product cannot be completely removed from the facility to be fumigated. These situations include when alternative space for storing food is not available, and/or does not provide the necessary security, environmental, or sanitation requirements to prevent spoilage or cross contamination of food ingredients. Sometimes packaged, processed foods must be fumigated in-situ. An example is when the product shipping or bundling materials

[1]Exception: Food not listed for commodity fumigation on the label for ProFume is removed from the facility to be fumigated when practical.

become infested and sufficient disinfested pallets and boxes may not available for re-bundling finished goods. Moving the infested pallets and boxes before fumigation will infest the temporary storage area, the destination location if shipped, and the food processing facility when returned after the fumigation.

The analysis of Cook and Ranville (2011) concluded that phosphine would be an economic and effective replacement for ProFume® gas fumigant for fumigation of commodities. Their analysis did not take into account many factors that prevent food processors from using phosphine instead of ProFume, including shipping and warehousing logistics, existing infrastructure for fumigation, and lack of space to expand fumigation facilities. In addition, insect resistance to phosphine is documented globally and in the United States. Recent research in the United States has verified high levels of phosphine resistance in stored product insects that would interfere with the applicator's ability to effectively control key stored-product pests using phosphine as currently labeled. Sulfuryl fluoride and phosphine have different modes of action, making ProFume the primary candidate for rotating with phosphine to combat resistance. The unique opportunity to use ProFume to efficiently remediate phosphine resistance in insects infesting grain storage has been initiated in Australia. The EPA's proposed removal of food tolerances for ProFume eliminates the only practical fumigant alternative for managing phosphine resistance in stored product insects in the United States.

If there are no food tolerances for ProFume, the analyses of EPA did not consider the unintended consequences resulting from the likely increased use of contact and residual insecticide treatments, including selection for insecticide resistance and reduced availability of natural pyrethrins for a broad range of pest control applications. In addition, removal of food tolerances for ProFume eliminates its use to eradicate structural infestations of new exotic, invasive stored product pests to prevent their dissemination and establishment. Sulfuryl fluoride has been used to efficiently, effectively, and readily eliminate structural infestations of introduced pest species, preventing their further dissemination**.**

The following information is being submitted by Dow AgroSciences in response to the proposal by the USEPA to phase-out food tolerances for sulfuryl fluoride, as published January 19, 2011 in the Federal Register.

Heat Treatment:

The analysis of Ranville and Cook (2011) predicted that if food tolerances were removed for sulfuryl fluoride, heat would be one of the two primary methods flour millers would use to disinfest mills. Heat treatment involves raising the ambient temperature of the whole or a portion of the facility to 50 - 60^{o}C and holding these elevated temperatures for 24 – 36 hours (Dowdy and Fields 2002, Wright et al. 2002).

Ranville and Cook (2011) did not compare the efficacy of fumigation with sulfuryl fluoride to heat treatment for disinfestation of mills. **Field research has repeatedly documented heat treatment is not as reliable or as effective as fumigation with sulfuryl fluoride for disinfestation of flour mills** (Subramanyam 2010a, Muck and Boye 2008, Suss and Savoldelli 2008). These studies have verified that accumulated flour deposits (Subramanyam 2010a), thermal cold spots in concrete (Muck and Boye 2008), and shortened treatment times due to production schedules (Suss and Savoldelli 2008) negatively impacted heat treatments, resulting in higher insect survival in heat treatments compared to fumigation with sulfuryl fluoride. These factors which adversely affect heat treatment efficacy either do not impact the efficacy of sulfuryl fluoride, or are readily remediated for sulfuryl fluoride,as described below. Other studies have further validated that sulfuryl fluoride provides control equivalent to that of methyl bromide for disinfestation of mills (Small 2007, Tsai et al. 2008) and is a suitable replacement for methyl bromide for control of post-harvest pest control in structures.

Milling facilities that have adopted heat as a treatment strategy still periodically require whole structure fumigation. There are at least three milling facilities in Canada that use existing boiler capacity and purchase or capital lease heat treatment equipment to incorporate frequent part-facility heat treatments into their integrated pest management programs. In spite of these treatments, infestations periodically increase above acceptable levels, indicating a long-term need for access to a commercially available chemical fumigant that performs similarly to methyl bromide (CNMA 2007), such as ProFume® gas fumigant.

Ranville and Cook (2011) state “It is always necessary to clean a flour mill before a heat disinfestation. The additional cleaning would not represent an increase in labor costs, however, since deep cleaning also precedes a chemical fumigation to ensure it is efficacious. Flour and other food particles are not easily penetrated by chemical fumigants or heat, so it is important that a facility is clean before disinfestation begins.” **Accumulated food residues significantly reduce the efficacy of heat treatment, but have far less impact on fumigants, particularly sulfuryl fluoride.** Based on research by Subramanyam (2010a), 2 cm of flour in bioassays resulted in significantly greater survival in adults and larvae of the red flour beetle, *Tribolium castaneum*, for heat treatments compared to fumigation with sulfuryl fluoride. Roesli et al. (2003) observed survival and significant increase in red flour beetle populations in a feed mill beginning two weeks post heat treatment, particularly on the 4th floor, where metal floor plates

retained and accumulated spilled feed. In contrast, sulfuryl fluoride has been documented to readily penetrate through flour 10 cm in depth, reaching 60% of surface concentrations within one hour or less (Bell et al. 2003). Therefore, facility heat treatments are labor intensive, because food and non-food items that are poor conductors of heat, such as paper bags, provide harborage for insects to escape heat and must be removed prior to treatment (Beckett et al. 2007). An additional reason for conducting intensive cleaning of equipment prior to heat treatment is the observation that food residues can bake during heating and become very difficult to remove during reassembly and mill start-up. This deep cleaning is complicated by design of older equipment, such as roller stands manufactured before 1970, which can be more difficult to clean manually and/or disassemble for cleaning (CNMA 2007). Fumigators attribute excellent results to the penetration capabilities of sulfuryl fluoride when fumigating facilities with deep-seated flour in cracks in mortar joints, wood beams, machinery, and other areas inaccessible for cleaning (Mueller 2009). **Therefore, the removal of food residues required before heat treatment is more extensive and more costly than that required prior to fumigation.**

The efficacy of heat is limited by diverse factors affecting its distribution, compared to the distribution of sulfuryl fluoride which is easily managed during fumigation. Temperature distribution in a heat-treated area is influenced by the type and intensity of the heating system, placement of heat sources, number and placement of fans to facilitate air movement, dimensions of the room, equipment present in the room, outside ambient temperature, structure of the building, and number of vents (Akdogen et al. 2005). During heat treatment, temperatures stratify both vertically and horizontally, causing non-uniform heating of a food-processing facility and resulting in areas where temperatures do not reach lethal levels (Dowdy and Fields 2002, Mahroof et al. 2003a, Roesli et al. 2003). Uneven temperature distribution in food processing facilities during heat treatments cannot be completely controlled by redistribution of hot air into cooler areas. Research has shown distribution of hot air into cooler areas can be facilitated with the use of fans but over- and under-heating can still occur (Brijwani et al. 2010). The rate of heating of different floors of a food-processing facility during heat treatment can vary between 3 and 14^{o}C/hour (Roesli et al. 2003), and on some floors heating rates can be as low as 0.3-0.9^{o}C/hour (Mahroof et al. 2003a). Electric heating resulted in substantial amounts of under-heated floor areas throughout a four-story pilot flour mill and cleaning house (Akdogen et al. 2005). Basements, outside walls, and windows can be difficult to heat to temperatures in excess of 50^{o}C to control target pests (Mahroof et al. 2003a, Dowdy and Fields 2002).

A facility's structural components and processing equipment (steel beams and cladding, concrete floors, masonry walls, metal and equipment components) can rapidly absorb heat. Recently built or modernized mills typically have substantial poured floor structures to support equipment. These areas have been documented in field trials to be challenged in reaching lethal temperatures due to the concrete acting as a heat sink (CNMA 2007). **The analysis of Ranville and Cook (2011) did not discuss the challenges of heat distribution, including heat sorption into structural matrices like concrete.** In contrast, the high volatility and low reactivity and sorption potential of sulfuryl fluoride results in its rapid distribution throughout the fumigated space with no detectable sorption into the structure or equipment.

Calculating the susceptibility of insects to heat treatment is complex and is still being evaluated. The susceptibility of insects to heat varies greatly based on species (Fields 1992),

life stage (Abdelghany et al. 2010), grain moisture content (Beckett et al. 1998) and rate of temperature increase (Mahroof et al. 2003b). The susceptibility to heat of even closely related species, or species with similar life histories, can vary greatly (Becket et al. 2007). Increasing grain moisture from 9% to 14% increased the LT_{99} by 40% for the lesser grain borer, *Rhizopertha dominica* (Beckett et al. 1998). There is conflicting data on heat required to control target pests. Laboratory data demonstrated that early instar red flour beetles, *T. castaneum*, were the most heat tolerant life stage (Mahroof et al. 2003b), requiring 7.2 hours exposure, compared to less than two hours for other life stages, at 50°C for 99% control. Yet field trials in a feed mill and flour mill resulted in survival of late instar and pupal red flour beetles in areas in which temperatures exceeded 50°C for up to 71 hours (Mahroof et al. 2003a). Mahroof et al. (2003a) attributed these differences to variation in acclimation of the different life stages to gradually increasing temperatures, which could affect subsequent susceptibility at high temperatures. Entomologists recommend heating a facility at 5°C per hour (Beckett et al. 2007) to prevent insects from acclimating to high temperatures. Conversely, industry experts state above 43°C, mills heat only 1 - 1.5°C per hour to minimize damage to diverse structural components that expand at different rates. **Experts agree that additional research is needed to verify rates of temperature increase and duration of lethal temperatures required to ensure mortality of target pests and the effect of these temperature regimes on building components and contents** (Beckett et al. 2007, Mahroof et al. 2003a).

No single, comprehensive calculation tool for planning and evaluating heat treatment for insects exists. A computer model (EARTH - Efficacy Assessment in Real Time during Heat Treatment), available through licensing from Kansas State University (Subramanyam 2010b), uses a thermal death kinetic model based on the heat tolerant stages of only two species; the confused flour beetle (*Tribolium confusum*) and red flour beetle (*T. castaneum*). The model did not include calculations for other stored product insects, such as lesser grain borer (*R. dominica*), the cigarette beetle (*Lasioderma serricorne)*, and warehouse beetle (*Trogoderma variabile*), which are considered more tolerant than flour beetles to heat treatment (Fields 1992, Fields and White 2002, Wright et al. 2002). This program requires that wireless temperature sensors be placed throughout the heated facility to transfer real time temperature data via a base station to a computer located outside the heated facility. The data are used to predict insect survival in real time, allowing the user to determine if certain areas are not heating properly and enabling corrective action. This software has limited field testing, is not required to be used when conducting heat treatments, and does not include calculations to estimate the heat energy required to treat a facility. Separate software called the Heat Treatment Calculator, also available through licensing from Kansas State University, estimates the heat energy required to conduct a heat treatment using various energy/fuel sources (Subramanyam 2010b). The calculator was validated during heat treatment of one large pasta facility.

In contrast, a comprehensive, extensively commercially validated calculation tool, the Fumiguide®, is required for use with ProFume® gas fumigant (sulfuryl fluoride). The Fumiguide is a Windows-based computer program that fumigators use to calculate the correct dose of ProFume for twenty pest species and a wide range of temperatures and exposure times (Anonymous 2005). It is available at no cost to fumigators who use ProFume. The data used to produce the Fumiguide is the result of ten years of research by six stored product research laboratories in the United States and Europe (Thoms et al. 2008), and nearly 1,200 bioassays of

the key U.S. stored product insects evaluated during 51 commercial fumigations (Williams 2008). When monitoring data are entered into the Fumiguide, the program will calculate the actual half loss time and accumulated dosage, predict the dosage outcome for the planned exposure period, and update instructions on exposure time (on target, shorten or lengthen) and fumigant concentration ("on target" or "add more"). The Fumiguide is used to plan and document fumigations and generate reports (Thoms et al. 2008). The Fumiguide has had three software enhancements, to expand calculations based on research data, since its introduction in 2004.

The efficacy of heat is adversely impacted by mobile life stages of insects leaving the heated areas, which has not been observed or reported to occur during structural fumigation with sulfuryl fluoride. Research has documented that fumigation does not stimulate insects to leave the fumigated area. Extensive interior and exterior trapping of stored product insects at a flour mill demonstrated that outdoor trap catches of red flour beetles, *T. castaneum*, declined after fumigation, indicating that red flour beetles did not vacate the fumigated facility (Campbell and Arbogast 2004). Recent research at Kansas State University in Hal Ross Flour mill documented marked red flour beetles moved between floors in the mill. Heat treatment of the mill increased movement of red flour beetles on each floor as indicated by significantly increased trap catches (Jim Campbell, personal communication, June 2011). Movement of insects away from heat-treated areas to infest untreated areas has been observed in other field research trials (CNMA 2007). This response of insects can reduce the utility of heating part of a food processing facility, and indicate whole structure heat treatment is necessary for efficacy. Heat treating entire facilities can be cost-prohibitive for some operations due to added energy requirements and added labor for preparation and start-up after treatment (CNMA 2007).

Unlike fumigation with sulfuryl fluoride, overheating can cause costly damage to the structure, equipment and other contents. Akdogen et al. (2005) documented gas heating of four-story pilot flour mill and cleaning house resulted in hot spots exceeding 80^{o}C (176^{o}F). This temperature can damage electrical components because it exceeds the 70^{o}C maximum approved for PVC electrical wire insulation (Fields and White 2002). Temperatures greater than 60^{o}C are not recommended for heat treatments because of possible damage to heat-sensitive contents, such as magnets, batteries, PVC, Tygon tubing, pneumatic connectors, belts, lubricants, and solid state electronics including electronic controllers, small computers, and photo eyes (Dosland et al. 2006, Mahroof et al. 2003b). Data have not been scientifically collected on the adverse effects of high temperatures on the structural integrity of the building, building materials, equipment and food grade-materials, such as gaskets, sifters, plastics, caulking, and paints (Beckett et al. 2007, Mahroof et al. 2003b). Therefore, the heat lability of many items, including construction elements, in food processing facilities may be unknown until damage occurs. A newly-laid, $300,000.00 epoxy-concrete floor in a bakery buckled and was completely destroyed when the temperatures were raised to prescribed insect-killing rates during heat treatment. Hardwood flooring in older processing plants is not suitable for heating (Thompson and Keigwin 2006). To prevent damage, known and suspected items that could be damaged by heat must be removed prior to heat treatment. Examples of these items include raw and finished food products, packaging and labeling materials, laboratory equipment such as testing refrigerators and freezers, foods and beverages in dispensing machines, and certain plastics such as those used in air hoses, water lines, brushes and brooms (Beckett et al. 2007,

CNMA 2007). None of these items, with the exception of food products not listed on the label for fumigation, would need to be removed prior to fumigation with ProFume® gas fumigant. Fifty years of application of sulfuryl fluoride (as Vikane® gas fumigant) to more than two million buildings, including museums, chemistry research laboratories, medical facilities, and 911 computer relay facilities, has validated sulfuryl fluoride will not damage building materials and contents, including sensitive equipment, when used according to label directions. Laboratory evaluations verified no effects on computers when fumigated five times with sulfuryl fluoride and at 10-fold the maximum labeled dosage for ProFume® gas fumigant at 40-50^{o}C (Bell et al. 2003).

The economic assessment by Ranville and Cook (2011) did not include the cost of labor, building modification, heat equipment replacement, repair and maintenance, and more frequent application of heat that would significantly increase the cost of heat treatment compared fumigation.

1. **The labor of the facility personnel for heat treatment includes removing food, heat labile items, and packaging before treatment and replacing them after treatment, conducting additional intensive cleaning and preparation of heat-sensitive equipment, sealing the heated space, and conducting and monitoring the heat treatment.** Heat has diverse adverse effects on food products, such as causing rancidity in butters and oils, denaturing proteins (Fields and White 2002), affecting the baking characteristics of mixes (Linda Mason, personal communication, March 2011), and reducing moisture content in grain. The labor to prepare for a heat treatment is similar to that estimated by Ranville and Cook (2011, Table 4) for conducting a fumigation with all the food removed. Heat treatment requires more time than current fumigation practices to move all food, heat-labile items (such as aerosol cans, carbon dioxide fire extinguishers, adhesives), and non-food items such as bags that can provide harborage to insects during heat treatment, then replacing these after heat treatment (Beckett et al. 2007, CNMA 2007, Fields and White 2002). Heat-sensitive equipment that cannot be removed needs to be sealed and provided with cool air. Rubber conveyor belts need to be slackened to prevent damage (Beckett et al. 2007).

   Milling personnel need to be present throughout the heat treatment, unlike a fumigation, to conduct hourly inspections to monitor and record temperatures, adjust heaters, move fans and other equipment to ensure proper heat distribution, and inspect for damage. Temperatures must be measured manually with an infrared thermometer for accuracy on surfaces inside the structure (Dosland et al. 2006). At least two people should be present when entering heated areas (Beckett et al. 2007). Signs of damage, such as flickering lights, sagging tubing, water or pressurized container releases, leaking fluids, and structural cracks (Dosland et al. 2006), may indicate temperatures are too high or were increased too quickly. After heat treatment, damage will need to be remediated, such as replacing heat-sensitive lubricants (Fields and White 2002).

2. Modification of a food processing facility can include replacement of sprinkler heads or entire sprinkler systems with a higher temperature tolerance of at least 95^{o}C, modification of other equipment to withstand heat, modification of electrical supply and distribution systems to accommodate heater units and circulation fans, and addition of manifold systems to connect to exterior gas tanks if propane heaters will be used (Beckett et al. 2007, CNMA 2007, Fields and White 2002). The cost of these upgrades has been determined not to be economically feasible for many food processing facilities in the western and southern United States (Thompson and Keigwin 2006).

3. The estimated cost of a fumigation by Ranville and Cook (2011, Table 4) includes overhead expenses to maintain, repair, and replace equipment, such as SCBAs, clearance and monitoring detectors, introduction hoses and connectors, fans, and other equipment required to conduct a fumigation. By comparison, Ranville and Cook (2011, Table 5) only included the cost to replace temporary ducting; they did not allocate funding for the ten year period to maintain, repair, and replace the heaters, fans and sensors required for heat treatment. For example, some fans may be expected to fail during heat treatment (Beckett et al. 2007).

4. Other miscellaneous expenses that Ranville and Cook (2011) did not include in the cost of heat treatment would be material supplies for sealing the facility, more frequent replacement of conveyor belts, motor seals, lubricants and other components in processing equipment (Fields and White 2002, Isbel 2009), and potentially increased insurance premiums for conducting heat treatments.

5. Ranville and Cook (2011) assumed heat treatments would be conducted as frequently as fumigations. Facilities that use heat treatment usually do so four times a year compared to one or two fumigations per year for facilities that fumigate (Fields and White 2002). Heat treated facilities are reported to be periodically fumigated to supplement heat treatment (CNMA 2007).

The revised total cost for heat treatment, including extra costs to move and store food, monitor the heat treatment, replace and maintain heat treatment equipment, and maintain the heated facility, are calculated in Table 1. **These calculations demonstrate that conducting three heat treatments, compared to three fumigations with ProFume® gas fumigant, per year at a 500,000 ft^3 facility will reduce total annual revenue by $409,300.**

Removal of food products prior to fumigation with ProFume® gas fumigant:

The analysis of Ranville and Cook (2011) predicted that if food tolerances were removed for sulfuryl fluoride, removal of all the ingredients and processed food from mill prior to fumigation with ProFume would be the other option that millers would use. **Removal of all raw and**

finished food products prior to fumigation will add significant and potentially unsustainable cost (CNMA 2007) and liability to fumigate with ProFume® gas fumigant.

There are currently numerous pre-fumigation actions taken by food processing facility managers that serve to minimize the raw and processed food products that need to remain in the facility during fumigation with ProFume. These steps include (from Rosenberg 2010):

1. Run only production needed for final orders until shut down for the fumigation to meet the needs of the last shipment and load the product on trucks for shipment prior to fumigation.

2. Plan production ahead of time so product ships or can be loaded onto trucks ready for shipment prior to fumigation.

3. Delay delivery of inbound ingredients until after the fumigation.

4. Draw down ingredient production bins.

5. Clean food debris out of equipment and production lines and sweep/clean the facility to maximize exposure of insect harborages to the fumigant.

6. Move finished goods to an area of the facility not included in the fumigation, including loading on truck cargo containers.

Even after all these steps are taken in preparation for fumigation, in some circumstances there are situations in which the finished food product cannot be completely removed from the facility to be fumigated. These situations include the following examples (from Rosenberg 2010):

1. The food processing facility does not have alternate space available for temporary storage of the remaining finished food during the fumigation.

2. The food processing facility does not have alternate storage space that provides the necessary security to prevent product tampering, and/or environmental or sanitation requirements to prevent spoilage and/or cross contamination of food ingredients (per American Institute of Baking requirements).

   Environmental requirements include strict control of required temperature and humidity to prevent spoilage. Generally, processed foods containing protein (like soy) and fats (like chocolate) cannot tolerate high or low temperatures and must be maintained in air conditioned warehouses and refrigerated truck cargo containers. Processed foods containing starch and carbohydrates may be more temperature tolerant, but can require

controlled humidity.

3. At times, the product shipping/bundling materials become infested. Pests harbor in pallets, boxes, and other shipping materials used to contain processed food for shipment and pallets, boxes and similar materials need to be fumigated for disinfestation. Sufficient disinfested pallets and boxes are not available for re-bundling finished goods. Moving the infested pallets and boxes before fumigation will infest: 1) the temporary storage area, 2) the destination location if shipped, and 3) the food processing facility when returned after the fumigation.

The above situations also limit the utility of heat as a treatment for food processing facilities, since removal of food products from a facility is necessary prior to heat treatment.

Sanitation:

Ranville and Cook (2011) included that sanitation can keep insect populations low and is needed to increase the efficacy of control treatments, such as heat. Nonetheless, **building construction, equipment design, and frequent changes between batches of raw products during processing can make effective sanitation programs in mills difficult** (CNMA 2007, Roesli et al. 2003). This is why fumigation with methyl bromide, and now ProFume, has been the established method for control of stored product pests in food processing facilities (Roesli et al. 2003). In addition, the microsanitation described by Ranville and Cook (2011) may not be possible due to areas inaccessible for cleaning and often is considered too costly by managers of food processing facilities. Microsanitation does not replace the need for periodic disinfestation of mills and food processing facilities by fumigation (Linda Mason, personal communication, March 2011). In addition, mills and other "dry" food processing facilities, such as pasta plants, are limited in using water to assist in cleaning because water increases the potential for bacteria.

Phosphine:

The analysis of Cook and Ranville (2011) concluded that phosphine would be an economic and effective replacement for ProFume for fumigation of commodities, such as walnuts and cocoa. **Their analysis did not take into account many factors that prevent processors from using phosphine instead of ProFume, including shipping and warehousing logistics, existing infrastructure for fumigation, and lack of space to expand fumigation facilities.** The cocoa industry used methyl bromide, and now uses ProFume, to meet time-critical logistics needs and strict FDA sanitation requirements (CMAA 2010). The significantly longer exposure time required to fumigate with phosphine compared to that for ProFume® require the construction of new, expanded, and separate facilities. Many facilities, such as warehouses, where commodity fumigations are now conducted using ProFume are not suitable for phosphine fumigation (Kip Walk, personal communication, March 2011). Land is not available due to cost, zoning restrictions, permitting, or previous development for processors to acquire to build additional chambers needed to conduct phosphine fumigations.

The analysis of Cook and Ranville (2011) did not discuss the insect resistance to phosphine which has been well documented globally (Collins et al. 2003) and is increasing in the United States (Hosoda 2009; Thoms et al. 2008). Worldwide, phosphine is the fumigant of choice for grain and other durable commodities for numerous reasons: it is relatively easy to apply, versatile, inexpensive, and is a nearly residue-free treatment (Collins et al 2003). Widespread and repeated fumigation of poorly sealed commodities has resulted in sub-lethal exposure and selection of resistance to phosphine (Chaudhry 2000). Phosphine resistance was first detected in the 1970s; by 2000 was documented in 11 species of key stored product insects in 45 countries (Chaudhry 2000); and continues to expand in distribution (Benhalima et al. 2004) and number of affected species (Pimentel et al. 2009).

Resistance to phosphine has two unusual characteristics (Chaudhry 2000). It is selected relatively easily from field populations of most stored product insects, suggesting the frequency of resistance gene(s) is relatively high. Resistance to phosphine is quite stable once selected: levels of resistance in most laboratory-maintained insect cultures has not changed over many years, even though they are not maintained under the selection pressure of phosphine.

Researchers at the USDA-ARS Stored Product Insect Research Laboratory in Savannah GA documented phosphine resistance in key stored product insects in the United States in surveys conducted from 1986 through 1991. This research verified phosphine resistance at high levels for the cigarette beetle, *L. serricorne*, in tobacco (Zettler and Keever 1994), and at moderate levels in some populations of the lesser grain borer, *R. dominica*, in wheat (Zettler and Cuperus 1990), the red flour beetle, *T. castaneum*, in flour mills (Zettler 1991) and peanuts (Zettler et al. 1989), and the Indian meal moth, *Plodia interpunctella*, in peanuts (Zettler et al. 1989). At the time, these researchers concluded control failures were due to inefficient fumigation practices resulting in low dosage accumulation rather than the resistance (Zettler and Cuperus 1990, Zettler and Keever 1994, Zettler et al. 1989). In fact, fumigation of poorly sealed peanut storage facilities was compared to aerosol treatment because of the resulting significant insect survival (Zettler et al. 1989).

USDA insecticide resistance research on stored product insects ceased when the USDA Stored Product Insect Lab closed in 1994 and researchers were relocated to other facilities. Currently, the USDA-ARS management discourages researchers from conducting insecticide resistance monitoring studies. University researchers in the United States have recently initiated studies evaluating phosphine resistance in stored product insects. **Their research has verified high levels of phosphine resistance in stored product insects that would interfere with the applicator's ability to effectively control key stored-product pests using phosphine as currently labeled**.

Rotating two or more insecticide classes with different modes of action allows any resistance developed to the first insecticide to decline over time when the second insecticide class is introduced and is a widely adopted method to manage resistance (IRAC 2011). Sulfuryl fluoride and phosphine have different modes of action (Thoms and Phillips 2004) and phosphine-resistant insects are not cross-resistant to sulfuryl fluoride (Bell et al. 2003). There is no known insect resistance to sulfuryl fluoride (Thoms and Phillips 2004). These characteristics make ProFume® gas fumigant a primary candidate for rotating with phosphine to combat resistance. The unique

opportunity to use ProFume to efficiently remediate phosphine resistance has been initiated in Australia. For more than two decades a monitoring and management program for phosphine resistance, funded and executed by a coalition of industry and government agencies, has been conducted in Australia (Collins et al. 2003). Currently, high levels of phosphine resistance in the flat grain borer, *Cryptolestes ferrigineus*, are resulting in control failures for phosphine treatment of central grain storages in Australia. Recent surveys have determined that 156 populations of flat grain borers collected from 52 sites in Australia have strong resistance to phosphine, requiring up to 500-fold the dosage for susceptible insects to obtain control (Collins 2011, Holloway 2011). This situation has prompted the coalition to fund research on rotational use ProFume in grain as part of a comprehensive plan for managing insect resistance to phosphine (Collins 2011**).** In the US, phosphine-resistant lesser grain borer has been reported by fumigators to occur in California, where fumigations in selected rice and corn storages have converted from phosphine to ProFume (Thoms et al. 2008). **The EPA's proposed removal of food tolerances for ProFume eliminates the only practical fumigant alternative for managing phosphine resistance in stored product insects in the United States.** This proposed action by EPA will limit the ability of the post-harvest industry in the United States to extend the long-term viability of phosphine as an effective, economical fumigant for grain and other durable commodities.

Additional Adverse Impacts of Removal of Food Tolerances for ProFume® gas fumigant:

The assessments by EPA (Cook and Ranville 2011, Ranville and Cook 2011) did not include additional unintended impacts on the post-harvest industry and other industries from the removal of food tolerances for ProFume. **If food tolerances for ProFume are removed, food processing facilities will increase reliance on contact and residual insecticides for stored product pest control.** Besides fumigants like ProFume, there are few insecticides that can be applied in food processing facilities. These insecticides include pyrethrins synergized with piperonyl butoxide (PB), insect growth regulators (IGRs, such as pyriproxifen and methoprene), some pyrethroids, diatomaceous earth, and few other active ingredients such as dichlorvos and chlorfenapyr. Fogging using aerosol formulations of synergized pyrethrins, often combined with an IGR, is a common practice in food processing facilities (Frank Arthur, personal communication, June 2011). Fogging every two to four weeks with synergized pyrethrins and methoprene in combination with sanitation or insecticide treatment of infestation "hot spots" has been documented to extend the time to reach a threshold of infestation of red flour beetles, *T. castaneum*, that would require fumigation in a mill, from a mean of 49 days to eight months (Campbell et al. 2010). **Nonetheless, even with increased application of residual insecticides and sanitation, fumigation is often still required to disinfest food processing facilities. The efficacy of insecticides applied as surface, spot, crack and crevice, or aerosols are limited by many factors**, including variable susceptibility of different species and life stages to the active ingredient (Arthur 2008a, Arthur et al. 2009, Arthur 2010a, Jenson et al. 2010a), inability of the insecticide to penetrate to contact the target pest (Arthur 2000, Toews et al. 2010), and longevity of residual insecticidal activity on surfaces (Arthur 2008b, Arthur et al. 2009, Arthur 2010a, Jenson et al. 2010b). Research has documented the presence of flour or other food substrates can reduce the residual efficacy of insecticides by forming a barrier so that insects do not come in contact with the residues or by providing a food source enabling insects to recover from exposure (Arthur 2000, Arthur and Campbell 2008, Arthur 2009, Toews et al. 2010). In addition, aerosol formulations do not distribute and penetrate like fumigants. The survival of insects increases as their distance from the aerosol application nozzle increases (Arthur and Campbell 2008, Jenson et al. 2010b). Insects under pallets can have greater survival than insects directly exposed to aerosol treatments (Toews et al. 2010).

If there are no food tolerances for ProFume, **the analysis of Ranville and Cook (2011) did not consider the unintended consequences resulting from increased use of contact and residual insecticide treatments, including selection for insecticide resistance and reduced availability of natural pyrethrins for a broad range of pest control applications.** Labeling for synergized pyrethrins permits application to more than 135 types of sites/structures and has no limitations on the frequency of application (Anonymous 2007). Methoprene is labeled for direct application to grain as a grain protectant (Anonymous 2008) in addition to use as a surface spray and fogging agent in wide range of food processing and storage facilities. Repeated exposure to pyrethrins (Parkin and Lloyd 1960) and methoprene (Brown et al.1978) can select for pesticide resistance in stored product insects. Stored product insects already have been documented to be resistant to pyrethrins and pyrethroids synergized with PB (Lloyd and Ruczkowski 1980) and to methoprene (Benezet and Helms 1994, Daglish 2008). **Intensifying the use of contact and residual insecticides by removing food tolerances for ProFume® gas fumigant will only accelerate**

selection for resistance to the limited insecticides registered for use in food processing facilities, further reducing the ability of this industry to effectively disinfest facilities and food products.

There has been a long term global shortage of natural pyrethrin for pesticide formations (Namata 2009, WBCSD 2004). In 2009, the total world demand for refined pyrethrin extract, estimated to be 400 metric tons, was four-fold greater than the supply of 100 metric tons (Namata 2009). Pyrethrin is extracted from flower *Chrysanthemum cinerariaefolium* grown in eastern Africa, of which 70% comes from Kenya and the United States is the largest importer (Mueller 2008). One of the largest users of natural pyrethrins in the United States is SC Johnson, which incorporates pyrethrins in a variety of household insecticide products under the trade names of RAID® and Baygon® (WBCSD 2004). Reliability in quality and volume of natural pyrethrin extract supplied from Kenya is plagued by political unrest, mismanagement, and graft (Patton 2008, Omondi 2009, Cheploen 2010). Synergized pyrethrins also are used for control of public health pests, arthropod pests of domestic and captive animals, and general pest control. Synergized pyrethrins are applied indoors and outdoors to a broad range of sites, such as residences, commercial and public buildings including restaurants, super markets, schools, and hospitals, and animal areas including zoos (Anonymous 2007). **If food tolerances for ProFume were removed, increased use of synergized pyrethrins could further reduce the availability of natural pyrethrin for pest management for public and animal health pests, general household pests (including consumer use), as well as stored product insects at food processing facilities.**

Removal of food tolerances for ProFume also prevents its use to eliminate structural infestations of new exotic, invasive stored product pests to prevent their dissemination and establishment. The USDA Animal and Plant Inspection Service, Plant Protection and Quarantine division (APHIS PPQ) is responsible for excluding nonindigenous pests of plants and noxious weeds from the United States. Inspections of baggage of international travelers and international cargo that arrive at U.S. ports and border crossing focus on agricultural and plant–related commodities that are likely to harbor live plant pests (McCullough et al. 2006). Travelers bring food on flights as snacks and gifts: fruit, nuts, seeds, spices and similar items are most commonly intercepted (Liebhold et al. 2006, McCullough et al. 2006). From 1984-2000, 62% of intercepted pests were in baggage from international travelers (McCullough et al 2006). Nonetheless, the United States has a lower pest interception rate in baggage compared to that of Australia and New Zealand which have more aggressive inspection procedures for baggage (Liebhold et al. 2006). From 1984-2000, 30 % of intercepted pests were in cargo, of which only 2% is targeted for inspection (McCullough et al 2006).

As a result of current U. S. trade and inspection practices, new pests are introduced and established annually in the United States. In Florida, ten invasive insect species become established each year on average (Frank and Thomas 2009). The khapra beetle, *Trogoderma granarium*, is the only stored product pest in the United States that is classified as a quarantine pest (Arthur 2010b). Other stored product pests have the potential to be introduced and established in the United States, such as the larger grain borer, *Prostephanus truncates*. This native species from Central America was introduced into Africa where it has become a major pest of stored corn and cassava (Nansen et al. 2004). **The introduction rate of new pests in the**

United States and geographical proximity of exotic stored product pest species to the United States indicate a real potential for new stored product pests to be introduced into this country.

Sulfuryl fluoride has been used to eradicate structural infestations of exotic pest species before they have been further disseminated to become invasive. Sulfuryl fluoride was used to fumigate a home in Winter Haven, FL in 2002 to eradicate an infestation of the Chilean Recluse spider, *Loxosceles laeta* (Edwards and Skully 2002). The Chilean Recluse has the most toxic venom of any *Loxosceles* species and has been implicated in deaths in South America. This was the first documentation of this species in Florida and none have been observed since the fumigation. Spiders are common hitchhikers on pallets. ProFume® gas fumigant is used to control pervasive infestations of spiders that are human health pests, such as black and brown widow spiders, on wooden pallets (Rosenberg 2010). Fumigation with ProFume prevented workers from being envenomated while handling pallets and stopped the transfer of widow spiders to customer locations. In Dania Beach, FL in 2003, sulfuryl fluoride was used to eradicate aerial infestations of introduced arboreal termite, *Nasutitermes costalis*, which could not be contacted and controlled using residual insecticides (Dwinell 2003). It was the first record of a non-native geographical infestation in any continent by a termite species in the family Termitidae (Scheffrahn et al. 2002). Two mobile homes, serving as offices, and two boats in dry dock were fumigated with sulfuryl fluoride. Inspection to termite carton nest (author present) after the fumigation documented that all termites were killed by the treatment. These eradication fumigations were efficient, effective, and readily executed because the applications made within label parameters and experienced fumigators were available with all required equipment. **Similar eradication fumigations could not be done with ProFume in situations involving food processing facilities and storages if food tolerances for ProFume are removed per EPA's proposal.**

Conclusions:

The proposed removal of tolerances for ProFume® gas fumigant will result in treatments that are less effective and more expensive for pest control in food processing facilities. For commodity treatment, use of phosphine will significantly increase the cost of treatment due to substantial infrastructure changes and will increase the potential for insect resistance to phosphine without ProFume being available as a resistance management tool. Additional unintended consequences include: increased selection of insect resistance to the limited contact and residual insecticides labeled for treatment of commodities and food processing facilities, intensified shortages of natural pyrethrins for a broad spectrum of pest control uses, and no fumigant available for whole structure treatment to eradicate newly introduced stored product pests. For these reasons, the US EPA should not withdraw the food tolerances for sulfuryl fluoride.

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Table 1. Summary of Flour Mill Annual Income and Expenses Based on a Ten Year Average: Comparing Heat Treatment with Current Fumigation with ProFume® gas fumigant (500,000 ft^3 facility); Modified from Ranville and Cook (2011).

		Heat Treat	Sulfuryl fluoride (SF)	Heat vs. SF
	Total Shipped (cwt)	2,418,500[1]	2,450,000	
	Total Revenue/Sales	**31,426,400.00**	**31,835,700.00**	(409,300.00)
	Cost of Goods (raw material)	26,399,900.00	26,743,700.00	
	Mfg & Sales Cost (operating costs)	1,550,670.00	1,537,300.00	(13,370.00)
	Sub-total Operating Cost	27,950,570.00	28,281,000.00	330,430.00
Gross Margin	**Net Revenue**	**3,475,830.00**	**3,554,700.00**	(78,870.00)

Further Detail of Manufacturing Cost:		Heat	SF	Heat vs. SF
	BASE - Mfg & sales Cost	1,479,700.00	1,479,700.00	
Included in Original Table	Disinfestation		57,600.00	57,600.00
	Equipment	12,500.00		(12,500.00)
	Energy & Other	16,600.00		(16,600.00)
Missing Costs:	Labor to move product[2]	23,000.00		(23,000.00)
	Rental of trailers[2]	6,000.00		(6,000.00)
	Labor to monitor heat treatment[3]	7,200.00		(7,200.00)
	Equipment Repair/Maintenance[4]	2,500.00		(2,500.00)
	Replacement of fans[5]	770.00		(770.00)
	Replacement of sensors[6]	400.00		(400.00)
	Increased facility maintenance Cost	2,000.00		(2,000.00)
	Updated Manufacturing & Sales Cost	1,550,670.00	1,537,300.00	(13,370.00)

[1] Units reduced due to extra time to prepare and conduct a heat treatment; same units as product removal scenario for fumigation, Table 4, Ranville and Cook (2011)

[2] Same cost as product removal scenario for fumigation, Table 4, Ranville and Cook (2011)

[3] Assumed two people at $25.00/hour for 48 hours per heat treatment (3 times/year)

[4] Assumed 2% value of the heat treatment equipment for maintenance and repair

[5] Assumed 20% of 70 fans replaced over 10 years ($550/fan)

[6] Assumed 20% of sensor system ($20,000 total value) replaced over 10 years

Appendix II – Detailed Science Comments Pertaining to EPA's Proposed Tolerance Revocation for Sulfuryl Fluoride

DETAILED SCIENCE COMMENTS PERTAINING TO EPA'S PROPOSED TOLERANCE REVOCATION FOR SULFURYL FLUORIDE

I. INTRODUCTION

On January 19, 2011, the U.S. Environmental Protection Agency (EPA) published a proposed order in the Federal Register that would grant objections to tolerances for sulfuryl fluoride and fluoride established in 2004 and 2005 and would deny a stay for those tolerances (EPA, 2011a). The objection and stay request were filed by the Fluoride Action Network, the Environmental Working Group and Beyond Pesticides. EPA proposed granting the objections "because it agrees that aggregate exposure to fluoride for certain major identifiable population subgroups does not meet the safety standard in FFDCA section 408." At the same time, EPA proposed to deny the stay because "risks from continued sulfuryl fluoride use in the short term is insignificant while the environmental and economic consequences from a sudden withdrawal of sulfuryl fluoride, a methyl bromide replacement, are considerable." On April 6, 2011, EPA issued an addendum to the original proposed order which clarified some issues in the original proposed order and granted comment period extension requests. These comments are being submitted in response to the extended deadline of July 5, 2011.

The focus of these comments is on the technical aspects of the issues raised by the objections and EPA's proposal to grant the objections. Specifically, the theme of these comments is that EPA's proposal to grant the objections to the sulfuryl fluoride and fluoride tolerances does nothing to address the public health concerns with regard to aggregate exposures to fluoride whereas removal of sulfuryl fluoride as a pest control tool would increase risks for the whole food system and increase the need for further use of methyl bromide.

To put the issue into context, a major contributor to current views of fluoride toxicity is the recent decision by EPA to re-classify severe dental fluorosis (SDF) as an adverse health effect associated with fluoride exposure and the attendant revision of the fluoride reference dose (RfD) to 0.08 mg/kg/day (EPA, 2010a). SDF is currently observed in <1% of the population aged 6-49 years, and moderate dental fluorosis is currently observed in 2% of the population aged 6-49 years (Beltrán-Aguilar, et al., 2010). Thus, dental fluorosis impacts only a small portion of the total US population. There is clearly considerable conservatism in EPA's exposure assessments, because the high aggregate exposures estimated for some populations would suggest much higher prevalence of dental fluorosis than what is observed in the population.

In short, these comments demonstrate that EPA's proposal to phase out sulfuryl fluoride will have no appreciable impact on aggregate fluoride exposures and will therefore not reduce the overall prevalence of severe dental fluorosis. At the same time, removing the food-related uses of sulfuryl fluoride will increase risks associated with contamination of the food supply and may delay U.S. efforts to discontinue methyl bromide critical use exemptions, as the country has committed to doing under the Montreal protocol. Therefore, Dow AgroSciences contends that the proposal to phase out sulfuryl fluoride as a food and structural fumigant is not in the public's best interest.

These comments are structured to address the following issues:

- The proposed phase-out of sulfuryl fluoride tolerances will have negligible impact on aggregate fluoride exposures. In fact, aggregate fluoride exposures for those subpopulations currently estimated by EPA to exceed the Agency's newly proposed reference dose (RfD) will still exceed the new RfD after the proposed phase-out of sulfuryl fluoride. Simply stated, the use of sulfuryl fluoride contributes insignificantly to aggregate fluoride exposure, and therefore removing the use of sulfuryl fluoride will not address EPA's public health concerns for aggregate fluoride exposures.

- Additional analyses demonstrate that the revised proposed beneficial level for fluoridation of drinking water (0.7 mg/L) would result in aggregate exposures greater than the newly proposed reference dose (RfD) of 0.08 mg/kg/day for some age groups, even when all sulfuryl fluoride tolerances have been terminated.

- An analysis of data on fluoride concentrations in public water systems from the EPA Office of Water and data on the prevalence of dental fluorosis from NHANES indicates that fluoride concentration in water is a significant determinant in the occurrence of moderate and severe dental fluorosis.

- Fluoride is intentionally added to toothpaste for the express purpose of preventing dental caries. Unfortunately, there appears to be little documentation available concerning how the recommended fluoride concentration in toothpaste was determined. In addition, there is ambiguity about best use practices and labeling, including possible scenarios where the use of fluoridated toothpaste is not warranted due to either water treatment or naturally-occurring levels of fluoride. Consequently, potential fluoride exposure associated with toothpaste may warrant re-evaluation by FDA.

- Removal of sulfuryl fluoride as a tool to control pests in food handling and storage facilities and on certain commodities will entail major disruption in the food processing sector. Removal of sulfuryl fluoride could give rise to increased risk of disease due to lack of alternatives, delay in putting alternatives into place, and the use of alternatives that are less effective and/or more costly. Further delays in the complete phase-out of methyl bromide and increased costs associated with the expensive transitions to other technology and active ingredients could also result.

Each of these issues is discussed in the sections below.

II. AGGREGATE FLUORIDE EXPOSURE ISSUES

A. Impact of Dietary Exposures of Proposed Phase-Out

As outlined in recent Federal Register notices (76 FR 3422-3449; 76 FR 19001-19003), EPA is proposing to phase out all food-related uses of sulfuryl fluoride. The proposed phase-out will consist of three phases. For commodities with previously cancelled tolerances (dried eggs and

powdered milk), sulfuryl fluoride tolerances will terminate immediately upon implementation of the order. Next, sulfuryl fluoride tolerances for commodities with little or no actual use will be terminated within 90 days of implementation of the order. And finally, a three year period will be allowed for tolerances for those directly treated commodities with significant use of sulfuryl fluoride and for tolerances covering residues that result from structural fumigation uses of sulfuryl fluoride.

EPA (2011b) has produced a series of fluoride aggregate exposure assessments for the purposes of understanding the potential fluoride exposures in the population. The EPA human health risk assessment includes three scenarios conducted under the auspices of the Federal Food, Drug and Cosmetic Act (FFDCA) in which drinking water is assumed to contain 1.76 mg/L fluoride, 2.28 mg/L fluoride or 2.59 mg/L fluoride, respectively. These concentration estimates represent the average detected concentration in water systems in which at least one sample was measured greater than 2 mg/L, one sample was measured greater than 3 mg/L and one sample was measured greater than 4 mg/L, respectively, as summarized from public water system fluoride monitoring data from 2002-2005 (EPA, 2011b). The so-called "FFDCA estimates" include average fluoride exposure from drinking water, commercial beverages and soil; average exposure to fluoride residues from sulfuryl fluoride treatment, and two brushings per day with fluoridated toothpaste. EPA (2011b) has concluded that these estimates apply to relatively small but highly exposed subpopulations. Another scenario included in the analysis was the Office of Water's Relative Source Contribution Analysis (EPA, 2010b), which assumes 90th percentile consumption of drinking water containing 0.87 mg/L fluoride, average exposure from food, commercial beverages and soil; average exposure to fluoride residues from sulfuryl fluoride treatment, and one brushing per day with fluoridated toothpaste. Finally, EPA included an "Average" scenario, which assumes average consumption of drinking water containing 0.87 mg/L fluoride, average exposure from food, commercial beverages and soil; average exposure to fluoride residues from sulfuryl fluoride treatment, and one brushing per day with fluoridated toothpaste. The main focus of EPA's evaluation was on the FFDCA scenarios, however, so these comments focus on the FFDCA scenarios, with some mention of the relative source contribution (RSC) scenario.

For these comments, two new aggregate exposure assessments were conducted to evaluate the impact of (1) the immediate and 90-day phase-out and (2) the total phase-out of sulfuryl fluoride on total aggregate fluoride exposures. Thus, only dietary fluoride exposures associated with the use of sulfuryl fluoride were changed in these aggregate calculations – all other inputs calculated by EPA (2011b) were used without modification. A dietary assessment was conducted to estimate the reduction in fluoride dietary exposure associated with the immediate and 90-day phase-outs (i.e., the intermediate step en route to the complete phase-out in 3 years). In addition, the impact of the reduced exposures from the phase-out of sulfuryl fluoride on total fluoride aggregate exposures was calculated. The result is a series of dietary and aggregate exposures which illustrate the negligible reductions in aggregate fluoride exposure achieved with the proposed phase-out of sulfuryl fluoride, which allows appreciation of the nominal impact that this action has on exposure and risk.

EPA (2011b) recently estimated that fluoride dietary exposures associated with all food-related, labeled structural and commodity uses of sulfuryl fluoride are 0.0011-0.0030 mg/kg/day

(depending on the age group), which accounts for 1.7%-4.0% of the aggregate fluoride exposure (depending on age group and assumption regarding fluoride concentration in drinking water).[15] From this starting point, the question to answer is "What reduction in aggregate fluoride exposure would result from EPA's proposed phase-out of sulfuryl fluoride?" The answer to that question is two-part: (1) the reduction in aggregate fluoride exposure associated with the initial phase-out and (2) the reduction in aggregate fluoride exposure associated with the total phase-out of sulfuryl fluoride. Obviously, the dietary fluoride exposure attributed to sulfuryl fluoride will be zero at the time when the phase-out is complete. In the interim, however, a dietary assessment is required to calculate the reduction in fluoride exposure due to the proposed initial phase-out.

The proposed initial phase-out will eliminate all tolerances for sulfuryl fluoride uses except: (1) structural fumigation and (2) commodity fumigation for walnuts, dried fruit (other than raisins) and cocoa. The fluoride dietary exposure assessment reflecting the initial phase-out required no change to the structural fumigation assessment conducted by EPA (2011b), but the direct food treatment assessment was revised to include only walnuts, dried fruit (other than raisins) and cocoa. EPA's residue input file for the direct commodity fumigation dietary assessment was revised to include only these few select commodities. Dietary fluoride exposures reflecting the initial phase-out were calculated using the revised fluoride residue input file. The results are summarized in Table 1 below. At the initial 90-day phase-out, fluoride exposures associated with commodity fumigations would be reduced 51.3%-76.7% (depending upon the age group), but there is no reduction in the fluoride exposure from structural uses at the initial phase-out period, so the overall total reduction in fluoride exposures from remaining sulfuryl fluoride uses at this point would be 39.1%-54.4% (depending on the age group). Currently, EPA (2011b) estimates fluoride dietary exposure from sulfuryl fluoride uses to be 0.0011-0.0030 mg/kg/day. At the initial phase-out, fluoride exposures associated with the remaining sulfuryl fluoride uses will decline to 0.0005-0.0017 mg/kg/day and would account for 0.8% to 2.1% of the total aggregate fluoride exposure. Upon the complete elimination of sulfuryl fluoride, the fluoride exposures attributable to sulfuryl fluoride will obviously decline to zero.

[15] The range of exposures attributed to food uses of sulfuryl fluoride (0.0011-0.0030 mg/kg/day) is only slightly greater than the range attributed to airborne fluoride (0.0006-0.0020 mg/kg/day or 0.013-0.042 mg/day) as estimated by EPA (2004) and the range in urban areas (0.020-0.040 mg/day) as estimated by NRC (2006). NRC (2006) estimated exposures via airborne fluoride of 2-4 µg/day in rural areas and 20-40 µg/day in urban areas. Whereas EPA (2010b) reported both ranges on page 84, the summary on page 88 lists only the rural range. EPA (2011b) concluded that air exposures to fluoride were insignificant based on the range for rural exposures. However, fluoride exposures from airborne sources in urban areas are comparable (one-half to two-thirds) to those from food uses of sulfuryl fluoride. Consequently, this brings into question EPA's conclusion that air exposures are insignificant and therefore not included in the aggregate assessment, whereas those from food uses of sulfuryl fluoride are included in the aggregate assessment.

Table 1. Impact of the Initial Phase-Out of Sulfuryl Fluoride Uses on Related Fluoride Dietary Exposures

Age Group (years)	Fluoride Exposure from Food Fumigation				Fluoride Exposure from Structural Fumigation (mg/kg/day)	Total Fluoride Exposure from All Sulfuryl Fluoride Treatments		
	From EPA (2011b) (mg/kg/day)	At Initial 90-Day Phase-Out (mg/kg/day)	Reduction (mg/kg/day)	Reduction (%)		From EPA (2011b) (mg/kg/day)	At Initial 90-Day Phase-Out [A] (mg/kg/day)	Reduction (%)
0.5 - < 1	0.0019	0.0005	0.0015	76.7%	0.0008	0.0027	0.0012	54.4%
1 - < 4	0.0022	0.0008	0.0014	63.5%	0.0008	0.0030	0.0016	46.4%
4 - < 7	0.0022	0.0010	0.0012	54.4%	0.0007	0.0030	0.0017	40.9%
7 - < 11	0.0017	0.0008	0.0009	51.3%	0.0005	0.0022	0.0014	39.1%
11 - < 14	0.0014	0.0006	0.0009	61.3%	0.0004	0.0018	0.0009	48.3%
14+	0.0008	0.0002	0.0006	72.1%	0.0003	0.0011	0.0005	54.4%

[A] Due to rounding of reported exposure estimates in the table, total exposure may not correspond exactly to sum of the component values.

The next step was to determine the impact of removing sulfuryl fluoride uses (for both the initial and complete phase-out) on aggregate fluoride exposures. Aggregate fluoride exposure includes exposures from the several sources: background (i.e., naturally-occurring) fluoride levels in food, commercial beverages, toothpaste, ingestion of soil, fluoride residues attributable to sulfuryl fluoride, and drinking water. Table 2 summarizes the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposure for all subpopulations of interest. The exposure estimates summarized in Table 2 clearly demonstrate that eliminating sulfuryl fluoride will have no meaningful impact on aggregate fluoride exposures for any subpopulation. Consider, for example, aggregate fluoride exposures for those who consume drinking water containing 2.59 mg/L fluoride (i.e., the highest fluoride water concentration evaluated in the FFDCA assessments). Aggregate fluoride exposures estimated by EPA range from 0.056 mg/kg/day to 0.160 mg/kg/day (depending on the age group). When sulfuryl fluoride's food-related uses are completely eliminated, aggregate fluoride exposures will range from 0.055 mg/kg/day to 0.157 mg/kg/day. Thus, elimination of sulfuryl fluoride will have no discernible impact on aggregate fluoride exposures – and aggregate fluoride exposures for those subpopulations which are currently estimated by EPA to exceed the Agency's newly calculated RfD will continue to exceed the new RfD.

Table 2. Impact of Removing Sulfuryl Fluoride Uses on Aggregate Fluoride Exposure

Age Range (years)	Exposure Estimates (mg/kg/day)						Aggregate Exposure Estimates (mg/kg/day)				
	Dietary (food-background)	Dietary (beverages)	Toothpaste (1/day)	Toothpaste (2/day)	Soil	SF	Average [A]	OW RSCA [B]	FFDCA [C]		
									1.76 mg F/L	2.28 mg F/L	2.59 mg F/L
EPA Estimates - Table 9, 7-Jan-2011 Human Health Risk Assessment											
0.5 - < 1	0.029	0	0.0078	0.016	0.0022	0.0027	0.080	0.135	0.127	0.150	0.160
1 - < 4	0.011	0.026	0.024	0.049	0.0029	0.0030	0.087	0.112	0.132	0.144	0.151
4 - < 7	0.017	0.026	0.010	0.021	0.0019	0.0030	0.074	0.097	0.102	0.112	0.118
7 - < 11	0.013	0.019	0.0056	0.011	0.0013	0.0022	0.053	0.068	0.071	0.078	0.082
11 - < 14	0.0092	0.0075	0.0039	0.0078	0.00078	0.0018	0.032	0.047	0.045	0.051	0.054
14+	0.0054	0.0084	0.0014	0.0029	0.00029	0.0011	0.030	0.042	0.044	0.051	0.056
Initial 90-Day Phase-Out – Remove Certain SF Uses											
0.5 - < 1	0.029	0	0.0078	0.016	0.0022	0.0012	0.078	0.133	0.125	0.148	0.158
1 - < 4	0.011	0.026	0.024	0.049	0.0029	0.0016	0.086	0.111	0.131	0.143	0.150
4 - < 7	0.017	0.026	0.010	0.021	0.0019	0.0017	0.073	0.096	0.101	0.111	0.117
7 - < 11	0.013	0.019	0.0056	0.011	0.0013	0.0014	0.052	0.067	0.070	0.077	0.081
11 - < 14	0.0092	0.0075	0.0039	0.0078	0.00078	0.0009	0.031	0.046	0.044	0.050	0.053
14+	0.0054	0.0084	0.0014	0.0029	0.00029	0.0005	0.029	0.041	0.043	0.050	0.055
Complete Phase-Out – Remove all SF Uses											
0.5 - < 1	0.029	0	0.0078	0.016	0.0022	- -	0.077	0.132	0.124	0.147	0.157
1 - < 4	0.011	0.026	0.024	0.049	0.0029	- -	0.084	0.129	0.129	0.141	0.148
4 - < 7	0.017	0.026	0.010	0.021	0.0019	- -	0.071	0.094	0.099	0.109	0.115
7 - < 11	0.013	0.019	0.0056	0.011	0.0013	- -	0.051	0.066	0.068	0.075	0.079
11 - < 14	0.0092	0.0075	0.0039	0.0078	0.00078	- -	0.030	0.045	0.043	0.049	0.052
14+	0.0054	0.0084	0.0014	0.0029	0.00029	- -	0.028	0.040	0.043	0.050	0.055

[A] Assumes average dietary exposure from background levels in food + average water consumption of drinking water (0.87 mg F/L + 1 brushing per day + average exposure estimates from soil + average exposure estimates from sulfuryl fluoride uses.

[B] Assumes 90th percentile consumption of drinking water (consumers only) at 0.87 mg F/L + average exposure from food (background) and commercial beverages + 1 brushing per day + average exposure estimates from soil + average exposure estimates from sulfuryl fluoride uses.

[C] Assumes drinking water exposure from water at indicated concentration + average exposure from food (background) and commercial beverages + 2 brushing per day + average exposure estimates from soil + average exposure estimates from sulfuryl fluoride uses.

A series of graphs visually demonstrate the negligible impact that the proposed phase-out of sulfuryl fluoride's food-related uses will have on total aggregate fluoride exposures. The focus of these figures is on the age groups with the highest estimated aggregate fluoride exposure (i.e., infants 0.5 to 1 yr, children 1 to 4 yrs, and children 4 to 7 yrs). The sources of fluoride exposures are indicated on each graph, which allows an appreciation of the relative contribution of the various sources to the total aggregate exposures. The exposure estimates presented in Figures 1 through 9 are also summarized in tabular form in Table 3.

- Figures 1 through 3 illustrate the sources of aggregate fluoride exposure for infants (0.5 to 1 yr). Figure 1 shows the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposures for infants whose drinking water contains 2.59 mg/L fluoride, and Figure 2 shows the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposures for infants whose drinking water contains 1.76 mg/L fluoride. Figure 3 shows the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposures for infants when the EPA Office of Water's Relative Source Contribution (RSC) analysis is used. From these Figures, it is clear that drinking water is the major source of fluoride exposure for this age group, with drinking water alone accounting for sufficient exposure to nearly equal or exceed the RfD (0.08 mg/kg/day). Naturally-occurring fluoride residues in food and toothpaste are also major contributors to aggregate fluoride exposure. Finally, Figures 1 through 3 also demonstrate that eliminating sulfuryl fluoride will not result in total aggregate fluoride exposures below the RfD for infants 0.5 to 1 yr.

- Figures 4 through 6 illustrate the sources of aggregate fluoride exposure for children (1 to 4 yrs). Figure 4 shows the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposures for children (1 to 4 yrs) whose drinking water contains 2.59 mg/L fluoride, and Figure 5 shows the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposures for children (1 to 4 yrs) whose drinking water contains 1.76 mg/L fluoride. Figure 6 shows the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposures for children (1 to 4 years) when the EPA Office of Water RSC analysis is used. From these Figures, it is clear that drinking water and commercial beverages are major sources of fluoride exposure for this age group with drinking water and beverages constituting exposure nearly equal to or exceeding the RfD. Toothpaste and naturally-occurring fluoride residues in food are also major contributors to aggregate fluoride exposure. Finally, Figures 4 through 6 also demonstrate that eliminating sulfuryl fluoride will not result in total aggregate fluoride exposures below the RfD for children (1 to 4 yrs).

- Figures 7 through 9 illustrate the sources of aggregate fluoride exposure for children (4 to 7 yrs). Figure 7 shows the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposures for children (4 to 7 yrs) whose drinking water contains 2.59 mg/L fluoride, and Figure 8 shows the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposures for children (4 to 7 yrs) whose drinking water contains 1.76 mg/L fluoride. Figure 9 shows the impact of the sulfuryl fluoride phase-out on aggregate fluoride exposures for children (4 to 7 years) when the EPA Office of Water's RSC analysis is used. From these Figures, it is clear that drinking water and commercial beverages are

major sources of fluoride exposure for this age group with drinking water and beverages constituting exposure equal to 74%-94% of the RfD. Toothpaste and naturally-occurring fluoride residues in food are also major contributors to aggregate fluoride exposure. Finally, Figures 7 through 9 also demonstrate that eliminating sulfuryl fluoride will not result in total aggregate fluoride exposures below the RfD for children (4 to 7 yrs).

In conclusion, this analysis shows that the proposed phase-out of sulfuryl fluoride tolerances will have negligible impact on total aggregate fluoride exposures.

Table 3. Summary of Aggregate Exposure Calculations Showing Impact of Sulfuryl Fluoride Phase-Out

	Fluoride Exposure (mg/kg/day)						
	Drinking Water	**Beverages**	**Food (Background)**	**Tooth Paste**	**Soil**	**Sulfuryl Fluoride**	**Total**
INFANTS (6 MONTHS – 1 YEAR OLD)							
"High" Drinking Water Concentration = 2.59 mg F/L							
Current Estimate	0.11	n.a.	0.029	0.016	0.0022	0.0027	0.160
Initial Phase-out						0.0012	0.158
Complete Phase-out						n.a.	0.157
"Low" Drinking Water Concentration = 1.76 mg F/L							
Current Estimate	0.077	n.a.	0.029	0.016	0.0022	0.0027	0.127
Initial Phase-out						0.0012	0.125
Complete Phase-out						n.a.	0.124
Office of Water Relative Source Contribution Assessment							
Current	0.093	n.a.	0.029	0.0078	0.0022	0.0027	0.135
Initial Phase-out						0.0012	0.133
Complete Phase-out						n.a.	0.132
CHILDREN (1 - 4 YEARS OLD)							
"High" Drinking Water Concentration = 2.59 mg F/L							
Current Estimate	0.059	0.026	0.011	0.049	0.0029	0.0030	0.151
Initial Phase-out						0.0016	0.150
Complete Phase-out						n.a.	0.148
"Low" Drinking Water Concentration = 1.76 mg F/L							
Current Estimate	0.040	0.026	0.011	0.049	0.0029	0.0030	0.132
Initial Phase-out						0.0016	0.131
Complete Phase-out						n.a.	0.129
Office of Water Relative Source Contribution Assessment							
Current Estimate	0.045	0.026	0.011	0.024	0.0029	0.0030	0.112
Initial Phase-out						0.0016	0.111
Complete Phase-out						n.a.	0.109
CHILDREN (4 - 7 YEARS OLD)							
"High" Drinking Water Concentration = 2.59 mg F/L							
Current	0.049	0.026	0.017	0.021	0.0019	0.0030	0.118
Initial Phase-out						0.0017	0.117
Complete Phase-out						n.a.	0.115
"Low" Drinking Water Concentration = 1.76 mg F/L							
Current	0.033	0.026	0.017	0.021	0.0019	0.0030	0.102
Initial Phase-out						0.0017	0.101
Complete Phase-out						n.a.	0.099
Office of Water Relative Source Contribution Assessment							
Current	0.039	0.026	0.017	0.01	0.0019	0.0030	0.097
Initial Phase-out						0.0017	0.096
Complete Phase-out						n.a.	0.094

Figure 1. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Infants (6 months to 1 year) in Areas with Drinking Water Containing 2.59 mg/L Fluoride

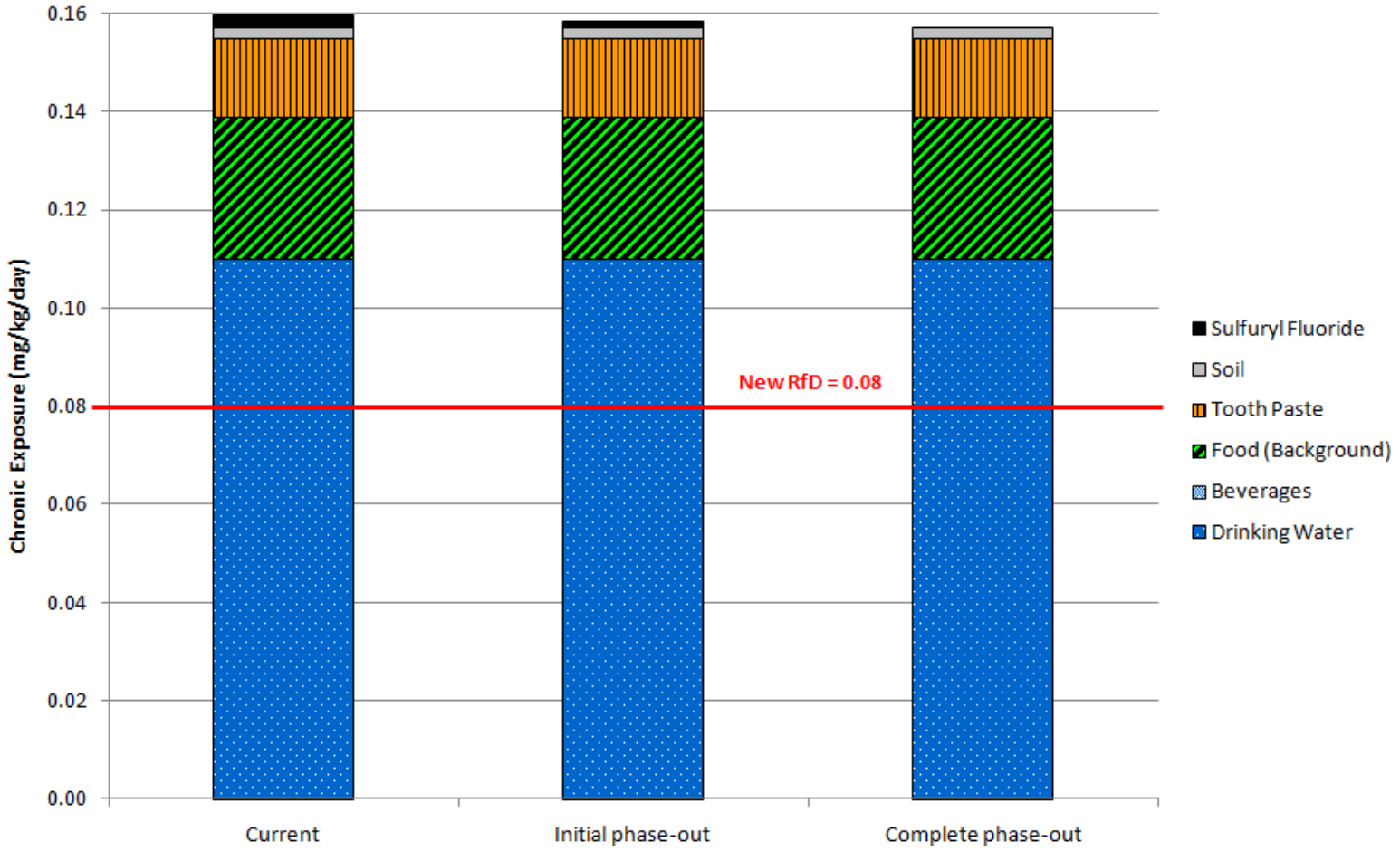


Figure 2. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Infants (6 months to 1 year) in Areas with Drinking Water Containing 1.76 mg/L Fluoride

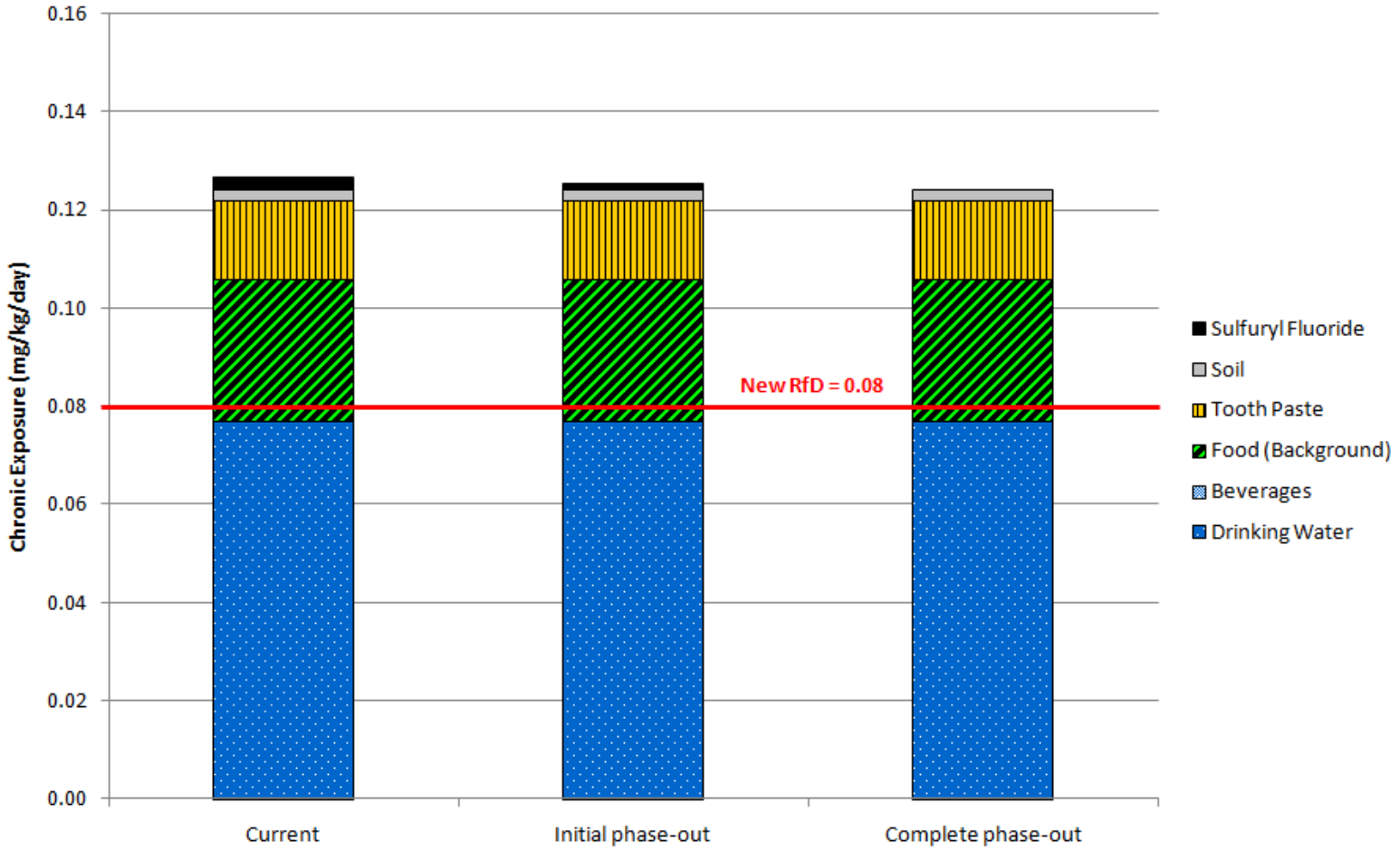


Figure 3. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Infants (6 months to 1 year) Using the Relative Source Contribution (RSC) Exposure Estimates

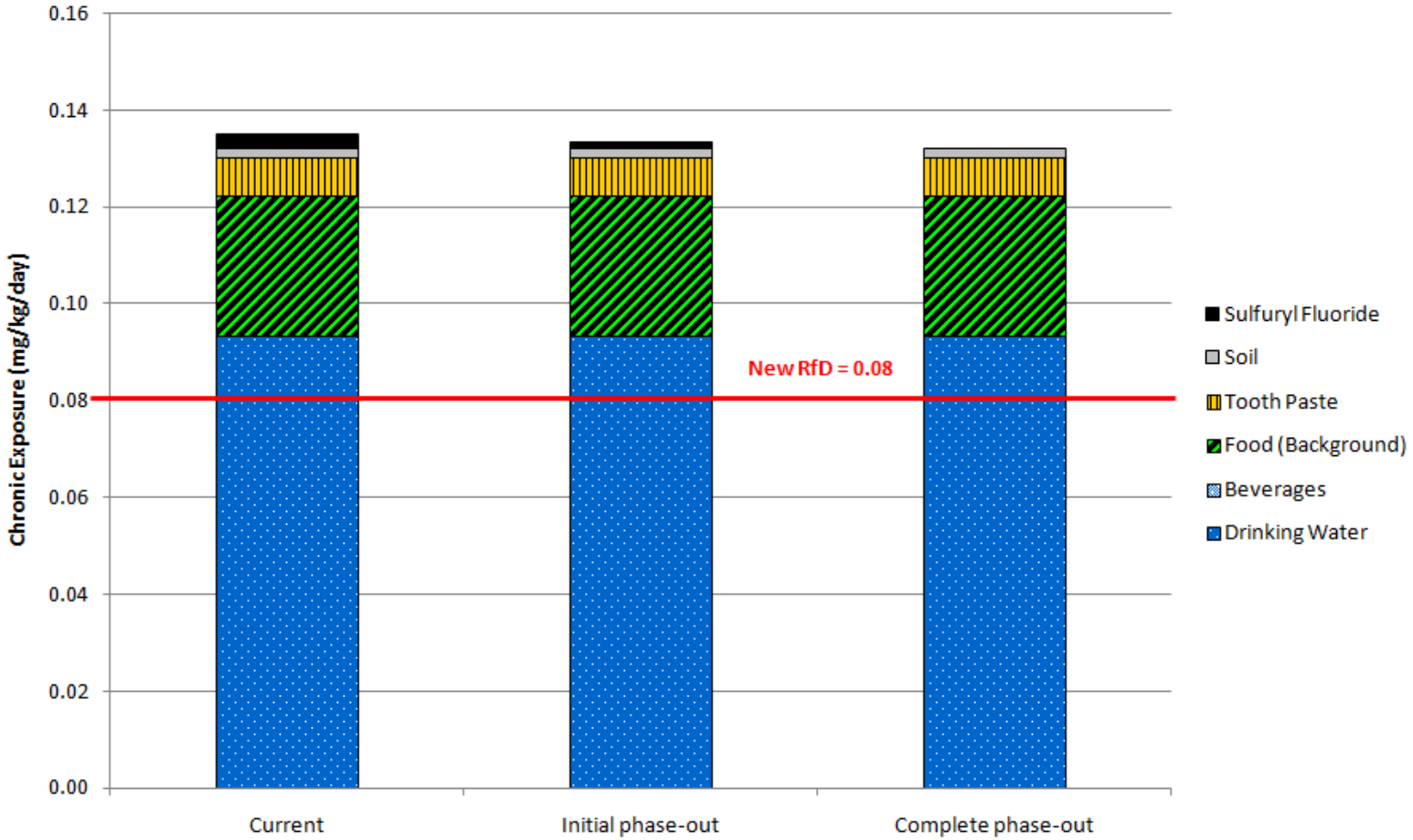


Figure 4. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Children (1 to 4 years) in Areas with Drinking Water Containing 2.59 mg/L Fluoride

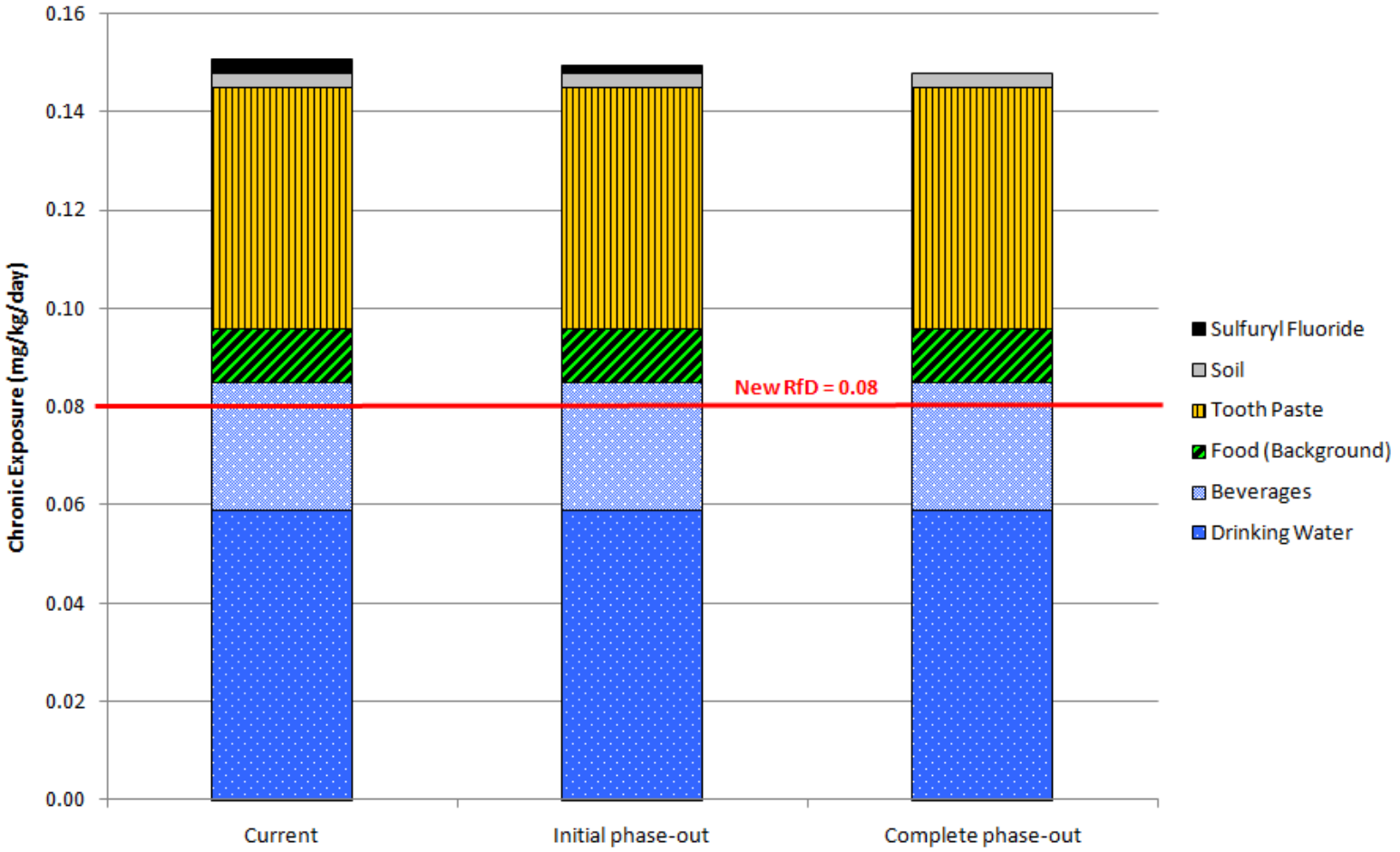


Figure 5. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Children (1 to 4 years) in Areas with Drinking Water Containing 1.76 mg/L Fluoride

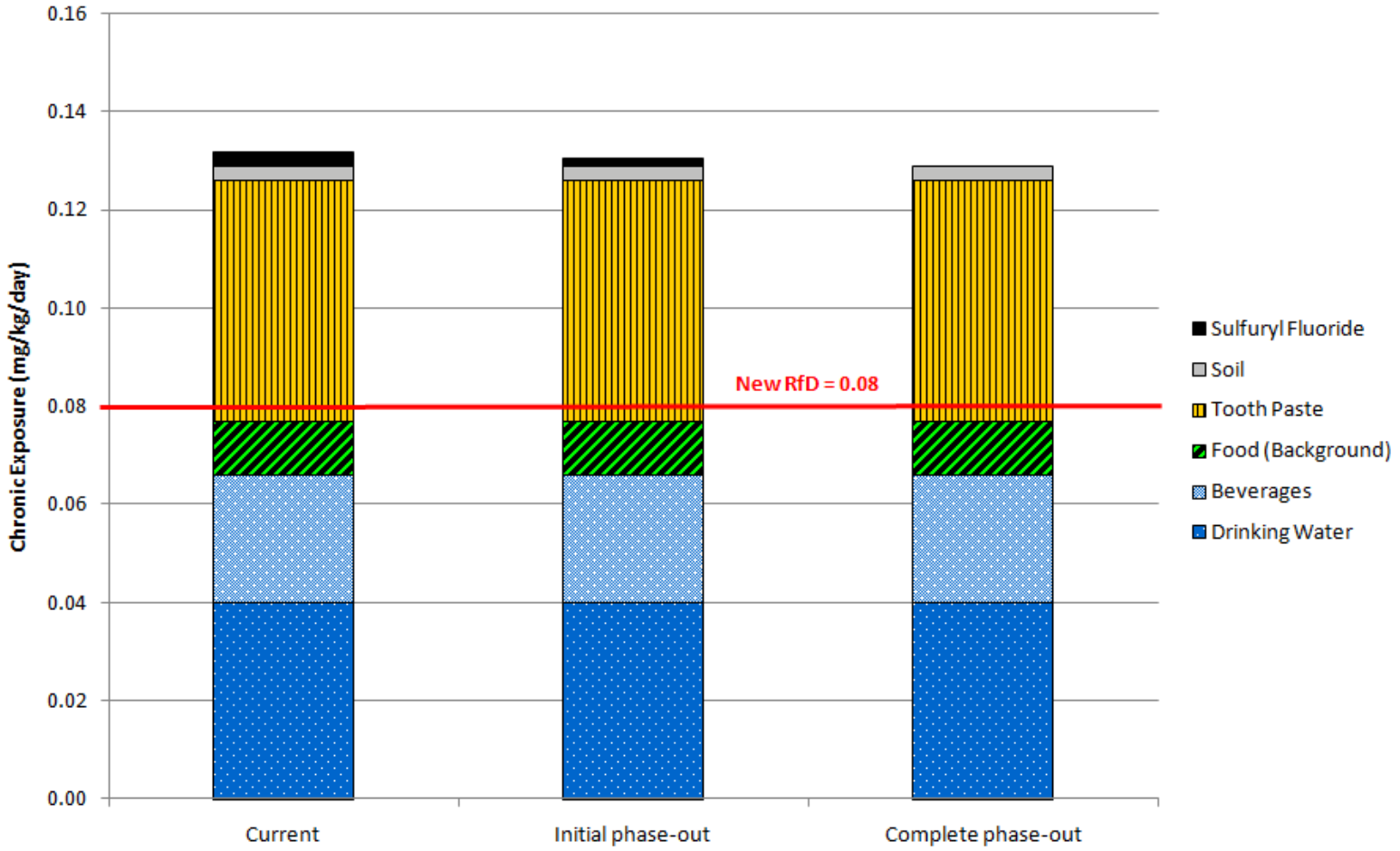


Figure 6. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Children (1 to 4 years) Using Relative Source Contribution (RSC) Exposure Estimates

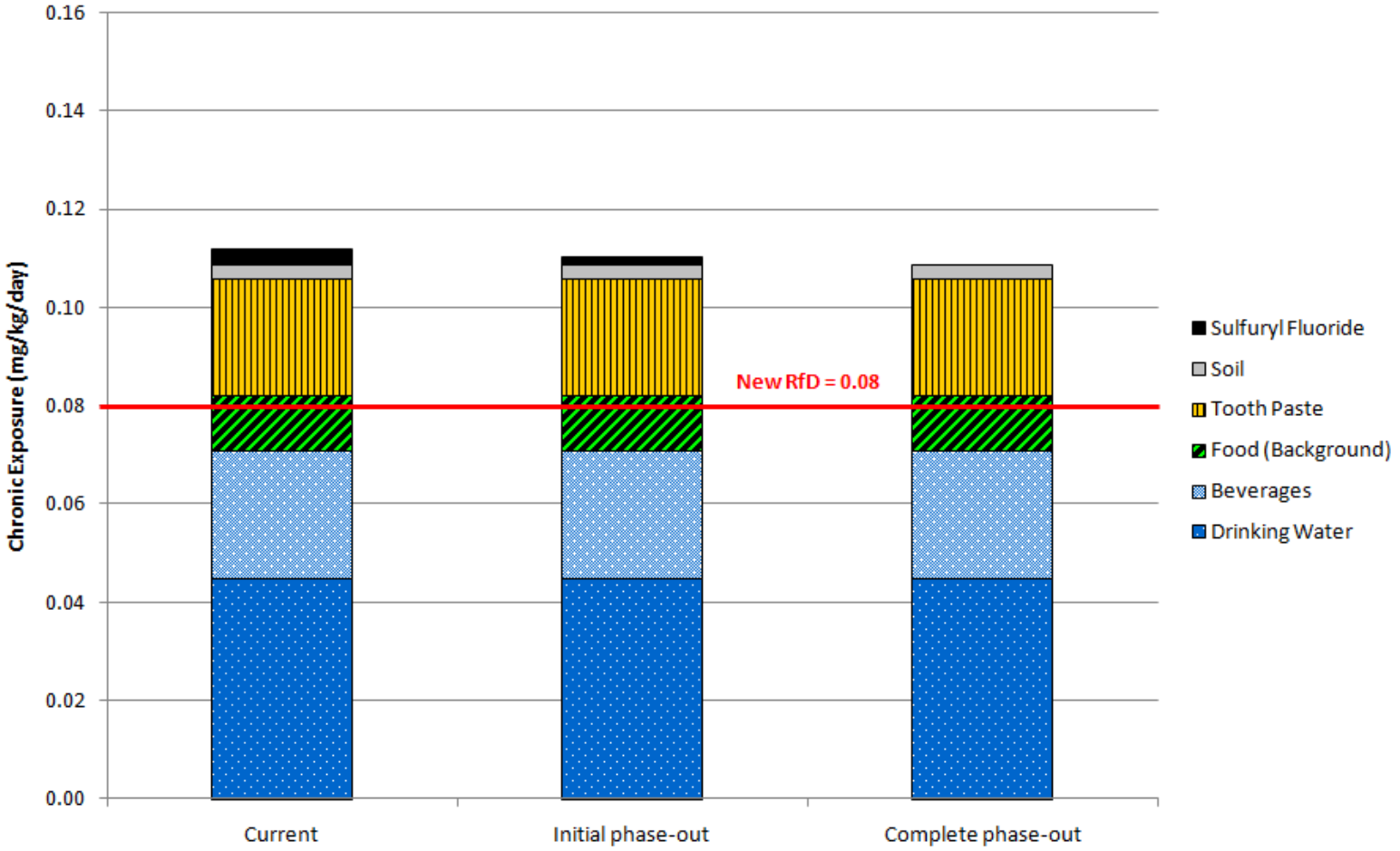


Figure 7. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Children (4 to 7 years) in Areas with Drinking Water Containing 2.59 mg/L Fluoride

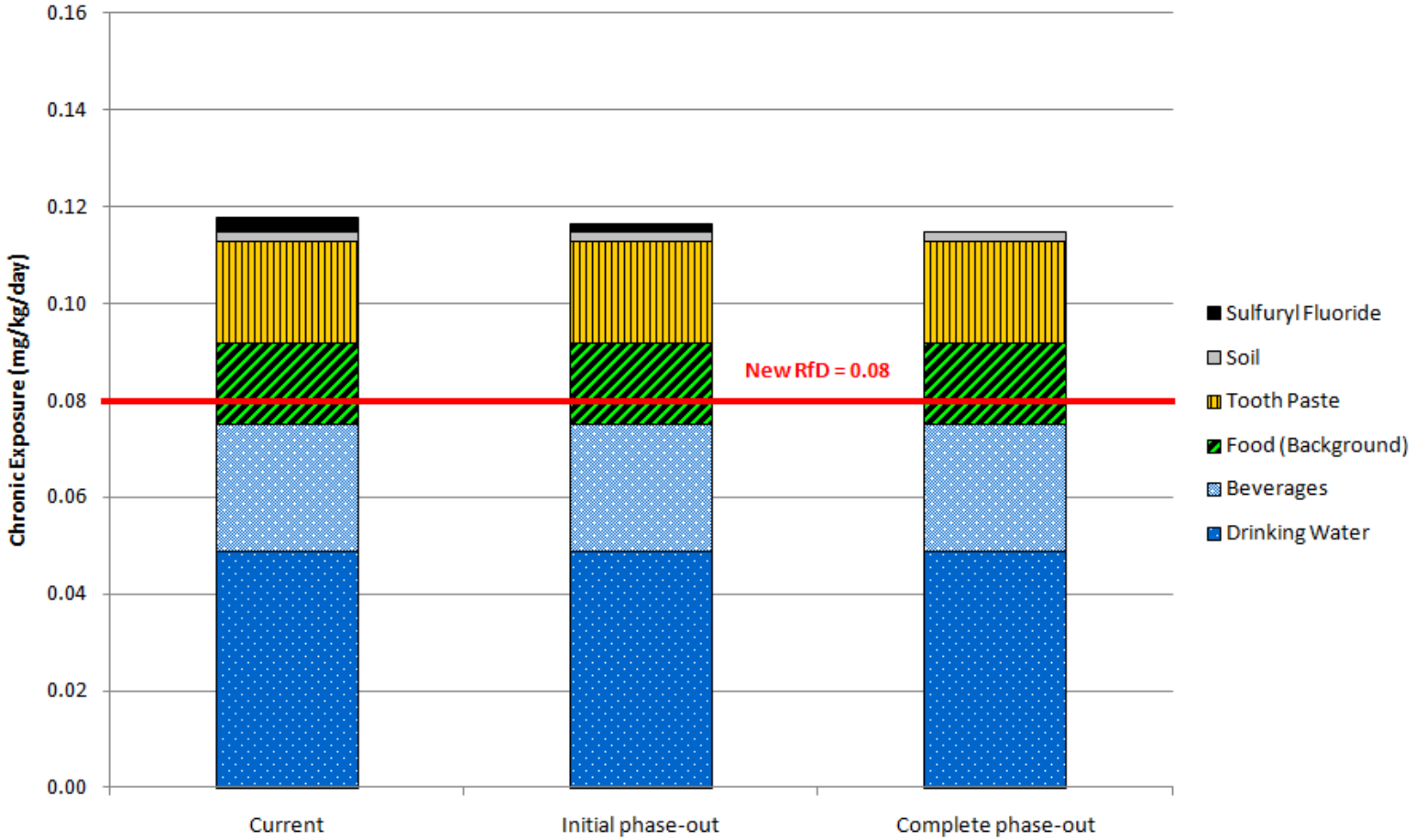


Figure 8. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Children (4 to 7 years) in Areas with Drinking Water Containing 1.76 mg/L Fluoride

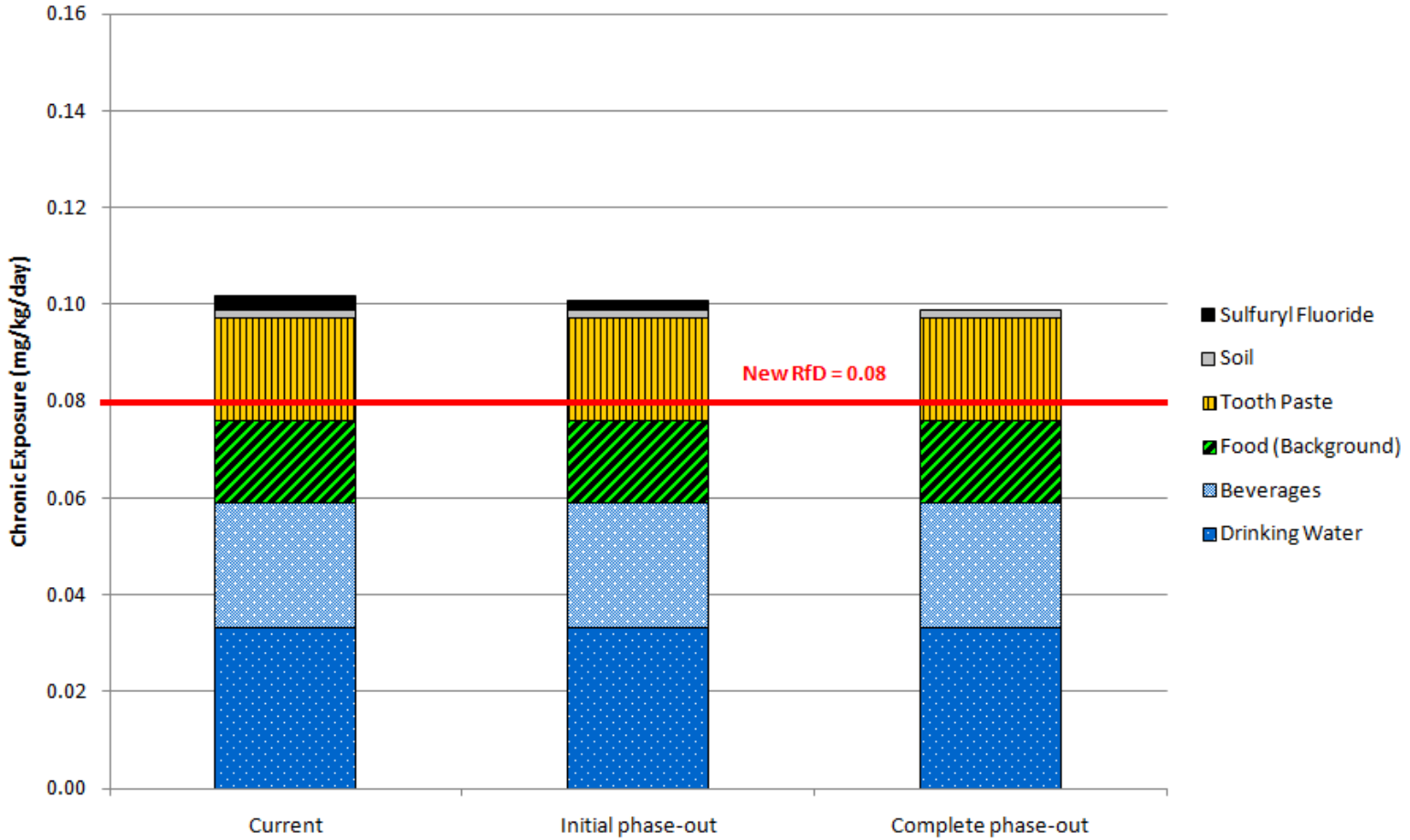
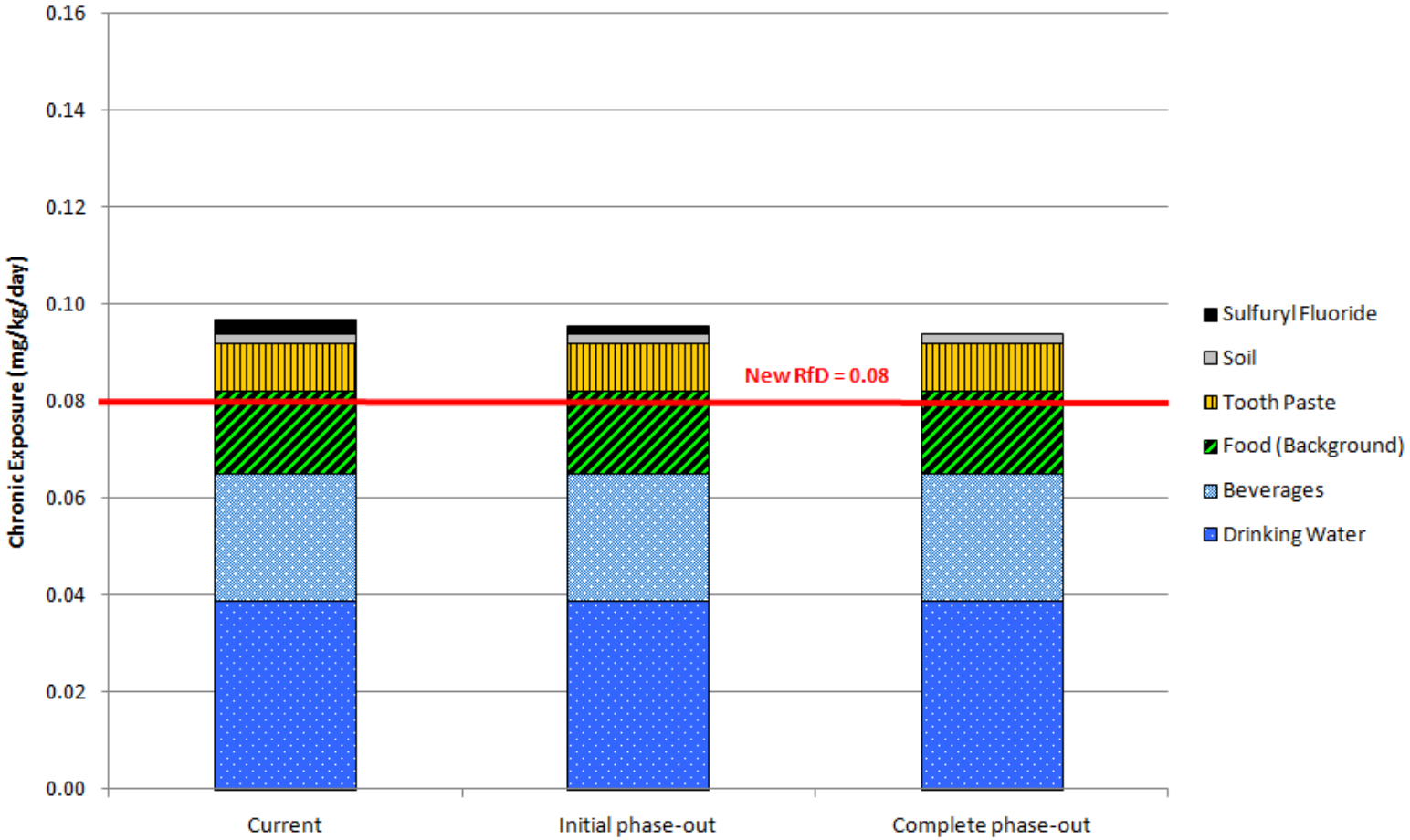


Figure 9. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Children (4 to 7 years) Using Relative Source Contribution (RSC) Exposure Estimates



B. Impact on Aggregate Fluoride Exposures if Water Contains Fluoride at the Proposed Beneficial Level (0.7 mg/L)

The U.S. Department of Health and Human Services (HHS) has recently proposed that the recommended level of fluoride in water for the prevention of dental caries be revised from a range of 0.7 to 1.2 mg/L to the low end of that range, i.e., 0.7 mg/L (HHS, 2011). The proposed revision raises the question of what aggregate fluoride exposures would be for select subpopulations if all water were to contain no more than 0.7 mg/L. The purpose of this section of these comments is to explore this question.

Fluoride exposures associated with commercial beverages and drinking water were reported by EPA in the January 7, 2011, aggregate assessment (EPA, 2011b). Commercial beverages were assumed to contain an average of 0.87 mg/L fluoride, and various concentrations were assumed for drinking water (up to 2.59 mg/L). In this assessment, the EPA fluoride exposure estimates were adjusted by the ratio of the proposed beneficial concentration (0.7 mg/L) to that in commercial beverages (0.87 mg/L) or drinking water (e.g., 2.59 mg/L). When these adjustments are made, the aggregate exposures in Table 4 result. For infants and children 4-7 years old, the aggregate exposures are just at or below the RfD (0.08 mg/kg/day), but for children 1-4 years old, aggregate fluoride exposures would be approximately 0.1 mg/kg/day, which is greater than the RfD. This analysis demonstrates that, even at the recommended beneficial level of fluoride in water (0.7 mg/L), at least some segments of the population (i.e., young children most at risk of SDF) would potentially experience aggregate fluoride exposures greater than the RfD. For children 1-4 years old, toothpaste constitutes approximately one-half the total fluoride exposure. Thus, this analysis points to the important role of dental professionals in recommending appropriate use of fluoridated toothpaste for young children in areas where the water contains fluoride, particularly high levels of naturally-occurring fluoride. The increase in the incidence of dental fluorosis noted by CDC between 1986–1987 and 1999–2004 (Beltrán-Aguilar, et al., 2010) can be attributed, at least in part, to excess fluoride exposures arising from unnecessary use of fluoridated toothpaste.

An additional point demonstrated by Table 4 is that the proposed phase-out of sulfuryl fluoride tolerances will have a negligible impact on total aggregate fluoride exposures, even if all water were to contain no more than 0.7 mg/L fluoride. In other words, potential fluoride exposures associated with the use of sulfuryl fluoride contribute insignificantly to total aggregate fluoride exposures and risks. Figures 10-12 illustrate this point graphically for select age groups. Removing sulfuryl fluoride will not result in sufficient reductions in exposures for EPA to demonstrate that any subpopulation is at lower risk for dental fluorosis than they were prior to the removal of sulfuryl fluoride.

Table 4. Impact of Proposed Sulfuryl Fluoride Phase-Out on Aggregate Fluoride Exposures with All Water Sources at 0.7 mg/L Fluoride

	Fluoride Exposure (mg/kg/day)						
	Drinking Water	**Beverages**	**Food (Background)**	**Tooth Paste**	**Soil**	**Sulfuryl Fluoride**	**Total**
Infants <0.5 - 1 years							
Current	0.0297	n.a.	0.029	0.016	0.0022	0.0027	0.080
Partial Phase-out						0.0012	0.078
Complete Phase-out						n.a.	0.077
Children 1 - <4 years							
Current	0.0159	0.0209	0.011	0.049	0.0029	0.0030	0.103
Partial Phase-out						0.0016	0.101
Complete Phase-out						n.a.	0.100
Children 4 - <7 years							
Current	0.0131	0.0209	0.017	0.021	0.0019	0.0030	0.077
Partial Phase-out						0.0017	0.076
Complete Phase-out						n.a.	0.074

Figure 10. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Infants (6 months to 1 year) if All Water Contains Beneficial Level of Fluoride (0.7 mg/L)

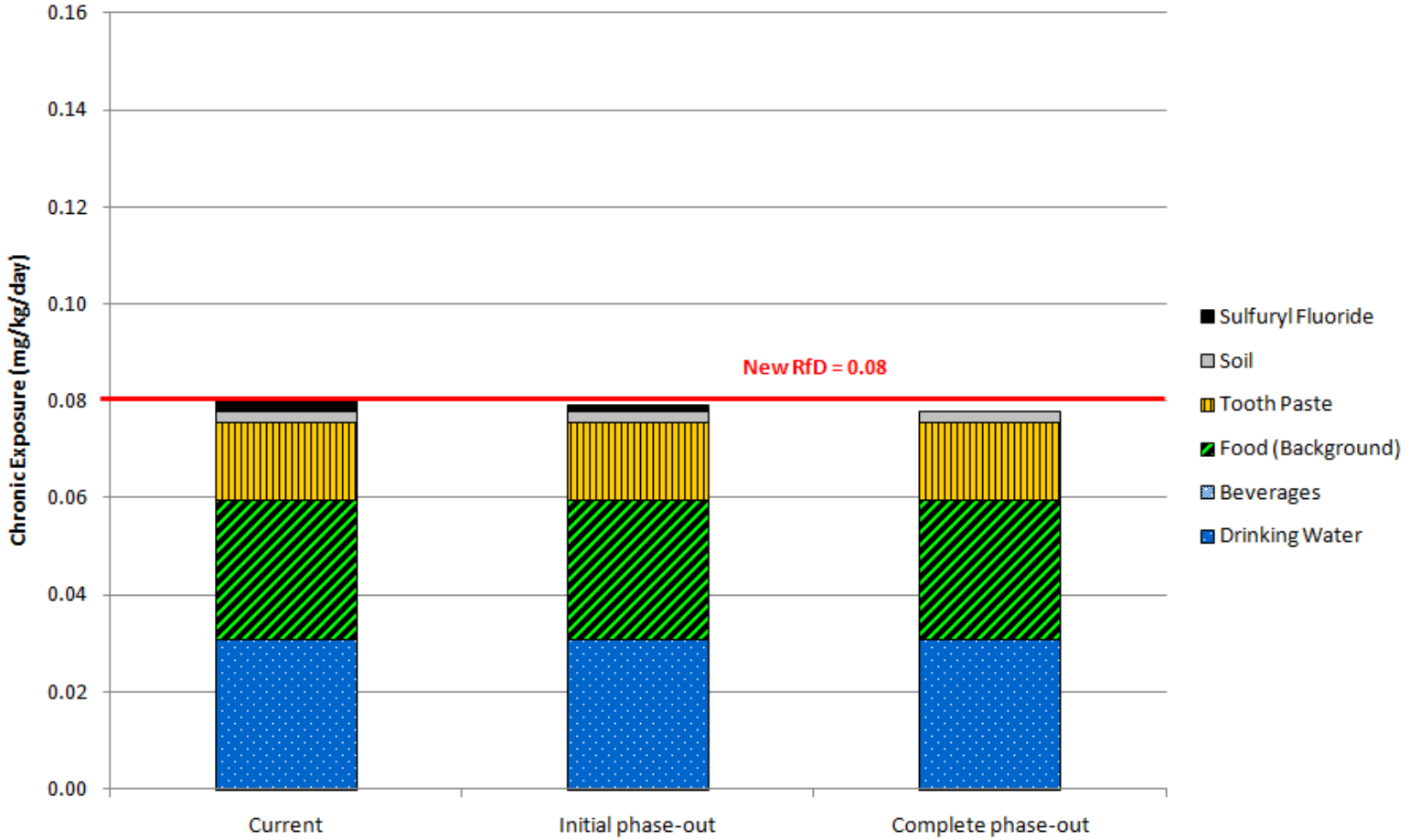


Figure 11. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Children (1 to 4 years) if All Water Contains Fluoride at the Beneficial Level (0.7 mg/L)

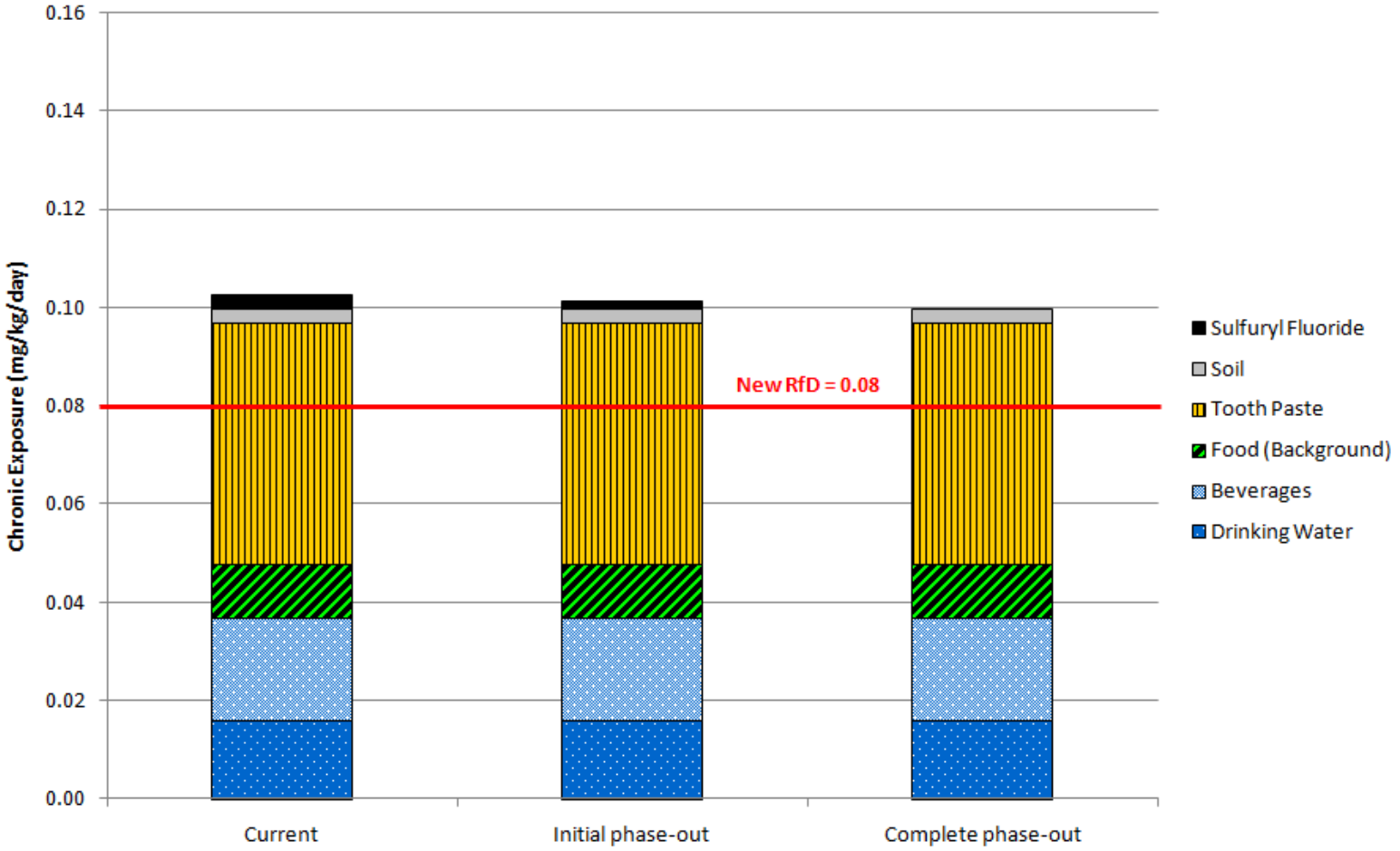
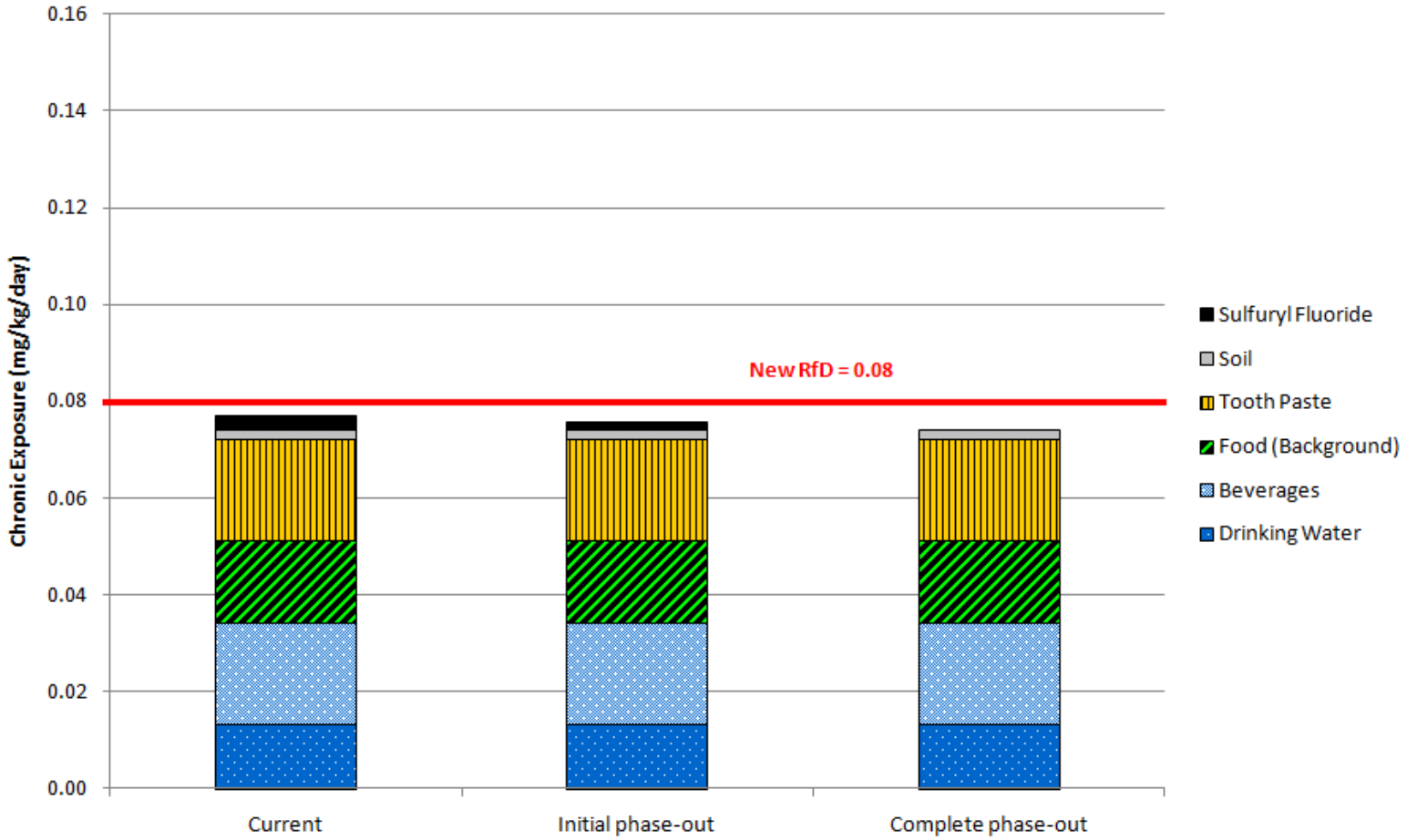


Figure 12. Impact of Sulfuryl Fluoride Phase-Out on Total Aggregate Fluoride Exposure for Children (4 to 7 years) if All Water Contains Fluoride at the Beneficial Level (0.7 mg/L)



C. Conclusion – Aggregate Fluoride Exposure Issues

The discussion above demonstrates that the proposed phase-out of sulfuryl fluoride will have negligible impact on aggregate fluoride exposures. In fact, aggregate fluoride exposures for those subpopulations which are currently estimated by EPA to exceed the Agency's newly calculated RfD will still exceed the new RfD after the proposed phase-out of sulfuryl fluoride tolerances. Use of sulfuryl fluoride contributes insignificantly to aggregate fluoride exposure, and removing the use of sulfuryl fluoride will not address public health concerns for aggregate fluoride exposures. Additional analyses demonstrate that the proposed beneficial level for fluoridation of drinking water (0.7 mg/L) would result in aggregate exposures greater than the new fluoride RfD of 0.08 mg/kg/day for some age groups, even when all sulfuryl fluoride tolerances have been terminated.

II. ASSOCIATION BETWEEN PREVALENCE OF DENTAL FLUOROSIS AND FLUORIDE CONCENTRATION IN DRINKING WATER

The CDC reported that the prevalence of dental fluorosis among adolescents aged 12-15 years has increased from 22.6% in 1986-87 to 40.7% in 1999-2004 (Beltrán-Aguilar et al., 2010). The EPA (2010a) conducted a Benchmark Dose analysis using data on severe dental fluorosis from a study involving 5824 children in 22 US communities in 10 states where fluoride levels in drinking water ranged from 0.0 to 14.1 ppm (Dean, 1942). Presumably no more recent data were available, which would explain EPA's reliance on a nearly 70-year old study. EPA's analysis estimated the BMD and BMDLs for 0.5%, 1% and 5% severe fluorosis. The BMD for 0.5% severe dental fluorosis is 2.14 ppm, and the BMDL is 1.87 ppm (EPA 2010a).

Dental fluorosis occurs over a range of severity from very mild fluorosis (characterized by small, opaque, white areas scattered irregularly over the tooth involving at most 25% of the tooth surface) to severe (characterized by discrete or confluent pitting, presence of widespread brown stain, and appearance of corrosion in teeth). CDC estimates that 16% of the US population aged 6-49 years has very mild dental fluorosis, 4.8% has mild dental fluorosis, 2.0 % has moderate dental fluorosis, and <1% has severe dental fluorosis (SDF). The estimates are based on data from the oral examination component of the National Health and Nutrition Examination Survey (NHANES) 1999-2004 (Beltrán-Aguilar, et al., 2010).

The US EPA (EPA 2010b) used data on fluoride concentrations in drinking water from the National Primary Drinking Water Regulations (NPDWR) database to estimate fluoride exposure from drinking water. The database, i.e., the National Compliance Monitoring ICR Dataset for the second Six-Year Review (or "Six-Year Review-ICR Dataset"), includes fluoride concentrations in 333,211 samples from 48,600 water systems located in 45 states. The water samples were collected between 1998 and 2005. The county location of the water systems was identified and summary estimates at the county levels were derived.

The NHANES dental fluorosis data were merged with the fluoride concentrations in drinking water data to confirm that fluoride concentration in water is a significant determinant in the occurrence of moderate and severe dental fluorosis. Geographic variables including state and

county of residence are restricted access variables collected by NHANES. These geographic data, which were needed to merge in the fluoride drinking water concentration data, were accessed through CDC's Research Data Center (RDC). A total of 12,783 subjects had non-missing dental fluorosis scores and were "mapped" to a county with drinking water fluoride concentration data.

The association between dental fluorosis and fluoride concentrations in drinking water was assessed at the person level. Specifically, each subject in the NHANES 1999-2004 survey with oral health examination data was assigned the fluoride concentration associated with the state/county in which they currently reside. Logistic regression was used to model the association between the probability of severe or moderate dental fluorosis and drinking water fluoride concentration. Analyses were conducted using the entire distribution of fluoride concentrations in water as well as using grouped water fluoride concentrations. Two approaches for grouping the fluoride levels were considered. In the first, fluoride levels were classified into quartiles, and the second approach classified the fluoride concentrations as less than or greater than the BMDL (1.87 ppm).

Analyses were run using Microsoft Excel 2007 and STATA statistical software package versions 10 and 11 (Stata-Corp, College Station, TX, USA). All summary statistics and analyses involving the NHJANES data were adjusted for survey design with appropriate statistical weights provided by NHANES and standard errors and associated confidence intervals (CI) were derived using the Taylor series (linearization) method.

Table 5 summarizes the logistic regression models using moderate or severe dental fluorosis as response and drinking water fluoride concentrations as a predictor. Two models were fit to the data. Model 1 used all subjects in the database, while Model 2 was restricted to those subjects who had moved to their current residence when they were 10 years of age or younger, i.e., were living in their current residence at an age where their teeth would have been vulnerable to fluoride exposure. The odds ratios (ORs) for both models were equal to 2.70 and were statistically significantly greater than 1, indicating a statistically significant increase in the odds of developing moderate or severe dental fluorosis with increased fluoride concentrations in drinking water. These analyses were repeated using severe dental fluorosis and mild, moderate or severe dental fluorosis as response. The results of these analyses were comparable to the results presented in Table 5 and are presented graphically in Figure 13. Figure 13 summarizes the estimated ORs and associated 95% CIs. Odds ratios higher than 1 indicate a positive association between dental fluorosis and fluoride concentrations in drinking water. If the confidence interval does not include one, i.e., if the lower limit of the CI is above 1 then the OR is statistically significantly different from one. In Figure 13, four of the 6 odds ratios were statistically significantly different from 1.

Two additional analyses were run using indicator variables for the grouped fluoride concentrations in drinking water described above. The results of the first analysis using the quartile indicator variables as predictors and moderate or severe dental fluorosis as outcome are summarized in Table 6. The prevalence of dental fluorosis in the first quartile is used as a reference category. Subjects living in counties with fluoride water content in the fourth quartile are 2.60 times more likely to have moderate or severe dental fluorosis than subjects living in

counties with fluoride water content in the first quartile (statistically significantly greater than 1). A slightly higher (2.75) OR was estimated when the analysis was restricted to subjects who moved to their current residence when they were 10 years of age or younger.

The results of the second analysis using indicator variables for whether the water fluoride levels were less than or greater than the BMDL as predictors and moderate or severe dental fluorosis as outcome are summarized in Table 7. Subjects living in counties with fluoride water content higher than the BMDL are 5.04 times more likely to have moderate or severe dental fluorosis than subjects living in counties with fluoride water content below the BMDL. Similar results were observed when the analysis was restricted to subjects who moved to their current residence when they were 10 years of age or younger. The ORs summarized in Table 7 are not statistically significantly different from 1, but the p-values are borderline significant (<0.10) and the upper limits of the 95% CI were above 30. These results indicate an increase in the likelihood of developing moderate or severe dental fluorosis for subjects living in counties with fluoride concentrations in drinking water higher than the BMDL, and the results suggest that the lack of statistical significance is most likely due to the small number of subjects in counties with average fluoride concentrations in water higher than the BMDL rather than a lack of association.

Our analysis, which is based on data from US EPA concerning fluoride concentrations in drinking water and dental fluorosis data from NHANES, shows that there is a statistically significant association between the prevalence of dental fluorosis and the fluoride concentration in drinking water. Stronger associations were detected when the analyses were restricted to subjects who had moved to their current residence at age 10 or younger, i.e., at an age when they were susceptible to the effects of fluoride exposure.

Table 5. Odds Ratio for Moderate or Severe Dental Fluorosis per Unit Increase in Fluoride Concentration in Drinking Water

Model	**Model 1** [A]	**Model 2** [B]
N	12,783	5,223
OR	2.70	2.70
95% CI	(1.05 - 6.95)	(1.09 - 6.68)
P-value	0.040	0.033

[A] Model 1 includes all subjects.
[B] Model 2 includes subjects who moved to their current residence when they were 10 years of age or less

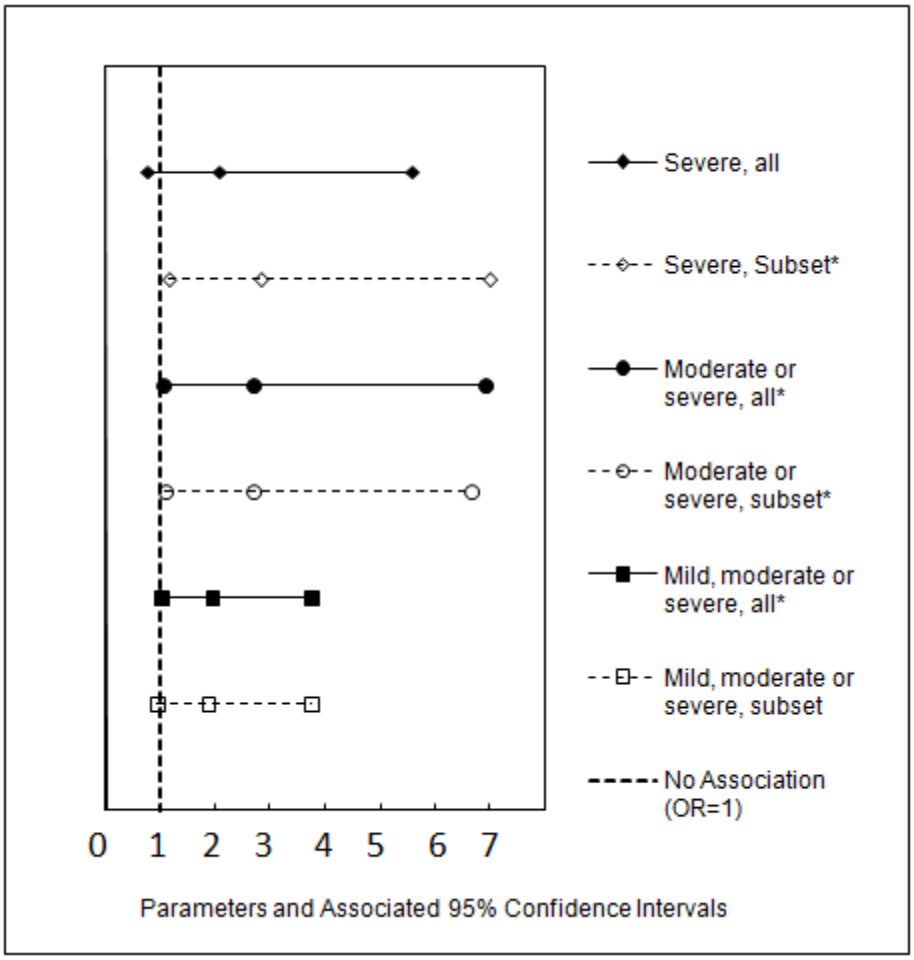
Table 6. Odds Ratio for Moderate or Severe Dental Fluorosis per Quartile of Fluoride Concentration in Drinking Water

	Q1 (<0.40 ppm)	**Q2 (0.40 - 0.73 ppm)**	**Q3 (0.73 - 0.91 ppm)**	**Q4 (>0.91 ppm)**
Population	All subjects (N=12,783)			
OR	1 (Reference)	1.68	1.79	2.60
95 % CI	-	(0.84 - 3.37)	(0.73 - 4.41)	(1.07 - 6.32)
P-value	-	NS	NS	0.036
Population	Subjects who moved to their current residence when they were 10 years of age or less (N=5,223)			
OR	1 (Reference)	1.68	1.52	2.75
95 % CI	-	(0.64 - 4.43)	(0.63 - 3.66)	(0.97 - 7.80)
P-value	-	NS	NS	NS (0.056)

Table 7. Odds Ratio for Moderate or Severe Dental Fluorosis per Subjects with Fluoride Concentrations in Drinking Water above the BMDL

	Group 1 (<1.87 ppm)	**Group 2 (≥1.87 ppm)**
Population	All subjects (N=12,783)	
OR	1 (Reference)	5.04
95 % CI	-	(0.76 - 33.47)
P-value	-	NS (0.092)
Population	Restricted to subjects who moved to their current residence when they were 10 years of age or less (N = 5,223)	
OR*	1 (Reference)	5.01
95 % CI	-	(0.83 - 30.10)
P-value	-	NS (0.077)

Figure 13. Estimated Odds Ratios (and 95% CI) for Dental Fluorosis Associated with a Unit (ppm) Increase in Drinking Water Fluoride Levels [A]



[A] The "All" analysis includes all subjects, while the "Subset" analysis includes only those subjects who moved to their current residence when they were 10 years or age or less. An asterisk (*) indicates an OR that is statistically significantly different from 1.

III. FLUORIDATED TOOTHPASTE AND FLUORIDE EXPOSURE

As noted above fluoridated toothpaste is a significant contributor to fluoride exposure to many subpopulations, particularly children who are susceptible to the effects of fluoride. Thus, consideration of the assumptions of the toothpaste assessment and factors that could be altered to mitigate the contribution of fluoride in toothpaste to aggregate exposures is warranted.

EPA's FFDCA assessment assumed two-brushings per day, which they indicated was a conservative assessment based upon available use data (EPA, 2011b). EPA indicates that the uncertainty in the toothpaste assessment is attributable to the number of brushings per day and the amount ingested, which is dependent upon actions such as spitting ability and rinsing. In addition, the amount of toothpaste applied to the brush plays a role. Specifically, older guidelines recommended a full strip of toothpaste be applied to the brush, while more contemporary guidelines suggest that a pea-sized portion be used (EPA, 2010b).

The approval of fluoride in toothpaste as a drug for the preventative treatment of dental caries dates back to the mid 1950s (see, for example, FDA, 1955). FDA published conclusions that dentifrices containing stannous fluoride and sodium fluoride monophosphate would reduce the incidence of dental caries in 1970 (35 FR 11643). Fluoride sources for toothpastes were listed in the Federal Register notice as sodium fluoride, stannous fluoride, and sodium monofluorophosphate.

After receiving public comments on a proposed rule and a tentative final rule in 1980 and 1985, respectively, FDA published a Final Rule in 1995 entitled "Anticaries Drug Products for Over-the-Counter Human Use; Final Monograph" (60 FR 52474-52510). This final rule established the "conditions under which the over-the-counter (OTC) anticaries drug products … are generally recognized as safe and effective and not misbranded." The Monograph was codified in Part 355 of the Code of Regulations, which is subdivided into "General Provisions" (sections 355.1 and 355.3), "Active Ingredients" (sections 355.10 and 355.20), "Labeling" (sections 355.50, 355.55, and 355.60), and "Testing Procedures (section 355.70).

Throughout the Final Monograph (and the Proposed and Tentative Final Monograph as well), the FDA made findings on the levels of sodium fluoride, sodium monofluorophosphate, and stannous fluoride that could be used as active ingredients in OTC Anticaries Drug Products, and in the process discussed whether certain levels could cause fluorosis. See, e.g., 60 Fed. Reg. 52478, et seq. In addition, the Agency also provided for Warnings and Directions for the use of anticaries products for various categories of children which were incorporated into the Final Rule. For example:

- For all fluoride dentifrice (gel, paste, and powder) products: "Keep out of reach of children under 6 years of age."

- For gel or paste dosage forms containing 850 to 1150 ppm: "Adults and children 2 years of age and older: Brush teeth thoroughly, preferably after each meal or at least twice a day, or as directed by a dentist or doctor. Instruct children under 6

years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 2 years of age: Consult a dentist or doctor."

- For gel or paste dosage forms containing 1500 ppm: "Adults and children 6 years of age and older: Brush teeth thoroughly, preferably after each meal or at least twice a day, or as directed by a dentist or doctor. Instruct children under 12 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise children as necessary until capable of using without supervision. Children under 6 years of age: Do not use unless directed by a dentist or doctor."

See 21 CFR § 355.50.

For dentifrice products containing 1500 ppm, the following optional additional labeling statement was provided: "Adults and children over 6 years of age may wish to use this extra-strength fluoride dentifrice if they reside in a nonfluoridated area or if they have a greater tendency to develop cavities." However, no indication was given as to how an individual would know if their water was fluoridated (i.e., if they resided in a nonfluoridated area). Further, there was no mention of the possibility that an individual could reside in a nonfluoridated area which in fact had high naturally-occurring fluoride levels.

In December, 2000 the FDA's Associate Commissioner for Legislation responded to questions posed by the House Subcommittee on Energy and Environment regarding the use of fluoride in drinking water and drug products (FDA, 2000) The letter cites the above referenced final rule publishing in the Federal Register (1995) which stipulated anticaries products as OTC drugs as well as generally recognized as safe and effective and not misbranded, as well as indicating that a new drug application (NDA) could be filed for a product containing fluoride which does not meet the previsions stipulated in the final rule. The letter continues, stating that drugs approved prior to 1962 are being reviewed under a process known as drug efficacy study implementation (DESI), which had not been completed at the writing of the letter. Evidence of the completion of this process could not be found at the writing of these comments. FDA clearly states that their principal safety concern regarding fluoride in OTC drugs is fluorosis in children under age two years. However, the letter indicates that these concerns are addressed in the monograph by mandating maximum concentrations of fluoride in these products. The results of the EPA's recent assessment suggest that potential fluoride exposure associated with the use of these products warrants re-evaluation. Key aspects for consideration are: concentration of fluoride in products, instructions for use, precautionary language, and acceptable marketing messages (verbal and visual).

IV. IMPACT OF PROPOSED SULFURYL FLUORIDE PHASE-OUT ON FOOD SAFETY

Sulfuryl fluoride is used to control insect infestations, such as cockroaches, flour beetles (red and confused) and moths. In addition, sulfuryl fluoride is also used as a fumigant to control rodents. Insects, rodents and birds have been shown to carry and transfer microbes. In addition, many

insect pests have the potential to cause allergic reactions from contamination of food products including grains and their milled products. Therefore foods processed in inadequately fumigated facilities may have an increase incidence of contamination with whole insects, insect body parts, insect waste and secretions, and rodent parts, as well as microbial pathogens and insect allergens. Thus the proposed termination of sulfuryl fluoride tolerances will result in more frequent filth contamination (insect and rodent infestations), and associated microbial pathogen and allergen contamination of food commodities if other effective and practical alternatives to sulfuryl fluoride are not readily available or cannot be implemented.

A. Filth

Several provisions under the FFDCA relate to filth. For many decades FDA primarily used the adulteration provision in Title 21 Section 402(a)(3) to regulate filth. Section 402(a)(3) states that food is adulterated "*if it consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food*." This section is supplemented by the insanitation provision Section 402(a)(4) which states that food is adulterated "*if it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.*"

FDA recognized that there is natural and unavoidable filth such as insect fragments from field production of raw materials, that elimination of "any" filth was not possible to achieve and that the courts considered there to be a *de minimis* level below which such contamination was too trivial to pursue under the law. Consequently FDA developed Defect Action Levels (DALs) to address such aesthetic and unavoidable filth (Olsen, et al., 2001; FDA, 1999). The DALs were developed for only some of the filth/product combinations as resources permitted and compliance decisions were made on a case-by-case basis where DALs were not available.

In the late 90s, the FDA developed a new strategy for filth. This strategy was intended to facilitate implementation of HACCP (Hazard Analysis Critical Control Point) preventive control systems which focus on health hazards and to assist FDA in prioritizing its filth enforcement resources to the most serious situations (Olsen, et al., 2001; FDA, 1999). The strategy divided filth into unavoidable and avoidable filth, and further divided the avoidable filth into health hazards and insanitation. Health hazards were considered the most serious filth category.

Health Hazards

Section 402(a)(1) of FFDCA states that food is adulterated "if it bears or contains any poisonous or deleterious substance which may render it injurious to health….". Although at the time of writing of the 2001 paper on regulatory action criteria (Olsen, et al., 2001), the dose-response data were not yet developed that would allow 402(a)(1) to be applied to the finding of allergenic mites in food, there is clear evidence that they can cause ingestive anaphylaxis and pose a significant health risk to sensitive individuals as discussed below. In absence of the use of 402(a)(1), the FDA could still address such mite contamination under the insanitation (402(a)(4)) or filth (402(a)(3)) provisions.

Insanitation

Infestations by pests that can carry pathogens are an example of insanitation adulteration that may render food injurious to health as discussed in the section on microbial contamination of flour below.

Visible objectionable avoidable filth also falls under the insanitation provisions of 402(a)(4) as this section covers insanitation from conditions where food may have become contaminated with filth. Consumers react very negatively to such filth especially large visible filth such as cockroaches, a dead mouse, a rat's tail, or a mouse foot (Olsen, et al, 2001; FDA, 1999). Clearly the public would reject food crawling with flour beetles and other insects that make a home in the foods if they can colonize it.

Unavoidable Filth

Natural and unavoidable aesthetic filth is considered the least serious in the view of FDA. This filth is normally not visible to the naked eye. DALs that establish limits on how much of such filth can be present in food have been issued in some cases. For instance, in the case of wheat flour, the DALs for insect and rodent filth are an average of 75 or more insect fragments per 50 grams, and average of 1 or more rodent hair per 50 grams, respectively. Consumers are not likely to accept insect fragments in their wheat flour, even though guidance allows up to 74 such insect fragments per 50 grams (FDA 2009; FDA, 1999).

Conclusion

Filth is largely avoidable in FDA's view if proper sanitation and good manufacturing practices are used. These would include appropriate pest control at facilities, and terminating the use of sulfuryl fluoride without effective practical alternatives increases the likelihood of occurrence of such insanitation filth and adulteration of foods.

B. Microbial Pathogens Linked to Flour

Rodents, birds and insects have long been considered potential vectors for microbial contamination of food (Olsen, et al., 2001). Several studies have been published demonstrating the ability of insects to carry and transfer bacteria. Flies and moths have been demonstrated to transmit pathogens to food from contact with the sponging mouthparts, body and leg hairs, on the sticky parts of the feet, and through the intestinal tract (Olsen, 1998b). FDA characterized the housefly as an important contributing factor in the dissemination of various infectious foodborne diseases such as cholera, shigellosis, and salmonellosis (Olsen, et al., 2001). Vinegar flies and beetles transferred fungi to injured peach fruit and fruit flies were found to transfer *E. coli* O157:H7 to apple wounds (Michailides and Spotts, 1990). In an epidemic of enterohemorhagic colitis in a nursery school in Japan, *E. coli* O157:H7 was isolated from both patients and houseflies collected in the area and all isolates were indistinguishable by molecular typing methods (Moriya, et al., 1999). Cockroaches have been found to bear *E coli, Salmonella spp., Shigella spp.,* and *Staphylococcus spp.* (Olsen, et al., 2001). *Salmonella* was reported to survive on contaminated cockroaches for over 100 days (Klowden and Greenberg, 1977).

Considering that populations of enteric pathogens can be as high as 10^6 per gram in animal (i.e., cattle feces) or human feces, and that studies have estimated an E. *coli* transfer coefficient of 1/1000 from inoculated flies to food surfaces (e.g., De Jesús, et al., 2004), the scenario of pathogen transfer from the environment to insects and insects to food at levels that can cause foodborne illness is probable.

Pests, like flies, moths, cockroaches, and beetles can transfer pathogens from moist environments to equipment and food. Therefore pest infestations within a food processing facility or storage facility, increase the potential of pathogen contamination of the food being produced. These pathogens could then cause foodborne illness if the final product at the processing plant, food service facility, or home was minimally heat processed. Even if the contaminated food was eventually heated to eliminate all likely levels of the pathogens (i.e. flour), the product could still indirectly cause foodborne illness by cross contamination through transporting pathogens into an area where multiple products are produced (i.e. foodservice or home kitchen). Once the pathogen is brought into an area where food is prepared, cross contamination to a minimally processed or ready-to-eat food could occur.

Salmonella is considered to be the pathogen of primary concern for bacterial contamination within flour and grain mills and has been isolated in wheat flour at a frequency of 0.3 to 3% (ICMSF, 2005; Richter, et al., 1993). *Salmonella* can become established in wet or moist locations of flour and grain processing facilities (ICMSF, 2005) and can remain in flour for several months and can cause illness at low contamination levels if uncooked, or added after cooking.

An outbreak of salmonellosis in 2005 was attributed to cake mix that was added to ice cream without proper cooking (Zhang, et al., 2007). A review of FDA's recall data base revealed that since 2006, 29 recalls (all due to the presence of *Salmonella*) have been initiated due to pathogen contamination of dry cereal products (flour mixes/seasonings).

CDC monitors the occurrence of 9 known pathogens in the population through its FoodNet sites. Recent CDC reviews estimate that 9.1 million episodes of foodborne illness occur annually in the United States from 31 known pathogens (Scallan, et al., 2011). CDC further estimates that these episodes result in 55,961 hospitalizations and 1,351 deaths annually. Of the pathogens monitored by CDC surveillance, *Salmonella* accounts for over one million illnesses, 54% of all hospitalizations and 43 percent of the total deaths report (CDC, 2011). The direct medical cost in the United States from *Salmonella* alone is estimated to be $365 million annually. Despite a reduction in the number of reported illness from several pathogens in the past 10 years, *Salmonella* cases have increased by 10% (CDC, 2011).

In conclusion, failure to control for potential microbial pathogen contamination in food production facilities could result in an increase in the number of Salmonella cases. Use of sulfuryl fluoride to control insect and rodent infestations will reduce the risk of microbial contaminations associated with such infestations in food production facilities.

C. Allergens

Many insect pests have the potential to cause allergic reactions from contamination of food products including grains and their milled products. The allergen hazard from insects is outlined in FDA's report: Regulatory Action Criteria for Filth and Other Extraneous Materials V. Strategy for Evaluating Hazardous and Nonhazardous Filth (Olsen, et al., 2001). Among insects that present an allergen risk are allergenic mites, cockroaches, and other insects, such as the confused flour beetle and the red flour beetle.

The case for allergenic risk from exposure to allergenic mites is laid out in a review of the literature conducted by Olsen (1998a). The review identified 36 patients with IgE-mediated systemic allergic reactions to mites, including anaphylaxis in two children from consuming baked products made from infested flour. Additional research cited by Olsen (1998a) demonstrated that some mite allergens were heat stable to at least 100^{o}C. There are as many as 114 species of mites that infest stored food. In an FDA survey, Olsen (1998a) found 22 species of mites in 149 processed food samples of which 8 were known to induce IgE-mediated reactions. Four of these 8 species have been associated with ingestive IgE-mediated anaphylaxis. The amount of mite allergens that can trigger an allergic response is not well known. However, Olsen stated that: '*Individuals who are extremely hypersensitive to mite contamination may be at risk from any level of mite contamination in their food.*'

Like mites, cockroach allergens cause IgE-mediated reactions. FDA and other public health organizations have had to deal with cockroach contamination of food for many years. Cockroach allergens are found in cockroach bodies, cast skins, egg cases and feces (Olsen, et al., 2001).

Many other insects that infest food have potential to cause sensitization and allergic reactions, including the confused flour beetle (*Tribolium confusum*) and red flour beetle (*Tribolium castaneum*). These reactions may occur either from occupational exposure such as in the case of bakers and millers, but also potentially from ingestion of contaminated food products.

Several studies (Alanko, et al., 2000; Schultze-Werninghaus, et al., 1991 and 1987; Musk, et al., 1989; Popa, et al., 1970; and Herling, et. al., 1995) reported on sensitization and allergic reactions among bakery employees:

- Alanko, et al. (2000) reported on a case of a mechanic that worked in a rye crisp factory who had occupational contact urticaria, rhinitis, conjunctivitis, and asthmatic symptoms from exposure to flour. The mechanic developed work-related rhinitis after 4 years of work. Testing showed an IgE mediated reaction due to confused flour beetles in the flour. He also tested positive to specific IgE antibodies to *Blattella germanica* (cockroach), *S. granarius* (grain weevil), and *Trogoderma angustum solier* (Berlin beetle), although they were not as strongly elevated as the IgE antibodies to *Tribolium confusum*.

- Schultze-Werninghaus, et al. (1991) found IgE antibodies to adult *Tribolium confusum* in nine of 125 (7.2 %) sera from bakers. The authors concluded that 'These findings

suggest that TC [*Tribolium confusum*] might act as an occupational allergen in a proportion of bakers.' The authors point out the baker's asthma is the most common type of occupational asthma in many countries with allergies to wheat and rye flour and alpha-amylase being very common.

- Schultze-Werninghaus, et al. (1987) reported that 8.3 % of 133 bakers had a positive skin prick test to *Tribolium confusum*.

- Musk, et al. (1989) studied sensitization to flour in a British bakery. The study included 279 of 318 bakery employees and employees were exposed to flour dust levels exceeding 10 mg/m^3 (9/79 dust samples were >10 mg/m^3). One third had a positive skin prick test for one or more grain mites and 11 percent were positive to *Tribolium confusum*. In total 38 percent had positive skin tests to bakery allergens (such as flour, wheat grain and mould mix), grain mites and *Tribolium confusum*. Forty percent had positive tests for common allergens (house mite, cat fur and grass pollen). Thirty five percent had chest symptoms of which 13 percent (about $1/3^{rd}$) were work related and 38 percent had nasal symptoms of which 19 percent were work related. Both work related symptoms and positive skin prick tests were more common in workers with higher dust exposure. The authors also noted that some symptoms, including nasal, were likely due to non-specific irritation.

- Popa, et al. (1970) studied allergy in 43 Romanian bakers (3 were managers), who had occupational exposure to wheat flour and allergic respiratory complaints including rhinitis, bronchitis, asthmatic bronchitis, and/or asthma. Rhinitis with or without bronchitis symptoms appeared after 9.1 years (mean) and asthma after 14.0 years (mean). The study included the main insects contaminating flour in the country (7 insects) and included red flour beetles (*Tribolium castaneum*). There were 50 controls, who were non allergic subjects that were not occupationally exposed to flour. In intradermal skin tests 100 percent of the bakers were positive to flour extracts. 53 percent of bakers (23 bakers) and 14 percent of controls were positive to red flour beetle extract. However, on nasal and/or bronchial provocation, only 1 of 43 bakers (2.3 percent) was positive to red flour beetle extract. One other subject was positive to a combination extract from *Calandra granaria* beetles and red flour beetles as *Calandra granaria* was cultivated from a mixture of *Calandra granaria* and *Tribolium castaneum*. There were no positive reactions to bronchial provocation.

- Herling, et al. (1995) demonstrated specific IgE antibodies to granary weevil extracts in Danish bakers whose skin prick tests were positive to extracts of granary weevils. This adds to the breath of the insects that infest grains and milled products that can be occupational allergen hazards and potentially ingestive allergen hazards.

Other studies have also reported reactions among non-occupationally exposed subjects. For instance, Bernton and Brown (1967) investigated the sensitization to 7 insects (red flour beetle larvae, red flour beetle adults, confused flour beetles, black weevil, fruit fly, Indian meal moth and Saw-toothed grain beetle) that infest food, including grain and milled products. They studied 2 groups, patients with allergies and a non-allergic group. Subjects in both groups had a

positive reaction to one or more extracts (30 % of the 'allergic' group and 25 % of the non-allergic group), indicating sensitization. Bernton and Brown also noted similar, but less vigorous reactions with heat-treated extracts, indicating that these allergic reactions could still occur with heat processed foods. As the subjects in the study were city dwellers and unlikely to have substantial respiratory exposure, this suggests that the positive skin prick results stem from generation of antibodies from ingestion of the allergenic components of the insects.

Rudolph, et al. (1987) reported that 430 patients suffering from perennial asthma and/or rhinitis and a proven sensitization to indoor allergens responded to whole-body *T. confusum* extracts (16.5 % and 30.7 % positive skin prick and intradermal test, respectively). As many of these patients did not have a profession where they would be exposed to the allergens by inhalation, positive responses may well be due to development of confused beetle antibodies from ingestion of wheat products.

In conclusion, the scientific literature clearly shows that insects that infest food may pose a serious health hazard to sensitive consumers as in the case of ingestion of allergenic mites that has been shown to cause anaphylaxis. There is substantial evidence that many granary insects present an occupational allergen risk based on the demonstration of allergenic sensitivity in bakers, millers and granary workers to allergens from insects such as flour beetles and grain weevils. To determine the true extent of allergenic risk to insects that infest flour and other foods still requires substantial research, but the research to date indicates that such allergens may pose a significant risk to health. Banning the use of sulfuryl fluoride without an effective practical alternative can only be expected to increase consumer and worker exposure to these allergens, increase the consequent sensitization to such allergens and subsequent adverse allergic responses despite the food industries efforts to minimize such infestations. Use of sulfuryl fluoride to control insect infestations will reduce the risk allergic contaminations associated with such infestations in food production facilities.

D. Conclusion

Avoidable pest infestation of food products would be more likely to occur without sulfuryl fluoride in the pest control toolbox of food processors. These infestations would likely be considered serious violations of the FFDCA and such food would be considered adulterated and enforcement action would be taken, such as seizure, injunction of manufacturing establishment, etc. It is quite likely that more food with increased levels of allergenic components, more pathogen contamination from pest transfer and increased visible and invisible filth will find its way to consumers despite industry efforts to minimize infestations by other less effective means without sulfuryl fluoride. While this increased risk of harm to workers and consumers cannot be quantified at this time for the transfer of foodborne pathogens by pests and insect allergens, it does appear to be a significant risk. And the risk may indeed be greater than the increased risk of severe dental fluorosis from the insignificant percentage increase in fluoride exposure that EPA has found to result from the food-related uses of sulfuryl fluoride. While we cannot quantify the increased risk of harm to consumers from terminating the food-related uses of sulfuryl fluoride, EPA also has only quantified the change in exposure, and has not quantified the increased risk of adverse fluorosis. EPA should compare the health impact of fluoride exposure from sulfuryl fluoride uses to the health impact of increased pathogen and allergen exposures resulting from

terminating use of sulfuryl fluoride. Indeed, with the growing salmonellosis illness burden (CDC, 2011), the life-threatening danger of foodborne pathogens and the seriousness of allergenic reactions including the potential for anaphylaxis and death, it is quite possible that eliminating the food-related uses of sulfuryl fluoride without an effective and practical alternative will result in net harm.

Exposure to fluoride from the registered use of sulfuryl fluoride is a very small percentage (ranging from 1.7 to 3.1% for children less than 7 years old) of total fluoride exposure, and indeed can be considered miniscule in the context of intentionally added fluoride to toothpaste and municipal water or the relatively elevated levels of naturally occurring fluoride in some drinking water as a result of the geological formations from which the water is extracted. In the context of such other exposures, a reduction of 3.1% or less from elimination of sulfuryl fluoride's food-related uses will have trivial if any public health impact and in this context, such miniscule added fluoride exposure from sulfuryl fluoride could be and should be considered *de minimis* under the law for purposes of evaluating its extremely important use to reduce filth in food, particularly filth that poses a health hazard and a source of insanitation in food. Alternatively, EPA should use its discretion to not take regulatory action and decline to terminate the sulfuryl fluoride tolerances. As the added fluoride exposure is a very small portion of total aggregate fluoride exposure, termination is unlikely to result in any meaningful health gain with respect to potential adverse health impacts of fluoride, and may very well result in net harm when the impacts of increased foodborne pathogen and allergen risks are considered.

Finally, terminating the sulfuryl fluoride tolerances will likely increase the regulatory burden to deal with the increased occurrences of pest infestations in food which will unnecessarily add to regulatory agencies' burden to keep food safe. The loss of food as an increased amount of product that needs to be destroyed would result in reduced productivity in the food sector, increased prices passed on to consumers, and an increased risk of food insecurity in the U.S. Again while these economic, regulatory and nutrition impacts cannot be quantified, they are nevertheless qualitatively important negative impacts that must be considered before EPA takes action with respect to the sulfuryl fluoride tolerances.

V. CONCLUSION

In summary, these comments focus on several points:

- The proposed phase-out of sulfuryl fluoride's food-related uses will have negligible impact on aggregate fluoride exposures. Because use of sulfuryl fluoride contributes insignificantly to aggregate fluoride exposure, removing the use of sulfuryl fluoride will not address public health concerns for aggregate fluoride exposures.

- Even at the revised beneficial level for fluoridation of drinking water (0.7 mg/L), aggregate fluoride exposures for some age groups will be greater than the newly proposed reference dose (RfD) of 0.08 mg/kg/day, even when all sulfuryl fluoride tolerances have been terminated.

- Fluoride concentration in water is a significant determinant in the occurrence of moderate and severe dental fluorosis, as demonstrated by an analysis of data on fluoride concentrations in public water systems from the EPA Office of Water and data on the prevalence of dental fluorosis from NHANES.

- Fluoride is intentionally added to toothpaste for the express purpose of preventing dental caries. With limited documentation available concerning the establishment of the recommended fluoride concentration in toothpaste and ambiguity about best use practices and labeling, including possible scenarios where the use of fluoridated toothpaste is not warranted due to either water treatment or naturally-occurring levels of fluoride, potential fluoride exposure associated with toothpaste warrants re-evaluation by FDA.

- Removal of sulfuryl fluoride as a pest control tool in food handling and storage facilities and on certain commodities will entail major disruption in the food processing sector, and it could give rise to increased risk of disease due to the lack of alternatives, delay in putting alternatives into place, or the use of alternatives that are less effective and/or more costly. Further delays in the complete phase-out of methyl bromide and increased costs associated with the expensive transitions to other technology and active ingredients could also result.

Thus, these comments demonstrate that EPA's proposal to phase out the food-related uses of sulfuryl fluoride will have no appreciable impact on aggregate fluoride exposures and will therefore not reduce the overall prevalence of severe dental fluorosis. At the same time, removing the use of sulfuryl fluoride will increase risks associated with contamination of the food supply and may delay U.S. efforts to phase out methyl bromide. Therefore, Dow AgroSciences contends that the proposal to phase out the food-related uses of sulfuryl fluoride is not in the public's best interest.

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