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ENVIRONMENTAL PROTECTION AGENCY

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**OBJECTORS' CONSOLIDATED OBJECTIONS TO FINAL RULES
ESTABLISHING TOLERANCES FOR RESIDUES OF SULFURYL FLUORIDE
AND FLUORIDE ANION**

Objectors Environmental Working Group (EWG), Fluoride Action Network

(FAN) and Beyond Pesticides/National Coalition Against the Misuse of Pesticides (BP)

(Objectors), by and through counsel, and as requested by the Director of the Office of

Pesticide Programs (OPP) of the Environmental Protection Agency (Administrator of EPA), hereby submit these Consolidated Objections to Final Rules Establishing Tolerances for Residues of Sulfuryl Fluoride and Fluoride Anion. (Objections)

These Objections challenge certain EPA rulemaking proceedings establishing tolerances for residues of sulfuryl fluoride and fluoride anion (fluoride) in or on raw and processed food commodities. (Regulations)   The first regulation (2004 Regulation) was promulgated as a final rule on January 23, 2004. Fed. Reg., Vol. 69, No. 15, January 23, 2004. The second regulation (2005 Regulation) was promulgated as a final rule on July 15, 2005. Fed. Reg., Vol. 70, No. 135, July 15, 2005. The process leading to issuance of the Regulations was initiated by petitions for rulemaking submitted by Dow AgroSciences, LLC (USEPA 2001a, 2002a, 2002c, 2005a). Those petitions requested that EPA amend 40 CFR Part 180 to set the tolerances at issue here. Objectors timely filed their Objections and Requests for Hearing with respect to both Regulations as provided for in the Federal Food, Drug and Cosmetic Act (FFDCA) Sections 408(g)(2)(A) and (B), 7 USC § 346a (g)(2)(A) and (B).

At the request of EPA's Office of Pesticide Programs, Objectors have consolidated their positions advanced in various past objections and supplements, and in other communications, into these Consolidated Objections to Final Rules Establishing Tolerances for Residues of Sulfuryl Fluoride and Fluoride Anion.

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INTRODUCTION AND SUMMARY OF OBJECTIONS

Introduction

Objectors challenge the subject Regulations on the grounds that EPA promulgated them in violation of the FFDCA, as amended by the Food Quality Protection Act, (FQPA) and the Administrative Procedure Act (APA). Essentially, EPA failed to evaluate the exposures and risks associated with the tolerances in the complete, thorough and detailed manner required by the FFDCA and the APA.

Objectors object to the substantive lack of adequate factual and scientific support underpinning critical assumptions and choices made in evaluating the tolerance petitions. Notable among these was EPA's choice, now thoroughly rejected by the National Research Council (NRC) of the National Academies, to use a Maximum Contaminant Level Goal (MCLG) for fluoride of 4 milligrams per liter (mg/L) as the foundation of a safe exposure level for setting tolerances for sulfuryl fluoride under the Food Quality Protection Act. Indeed, the NRC study concluded that serious adverse health effects would occur at exposure to 4 mg/l fluoride, a finding that undermines the notion that the tolerances meet the legal requirement in FQPA of a reasonable certainly of no harm for infants and children. EPA's reliance on an unsafe MCLG as the foundation of food tolerances for sulfuryl fluoride made it impossible for the process that established these tolerances to meet the legal requirements of the FFDCA, which mandate a careful, logical and sound assessment of the health risks associated with fluoride exposure. Necessarily, this failure pervaded and flawed the entire decisional process.

An equally serious flaw in EPA's risk assessment concerns the "reference dose" (RfD) promulgated for infants. The RfD is a mg/kg daily exposure value with a built in

safety factor designed to ensure that exposures are safe, even for potentially vulnerable populations such as infants. Objectors note that *EPA has changed the fluoride RfD for a 7 kilogram infant twice over four years, with no formal public input or comment on the scientific rationale underlying these changes, each time increasing the RfD and thus allowing for higher levels of fluoride for infants*. Notably, these increases – which have resulted in the highest allowable dosage of fluoride ever sanctioned by a government agency in the nation's history – were not based on new scientific information, but on changing interpretations of the same, twenty-year old standard (MCLG). The disturbing culmination of the increases is that the final RfD for infants (1.14 mg/kg/day) is now ten times higher than the first RfD (0.114 mg/kg/day) and ten times higher than the RfD for adults (0.114 mg/kg/day). This makes sulfuryl fluoride the only pesticide ever registered where the allowed safe dosage (RfD) for infants and children is higher that it is for adults. It is an unprecedented decision that warranted a high burden of proof that was not met.

Objectors further note that many adults are already exceeding the RfD (0.114 mg/kg/day), while many children are exceeding the dose (2 mg/day) that EPA acknowledges can cause severe dental fluorosis. There is, therefore, no safe room for the additional fluoride exposures posed by the tolerances. In addition to the risk for chronic toxicity, Objectors also note the risk of acute toxicity that is presented by some of the approved tolerance residues.

Objectors also object to certain agency procedural missteps that have compromised the transparency and integrity of the rule-making process. Notable among these procedural inadequacies is *the issuance of the 2005 Regulation six months before providing Objectors with a copy of the Health Risk Assessment on which that Regulation*

was supposed to have been based. Also, numerous important documents used in the decision-making process were not made a part of the publicly available record. Finally, the issuance of the Regulations before completion of the NRC report, which EPA had itself requested, was similarly a procedural shortcoming whose implications are considerable. The procedures for establishing tolerances are not trivial matters lacking substantive consequences. Indeed, the APA reflects the basic view that good, sound decision-making about important matters demands adequate information, public comment and an overall process designed to provide a fair opportunity to assess that information and commentary. The aforementioned procedural failings, and others described herein, severely thwarted the process leading to issuance of the Regulations.

The overall result of these procedural inadequacies, and substantive errors of fact, was an inadequate and incomplete decision-making, yielding Regulations that pose precisely the kinds of health threats sought to be avoided by the FFDCA.

Summary of Specific Objections

Section I of these Objections explains why the 4 mg/L MCLG used by EPA in establishing the tolerances is not a protective standard and therefore is not a sufficiently protective foundation for the establishment of tolerances for sulfuryl fluoride, which must meet a standard of reasonable certainly of no harm for the infant and child. Significantly, a report of the National Research Council (NRC) of the prestigious National Academies entitled *Fluoride in Drinking Water: A Scientific Review of EPA's Standards,* found that the EPA MCLG fluoride standard does not protect children from severe dental fluorosis, does not protect the population from bone fractures or arthritic symtptoms, and "should be lowered." The NRC also has identified a range of other plausible effects that may be

caused by excess fluoride exposure, including damage to the nervous, endocrine and renal systems, and bone cancer. This Section asserts that these threats are sufficiently recognized in the peer-reviewed literature and by the NRC to justify the application of safety factors required to meet the standard of safety infants and children in the Food Quality Protection Act. Especially susceptible to fluoride at the levels allowed by the MCLG are sensitive groups, including children and persons with nutrient deficiencies, diabetes and kidney disease.

Section II of these Objections describes certain violations of the FFDCA, as amended by FQPA, that relate to the agency's derivation of a reference dose (RfD) for children. The RfD for children adopted by EPA, which is up to ten times higher than the RfD for adults, is the highest RfD ever promulgated for fluoride in the nation's history. It violates both basic toxicological principles and the requirements for demonstrating safety as set forth under FFDCA.

Section III of these Objections addresses EPA's waiver of an inhalation developmental neurotoxicity (DNT) study, taking the position that such a waiver compromised the integrity of the tolerances. EPA's explanation of the waiver is lacking. Objectors demonstrate that performance of an oral DNT study of fluoride is imperative under the circumstances and cite from the NRC study for support.

Section IV of these Objections demonstrates that there is no safe room for additional fluoride exposures. This Section addresses the requirement of the FFDCA that EPA, in establishing pesticide tolerances, must consider the "aggregate" exposures of humans to fluoride. The main point here is that many Americans are already exceeding EPA's established RfD, which in and of itself is a violation of FFDCA, as amended by

FQPA, and that adding more exposure via the food supply is further violation of the law.

Section V of these Objections asserts that EPA's evaluation of acute toxicity risk in establishing the tolerances was based on misleading and false premises. Whereas EPA's evaluation of acute toxicity was limited to extreme doses that can cause fatalities, Objectors note that much lower doses – not considered by EPA and relevant to doses achievable by consuming foods fumigated at permitted levels (e.g. dried eggs and wheat products) – can cause non-lethal symptoms of acute toxicity, including stomach pain, nausea, and vomiting.

Section VI of these Objections focuses on the significant problems persisting regarding EPA's estimate of chronic fluoride exposure from tolerances. Here, Objectors note that EPA's risk assessment only considered individuals whose consumption of fumigated foods was average and did not take into account anyone who eats more than an average amount of a particular food, even though the agency has on many occasions assessed the risk to individuals who eat more than the average amount of specific foods, and is clearly aware of the method and the need to use it in this case.

Section VII of these Objections addresses the procedural errors that hampered the tolerance issuance process. Failures (1) to allow fair opportunities for public participation, (2) to issue health risk assessments in a timely manner, (3) to place numerous important documents in the public record, and (4) to wait for the completion of the NRC report, all constituted violations of the APA.

Applicable Law

Section 408(b)(2)(A)(1) provides that the Administrator may modify or revoke a tolerance if the Administrator determines the tolerance is not "safe." 7 U.S.C.

§346a(b)(2(A)(i) Significantly, the determination of safety was raised to an appropriately

demanding standard by the Food Quality Protection Act (FQPA), which modified

FFDCA:

> [T]he term "safe", with respect to a tolerance for a pesticide chemical residue,
> means that the Administrator has determined 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.

7 U.S.C. § 346a(b)(2)(A)(ii)

Further, the stringency of the process for the establishment of tolerances is

particularly well reflected in the requirements of FFDCA Section 408((b)(2)(C) that the

Administrator assess the risk of a subject pesticide chemical residue based on available

information on infants and children regarding the following:

> (1) consumption patterns likely to result in disproportionately high consumption
> of foods containing or bearing pesticide chemical residues in comparison to the
> general population;
>
> (2) special susceptibility to pesticide chemical residues, including neurological
> differences between infants and children and adults and effects of in utero
> exposure to those residues, and
>
> (3) the cumulative effects on this group of such residues and other substances
> having a common mechanism of toxicity.

7 U.S.C. § 346a(b)(2)(C)

Additionally, that section requires that the Administrator "shall ensure that there

is a reasonable certainty that no harm will result to infants and children from aggregate

exposure to the pesticide chemical residue." In cases of pesticide chemical residues

demonstrating "threshold effects," the standard determination of a "safe" tolerance

requires an "additional ten-fold margin of safety for the pesticide chemical residue and

other sources of exposure …to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure."

FFDCA Section 408(b)(2)(D) sets forth the nine factors that the Administrator shall consider, among other relevant factors, in establishing, modifying, leaving in effect, or revoking a tolerance. These include the available information, with respect to the subject pesticide chemical residue, (1) concerning the validity, completeness, and reliability of the available data, (2) the toxic effect, (3) the relationship of the results of studies to human risk, (4) the dietary consumption patterns of consumers (and major consumer groups), (5) the cumulative effects of such residues and other substances having a common mechanism of toxicity, (6) the aggregate exposure levels of consumers (and major identifiable subgroups), (7) the variability of the sensitivities of major identifiable subgroups, (8) information the Administrator may require as to the potential effect on humans of a pesticide chemical residue similar to that produced by endocrine effects, and (9) safety factors that qualified experts on the safety of food additives recognize as appropriate for the use of animal experimentation data. 7 U.S.C. § 346a(b)(2)(D)

Sections I through VI of these Objections rely upon the foregoing legal provisions. Additionally, FFDCA Sections 408((g)(2)(A), (B), 7 USC §346a(g)(2)(A),(B), provide that "any person" may file "objections" to a regulation establishing a tolerance and request a hearing. FFDCA Section 408(g)(2)(B), 7 USC § 346a(g)(2)(B), requires that findings of fact made pursuant to a hearing must be "based only on substantial evidence of record." Further, Objectors demonstrate in the Objections

that the criteria for justification of a public evidentiary hearing, 40 C.F.R. § 178.32(b), have been met.

Finally, relevant APA provisions include Section 706(2)(E), 5 USC § 706(2)(E) (substantial evidence test), Section 553 (c), 5 USC § 553 (c) (opportunity for public participation and completeness of the administrative record), and Section 706(1), 5 USC § 706(1) (agency action unlawfully withheld or unreasonably delayed). These provisions provide the legal basis for Section VII of these Objections.

I. THE MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) IS A NON-PROTECTIVE STANDARD

The adequacy, or lack thereof, of EPA's risk assessment of the sulfuryl fluoride tolerances is heavily dependent on the adequacy, or lack thereof, of EPA's safe drinking water standard known as the Maximum Contaminant Level Goal, or "MCLG."

The MCLG was established by EPA's Office of Drinking Water (ODW) in 1985. The MCLG is 4 milligrams of fluoride per liter of water (4 mg/L, or 4 ppm).

In its health risk assessments of the tolerances, EPA's Office of Pesticide Programs (OPP) utilized the MCLG as the basis for its three reference doses[1]. A reference dose (RfD) is the key indicator by which EPA assesses the safety of tolerances, as it represents the maximum dosage (mg/kg/day) of the chemical that EPA considers safe for each age range.

Since the MCLG is the scientific basis for OPP's RfD for fluoride, if the science underpinning the MCLG is flawed, then the RfD will be flawed as well. In other words, the MCLG is to the RfD what a foundation is to a house. If the foundation is faulty, the house is at risk.

As Objectors have detailed in their many written objections to OPP[2], and as the foregoing discussion makes clear, the MCLG is, in fact, an unsafe and severely deficient standard – particularly when judged by the criteria for assessing safety set forth by the Federal Food Drug and Cosmetic Act (FFDCA), as amended by the Food Quality

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[1] As detailed in Section II, OPP derived three different reference doses (RfDs) for fluoride in its three health risk assessments of sulfuryl fluoride tolerances. *All three RfDs are based on the same MCLG.* The 1st RfD (0.114 mg/kg/day for _all ages_), was used in OPP's initial risk assessment of sulfuryl fluoride in September 2001. The 2nd RfD increased the allowable dosage for children by up to a factor of five ($\leq$0.571 mg/kg/day) and was used in EPA's January 2004 risk assessment. The 3rd RfD increased the allowable dosage for children by an additional factor of two ($\leq$1.14 mg/kg/day) and was used in EPA's January 2006 risk assessment.

[2] See Appendix A for a chronology of Objectors' submissions to OPP.

Protection Act (FQPA). Thus, by using ODW's 20-year old MCLG as the basis for its RfD[3], OPP's risk assessment of the tolerances was incapable of making a true determination of safety.

ISSUE 1.1: MCLG unsafe according to National Research Council

Objectors' contention that the MCLG is an unsafe and inadequate standard is now supported by the highest scientific authority in the country - the National Research Council (NRC) of the National Academies.

At the request of EPA, a committee appointed by NRC reviewed the scientific adequacy of the Maximum Contaminant Level Goal (MCLG).

On March 22, 2006, the NRC released a 400+ page report detailing the conclusions (NRC 2006). The report, titled "Fluoride in Drinking Water: A Scientific Review of EPA's Standards" confirms in great detail the key positions taken by the Objectors regarding the MCLG.

Most importantly, the NRC report concurs with Objectors' primary contention that the MCLG is not a safe standard and "should be lowered." According to NRC:

> "In light of the collective evidence on various health end points and total exposure to fluoride, the committee concludes that EPA's MCLG of 4 mg/L should be lowered. Lowering the MCLG will prevent children from developing severe enamel fluorosis and will reduce the lifetime accumulation of fluoride into bone that the majority of the committee concluded is likely to put individuals at increased risk of bone fracture and possibly skeletal fluorosis, which are particular concerns for subpopulations that are prone to accumulating fluoride in their bone"

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[3] One of the many problems with OPP's decision to utilize the MCLG as its health standard, is that the MCLG was developed by another division of EPA (Office of Drinking Water) using different methodologies for determining safety. Different methodologies for assessing safety are likely to apply different assumptions, different standards of cost/benefit weighting, different degrees of confidence, different levels of data completeness, different cumulative methods, different aggregation methods, different childhood risk methods, different standards of transparency and openness, etc. Considering OPP's unique requirements (as defined by FFDCA) for determining safety, its decision to use a standard from an EPA division which does not need to adhere to FFDCA's rigorous and protective requirements, fundamentally impaired OPP's risk assessment from making a true determination of safety.

(NRC, p. 299).

The NRC's conclusion that the MCLG is unsafe undermines the scientific basis of OPP's risk assessment for sulfuryl fluoride, since the health risk assessment is entirely predicated on the assumption that the MCLG is a safe and adequate standard. According, for example, to the New York State Attorney General's Office:

> "extrapolating from the conclusions of the NRC report, the tolerances established by EPA are not sufficiently protective against adverse health effects" (Kaufmann 2006).

The tolerances, therefore, cannot be considered "safe" because they are not based on a determination of "reasonable certainty that no harm will result" as required by the FFDCA.

ISSUE 1.2: Severe dental fluorosis is an adverse health effect

It has been known for a long time that a significant percentage of children who drink water with 4 ppm fluoride (the current MCLG) will develop a condition known as "severe dental fluorosis." Severe dental fluorosis is a serious mineralization disorder of the teeth that results in a highly porous, discolored, and weakened enamel. The enamel of the teeth become so porous that the teeth are "prone to fracture and wear" (ATSDR 2003), "subject to extensive mechanical breakdown of the surface" (Aoba & Fejerskov 2002), with a "friable enamel that can result in loss of dental function" (Burt & Eklund 1999).

Because of the widespread staining and mechanical damage that severe fluorosis can cause to teeth, there has been a longstanding concern that it could adversely affect a child's health. As noted by Victor Kimm, the head of EPA's ODW, in 1984:

> "It is difficult to conclude a priori that teeth which spontaneously pit are stronger teeth. Further, data suggest that the effects of fluorosis are not merely

discoloration and pitting, but fracturing, caries and tooth loss as well… We have some color photos of fluorotic teeth which shows the kind of chipping, pitting and fracturing individuals exposed to high fluoride levels must endure. It is difficult to examine such photos and conclude that such effects are not adverse" (Kimm 1984).

Despite the damage that severe fluorosis can cause to teeth, EPA's MCLG was established on the premise that severe fluorosis is only a "cosmetic" effect, and not a health effect. After reviewing the literature on dental fluorosis, however, the NRC has rebuked EPA's contention on this matter. According to NRC, severe dental fluorosis fits the requisite criteria of an adverse health effect. To quote:

> "One of the functions of tooth enamel is to protect the dentin and, ultimately, the pulp from decay and infection. Severe enamel fluorosis compromises that health-protective function by causing structural damage to the tooth. The damage to teeth caused by severe enamel fluorosis is a toxic effect that is consistent with prevailing risk assessment definitions of adverse health effects" (NRC, p. 3).

NRC's conclusion that severe fluorosis is an adverse health effect[4] which EPA needs to protect against is extremely important, since about 10% of children who drink water at ODW's MCLG of 4 mg/L develop severe fluorosis. Thus, on this issue alone, it can be seen that the current MCLG – and, by extension, OPP's risk assessment for the sulfuryl fluoride tolerances – is not protective of children's health. Accordingly, since OPP is duty bound under the Food Quality Protection Act to set tolerances that are safe

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[4] In addition to the damage that severe fluorosis can cause to teeth, there is also long-standing concern – as expressed by the National Institute of Mental Health (see: USEPA 1985a,b) -- that severe fluorosis may cause adverse psychological effects on the impacted child (due to the embarrassment produced by having marked disfiguration of the teeth). While NRC refrained from making any firm conclusions on this point, a study published after the NRC report was published has added compelling new evidence that severe fluorosis could adversely impact a child's psychological well-being (Williams 2006). The study found that people with severe fluorosis were consistently judged to be less intelligent, less hygienic, less social, and less attractive. Assuming that any of these highly unfavorable judgments would impact the child's psychological development, then severe fluorosis would be appropriately classified as an adverse health effect irrespective of any reduced functionality of the teeth.

for children, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.3: Fluoride can damage the skeletal system before it produces crippling fluorosis

Another key assumption underlying ODW's MCLG, and by extension OPP's sulfuryl fluoride risk assessment, is the belief that crippling fluorosis is the only adverse effect that fluoride can have on the skeletal system. In agreement with Objectors, the NRC has rejected this assumption. According to the NRC, fluoride can cause other adverse effects on bone besides crippling fluorosis, and these effects can occur before crippling fluorosis is present.

The two pre-crippling bone effects identified by NRC, but unaccounted for in the MCLG, include:

- Arthritic symptoms
- Bone fracture

We will discuss these effects one at a time.

ISSUE 1.3.1: Arthritic Symptoms: A pre-crippling effect of fluoride ignored by EPA

One of the most significant errors underlying the MCLG is the notion that the pre-crippling clinical stages of skeletal fluorosis (osteosclerotic changes in bone structure) are not associated with any adverse symptoms. In promulgating the current MCLG, ODW stated:

> "the Agency can find no evidence that fluoride induced increases in bone density, osteosclerosis, result in bodily harm or impaired functioning of the body. No new evidence or argument on this point was received in public comment. Therefore, the EPA reaffirms its conclusion that fluoride induced osteosclerosis is not an adverse health effect within the meaning of the SDWA" (US EPA 1985a).

ODW's contention that the pre-crippling, osteosclerotic phase of fluorosis does not result in "bodily harm or impaired functioning" has been directly contradicted by the NRC. According to NRC:

> "In clinical stage II, symptoms characterized by sporadic pain, stiffness of joints, and osteosclerosis of the pelvis and spine are observed… Because the symptoms associated with stage II skeletal fluorosis could affect mobility and are precursors to more serious mobility problems, the committee judges that stage II is more appropriately characterized as the first stage at which the condition is adverse to health. Thus, this stage of the affliction should also be considered in evaluating any proposed changes in drinking water standards for fluoride" (NRC, p. 139).

The NRC's conclusion is consistent with the assessment of the US Public Health Service. According to the US PHS (1991), fluoride-induced osteosclerosis can cause, depending on its severity, "sporadic pain", "stiffness of joints," "chronic joint pain," and "arthritic symptoms." As with NRC, the PHS concluded that these arthritic effects can occur <u>before</u> the crippling stage of fluorosis.

While not everyone with pre-crippling clinical fluorosis will experience arthritic pain (Franke 1975), the evidence is clear that some people *will* (Singh 1963; Singh & Jolly 1970; Vischer 1970; Cook 1971; Schlegel 1974; Franke 1975; Teotia 1976; Czerwinski 1977; Boillat 1980; Carnow 1981; Czerwinski 1988; PHS 1991; Roschger 1995; Savas 2001; Eichmiller 2005).

Thus, if skeletal fluorosis is OPP's endpoint of concern, it is imperative that OPP follow the advice of NRC and establish an RfD that will protect against the arthritic symptoms encountered in the pre-crippling, clinical stage of the disease. Because ODW's MCLG cannot – according to NRC – be relied on to protect against the pre-crippling stages of skeletal fluorosis, OPP's RfD cannot be considered safe with "reasonable

certainty" for all subsets of the population. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.3.2: Bone fracture: A pre-crippling effect of fluoride ignored by EPA

In addition to its ability to produce arthritic symptoms in the pre-crippling phase of fluorosis, the NRC also concluded that fluoride can reduce the strength of bone and thereby increase the risk of fracture and that these effects can occur at levels of exposure at, or below, the MCLG. According to NRC:

> "All members of the committee agreed that there is scientific evidence that under certain conditions fluoride can weaken bone and increase the risk of fractures. The majority of the committee concluded that lifetime exposure to fluoride at drinking water concentrations of 4 mg/L or higher is likely to increase fracture rates in the population, compared with exposure at 1 mg/L, particularly in some susceptible demographic groups that are more prone to accumulate fluoride in their bones" (NRC, p. 146).

Because ODW's MCLG does not protect against bone fracture, OPP's RfD cannot be considered safe with "reasonable certainty" for all subsets of the population as required by FFDCA.

There are three lines of evidence which NRC relied on to support its conclusions: human clinical trials, animal studies, and epidemiological studies of communities with varying levels of waterborne fluoride. We will discuss each in turn.

ISSUE 1.3.2A) Fluoride & Bone Fracture: Clinical Trials

Since 1985, a series of well-controlled clinical trials – including an NIH-sponsored 4 year double-blind trial (Riggs 1990) - have reported that osteoporotic patients treated with fluoride experience a higher rate of bone fractures, particularly hip fracture and other types of non-vertebral fracture (Dambacher 1986; Hedlund 1989; Bayley 1990; Orcel 1990; Riggs 1990; Schnitzler 1990; Haguenauer 2000; Gutteridge

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2002). Two studies published before 1985, including a double-blind trial – had also found this effect (Inkovaara 1975; Gerster 1983).

Especially relevant are the clinical trials of Inkovaara (1975), Gerster (1983), Hedlund (1989); Bayley (1989), Orcel (1990), and Gutteridge (2002), as the doses used in these trials ranged from just 21 to 25 mg per day. Also important was the short duration of these trials, and the fact that fractures were seen in some patients within just 8 and 11 months of exposure (Inkovaara 1975; Gerster 1983). Thus, at doses virtually identical to EPA's LOAEL[5] (20 mg/day for 10+ years), clear evidence of bone toxicity was experienced in less than a year of exposure – much less than EPA's purported 10-year minimum duration.

While OPP attempted to dismiss the relevance of these trials by pointing out that the doses greatly exceed the current LOAEL of 20 mg/day, OPP's argument was based on a fundamental error: the OPP had failed to convert the dose of sodium fluoride into the respective dose of fluoride ion (USEPA 2003b). Hence, OPP stated that the doses used by Hedlund (1989), Bayley (1990), and Gutteridge (2002) ranged from 50 to 60 mg/day, when in fact they ranged from 21 to 25 mg/day – or just a hair higher than the LOAEL.

OPP's dismissal of the clinical trials also overlooked the fact that the fractures in these trials occurred before crippling fluorosis was present, and they occurred in a notably shorter duration. Hence, it is incorrect for OPP to state that 1) crippling fluorosis is the first adverse effect that fluoride can have on bone, and that 2) an adverse effect on bone requires at least 10 to 15 years of exposure. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

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[5] LOAEL = "Lowest Observable Adverse Effect Level." For further discussion of the 20 mg/day LOAEL, see section 1.6.

ISSUE 1.3.2B) Fluoride & Bone Fracture: Animal studies

Lending support to the findings of the clinical trials, a series of well conducted animal studies – published after 1985 - have concluded that fluoride reduces bone strength (Mosekilde 1987; Turner 1992, 1993, 1995, 1996, 1997, 2001; Lafage 1995; Sogaard 1995).

According to NRC:

"Fracture risk and bone strength have been studied in animal models. The weight of evidence indicates that, although fluoride might increase bone volume, there is less strength per unit volume" (NRC, p. 5).

One of the important observations from these studies is that fluoride can reduce the strength of bone before any evidence of fluorosis is detectable on the microscopic level (Fratzl 1996; Turner 1995, 1997) and/or before bone mineral density is significantly altered (Mousny 2006). These findings underscore the problematic nature of OPP relying on ODW's 1985 contention that crippling fluorosis is the only bone effect to protect against.

Another important result from the animal studies is Turner's 1996 finding of increased osteomalacia and reduced bone strength in rats with kidney disease drinking water with the estimated human equivalent water-fluoride concentration of 3 ppm (Turner 1996). Moreover, the blood fluoride levels (9-10.8 umol/L) consistently associated with reduced bone strength in Turner's studies (Turner 1995, 1996, 2001), are equal to blood fluoride levels known to occur in humans with kidney disease living in communities with less than 2 ppm fluoride in water (Johnson 1979; Waterhouse 1980; Warady 1989; Torra 1998).

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ISSUE 1.3.2C) Fluoride & Bone Fracture: Epidemiology

Just as most of the clinical trials and animal studies investigating fluoride's impact on bone strength have been published after ODW's issuance of the MCLG, the same is true for epidemiological studies reporting an increased rate of fracture in communities with elevated fluoride in water. Indeed, all of the important studies on waterborne fluoride and fracture have been published since 1985.

A year after ODW issued the MCLG, Sowers (1986) reported a statistically significant increase in bone fractures in a 4 ppm community versus a control community with 1 ppm. In 1991, Sowers updated her findings and noted that in addition to an increase in bone fractures, there was also a statistically significant reduction in bone mass in the 4 ppm community.

A year earlier, Phipps (1990) reported the results of a separate study which looked at bone mass in a 3.5 ppm community. Consistent with Sowers' finding, Phipps found that the 3.5 ppm community had significantly less bone density than the 1 ppm community in the bone that she measured (the forearm). A follow-up study by Phipps (1996, 1998) found similar results (reduced bone density in the forearm) among a community with just 2.5 ppm.

While Phipps' studies did not investigate bone fracture rates in high-fluoride communities, a later study by Li (2001) did. As with Sowers, Li found a statistically significant increase in bone fracture rates, particularly hip fractures, in communities with excess fluoride. In a community with 4.3-8 ppm, Li found that the hip fracture rate was 3 times higher than the hip fracture rate in the control 1 ppm community. Li also found a

doubling of hip fractures at 1.5+ ppm, however, this effect was not statistically significant at the 95% confidence level.

According to the NRC, Li's finding of an increase in fractures at 1.5 ppm is consistent with findings from Kurttio (1999) and Alarcon-Herrera (2001) and gives "support to a continuous exposure-effect gradient" between 1 and 4 ppm (NRC 2006, p. 138). In other words, the findings from Li (2001), Kurttio (1999), and Alarcon-Herrera (2001) indicate – according to NRC - that fluoride may increase the risk for bone fracture at fluoride levels well below the 4 ppm MCLG.

A more recent study by Sowers (2005), again looking at a 4 ppm versus 1 ppm community, has again reported significantly higher osteoporotic fractures in a 4 ppm area, although the effect no longer reached statistical significance when the authors controlled for other covariates, including serum fluoride and bone density.

Based on the findings of these epidemiological studies and their consistency with the clinical and animal research discussed earlier, the NRC concluded that the weight of evidence supports the conclusion that fluoride increases the risk of fracture, and that ODW's MCLG does not protect against this risk. Since OPP's RfD is based on the MCLG, the RfD cannot be considered protective against bone fracture for all subsets of the population. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.4: Fluoride's effects are not just limited to teeth and bone

A fundamental assumption underlying ODW's MCLG, and by extension OPP's sulfuryl fluoride risk assessments, is the notion that fluoride's effects on human health are strictly limited to hard tissues (teeth and bone). A review of the science underpinning the

MCLG (US EPA 1985b) reveals that ODW had assumed fluoride could not affect soft tissues at water fluoride concentrations below 50 ppm. However, as with ODW's assertion that fluoride's only adverse bone effect is crippling fluorosis, ODW's assertion (and, by extension, OPP's assertion) that fluoride can have no adverse effects on soft tissue function has also been contradicted by the NRC report.

ISSUE 1.4.1: Fluoride may damage the brain

When ODW issued its MCLG in 1985, there was hardly any research available concerning fluoride's impact on the brain. Indeed, there is not a single mention of the word "brain" in any of the 190+ pages of the 1985 Criteria Document supporting ODW's MCLG (US EPA 1985b). It is understandable, therefore, that the MCLG in 1985 did not account for the concerns on fluoride's neurotoxicity. As the NRC report makes clear, however, the state of science on fluoride's neurotoxicity is much different, and much more compelling, today than it was in 1985.

For example, following a 1986 study by Guan et al, there have been over 40 studies indicating that fluoride can damage the brain. According to the NRC,

> "On the basis of information largely derived from histological, chemical, and molecular studies, it is apparent that fluorides have the ability to interfere with the functions of the brain and the body by direct and indirect means" (NRC, p187).

In some cases brain damage has been caused at very low doses. For example, Varner et al. (1998) exposed rats to 1 ppm fluoride in doubly distilled and de-ionized water for 1 year and showed kidney damage, brain damage and uptake of aluminum into the brain[6]. Studies on humans exposed to elevated fluoride in China, meanwhile, have

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[6] In a study of shorter duration, Zhao (1998) found adverse brain effects in rats drinking 5 ppm fluoride in water, while studies by Guan and colleagues (Guan 1998; Long 2002; Shen 2004) have consistently found neurotoxic effects among rats drinking 30 ppm fluoride (the lowest concentration they've used). When considering that blood fluoride levels are typically 5 times lower in rats than in humans when exposed to

found effects on IQ in children at levels as low as 0.9 ppm in areas of iodine deficiency (Lin Fa Fu 1991) and 1.8 ppm in areas with sufficient iodine (Xiang 2003a,b).

ISSUE 1.4.1A Fluoride & the Brain: Fluoride crosses the placenta.

In light of NRC's conclusion that "fluorides have the ability to interfere with the functions of the brain," it is significant – particularly in the context of FQPA – to note that the placenta does not prevent the passage of fluoride from maternal blood to the fetus (WHO 2002). As a result, pre-natal exposure to fluoride may present risks to the child. OPP's failure to address this issue, therefore, reflects a serious flaw and oversight in their risk assessment.

The potential for fluoride to damage the brain during fetal development was, in fact established by Du in 1992. Du compared the brains of 15 aborted fetuses at the 5-8th gestation month from an endemic fluorosis area and compared these with fetuses from a non-endemic area. Du's analysis of the brains revealed a significant reduction in the density of mitochondria and a reduction in the mean volume of neurons among the fetuses from the endemic fluorosis area (Du 1992).

While Du does not provide data on the water fluoride levels that the mothers were exposed to, he does provide data on their urine fluoride levels. The average urine fluoride levels of the exposed mothers was only 6.4 ppm which is not exceptionally higher than the urine fluoride levels found among some women in the U.S. In fact, were a pregnant woman to consume dried eggs or wheat products fumigated with permissible levels of sulfuryl fluoride (see section 5), they could easily have spikes in their urine fluoride levels that significantly exceed 6.4 ppm on a temporary basis. Based on current evidence,

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the same dose of fluoride (NRC 2006), Guan's studies are probably more indicative of human exposure to ~6 ppm fluoride in water.

it is not possible to rule out adverse effects on the developing fetus from such spikes in fluoride exposure. In fact, animal research by Mullenix (1995) indicates that spikes in fluoride exposure during sensitive periods of fetal development can have permanent neurotoxic effects. On this basis alone, the tolerances should be rejected.

ISSUE 1.4.1B Fluoride & the Brain: Fluoride crosses blood brain barrier

Adding to the concern about fetal exposure to fluoride is the fact that fluoride is able to pass through the blood brain barrier. While some, such as Whitford have questioned whether it can accumulate in the tissue (Whitford 1996), it is widely accepted that the fluoride circulating in the bloodstream will enter the brain (Zhai et al. 2003; Inkielewicz & Krechniak 2003; Vani and Reddy 2000; Long 2002; Guan et al 1998; Mullenix et al. 1995; Gerents et al. 1986; Tomomatsu 1981). Thus, were a pregnant women to consume a food fumigated with fluoride, the fluoride would not only enter the fetal bloodstream, it would also enter the fetal brain. In fact, since the blood brain barrier is not yet fully developed in the fetus, a greater percentage of fluoride in fetal blood will enter the brain than in older populations. (The blood brain barrier is also not fully developed at birth either, thus infants will also have less ability to prevent any ingested fluoride from entering the brain.)

ISSUE 1.4.1C Fluoride & the Brain: Fluoride can exacerbate effects of iodine-deficiency

According to the NRC, fluoride has the potential – at notably low doses - to exacerbate the neural developmental effects (e.g. IQ deficits and mental retardation) of low iodine intake. This is a serious finding – one which OPP did not consider in its risk assessment.

Iodine deficiency is the world's leading cause of IQ deficits, and the incidence of iodine deficiency has increased significantly in the US over the past 30 years. According to the CDC, iodine deficiency now affects about 12% of the US population (CDC 1998).

According to the NRC, fluoride may exacerbate the effects of iodine deficiency at dosages as low as 0.01-0.03 mg/kg/day (NRC, p. 218). To put this dosage in perspective, the OPP's current RfD for infants is 1.14 mg/kg/day. This is up to 100 times greater than NRC's estimate for the dosage associated with aggravation of iodine deficiency. NRC's conclusion is based, in part, on a UNICEF-funded study in China (Lin Fa-Fu 1991) which found that the effects of iodine deficiency (e.g. low IQ, mental retardation, and auditory problems) were greater and more severe in areas where the iodine deficiency was coupled with elevated fluoride exposure from water (0.9 ppm F). Supporting this finding are a series of animal studies which have reported that fluoride's effects on the brain, and thyroid, are significantly more severe if the animal has a deficient intake of iodine (Zhao 1998; Wang 2004a,b; Ge 2005).

In light of this evidence, the NRC report warns that:

"The recent decline in iodine intake in the United States could contribute to increased toxicity of fluoride for some individuals." p218

With about 12% of the US population experiencing some form of iodine deficiency, and considering the critically important role of iodine in fetal and childhood neurologic development, the failure of OPP to specifically assess the risk of fluoride to this major identifiable subset of the population represents a major flaw in the risk assessment.

ISSUE 1.4.1D Fluoride & the Brain: Fluoride may lower IQ

Consistent with the above-mentioned studies indicating that fluoride can have both direct, and indirect, neurotoxic effects, several studies from China have found an association between elevated fluoride exposure and decreased IQ. Some of these studies have not controlled for some key variables, but the latest study – a double-blind study by Xiang et al. (2003a,b) -- did control for both lead and iodine exposure, as well as other key factors associated with IQ (e.g. parental income & education) and found a lowering of IQ in children at fluoride levels as low as 2 ppm.

According to the NRC:

"A few epidemiologic studies of Chinese populations have reported IQ deficits in children exposed to fluoride at 2.5 to 4 mg/L in drinking water. Although the studies lacked sufficient detail for the committee to fully assess their quality and relevance to U.S. populations, the consistency of the results appears significant enough to warrant additional research on the effects of fluoride on intelligence" (NRC, p. 6).

ISSUE 1.4.1E Fluoride & the Brain: Fluoride may also affect elderly

In addition to fluoride's potential for damaging the developing brain, the NRC discussed several lines of evidence which indicate that chronic fluoride exposure may also damage the brain in the elderly.

As discussed by the NRC, studies on animals have found that fluoride can both facilitate the uptake of aluminum into the brain and increase the formation of beta-amyloid deposits (Varner 1998). Beta-amyloid deposits are the classic brain pathology of Alzheimers' disease. According to NRC:

"histopathological changes similar to those traditionally associated with Alzheimer's disease in people have been seen in rats chronically exposed to AlF [aluminum fluoride]" (NRC, p. 178).

The NRC report also discussed evidence indicating that fluoride can increase the production of free radicals in the brain via several mechanisms. According to NRC:

> "Fluorides also increase the production of free radicals in the brain through several different biological pathways. These changes have a bearing on the possibility that fluorides act to increase the risk of developing Alzheimer's disease" (NRC, p. 186).

In light of research indicating several plausible mechanisms[7] by which fluoride could cause, or contribute to, adverse effects on the adult brain, the NRC recommended that:

> "Studies of populations exposed to different concentrations of fluoride should be undertaken to evaluate neurochemical changes that may be associated with dementia. Consideration should be given to assessing effects from chronic exposure, effects that might be delayed or occur late-in-life, and individual susceptibility" (NRC, p. 187).

ISSUE 1.4.1F Fluoride & the Brain: The multitude of NRC's concerns belie EPA's claims

When coupling the multitude number of concerns clearly expressed by NRC on the potential for fluoride to adversely affect the brain, with the absence of any such consideration by ODW when promulgating the MCLG in 1985, OPP's RfD cannot be considered safe with reasonable certainty for all subsets of the population, particularly infants and children. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

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[7] Concerns about fluoride's potential to contribute to dementia are further supported by papers reporting that fluoride may damage the hippocampus (Zhai JX et al. 2003; Bhatnagar et al. 2002; Shivarajashankara YM et al. 2002; Chen J et al. 2002; Zhang Z et al. 2001; van der Voet et al. 1999; Varner et al. 1998; Mullenix et al. 1995; Kay et al. 1986). Damage to the hippocampus usually results in profound difficulties in forming new memories and affects access to memories prior to the damage. In Alzheimer's disease, the hippocampus becomes one of the first regions of the brain to suffer attack; causing memory problems and disorientation.

ISSUE 1.4.2: Fluoride is an "endocrine disrupter"

When ODW promulgated the MCLG in 1985, it did so – in part - on the

premise that fluoride had no effect on the endocrine system at water fluoride

levels less than 50 ppm (US EPA 1985b). OPP recently tempered this statement,

however, by saying that the "Agency is aware of potential effects of fluoride

being noted in the open literature" and that it would "re-examine" its assessment

of whether fluoride is an endocrine disrupter based on the findings of the NRC.

It is particularly significant, therefore, to look at what NRC concluded about

fluoride's effect on the endocrine system. According to NRC, there is sufficient evidence

to warrant the classification of fluoride as an "endocrine disrupter." To quote:

> "In summary, evidence of several types indicates that fluoride affects normal
> endocrine function or response; the effects of the fluoride-induced changes vary
> in degree and kind in different individuals. Fluoride is therefore an endocrine
> disruptor in the broad sense of altering normal endocrine function or response,
> although probably not in the sense of mimicking a normal hormone." (NRC, p.
> 223).

Moreover, whereas ODW set the MCLG with the belief – based on animal studies

- that fluoride had no effect on thyroid function at less than 50 ppm, the NRC stated that

fluoride could affect endocrine function at less than 4 ppm. According to NRC:

> "The chief endocrine effects of fluoride exposures in experimental animals and in
> humans include decreased thyroid function, increased calcitonin activity,
> increased parathyroid hormone activity, secondary hyperparathyroidism, impaired
> glucose tolerance, and possible effects on timing of sexual maturity. **Some of
> these effects are associated with fluoride intake that is achievable at fluoride
> concentrations in drinking water of 4 mg/L or less**, especially for young
> children or for individuals with high water intake" (NRC, p. 7; emphasis added).

In comparing NRC's conclusions with those underpinning ODW's MCLG, it is

clear that the body of scientific knowledge on fluoride's endocrine effects has either

changed considerably since 1985, or ODW's conclusions underpinning the MCLG were

significantly flawed. In any event, NRC's conclusion that fluoride is an endocrine disrupter associated with effects at levels lower than 4 ppm further undermines OPP's use of the 4 ppm MCLG as the basis of its RfD. Indeed, based on the evidence linking fluoride to endocrine disruption at levels below 4 ppm, OPP's RfD cannot be considered safe under the requirements set forth by FFDCA, as amended by FQPA. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.4.2A: Fluoride's Impact on Insulin Secretion/Glucose Tolerance

According to the NRC, fluoride's potential to affect the endocrine system is supported, in part, by evidence that fluoride can inhibit the secretion of insulin and/or interfere with glucose tolerance.

According to NRC:

"The conclusion from the available studies is that sufficient fluoride exposure appears to bring about increases in blood glucose or impaired glucose tolerance in some individuals and to increase the severity of some types of diabetes. In general, impaired glucose metabolism appears to be associated with serum or plasma fluoride concentrations of about 0.1 mg/L or greater in both animals and humans" (NRC, p. 217).

One of the studies underpinning NRC's discussion on fluoride/insulin secretion, is a study published by Menoyo (2005). As with earlier animal, human, and in-vitro studies (Rigalli 1990, 1995; Trivedi 1993), Menoyo found that fluoride can impair insulin secretion at notably low levels. The serum concentration of fluoride repeatedly found capable of inhibiting the secretion of insulin was, as the NRC stated, "about 0.1 mg/L". A non-significant reduction, meanwhile, has been reported at concentrations as low as 0.04 mg/L (Rigalli 1995; see Table 1).

Based on this research, Menoyo (2005) concluded that:

> "The overall information afforded by present experiments indicate
> that extracellular concentrations of fluoride above 5 umol/L [0.095
> mg/L] affect the insulin excretion. The results suggest that fluoride
> affects some stage of insulin secretion situated below the cascade
> of events that include the participation of calmodulin, protein-
> kinase C and cyclic AMP" (Menoyo 2005).

What's remarkable about this finding is that 5 umol/L (= 0.095 mg/L) is a

concentration that many individuals with kidney disease, even those living in ≤1 ppm

areas, will attain in their bloodstream (Johnson 1979; Waterhouse 1980; Warady 1989;

Torra 1998). Even some individuals without kidney disease living in <4 ppm areas will

attain this concentration (Parkins 1974; Singer 1979; Jackson 1997; Sowers 2005).

These findings, therefore, raise concerns about the potential for fluoride exposure

to increase either the incidence or severity of diabetes mellitus. As noted by the NRC,

individuals with diabetes mellitus can have markedly increased water consumption,

which, in turn, can lead to enhanced intakes of fluoride. According to NRC:

> "diabetic individuals will often have higher than normal water intake, and
> consequently, will have higher than normal fluoride intake for a given
> concentration of fluoride in drinking water. An estimated 16-20 million people in
> the U.S. have diabetes mellitus; therefore, any role of fluoride exposure in the
> development of impaired glucose metabolism or diabetes is potentially
> significant" (NRC, p. 217).

With millions of Americans affected by diabetes mellitus, and with published

evidence repeatedly finding that fluoride can inhibit insulin secretion at attainable blood

concentrations attainable in ≤4 ppm areas, OPP cannot state with reasonable certainty

that the 4 ppm MCLG is safe for all subsets of consumers. Accordingly, OPP's risk

assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.4.2B: Fluoride's Impact on the Thyroid Gland:

In addition to affecting insulin secretion, fluoride may also affect the thyroid gland. According to the NRC, "several lines of information indicate an effect of fluoride exposure on thyroid function" (NRC, p. 197).

Fluoride's potential to impair thyroid function is illustrated by the fact that – from the 1930s through to the 1970s -- doctors used sodium fluoride (at doses as low as 2-10 mg/day of F ion) to lower the activity of the thyroid gland of patients who suffered from hyperthyroidism. The doses used were remarkably low (2-10 mg fluoride/day)[8] (Galletti and Joyet, 1958).

Further, additional research – in both animals and humans – indicates that fluoride's impact on the thyroid and brain is exacerbated when coupled with an iodine deficiency – a fact emphasized in the NRC report (Guan 1998; Li-Lu 1991; Zhao 1998; Wang 2004a,b, Ge 2005). As noted by the NRC, this fact may help explain some of the contradictory findings in the literature on fluoride and thyroid. For instance, in 1985 ODW stated:

> "At concentrations of 50 mg/L or below of fluoride in drinking water, no structural or functional changes in the thyroid have been observed in animals" (US EPA 1985b, p. I-3).

Studies published after 1985, however, have shown that iodine-deficient animals are clearly affected when exposed to less than 50 ppm fluoride in water, including at the lowest tested level of 10 ppm (Guan 1988; Zhao 1998).

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[8] While promoters of water fluoridation have dismissed this fact on the premise that fluoride's anti-thyroid effects may be limited to people with hyperthyroid conditions (Demole 1970), Bachinskii has published data showing that fluoride may lower normal thyroid function as well -- at levels as low as 2.3 ppm fluoride in drinking water (Bachinskii 1985).

Similar findings have been reported in iodine-deficient humans. In fact, according to NRC, the doses causing adverse thyroid effects in humans are significantly <u>lower</u> than the doses causing effects in animals. According to the NRC:

> "In animals, effects on thyroid function have been reported at fluoride doses of 3-6 mg/kg/day (some effects at 0.4-0.6 mg/kg/day) when iodine intake was adequate; effects on thyroid function were more severe or occurred at lower doses when iodine intake was inadequate. In humans, effects on thyroid function were associated with fluoride exposures of 0.05-0.13 mg/kg/day when iodine intake was adequate and 0.01-0.03 mg/kg/day when iodine intake was inadequate" (NRC, p. 218).

As noted earlier, NRC's estimate of the dosages (0.01-0.03 mg/kg/day) associated with thyroid effects in iodine-deficient humans are well below OPP's RfD of 0.114 for adults, and even further below OPP's RfD for infants and children (≤1.14 mg/kg/day).

Again, this fact is quite significant when considering CDC's recent estimate that 12% of the US population has some form of iodine deficiency (CDC 1998). This represents an extremely large subset of consumers that are potentially at increased risk from fluoride exposure. As noted by the NRC:

> "The recent decline in iodine intake in the United States could contribute to increased toxicity of fluoride for some individuals" (NRC, p. 218).

Considering that the doses of fluoride that may exacerbate the anti-thyroid effects of iodine deficiency are easily exceeded in 4 ppm areas, OPP's RfD can not be considered safe with reasonable certainty for all subsets of the population. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.4.2C: Fluoride's Impact on the Pineal Gland

Yet another endocrine gland's function that fluoride may disturb is the pineal gland and it's regulation of the hormone melatonin.

As recently discovered by Luke (1997, 2001), the pineal gland is a significant site of fluoride accumulation. An analysis of human cadavers found that the calcified crystals within the pineal gland have the highest concentrations of fluoride (avg = 9,000 ppm) in the body (Luke 2001).

The discovery of high fluoride levels in the pineal prompted animal research to determine if the presence of fluoride in the gland could interfere with the cells (pinealocytes) responsible for synthesizing melatonin. The subsequent animal study, conducted by Luke (1997), found that the animals exposed to fluoride had reduced levels of circulating melatonin and an earlier onset of puberty than the animals not exposed to fluoride. According to the author, the findings suggest that fluoride accumulation in the pineal can damage cells in the gland in an analogous fashion as fluoride accumulation in the developing teeth can damage the ameloblasts (enamel-forming cells). To quote:

> "The safety of the use of fluorides ultimately rests on the assumption that the developing enamel organ is most sensitive to the toxic effects of fluoride. The results from this study suggest that the pinealocytes may be as susceptible to fluoride as the developing enamel organ (Luke 1997, p. 7)."

According to the NRC, Luke's study:

> "indicates that fluoride exposure results in altered melatonin production and altered timing of sexual maturity" (NRC, p. 221).

While fluoride's impact on melatonin levels in humans has never been directly studied, the NRC points out that:

"two studies of menarcheal age in humans show the possibility of earlier menarche in some individuals exposed to fluoride, but no definitive statement can be made" (NRC, p. 221).

As detailed by the NRC, any affect on melatonin production in humans would be a serious matter. For instance, the NRC report states that:

"Recent information on the role of the pineal organ in humans suggests that any agent that affects pineal function could affect human health in a variety of ways, including effects on sexual maturation, calcium metabolism, parathyroid function, postmenopausal osteoporosis, cancer, and psychiatric disease" (NRC, p. 221-222).

In every comment we submitted to EPA on sulfuryl fluoride (E Connett 2001, 2002, 2005a; P Connett 2002, 2004; Neurath 2005) we noted our concerns of fluoride's potential to accumulate in the pineal gland. (In October 2001 we sent Luke's thesis to EPA's Dennis McNeilly who was then coordinating responses to the proposed tolerances.) The NRC's report echoes our concerns on this matter, and has called for more research to investigate the matter. Before such research is done, it is simply not possible – under the conditions set forth by FFDCA – for OPP to state with reasonable certainty that increasing current fluoride exposures will have no adverse effect on pineal function. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.4.3C: Fluoride's Impact on the Kidneys

With the exception of the pineal gland, the kidney accumulates more fluoride than all other soft tissues in the body (Hongslo 1980; Ekstrand 1996; Whitford 1996). As a result, the kidney has long been recognized as a potential target site of toxicity for fluoride.

According to NRC:

"Human kidneys... concentrate fluoride as much as 50-fold from plasma to urine. Portions of the renal system may therefore be at higher risk of fluoride toxicity than most soft tissues" (NRC, p. 236).

When ODW, however, promulgated the MCLG in 1985, it did so on the premise that fluoride in water would not damage the kidneys if it were present in concentrations below 100 ppm. As noted in ODW's Criteria Document supporting the MCLG,

"renal injuries do not develop when drinking water contains less than 100 ppm fluoride" (USEPA 1985b, p. V-35).

While the NRC panel did not review the research on fluoride and kidney as extensively as they did other tissues, the studies they reviewed found effects at much lower levels than 100 ppm. According to NRC:

"On the basis of studies carried out on people living in regions where there is endemic fluorosis, ingestion of fluoride at 12 mg per day would increase the risk for some people to develop adverse renal effects" (NRC, p. 247).

The NRC also reported on animal studies (Borke & Whitford 1999; Guan 2000), which found adverse renal effects at 10 ppm and 30 ppm (the lowest levels tested in the two respective studies).

The Borke & Whitford (1999) study is particularly relevant since it found adverse effects on kidneys among rats with average blood fluoride levels of just 0.038 ppm (or 2 umol/L). This is a concentration commonly found in people living in 1 ppm and 2 ppm areas (Parkins 1974; Johnson 1979; Warady 1989; Jackson 1997; Torra 1998; Sowers 2005).

Lending support to Borke & Whitford's findings is the low-dose, long term rat study conducted by Varner (1998). This study found adverse effects on kidney tissue at just 1 ppm when the rats were exposed to fluoride in their drinking water for a full year.

Taken together, the animal studies by Borke & Whitford (1999), Guan (2000), and Varner (1998), as well as others by Manocha (1975) and Sullivan (1969), sharply contradict EPA's claim that fluoride does not affect kidney function at concentrations below 100 ppm.

A new study on humans, meanwhile, published after the NRC report was completed, has found that fluoride concentrations as low as 2.5 ppm are associated with adverse renal effects in children (Xiong 2006). According to the authors:

> "our results suggest that drinking water fluoride levels over 2.0 mg/L (ppm) can cause damage to liver and kidney function in children..." (Xiong 2006)

While many previous surveys of human populations have found evidence of kidney damage among patients with skeletal fluorosis (Ando 20001; Derryberry 1963; Jolly 1980; Kumar 1963; Lantz 1987; Reggabi 1984; Shortt 1937; Siddiqui 1955; Singh 1963; Singla 1976); the study by Xiong is notable in that the children were not identified as having skeletal fluorosis of any significant degree. Thus, Xiong's study raises yet further doubts about the appropriateness of EPA using crippling skeletal fluorosis as the only endpoint of regulatory concern.

Since multiple peer-reviewed studies have found effects on the kidney at levels 50 to 100 times lower than ODW's purported threshold and within the range of exposures allowed by the MCLG, it is clear that the premise on which EPA dismissed kidney effects when promulgating the MCLG is severely deficient. Since OPP's RfD is based on the MCLG, the RfD cannot be considered protective of adverse renal effects under the conditions set forth under FFDCA. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.5: Fluoride has the potential to cause cancer

Another pivotal basis on which ODW's MCLG is based is the contention that fluoride is not a carcinogen (a cancer causing agent).

However, while not definitive, the evidence linking fluoride to cancer is much more convincing today than it was when the MCLG was first promulgated in 1985.

According to the NRC (2006), studies on animals, cell-lines, and humans indicate that fluoride has the "potential to initiate or promote cancers[9], particularly of the bone." While NRC considered this evidence "tentative and mixed," their conclusion is a significant upgrade from NRC's previous conclusion – in 1993 - that there is "no credible evidence" linking fluoride in water to cancer.

Of particular concern, according to NRC, is the possible link between fluoride and osteosarcoma (bone cancer). The concern that fluoride may cause osteosarcoma has been fueled by 1) a National Toxicology Program (NTP) animal study reporting a dose-dependent relationship between fluoride exposure and osteosarcoma in male rats[10] (NTP 1990), 2) several epidemiological studies on human populations reporting an association between fluoridated drinking water and osteosarcoma in young males (Hoover 1991, Cohn 1992, Bassin 2006), and 3) the biological plausibility of fluoride causing cancer in the bone.

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[9] Bladder cancer is another cancer that has been associated with elevated fluoride exposure (Lynch 1984; Grandjean 1985, 1992, 2004; Connett M 2004; NRC 2006). The strongest evidence supporting the link comes from a series of studies on cryolite workers by Grandjean (1985, 1992, 2004; Connett M 2004). Since Grandjean's findings are based on the same cryolite plant studied by Roholm (1937), his findings of an association between fluoride and bladder cancer among the workers indicate that – if studies on cryolite workers are to form the basis of EPA's LOAEL for fluoride – it would be more appropriate to use bladder cancer as the endpoint of concern, rather than crippling skeletal fluorosis, particularly since some epidemiological evidence indicates an association between bladder cancer and fluoridated drinking water (Lynch 1984; see also Appendix D in DHHS 1991).

[10] Despite NTP's findings of a dose-response curve in osteosarcomas among fluoride-treated male rats, Dow does not appear to have carefully examined bone tissue in their 2-year carcinogenicity study of sulfuryl fluoride. In light of NTP's findings, the failure to carefully look for sarcomas in the bone must be viewed as a significant limitation with Dow's study.

According to NRC, an association between fluoride and bone cancer is biologically plausible because of:

> "fluoride's deposition in bone, the NTP animal study findings of borderline increased osteosarcomas in male rats, and the known mitogenic effect of fluoride on bone cells in culture. Principles of cell biology indicate that stimuli for rapid cell division increase the risks for some of the dividing cells to become malignant, either by inducing random transforming events or by unmasking malignant cells that previously were in nondividing states" (NRC, p. 275).

The fact that the link between fluoride and bone cancer is biologically plausible, and the fact that the research published since ODW's promulgation of the MCLG in 1985, discredits the appropriateness of OPP relying on ODW's MCLG in assessing the safety, or lack thereof, of the tolerances. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

For an extensive review of the scientific literature on fluoride/osteosarcoma, we refer EPA to our comprehensive review of matter, which we submitted as part of our December 16, 2005 submission; see: Connett P et al, 2005 a, b).

ISSUE 1.6: The 20 mg/day LOAEL is outdated and incorrect

The fundamental premises of ODW's MCLG, and by extension OPP's sulfuryl fluoride risk assessment, are ODW's assertions that A) crippling fluorosis is the only relevant adverse effect that can result from chronic fluoride exposure, and that B) this effect doesn't occur at doses lower than 20 mg/day. As detailed above, the former assertion is not credible. As we will now detail, the latter assertion is not credible either.

Before beginning the discussion, it will be helpful to first provide a brief explanation about the origins of the 20 mg/day LOAEL ("Lowest Observed Adverse Effect Level.")

The first published reference to the 20 mg/day LOAEL was a 1950 paper by

Harold Hodge. In the paper, Hodge stated that:

> "From analyses of the urinary excretion of fluoride by cryolite workers in
> Denmark, the opinion has been stated that crippling fluorosis develops in
> individuals whose intake of fluoride exceeds 20 mg. per day for a period of 10 to
> 20 years" (Hodge 1950).

The study on cryolite workers to which Hodge refers, and which formed the basis

of the 20 mg/day LOAEL, was published by Roholm in 1937 with a follow-up study by

Brun in 1941. If one reviews these two papers, one will find that the size of the

population studied was small (e.g. a few dozen workers), the length of exposure was

limited (~10 to 25 years), and the composition of the population was very homogenous

(e.g. adult male workers). One will also find that the authors of the study were very

hesitant to make any firm conclusions about the dose of fluoride that can, and cannot,

cause fluorosis.

Nevertheless, following the publication of Hodge's paper in 1950, the cryolite

study became routinely cited as having established the minimum dose of fluoride (20

mg/day) that can cause crippling fluorosis. There are several major problems with this

assumption and OPP's reliance on it.

ISSUE 1.6.1 20 mg/day LOAEL is based on outdated data.

As noted above, Harold Hodge was the first scientist to publish – in 1950 - the

estimate that 20 mg/day is the minimum dose that can cause crippling fluorosis. Hodge

went on to cite this estimate in many of his subsequent reviews of fluoride toxicity.

Eventually, however, Hodge revised this estimate by stating that doses as low as

10 mg/day could cause crippling fluorosis (Hodge 1979).

In 1979, Hodge wrote:

"Crippling fluorosis as an occupational disease follows exposures estimated at 10 to over 25 mg of fluoride daily during periods of 10-20 years" (Hodge 1979).

Despite the fact that Hodge made this revision in 1979 -- six years before ODW issued the MCLG – ODW used his original 20 mg/day estimate.

While EPA may have failed to notice Hodge's revision, the National Research Council appears to have noticed it in their 1993 review on the "Health Effects of Ingested Fluoride." According to NRC:

"Crippling skeletal fluorosis might occur in people who have ingested 10-20 mg of fluoride per day for 10-20 years."

With both Hodge and the NRC stating that crippling fluorosis may be caused at doses as low as 10 mg/day[11], it is clearly inappropriate for OPP to still be using 20 mg/day as the LOAEL for crippling fluorosis. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.6.2 LOAEL based on only 10 to 20 years of exposure

An additional problem with using the 20 mg/day estimate as a LOAEL, is that – according to its own adherents - it only applies to "10 to 20+ years" exposure. Put another way, the science supporting OPP's tolerances for sulfuryl fluoride assume that people are exposed to fluoride for only 10 to 20 years. Since skeletal fluorosis is dependent both on dose *and* duration of exposure, it is not possible - based on Roholm's research - to determine the LOAEL for people exposed to fluoride for longer periods of time than the workers in Roholm's study. Needless to say, humans live for more than "10 to 20 years", and as a result, an appropriate MCLG – and RfD - would be based on

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[11] Recent research from Asia further reinforces Hodge's (1979) and NRC's (1993) estimate that crippling fluorosis may be caused at doses as low as 10 mg/day. According to a carefully conducted study by Cao (2003), crippling fluorosis in Tibet was caused by average daily doses of between 9 and 12 mg/day.

lifetime exposure to fluoride. OPP cannot say with reasonable certainty, therefore, that lifetime doses lower than the 20 mg/day LOAEL are safe. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.6.3 LOAEL is not appropriate for major identifiable sensitive sub groups.

Another major problem with OPP's 20 mg/day LOAEL is that it is not representative of the full range of conditions found in society. The cryolite study on which the LOAEL is based cannot support conclusions about major identifiable sensitive sub groups since the study was based on only a few dozen well-nourished, otherwise healthy adults. Thus, it is impossible to determine from the cryolite study the safe dose for susceptible population subsets, including infants, children, pregnant women, people with kidney disease, diabetes, and dietary deficiencies.

It is entirely inappropriate, therefore, particularly in the context of FFDCA as amended by FQPA, for OPP to assume 20 mg/day is the minimum toxic dose for susceptible populations not represented in the cryolite study. The problem is underscored by the following comments[12] from Dr. Georges Boivin, a renowned bone researcher who spent nearly two decades studying the impact of fluoride on the skeletal system:

> CONNETT: In the US, they've created this safe standard of 10 milligrams a day for life. This is from the age of 8 through for the rest of your life. Do you think that for a kidney patient, what would you say about 10 milligrams a day for a kidney patient?
>
> BOIVIN: For a patient with bad kidney function?
>
> CONNETT: Yes.

---

[12] Boivin's comments were made in response to a question about the Institute of Medicine's 10 mg/day "Upper Tolerable Limit" for adults. Thus, in addition to highlighting the problems with ODW/OPP assuming 20 mg/day is the minimum toxic dose, Boivin's comments also underscore the problems with using the IOM standard as a replacement, which OPP has insinuated it may do (USEPA 2006).

BOIVIN: It is 10 milligrams of fluoride ion?

CONNETT: Yes, per day.

BOIVIN: Ah, it is too much. It is definitely too much. During all the life? I would be very surprised if you do not obtain skeletal fluorosis after some years of treatment with such a dose in patients suffering from a bad, a poor renal function.

CONNETT: So you think that's too high a level for the kidney patients?

BOIVIN: Absolutely. 1 milligram is perhaps correct, but 10 milligram is too much. It is half the therapeutic dose, and the therapeutic dose is for two years only...

CONNETT: Even getting it from little bits each day, not in one bolus dose?

BOIVIN: I think that a total of 10 milligrams per day is too much, whatever the source, whether it is one source or multiple sources. I think it is too much.

CONNETT: Do you think it is too much for just the everyday person, not just the kidney patient?

BOIVIN: It is too much because in the population you cannot say what patient is, or will be, suffering from renal insufficiency in the future. *(Video-taped interview with Michael Connett, October 7, 2005).*

The fact that doses as low as 10 mg/day cannot – with reasonable certainty – be considered safe for individuals with kidney disease underscores the inadequacy of OPP relying on 20 mg/day as the LOAEL Accordingly, OPP's RfD can not be considered safe for sensitive subsets of consumers as required by FFDCA.

ISSUE 1.6.4 Applying safety factor of 2.5 to LOAEL is inadequate to protect sensitive sub groups of population.

As discussed above, the 20 mg/day LOAEL underpinning ODW's MCLG, and by extension OPP's RfD, is based on a small study of cryolite workers from the 1930s. Because the study only looked at a small number of adult male workers, it is not possible from the study to determine the minimum toxic dose for susceptible subsets of the general population that were not included in the study (e.g. infants, children, pregnant women, people with kidney disease, malnourishment, diabetes, etc). Because of the uncertainties involved in extrapolating conclusions from the cryolite study to society as a whole, it was inappropriate, therefore, for ODW (and by extension the OPP) to have applied an abnormally low safety factor.

When deriving safe doses from LOAELs, EPA normally applies a safety factor of 10 in order to account for the range of sensitivity to the chemical that may exist among an entire population. For the reasons stated above, the cryolite study was exactly the kind of study that warranted a protective safety factor. However, rather than apply even the standard safety factor of 10, ODW applied an abnormally low safety factor of 2.5.

By applying a small safety factor to data derived from a small, non-representative study, ODW's purported safe dose of fluoride (8 mg/day) can not be considered safe for susceptible populations – a fact demonstrated by, among other things, Boivin's observation that 10 mg/day is unsafe for someone with kidney disease. (If 10 mg/day is unsafe for an individual with kidney disease, than 8 mg/day would provide a completely inadequate margin of safety for this major identifiable subset of the population[13].)

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[13] See Section 1.7 for further discussion on the risks fluoride poses to kidney patients at water concentrations below the 4 ppm MCLG.

Because the 20 mg/day and the 2.5 safety factor form such a pivotal basis of

OPP's analysis, the risk assessment supporting the tolerances is scientifically, factually

and legally inadequate.

ISSUE 1.6.5: EPA's attempt to justify low safety factor lacks merit

ISSUE 1.6.5A: The low safety factor is not justified by "large amounts of human epidemiological data."

One of the arguments utilized by ODW to justify its application of an abnormally

low safety factor to the 20 mg/day LOAEL is that the lack of reports of crippling

fluorosis in the US suggests there is negligible risk of the disease at the levels of fluoride

found in the US. To quote:

> "The fact that only two cases of crippling skeletal fluorosis have been observed in the US associated with the consumption of drinking water provides convincing evidence that the population at risk at 4 mg/L is negligible" (USEPA 1985a, p 47144).

There are several fundamental problems with this argument.

First, ODW's assertion that skeletal fluorosis is extremely rare in the US is based

on data concerning the most extreme form of the disease (crippling fluorosis). However,

as concluded by the NRC, earlier forms of the disease can also be adverse to a person's

health. Hence, any discussion about the prevalence of skeletal fluorosis should also

consider the earlier forms of the disease. According to the NRC, however, there is a

dearth of research by which to determine the prevalence of earlier forms (stage II) of

skeletal fluorosis. To quote:

> "The committee could not determine from the existing epidemiologic literature whether stage II skeletal fluorosis is occurring in U.S. residents who drink water with fluoride at 4 mg/L. The condition does not appear to have been systematically investigated in recent years in U.S. populations that have had long-term exposures to high concentrations of fluoride in drinking water" (NRC, p. 144).

NRC's observation about the absence of systematic studies investigating the prevalence of skeletal fluorosis directly contradicts EPA's claim that their low safety factor is warranted by the "large amounts of human epidemiological data surrounding fluoride and skeletal fluorosis" (USEPA 2004a).

A second problem with ODW's argument is that there has been an almost complete absence of systematic research on the prevalence of skeletal fluorosis in the most susceptible subset of the population: people with kidney disease.

In 1985, when the ODW issued the MCLG, there had yet to be (and there has still yet to be) a single systematic study on the prevalence of fluorosis among patients with kidney disease (Groth 1973; Johnson 1979; Hileman 1988). According to Groth (1973):

> "It seems probable that some people with severe or long-term renal disease, which might not be advanced enough to require hemodialysis, can still experience reduced fluoride excretion to an extent that can lead to fluorosis, or aggravate skeletal complications associated with kidney disease... It has been estimated that one in every 25 Americans may have some form of kidney disease; it would seem imperative that the magnitude of risk to such a large sub-segment of the population be determined through extensive and careful study**.** *To date, however, no studies of this sort have been carried out, and none is planned"* (emphasis added).

According to Hileman (1988):

> "[A] fairly substantial body of research indicates that people with kidney dysfunction are at increased risk of developing some degree of skeletal fluorosis. ... However, *there has been no systematic survey of people with impaired kidney function to determine how many actually suffer a degree of skeletal fluorosis that is clearly detrimental to their health."*

Thus, ODW's discussion on the prevalence of fluorosis in the US was predicated on data incapable of determining the prevalence among the very population most susceptible to developing the disease! Accordingly, since OPP's RfD is based on these

flawed assumptions, the risk assessment supporting the tolerances is scientifically,

factually and legally inadequate.

ISSUE 1.6.5 B: EPA's low safety factor is not justified by 1950s epidemiological studies from US

Another point made by EPA's Office of Water to justify its low safety factor

relates to the findings of several epidemiological studies conducted in high fluoride areas

in the US in the 1950s (Leone 1955; Stevenson 1957; Geever 1958; McClure 1958;

Zipkin 1958; as cited in US EPA 1985a, b). According to ODW, these studies

demonstrate the absence of adverse effects on the skeleton at water fluoride levels up to 8

ppm, thus giving the Agency confidence that the 8 mg/day RfD is adequate.

ODW's reliance on these studies, however, is deeply problematic for a number of

reasons – not least of which is the fact that the studies' findings have been repeatedly

contradicted by studies published in the past 50 years.

For example, whereas the early studies reported no defects in bone quality at 8

ppm, Arnala (1985) detected a statistically significant increase in mineralization defects

in communities with concentrations in excess of just 1.5 ppm.

Whereas Leone reported a reduced rate of bone loss among residents in an 8 ppm

community, recent studies from both Sowers (1991) and Phipps (1990, 1998) have

documented reductions in bone density at 2.5 to 4 ppm.

And, whereas Leone (1955) reported no symptomatic skeletal fluorosis at 8 ppm,

numerous studies published since then have found symptomatic skeletal fluorosis in

western populations at levels ranging from 1.7 to 9 ppm (Sauerbrunn 1965; Goldman

1971; Juncos 1972; Johnson 1979; Lantz 1987; Felsenfeld 1991; Whyte 2005; see

additional references cited in Nicolay 1997).

These later findings suggest, therefore, that the studies from the 1950s lacked the necessary sensitivity to detect symptomatic, but pre-crippling, fluorosis. Because of these limitations, the studies from the 1950s do not provide a compelling basis for ODW applying a reduced safety factor to the 20 mg/day LOAEL. Accordingly, since OPP's RfD is based on this flawed premise, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.6.5 C: EPA's low safety factor is not supported by epidemiological research on crippling fluorosis in India and other countries

A third point used to justify ODW's use of a high LOAEL, and low safety factor, is ODW's contention that crippling fluorosis has only been observed in other countries where the water contains more than 10 ppm fluoride.

In its November 14, 1985 Final Rule, ODW made a pivotal, yet incorrect assumption about the epidemiological data on skeletal fluorosis. To quote:

> "EPA notes that crippling skeletal fluorosis, rheumatic attack, pain and stiffness have been observed in a large number of individuals in other countries chronically exposed to fluoride in drinking water at levels of 10 mg/L to 40 mg/L" (US EPA 1985a, p. 47144).

Prior to 1985, however, there were at least 6 studies, published in the peer-reviewed literature, documenting crippling fluorosis in communities with less than 10 ppm fluoride (see Table 1-A). 2 of these 6 studies were actually from the U.S.

TABLE 1-A. Documented Cases, Prior to 1985, of Crippling Skeletal Fluorosis in Humans Consuming Water with < 10 ppm Fluoride			
Study	Water F Content Mean, ppm (range)	Crippling Skeletal Fluorosis?	Country
Singh 1961	1.2 & 1.3	Yes	India
Siddiqui 1970	1.35	Yes	India
Sauerbrunn 1965	(2.2-3.5)	Yes	U.S.
Krishnamachari 1973	(3.5-6.0)	Yes	India
Goldman 1971	(4.1-8.0)	Yes	U.S.
Siddiqui 1955	5.2	Yes	India

It is incorrect, therefore, for ODW to have stated in 1985 that the minimum water fluoride level producing crippling fluorosis was 10 ppm. Indeed, one of the most thorough and widely-cited studies on fluorosis in India, conducted by a scientific advisor to the WHO (Jolly 1970), clearly showed crippling fluorosis occurs at levels well below 10 ppm. Jolly published this data in 1970 (see Table 1-B), and there is therefore little excuse for the EPA to have omitted it in 1985 - and for OPP to perpetuate this oversight. Indeed, the burden is on OPP to clearly show why this information is not relevant – particularly since several recent comprehensive studies (e.g. Choubisa 2001; Cao 2003) have strongly re-enforced the earlier studies (see Tables 1-C & 1-D).

TABLE 1-B. Relation between Water Fluoride & Skeletal Fluorosis in Punjab, India (1970)					
	Fluoride Content of Water		Skeletal Fluorosis		
Village	Mean (ppm)	Range (ppm)	Individuals Examined	Skeletal Fluorosis %	Crippling Fluorosis
Gharachon	1.4	0.9-2.5	82	2.4	No
Laluwala	2.4	1.0-5.5	74	23.0	No
Dhapai	3.0	1.1-5.5	107	19.6	No
Bhodipura	**3.0**	**1.3-5.2**	64	42.2	**Yes**
Rajthai	3.3	0.5-6.5	160	10.0	No
Bhikti	**3.3**	**1.0-5.9**	160	45.6	**Yes**
Sanghera	**3.6**	**1.1-5.8**	154	33.1	**Yes**
Ramuana/ Ganjigulab	**5.0**	**1.5-11.5**	90	60.0	**Yes**
Singh	**8.5**	**3.7-14.0**	56	58.9	**Yes**
Khara	**9.7**	**6.0-16.2**	232	80.7	**Yes**
SOURCE: Jolly SS. (1970). Hydric fluorosis in Punjab (India). In: TL Vischer, ed. Fluoride in Medicine. Hans Huber, Bern. pp. 116					

TABLE 1-C. Documented Cases, Post-1985, of Crippling Skeletal Fluorosis in Humans Consuming Water with < 10 ppm Fluoride			
Study	Water F Content Mean, ppm (range)	Crippling Skeletal Fluorosis?	Country
Misra 1988	**2.4**	**Yes**	India
Cao 2003*	**(3.2-4.5)**	**Yes**	Tibet
Fisher 1989	**3.9**	**Yes**	Mexico
Haimanot 1990	**(4.0-7.0)**	**Yes**	Ethiopia
Misra 1988	**5.5**	**Yes**	India
Misra 1988	**7.0**	**Yes**	India
Brouwer 1988	**7.4**	**Yes**	Senegal

*Cao's data refers to the F content of brick tea, the sole significant source of F (99% of total intake) in the area studied.

TABLE 1-D. Relation between Water Fluoride & Skeletal Fluorosis in Rajasthan India (2001)					
	Fluoride Content of Water		Skeletal Fluorosis		
District/ Village	Mean (ppm)	Range (ppm)	Individuals Examined	% w/ Skeletal Fluorosis	Crippling Fluorosis?
Banswara					
Deolya	1.5	1.0-2.8	132	6.1%	No
Isarwada	1.6	1.2-2.1	108	6.5%	No
Gangertalai	1.9	1.2-3.0	102	14.7%	No
Vassioda	2.6	2.2-2.9	122	18.9%	No
Mangala	**3.3**	**2.7-4.1**	126	24.6%	**Yes**
Borda	**3.5**	**2.6-4.2**	120	30%	**Yes**
Chhotipadel	**3.7**	**2.9-4.6**	116	32.8%	**Yes**
Dungarpur					
Fatehpura	1.5	1.0-2.3	105	9.5%	No
Mewadi	1.6	1.1-1.8	112	8.9%	No
Jhariyana	1.8	1.7-2.0	104	19.2%	No
Indora	2.4	1.1-3.1	105	25.7%	No
Deotalab	**2.8**	**1.5-4.1**	98	39.8%	**Yes**
Dad	**3.1**	**2.8-3.9**	96	42.7%	**Yes**
Bokedsal	**3.2**	**2.9-3.5**	102	39.2%	**Yes**
Udaipur					
Matasula	1.5	1.2-1.7	103	6.8%	No
Amlu	1.6	1.3-1.6	94	8.5%	No
Dagar	1.9	0.2-3.0	90	15.6%	No
Thada	2.6	0.2-5.1	102	19.6%	No
Bhabrana	**3.0**	**2.6-3.5**	114	21.1%	**Yes**
Dhamodar	**3.8**	**3.0-4.7**	110	33.6%	**Yes**
Jhalara	**4.0**	**3.5-4.7**	142	36.6%	**Yes**

SOURCE: Choubisa SL. (2001). Endemic fluorosis in Southern Rajasthan, India. Fluoride 34: 61-70.

While nutritional deficiencies, and elevated water consumption, can exacerbate the impact of waterborne fluoride, these conditions can be found in the US (NCCNHR 2000; USDA 2003). It would not be surprising therefore if malnourished individuals in the US (particularly those with combinations of diabetes and/or kidney disease) exhibit a similar susceptibility to fluoride toxicity as found in India and elsewhere. This possibility, in fact, was articulated by the Surgeon General's 1983 panel on the "Non-Dental Health Effects of Fluoride." To quote:

> DR. KLEEREKOPER: The reports outside of the United States, taking everything into consideration, do get clinically observable adverse effects certainly at four (ppm) or above. There are plenty of papers.

> DR. SPENCER: I don't believe that we can compare a report in India which is a tropical country, where you don't know how much water you take in, where the nutritional status is very poor, where they don't have any milk and little meat; therefore, no calcium, no phosphorus and magnesium and one cannot compare this to the high fluoride areas in this country.

> DR SMITH: I think you are going to find some populations of that sort in this country too.

> DR. SPENCER: Then we should see more pathologic indication of myelopathy and fluorosis in this country. Why don't we see it in the areas of four ppm?

> DR. KLEEREKOPER: I think that you have to conclude that we haven't looked for it and we really don't know. (Surgeon General, 1983, p 412-413).

Thus, ODW was incorrect in stating that crippling fluorosis only occurs in other countries at >10 ppm F. This fact, which may be particularly significant for susceptible populations in the US, undermines one of ODW's arguments for using the low safety factor. Accordingly, since OPP's RfD is based on these flawed assumptions, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.7. MCLG does not protect people with kidney disease

By selecting a LOAEL (20 mg/day) based on a small, non-representative sampling of the population, and applying an unusually small safety factor (2.5x), the ODW's MCLG runs the risk of being non-protective for susceptible subsets of the population. Indeed, as mentioned earlier, and as discussed in greater detail below, data from the published literature clearly indicates that the MCLG is _not_ safe for people with kidney disease. Because OPP's RfD is based on the MCLG, and because the FFDCA requires OPP to protect sensitive subsets of consumers, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.7A MCLG is unsafe for kidney patients not on dialysis

When ODW adopted the MCLG in 1985, they failed to acknowledge or reference a key study – published in 1979 by Mayo Clinic scientists - demonstrating the existence of symptomatic skeletal fluorosis in kidney patients drinking water with less than half of the MCLG (Johnson 1979). In a group of 4 kidney patients drinking water with just 1.7 – 2.0 ppm, Johnson (1979) found several key indications of fluorosis, including: histological evidence of fluorotic changes to bone; accumulations of fluoride in the bone and blood known to be associated with bone damage in humans and animals; and the successful alleviation of bone pains following the provision of fluoride-free water.

The blood fluoride levels in Johnson's kidney patients were particularly noteworthy. They averaged 10.3 umol/L, and reached as high as 14.3 umol/L in the patient with the severest case of the disease. To put these concentrations in perspective, they exceed:

- The blood fluoride levels (5 - 9 umol/L) found in human populations with skeletal fluorosis (Li 1986, Li 1990; Savas 2001; Singla 1976);

- The blood fluoride levels (7.6 umol/L) found to increase bone osteoid volume in rats (Turner 1996, see figure 5).
- The blood fluoride levels (9-10.6 umol/L) found to reduce bone strength in Turner's animal studies (Turner 1995, 1996, 2001; see also: Dunipace 1995, 1998);
- The blood fluoride levels (10 umol/L) which Pak (1989) considers toxic to bone mineralization in short term exposures (< 5 years), especially in the absence of major calcium supplementation.

Based on these findings, Johnson (1979) concluded that 2 ppm fluoride in water presents a probable risk to the bones of people with advanced kidney disease and that the effect may also be experienced in 1 ppm areas as well. To quote:

"The available evidence suggests that some patients with long-term renal failure are being affected by drinking water with as little as 2 ppm fluoride... The finding of adverse effects in patients drinking water with 2 ppm of fluoride suggests that a few similar cases may be found in patients inbibing 1 ppm, especially if large volumes are consumed, or in heavy tea drinkers and if fluoride is indeed a cause" (Johnson 1979).

Other experts on skeletal fluorosis concur that skeletal fluorosis may occur in kidney patients at levels as low as 1 ppm. According to Bansal & Tiwari (2006):

"Individuals with kidney disease have decreased ability to excrete fluoride in urine and are at risk of developing fluorosis even at normal recommended limit of 0.7 to 1.2 mg/l."

According to Ayoob (2006):

"Persons with renal failure can have a four fold increase in skeletal fluoride content, are at more risk of spontaneous bone fractures, and akin to skeletal fluorosis even at 1.0 ppm fluoride in drinking water."

ODW, in fact, has actually acknowledged that the MCLG cannot be relied on to protect people with kidney disease. To quote:

"The Agency feels that this [MCLG] provides an adequate margin of safety *except* in those very extreme cases involving severely renally impaired individuals who consume unusually high levels of fluoride due in part to polydipsia and other confounding factors" (US EPA 1985a, p. 47152; emphasis added).

"Except" is the key word here, as it contradicts OPP's mandate under FFDCA to protect susceptible subsets of consumers. ODW's attempt to downplay the failure of the MCLG to protect people with kidney disease by highlighting the "unusual" amounts of water consumed is without merit since excessive thirst (polydipsia) is a common medical feature of kidney disease. The combination of kidney disease with excess thirst is, therefore, not an "unusual" combination. It is inappropriate, thereby, for OPP to have based its RfD on a standard that – according to published data the Office of Drinking Water – can not be expected to protect people with kidney disease. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 1.7B MCLG is unsafe for kidney patients on dialysis

Research published since 1985 has raised further concerns about the safety of the MCLG for people with kidney disease undergoing dialysis treatment.

Of particular concern are a series of studies showing that dialysis patients have an extremely impaired ability to clear fluoride from their body (Warady 1989; Huraib 1993; Tanimura 1994; Takahashi 1995; Cohen-Solal 1996; Al-Wakeel 1997; Usuda 1997; Torra 1998 Marumo 2001; Cohen-Solal 2002; Ng 2004).

Even when the dialysis unit filters the fluoride content to less than 0.05 ppm (as most now do), dialysis patients have still been found to accumulate strikingly high fluoride levels in their bones and blood – presumably from the fluoride in their drinking water and food.

For example, Torra (1998) found that a dialysis patients living in a 0.2 ppm area can have up to 185 ppb fluoride in their blood. This exceeds the concentration of fluoride

found in humans with skeletal fluorosis (Li 1986, Li 1990; Savas 2001; Singla 1976) and

the fluoride concentration found to weaken the bones of animals (Turner 1996).

Because of the marked inability of dialysis patients to excrete fluoride,

researchers such as Usuda (1997) have advised that:

> "HD (hemodialysis) patients need to practice dietary control for the restriction of oral F intake."

Torra (1998) made a similar recommendation, advising that:

> "it is important to control the intake of this element and the prolonged use of fluoridated dental products in the subjects with chronic renal insufficiency, to avoid a risk of fluorosis."

With over over 400,000 Americans on dialysis (NIDDK 2004), we find it

completely unacceptable that OPP is allowing a major new (and unavoidable) source of

fluoride to enter the food supply. Such a decision was made possible by OPP's utilization

of an outdated MCLG that is demonstrably unsafe for people with kidney disease.

Accordingly, the risk assessment supporting the tolerances is scientifically, factually and

legally inadequate.

II. OPP's CHILDHOOD REFERENCE DOSE (RfD) IS UNSAFE AND VIOLATIVE OF THE FQPA

As detailed above, there are many fundamental problems with ODW'S MCLG which OPP used to derive the reference dose (RfD) for its risk assessment. As we will now demonstrate, there are also fundamental problems with how OPP derived the RfD. In fact, the latest alteration that OPP has made to the RfD for fluoride is significantly less protective than the MCLG, despite being purportedly based on it[14].

Because it is commonly accepted that infants and young children are more susceptible to environmental contaminants than adults, the Food Quality Protection Act (FQPA), passed into law on August 3, 1996, amended FFDCA in such a manner as to mandate that OPP explicitly determine that tolerances are safe for children.

In order to issue tolerances that are safe for children, FFDCA now requires OPP to consider uncertainties in the database relative to children, and when appropriate, to issue an additional safety factor of ten-fold to account for children's enhanced sensitivity. To quote:

> "When setting new tolerances, or reassessing existing tolerances or tolerance exemptions, EPA must now focus explicitly on exposures and risks to children and infants. EPA must, 1) explicitly determine that the tolerance, or exemption from tolerance, is safe for children; 2) consider the need for an additional safety factor of up to ten-fold to account `for uncertainty in the data base relative to children unless there is evidence that a different factor should be used; and 3) consider children's special sensitivities and often unique exposure patterns to pesticides." (US EPA, 1997)

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[14] OPP's latest alteration of the RfD – the 3rd RfD it issued in as many years – assumes it is safe for children to receive twice as much fluoride (8 mg/day) as the dose (4 mg/day) OPP assumes children in a 4 ppm area would receive (USEPA 2004a, table 3.2.1). Thus, even if one assumes that the MLCG is safe (which it is not, as detailed in Section I), OPP's RfD for children is actually less protective than the MCLG by a factor of 2.

OPP's derivation of its third and final fluoride RfD for children violates virtually every key scientific premise of FQPA. Rather than carefully consider significant uncertainties relative to children, OPP recklessly ignored them. Rather than issue a childhood RfD that is equally protective, or more protective, as the adult RfD, OPP issued an RfD for childhood that is significantly <u>less protective</u>[15]. The end result is that *OPP has managed to make a bad standard (MCLG) worse by deriving from it a childhood RfD which is significantly more dangerous to children's health.*

ISSUE 2.1 Childhood RfD runs counter to previous OPP risk assessments

Prior to its health risk assessments of sulfuryl fluoride, OPP had utilized an RfD of 0.114 mg/kg/day to assess the risk from fluoride-based pesticides (e.g. cryolite). OPP had derived this RfD from the MCLG and had used it uniformly for all age groups. For instance, an OPP risk assessment of cryolite tolerances stated in 2002 that:

> "For the chronic dietary exposure assessment, **EPA has determined that the dose to be used for risk assessment for exposure to fluoride is 0.114 mg F/kg/day**, per the 1996 Cryolite RED. **This value is used for all population subgroups** ..." (USEPA 2002c, emphasis added)

In its initial risk assessment of sulfuryl fluoride tolerances, OPP continued its use of this 0.114 mg/kg/day RfD for all age groups. Thus, in its September 5, 2001 risk assessment OPP stated:

> "the Agency used the maximum concentration limit goal (MCLG) of 4.0 ppm (0.114 mg/kg/day)… " (US EPA 2002, emphasis added)

In Objectors' September 29, 2001 submission to OPP, however, Objectors pointed out that data already indicated that some children were exceeding the 0.114

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[15] According to the New York State Attorney General's Office, "the tolerance assessment at issue wrongly assumes that there is no special susceptibility of infants and children to the adverse health effects of fluoride exposure" (Kaufmann 2006).

mg/kg/day reference dose[16]. This fact was sufficient reason, in and of itself, for OPP to have rejected the tolerances since never before in OPP's history has OPP granted a tolerance for a pesticide where children are already exceeding the RfD for the residue of concern[17].

Table 2: The 3 Different Reference Doses (RfDs) used by OPP in SF Risk Assessments				
Population Subgroup	Toxicological Effect	Reference Dose (RfD)		
		Feb 2002 [a]	Jan 2004 [b]	Jan 2006 [c]
US pop (total)	Skeletal Fluorosis	0.114	0.114	0.114
Infants < 1 year	Skeletal Fluorosis	**0.114**	**0.571**	**1.143**
Child 1-2 years	Skeletal Fluorosis	**0.114**	**0.308**	**0.616**
Child 3-5 years	Skeletal Fluorosis	**0.114**	**0.182**	**0.364**
Child 6-12 years	Skeletal Fluorosis	0.114	0.100	**0.200**
Youth 13-19 yrs	Skeletal Fluorosis	0.114	0.133	0.133
Adult 20+ years	Skeletal Fluorosis	0.114	0.114	0.114
Females 13-49	Skeletal Fluorosis	0.114	0.131	0.131

(a) <u>Feb 2002 RfD</u>: 8 mg/day (the dose an adult would drink if consuming 2 liters of water with 4 mg/L - the MCLG) is divided by average weight of adult (70 kg). The resulting dosage (0.114 mg/kg/day) is applied uniformly to all age groups.

(b) <u>Jan 2004 RfD</u>: The adult RfD is based on same rationale as Feb 2002 RfD (2 liters of 4 mg/L water divided by average adult weight).. Childhood RfD is derived based on the dosage a child would receive if drinking 1 liter of 4 mg/L water. For a 7 kg infant, the RfD equals 0.571 mg/kg/day.

(c) <u>Jan 2006 RfD</u>: The adult RfD of 8 mg/day (based on 2 liters of 4 mg/L water) is applied directly to children without adjusting for bodyweight. For a 7 kg infant, the dosage equals 1.14 mg/kg/day.

Rather than reject DOW's request, OPP opted instead to increase the RfD for children. In its January 20, 2004 Final Rule, OPP stated that it had increased the RfD for children by up to a factor of five (see Table 2). This change to the childhood RfD was _not_ based on the emergence of new data; it was based instead on a re-interpretation of ODW's 1985 MCLG.

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[16] Upon further review of the peer-reviewed published literature, Objectors have identified an abundance of additional data showing that a significant percentage of children are exceeding OPP's initial RfD of 0.114 mg/kg/day (e.g. Levy 2003; Erdal 2005; NRC 2006).

[17] Approving a tolerance when children are already exceeding the RfD represents a significant change in policy. In theory, if OPP can grant food tolerances for pesticides in situations where there exists a significant body of peer reviewed literature showing that children are already exposed at levels above the RfD, then they could do it for any pesticide and the entire FQPA system would be broken.

In response to OPP's alteration of the RfD, Objectors' filed objections in March 2004 which – in addition to emphasizing the lack of new data to support this unprecedented move – documented that some children living in 1 to 2 ppm areas would still exceed the weakened RfD.

OPP never responded to this information. Instead, on July 15, 2005, OPP issued a second Final Rule where they announced that they had once again increased the RfD for children (see Table 2). In this latest alteration – which remains current at the present time – OPP concluded that the 8 mg/day "safe" dose for adults can be applied directly to children without accounting for the difference in bodyweight and sensitivity. When this single dose of 8 mg/day is divided by the weight of children at various ages, it can be seen that this new RfD for infants (1.14 mg/kg/day) is ten times higher than the initial RfD for infants and ten times higher than the RfD for an adult (0.114 mg/kg/day). In fact, 1.14 mg/kg/day is the highest purported safe dosage of fluoride ever approved by any governmental agency in US history (see NRC, table 2-18). Indeed, according to the best of Objectors' knowledge, the 1.14 mg/kg/day RfD is the *highest purported safe dosage of fluoride every approved by any governmental agency in human history!*

Despite the extraordinary and unprecedented nature of this new childhood RfD, OPP did not cite *any* new data to support it. In fact, in its attempt to justify why children could be exposed to a dose (8 mg/day) previously only considered safe for adults, OPP repeated the exact same two-sentence explanation it had used to justify the former RfD (which had considered 8 mg/day unsafe for children). Not only did OPP fail to provide any additional data or evidence to justify its alteration of the RfD, it failed to even

acknowledge that this new RfD represented a striking change from all previous risk assessments.

OPP's failure, therefore, to offer any new data or analysis to justify the adoption of the highest purported safe dosage of fluoride in human history, renders the entire risk assessment legally, factually, and scientifically invalid.

ISSUE 2.2: RfD violates basic toxicological principles

On the face of it, OPP's assumption that the safe daily dose for adults will also be safe for infants and children -- irrespective of the difference in weight and sensitivity -- is absurd. It is the toxicological equivalent of assuming that, because 250-500 mg of aspirin is safe for an adult, that therefore the same dose of aspirin will be safe for infants as well.

Objectors are not aware of any other instance in OPP regulatory history where the cardinal rule that bodyweight affects the impact of a chemical has been abandoned. Unprecedented actions warrant a high burden of proof. As described below, this burden of proof was not met by OPP.

ISSUE 2.3: "Safe dose" for children is 4 times greater than dose that causes severe dental fluorosis

In setting the safe dose at 8 mg/day for children, OPP created an RfD for children that is four times greater than the dose (2 mg/day) that OPP has conceded may cause severe dental fluorosis (USEPA 2006, Appendix II). As detailed earlier (see Section 1.2), the National Research Council has concluded that severe dental fluorosis is an adverse health effect.

Since FFDCA, as amended by FQPA, requires OPP to specifically protect the health of children, the fact that OPP's RfD greatly exceeds the dose that – according to

NRC - can specifically harm children's health is reason, in and of itself, to reject the RfD.

Accordingly, the risk assessment is legally, factually, and scientifically invalid.

ISSUE 2.4: OPP failed to adequately "consider uncertainty in data base relative to children"

In raising the RfD for children to a dosage up to ten times higher than adults

(≤1.14 mg/kg/day vs 0.114 mg/kg/day), OPP faced a tough burden of proof. Not only did

OPP need to demonstrate that 1) children do not have an enhanced sensitivity to fluoride,

they also needed to demonstrate that 2) children have a *reduced* sensitivity (by a factor of

10). To substantiate these two propositions in a manner consistent with the criteria set

forth by FFDCA, OPP needed to consider "uncertainty in the data base relative to

children", and thereupon demonstrate that there is no such uncertainty which would pre-

empt these conclusions.

As the record demonstrates, OPP failed to establish the safety of the childhood RfD in

a manner consistent with FFDCA. Accordingly, the risk assessment supporting the

tolerances is legally, factually, and scientifically invalid. This can be demonstrated by

examining the following two key health concerns relative to fluoride and childhood

health:

- Bone damage
- Neurotoxicity

ISSUE 2.4.1: Bone Damage

Since OPP set the RfD for children on the basis of a bone effect (crippling

skeletal fluorosis), it is instructive to examine how OPP justified its contention that 8

mg/day would not damage the bones of infants or children.

According to OPP, the 8 mg/day "safe dose" for adults is also safe for children

because:

"Skeletal fluorosis is an effect that requires chronic (10+ years) high exposures in order to be manifested. As such, infants and children will not exhibit this effect and **an additional factor to account for potential enhanced sensitivity is not necessary**" (USEPA 2006; emphasis added)

This statement by OPP – which the New York Attorney General Office has characterized as a "wholly illogical conclusion" (Kaufmann 2006) - is riddled with several fatal fundamental flaws, as we will now demonstrate.

ISSUE 2.4.1A: OPP failed to demonstrate why a higher reference dosage for children is safe.

Barring strong evidence to the contrary, basic toxicological principles dictate that the dosage of a chemical (expressed as mg/kg/day) is the relevant index for assessing risk, not the dose (expressed as mg/day). OPP's attempt, therefore, to characterize 8 mg/day for children as being the toxicological equivalent as 8 mg/day for adults –without acknowledging the striking difference in dosage – was highly inappropriate. *Before arguing why a lower RfD for children "is not necessary", OPP needed to first demonstrate that a higher RfD for children (when expressed in the relevant terms of mg/kg/day) is safe*. OPP's failure to do this, and its failure to acknowledge the fundamental need to do this, represents a flagrant violation of standard protocol and basic toxicological principles. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

To better underscore this critically important point, it is instructive to consider the following: A dose of 8 mg/day for children less than 2 years old provides a dosage (0.62 - 1.14 mg/kg/day) that is up to two times greater than the dosage (0.40 - 0.55 mg/kg/day) known to increase bone fractures in adults during 1-to-2 year clinical trials (Dambacher

1986; Hedlund 1989; Bayley 1990; Orcel 1990; Riggs 1990; Schnitzler 1990;

Haguenauer 2000; Gutteridge 2002).

ISSUE 2.4.1B: OPP failed to demonstrate that children's bones have a reduced sensitivity to fluoride

In order to demonstrate that children can withstand much higher dosages of

fluoride than adults without suffering adverse effects on the skeletal system, OPP needed

to make a convincing case that children's bones are less sensitive to fluoride than adults.

OPP failed, however, to make this case. Rather than argue that children are *less* sensitive

than adults, OPP simply argued that children are not *more* sensitive. These, however, are

two distinctly different arguments - both of which OPP needed to make in order to

establish the safety of the RfD in accordance with the requirements of FFDCA.

By foregoing any attempt to demonstrate that children's bones are, in fact, *less*

sensitive than adults, OPP did not demonstrate the safety of an RfD that allows 10 times

greater exposures for children. Accordingly, OPP's risk assessment supporting the

tolerances is scientifically, factually and legally inadequate.

ISSUE 2.4.1C: OPP failed to consider evidence indicating children's bones have an enhanced sensitivity to fluoride

The argument made by OPP to support their claim that children's bones do not

exhibit "enhanced sensitivity" to fluoride is also problematic and at odds with a

significant body of scientific literature.

According, for instance, to an expert body convened at the request of the Public

Health Service (PHS) to review the "Non-Dental Effects of Fluoride", it is, in fact,

probable that children's bones are *more* sensitive to fluoride-induced damage than adults,

not *less* (Shapiro 1983a,b; Surgeon General 1983).

Research published since the PHS review has elucidated a key mechanism by which children's bones might be expected to display an enhanced sensitivity to fluoride. According to Ekstrand (1994) and Whitford (1999), young children accumulate a much greater percentage of ingested fluoride than adults – thereby exposing developing bone cells to a significantly higher concentration of fluoride (Teotia 1998; Whitford 1999). Thus, at the very moment in life when bones are most prone to incorporating fluoride, OPP is allowing the greatest dosage. For instance, whereas the adult skeleton accumulates roughly 50% of an absorbed dose, the infant skeleton accumulates up to 87% of an absorbed dose (Ekstrand 1994). This finding provides a clear biological basis why it is deeply inappropriate for OPP to assume – without direct evidence to back it up - that children's bones will respond to fluoride in an identical manner as adults.

According to Teotia & Teotia (1998), the greater accumulation rate of fluoride in young children is probably one of the reasons explaining why – in research on skeletal fluorosis in India – children suffer more severe effects, at lower doses[18] and in shorter periods of duration than adults. (All of these findings directly contradict OPP's assumptions.) To quote:

> "Fluoride toxicity afflicts children more severely and over a shorter period of exposure (about 6 months) as compared to adults. This is because the rapidly growing bones of children are metabolically active[19] and more vascular and thus absorb and accumulate fluoride faster and in greater amounts than older bones, particularly at the sites of bone growth and physiological calcifications" (Teotia 1998).

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[18] According to Teotia & Teotia (1998), children with calcium deficiency may develop skeletal fluorosis at doses as low as 2.5 mg/day – significantly less than EPA's purported safe dose of 8 mg/day.

[19] The Teotia team's conclusion that increased metabolic activity makes children's bones more vulnerable to fluoride is supported by research on animals. According to Johnson 1965:"Mottling [a defect found in fluorotic bone] was the result of the action of fluoride on osteoblasts during bone formation. Young bones undergoing extensive remodeling showed extensive mottling, while old bones with scant remodeling showed little mottling" (Johnson 1965).

OPP's assumption, therefore, that a child's skeleton – with its more rapid rate of growth and its higher accumulation rate of fluoride - will respond to fluoride in the same manner as an adult runs counter to a significant body of scientific evidence[20]. By failing to even acknowledge or consider this evidence, OPP has failed its requirement to account for significant "uncertainty in the data base relative to children." Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 2.4.1D: OPP's claim that skeletal fluorosis takes 10+ years to develop is incorrect

OPP's contention that skeletal fluorosis will only develop after 10+ years of exposure is incorrect. According to Felsenfeld (1991), clinical skeletal fluorosis can develop after just 7 years, while, according to Roholm (1937) – the study on which the 10-year estimate is based -- the earlier stages of clinical fluorosis can be caused after just 2 years of exposure[21]. Research, meanwhile, by Christie (1980) and Teotia (1998), has documented the presence of clinical skeletal fluorosis in children as young as 2 and 4 years of age. Naturally, if a 2-year old child can develop skeletal fluorosis, then something must be wrong with OPP's contention that it requires at least ten years of exposure. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 2.4.1E: Even if skeletal fluorosis took 10+ years to develop, it does not excuse OPP allowing kids a higher RfD for *12 years*

Even if OPP were correct in stating that it takes 10 years for adverse skeletal fluorosis to develop, this does not excuse OPP for letting kids have a strikingly elevated

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[20] This evidence also includes Schlesinger's (1956) finding of a significantly increased rate of cortical bone defects among children living in a 1 ppm, vs <0.2 ppm, area and Alarcon-Herrera's (2001) finding of an increased risk for bone fracture among children with dental fluorosis.

[21] The fact that pre-crippling clinical fluorosis can develop in less than 10 years is particularly significant when considering NRC's conclusion that pre-crippling fluorosis can be an adverse health effect.

RfD for their first _12 years_ of life! As can be seen in Table 2 above, the RfD for children

remains almost twice as high as the RfD for adults all the way into a child's 12th year of

life. Since OPP wouldn't countenance this situation for adults, it is inconceivable that this

can be considered acceptable for children under the conditions set forth under FQPA.

Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually

and legally inadequate.

ISSUE 2.4.1F: OPP's RfD for children based on assumptions derived from adult studies, not on research specific to children

Finally, it bears emphasizing that OPP based its conclusion that 8 mg/day is safe

for childrens' bones on extrapolations from adult studies, not on research specific to

children. This highlights a significant inherent uncertainty in OPP's analysis, which

warranted the application of a safety/uncertainty factor to the data in order to account for

the foreseeable limitations with applying adult-based data to children. The application of

a safety/uncertainty factor was particularly crucial since, to the best of Objectors'

knowledge, there is no relevant, primary data in the published literature that would

directly attest to the safety of 8 mg/day for infants and children. Accordingly, OPP's risk

assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 2.4.2: OPP violated FQPA by failing to account for "uncertainty in the data base relative to children" regarding neurotoxic effects

Whereas very little was known about fluoride's neurotoxic potential in 1985 when

ODW promulgated the MCLG[22] on which OPP's reference dose is based, numerous

studies since that time indicate a clear potential for fluoride to damage the developing

brain. For example, studies have found that:

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[22] As discussed earlier (see Section 1.4.1), the word "brain" is not mentioned once in the 190-page Criteria Document supporting ODW's 1985 MCLG. This bears a sharp contrast to the recent NRC report which dedicated an entire chapter to fluoride's effects on the brain.

- fluoride crosses the placenta exposing the fetus to fluoride ingested by the mother (WHO 2002);
- fluoride crosses the blood-brain barrier (Inkielewicz & Krechniak 2003; Long 2002; Mullenix et al. 1995);
- adverse brain effects occur in human fetuses exposed to elevated fluoride (Du 1992);
- fluoride exposure – at levels as low as 1 ppm – can damage the brains of animals (Varner 1998; NRC 2006);
- fluoride levels as low as 0.9 ppm may intensify the neurological damage (e.g. low IQ, mental retardation) caused by iodine deficiency (Lin Fa-Fu 1991);
- fluoride levels as low as 1.8 to 2.5 ppm may reduce the IQ of children with normal iodine levels (Xiang 2003a,b; NRC 2006).

In light of this research, and in light of the requirements set forth by FQPA, it was unacceptable for OPP to have increased the RfD for children, over and above the levels intended by the MCLG, without citing any data or explanation that would demonstrate, with reasonable certainty, the absence of neurotoxic risk from the new RfD.

OPP's failure to acknowledge the "uncertainty in the database relative to children" regarding fluoride's neurotoxic effects, combined with its failure to demonstrate the safety of the new RfD with regard to these effects was deeply violative of the requirements for determining safety set forth by FQPA. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 2.5: NRC's findings on endocrine disruption undermine safety of RfD

In its health risk assessment, OPP stated it was "aware of potential endocrine effects of fluoride being noted in the open literature" but that, based on its "preliminary review", it did not feel there was enough evidence to "permit confident conclusions" (USEPA 2006). OPP noted, however, that they would "reexamine this conclusion" upon receipt of the NRC report.

NRC's findings on endocrine disruption underscore the need for OPP to "reexamine" its conclusion that fluoride does not affect the endocrine system[23]. For, in contrast to OPP, NRC concluded that there is sufficient evidence to warrant the classification of fluoride as an "endocrine disrupter." According to NRC:

> "In summary, evidence of several types indicates that fluoride affects normal endocrine function or response; the effects of the fluoride-induced changes vary in degree and kind in different individuals. Fluoride is therefore an endocrine disruptor in the broad sense of altering normal endocrine function or response, although probably not in the sense of mimicking a normal hormone" (NRC, p. 223).

In addition to concluding that fluoride is an endocrine disrupter, the NRC also found that:

> "some of these [endocrine] effects **are associated with fluoride intake that is achievable at fluoride concentrations in drinking water of 4 mg/L or less**, especially for young children or for individuals with high water intake" (NRC, p. 7; emphasis added).

In light of NRC's findings that 1) fluoride is an "endocrine disrupter", and that 2) some of fluoride's effects on the endocrine system may occur at doses achievable at, or below, the MCLG, it would appear impossible for OPP to assert it has "reasonable certainty" that the RfD is safe for children's endocrine system. It seems particularly difficult to fathom when considering that OPP's RfD allows children twice as much fluoride (8 mg/day) as the "toxicological dose" (4 mg/day) which OPP associates with the MCLG (USEPA 2004a, table 3.2.1). Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

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[23] For more details on NRC's findings regarding fluoride and the endocrine system, see Section 1.4.2 above.

III. OPP's WAIVER OF DEVELOPMENTAL NEUROTOXICITY (DNT) STUDIES HAS COMPROMISED INTEGRITY OF THE TOLERANCE

When OPP first approved permanent food tolerances for sulfuryl fluoride in 2004, it set forth as a condition of registration that Dow conduct an inhalation Developmental Neurotoxicity[24] (DNT) study on sulfuryl fluoride. OPP repeated the need for a DNT study on at least 7 occasions between 2001 and 2005, including in the two Final Rules where OPP approved permanent tolerances for sulfuryl fluoride for all processed foods and a large number of raw foods (US EPA 2001, 2002, 2003, 2004a, 2004b, 2005a, 2005b).

OPP's requirement that Dow conduct a DNT study was made in response to Dow's animal studies which indicated that the brain is the "primary target" for sulfuryl fluoride's toxic effects. According, for example, to Anna Fan of the California Office of Environmental Health Hazard Assessment:

> **"In the light of the results… that show the brain is a primary target for sulfuryl fluoride toxicity we are concerned that younger populations may be especially sensitive to sulfuryl fluoride exposures.** The developing organism with rapid cell proliferation, migration, and differentiation is uniquely sensitive to any kind of disruptions. In the brain these processes are unidirectional and occur at very specific times for different structures. Prenatal events include closure of the neural tube, proliferation of neurons, and migration of cortical neurons. During infancy and early childhood, proliferation and migration continue along with synaptogenesis, myelination, and development of the blood-brain barrier. Structural maturation of neural pathways, including an increase in the diameter and myelination of axons, continues through adolescence. During adolescence the rate of synaptic pruning peaks**. Sulfuryl fluoride exposures can have profound effects on all of these neurologic developmental processes."** (Fan A, 2004, emphasis added)

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[24] "DNT studies investigate neuropathology, endocrine disruption, behavioral/functional effects, structure-activity relationship, and neurotoxic potency" (Cal EPA 2005).

Based on the severe and rare effects in the brains of sulfuryl fluoride treated animals, OPP repeated its requirement of a DNT study in its July 15, 2005 Final Rule. According to the Final Rule:

"… the Agency is requiring an inhalation DNT study in rats (OPPTS Harmonized Guideline 870.6300) as a condition of registration in order to more clearly and fully characterize the potential for neurotoxic effects in young animals… It is considered possible that the results of the DNT study could impact the endpoint selection for risk assessments…" (US EPA, 2005a)

In January of 2006, however, Objectors became aware – via a third party - that OPP had waived the DNT study requirement. While OPP's team leader on sulfuryl fluoride (Dan Kenny) assured Objectors at this time that the DNT study had not been waived, OPP's Legal Counsel, Jonathan Fleuchaus, confirmed in February 2006 that the DNT study had, in fact, been waived. According to the documents provided to us by Fleuchaus, the DNT study had been waived on April 22, 2004 – 15 months prior to the issuance of the July 15, 2005, Final Rule.

Not only were OPP's actions confusing and inconsistent by stating the need for a DNT study on July 2005, when it had waived the DNT study in April 2004, but, as we will discuss below, the justifications offered by OPP for why a DNT study is not necessary are riddled with logical and scientific fallacies.

ISSUE 3.1 OPP's justifications for waiving DNT study lack merit

ISSUE 3.1.1 The fact that sulfuryl fluoride metabolizes into fluoride ion does not diminish need for DNT

In justifying its approval of Dow's request for the waiver, OPP stated:

"Dow indicated in their waiver justification that they recently conducted a rat metabolism study that showed sulfuryl fluoride is rapidly released to fluoride. Thus, given the known toxicology of fluoride coupled with the minimal inhalation

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exposure to humans, neurotoxicity to the adult or developmental neurotoxicity would be highly unlikely (Dellarco et al. 2004)."

The fact that sulfuryl fluoride may rapidly metabolize into fluoride anion does <u>not</u> diminish the need for a DNT study. Indeed, as detailed by the NRC, the weight of scientific evidence supports the conclusion that fluoride – in and of itself - is a neurotoxin. According to NRC:

"On the basis of information largely derived from histological, chemical, and molecular studies, it is apparent that fluorides have the ability to interfere with the functions of the brain and the body by direct and indirect means." (NRC, p. 187)

Because of the evidence linking fluoride to neurotoxic effects (see Section 1.4.1 above), the NRC specifically has recommended more animal and human studies "to clarify fluoride's biochemical effects on the brain" (NRC, p. 186). OPP's claim, therefore, that sulfuryl fluoride's quick release into fluoride ion relieves the need of having a proper DNT study is directly contradicted by the findings and recommendations of the NRC.

Indeed, we find it hard to understand – in light of the severe and rare neurotoxic effects reported in Dow's studies – why it should be of any relief to know that the sulfuryl fluoride is rapidly metabolizing into fluoride ion. It is obvious that something is causing damage to the animal's brains. Moreover, Dow scientists have stated, and OPP concurs, that the "the likely cause of SO2F2 [sulfuryl fluoride] toxicity is the metabolic release of fluoride ions" (Nitschke et al 1986), and that the "toxicity elicited by SO2F2 may be due to the release of fluoride ions, rather than a direct toxic action of SO2F2" (Mendrala et al. 2005). Considering that the tolerances will produce much higher fluoride ion residues than sulfuryl fluoride residues, the fact that the fluoride ion is the

probable cause of the neurotoxic effects in Dow's studies is not reason to waive a DNT study.

ISSUE 3.1.2 OPP's contention that there will be "essentially no chronic dietary exposure" from tolerances is no longer true

Another reason given for waiving the DNT study was OPP's contention that there will be "essentially no chronic dietary exposure" from the tolerances. Objectors note, however, that since this waiver was granted, OPP has approved a new set of broad-reaching tolerances that have significantly increased the expected exposure to fluoride anion. When OPP issued the waiver, it estimated that the tolerances would result in an average fluoride exposure of 0.028 mg/day. (USEPA 2004b) OPP now estimates, however, that the tolerances will result in a daily exposure of 0.667 mg, <u>a 24-fold increase</u> since the waiver and enough fluoride to make sulfuryl fluoride the second largest source of fluoride anion in the U.S. (USEPA 2006). Thus, it is no longer valid for OPP to maintain that the tolerances will result in "essentially no chronic dietary exposure" – particularly if considering (as required by FFDCA) the aggregate exposure to fluoride from all other sources (see Section IV below).

ISSUE 3.1.3 Concerns about lack of applicability of inhalation DNT study does <u>not</u> apply to oral DNT study

An additional reason for waiving the DNT study is the argument that an inhalational DNT study is not needed since the tolerances are not expected to result in significant inhalational exposures to sulfuryl fluoride. This concern is not applicable, however, to an <u>oral</u> DNT study with fluoride anion. An oral DNT study is critical because – according to OPP's own estimates - the tolerances are expected to become the

second largest source of fluoride exposure in the US and because the majority of these residues will be <u>ingested</u>, not inhaled.

The need for an oral DNT study for fluoride ion is further underscored by the following facts:

A. As discussed in Section II, OPP has approved the highest allowable dose for fluoride for infants and children (8 mg/day) in the nation's history. There is no published study in the peer-reviewed literature that has ever examined the neurological effects of this extremely high dose on infants and children.

B. No oral DNT study for fluoride has ever been performed.

C. The only oral toxicity data cited by OPP for sulfuryl fluoride was an Acute Oral Toxicity Category of 2. OPP presented no other information from oral studies. California EPA (2005) stated that the available oral studies on sulfuryl fluoride did not provide sufficient data for toxicity evaluation (page 27) and also noted: "<u>U.S. EPA considered the submitted acute oral study as unacceptable</u> and a Toxicity Category II was assigned for this route" (page 23, *our emphasis*).

D. The brain was a major target organ in Dow's animal studies (rat, mouse, dog, rabbit) conducted with sulfuryl fluoride, but "the long-term and functional consequence of such damage has not been studied …" (CA EPA 2005 at 54-55).

E. No histological examination of the fetal and pup brains was performed in the critical developmental toxicity studies in rats and rabbits exposed to sulfuryl fluoride and in the 2-generation rat reproductive toxicity study. According to the California EPA:

> "In majority of the studies, the presence of brain vacuoles occurred without clinical signs (Table 16). It was unknown if the same lesion [brain vacuoles] would occur from in utero or milk exposure because fetal and pup brains were not examined

histologically in the developmental toxicity studies and 2-generation reproductive toxicity study… Results from a developmental neurotoxicity study would provide important information regarding potential effects in the young that were not examined in these developmental and reproductive toxicity studies." (CA EPA, 2005 at 95)

F.   In Dow's teratology studies with rats and rabbits, no histological examination of the brain was performed (Fanley et al. 1981, US EPA 1982).

G.   It is unknown if there is a particular time in the stages of human brain development for adverse effects to occur from exposure to fluoride or to sulfuryl fluoriode. However, we do know that sulfuryl fluoride takes fluoride into the brain, that fluoride has been detected in the brain of human fetuses, and that studies with sulfuryl fluoride and sodium fluoride have reported serious brain effects[25]. For example:

i.   Dow's scientists reported elevated levels of fluoride ion detected in the brain during and after exposure to sulfuryl fluoride (CA EPA 2005, pp 25-26, citing Mendrala et. al. 2002).

ii.   Independent animal studies – investigating the effect of <u>oral</u> fluoride intake from water – have also reported elevated levels of fluoride ion in the brain (Zhai et al. 2003; Inkielewicz & Krechniak 2003; Vani and Reddy 2000; Long 2002; Guan et al 1998; Mullenix et al. 1995).

iii.   Fluoride crosses the placenta (WHO 2002) and has been found in the brains of aborted human fetuses. Du (1992) examined the brains from 15 aborted human fetuses from an endemic fluorosis area and 16 aborted brains from a non-endemic area in China. He found:

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[25] See Appendix B for a listing of the brain effects reported in Dow's animal studies on sulfuryl fluoride. See Section 1.4.1 above for a discussion on the brain effects associated with fluoride. (See also Tables 3 & 4 n Neurath et al 2005)

- the "fluoride levels in fetus brain from the endemic fluorosis area was 0.28±0.14ug/g which was higher than the levels in the non-endemic area at 0.19±0.06ug/g (p <0.05)."
- the "numerical density of volume, the volume density and surface density of the mitochondria were significantly reduced" in the brains of fetuses from the endemic area as compared to the non-endemic area."
- the "mean volume of the neurons was reduced" in the fetal brains from the endemic area.
- The author concluded, "fluorine passes through the placenta of chronic fluorosis mothers and accumulation within the fetus brain impacts the developing central nervous system and stunts neuron development."

H. Calvert et al. (1998) reported the following in their study of fumigation workers:

"Occupational sulfuryl fluoride exposures may be associated with subclinical effects on the central nervous system, including effects on olfactory and some cognitive functions..."

I. Animals (rabbits, rats, and dogs) exposed to sulfuryl fluoride have developed

"malacia (necrosis)" of the brain. This is a very rare effect defined by Dow scientists as

"liquefaction necrosis" (Quast et al., 1993). A more explanatory definition of

liquefactive necrosis (Uppsala University) is:

• Necrosis characterized by dissolution of tissue
• Necrotic area is soft and filled with fluid
• No cell architecture remains.
• Results from enzymatic degradation of tissue

J. Sulfuryl fluoride is the only pesticide with food tolerances in OPP's database that

produces liquefactive necrosis. The only other non-pesticide chemical that we could find

that produces liquefactive necrosis in the brain is soman (Armed Forces Institute of

Pathology, 2002, at 1). Soman is an organofluorine warfare nerve agent.

K. Vacuolation of the brain[26] is a rare effect that is seldom found in animal experiments

with pesticides. There are only seven current pesticides[27] used in the U.S. that are known

to produce vacuolation in the brain of experimental animals. Of these seven:

> • 1 is sulfuryl fluoride
> • 2 are fluorinated (fluazinam and indoxacarb)
> • 2 are fluorinated and brominated (bromethalin and chlorfenapyr)
> • 2 are non-fluorinated (propamocarb hydrochloride and propetamphos)

L. According to a July 1, 2005, California EPA Health Risk Assessment:

> "The cause of the vacuolation and malacia in the brain after sulfuryl
> fluoride exposure is unknown... In neural diseases, the formation of
> intracellular vacuoles in the brain is a marker for the diagnosis of a group
> of neural degenerative diseases called spongiform encephalopathies (De
> Girolami et al., 1999). Vacuolation of the neurons in the cerebrum,
> cerebellum, and other nuclei is also a finding in aging rats (Solleveld and
> Boorman, 1990)." (page 54)

M. In its brief review of central nervous effects, the California EPA in its June 2005

Health Risk Assessment noted:

> "Subchronic exposure to 0.03 or 0.1 ppm fluoride as hydrogen fluoride for
> 5 months showed central nervous system dysfunction (diminished
> conditioned responses and increased time before motor nerve response).
> The 0.1 ppm rats showed changes in the nerve cell synapses." (pp B-9-10)

N. Vacuolation of the <u>white matter</u> of the brain has also been reported in animal studies

with sulfuryl fluoride. This is another rare effect as we only found it reported in three

other pesticides in OPP's database. These three pesticides are all fluorinated:

bromethalin, chlorfenaphyr, fluazinam. According to Christopher Filley, author of *The

Behavioral Neurology of White Matter* (Oxford University Press, 2001),

> "Early clinical features of cerebral white matter involvement typically include
> confusion, inattention, memory dysfunction, and personality change... Measures of

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[26] Females may be at greater risk. Rats in a 2-year study had significantly higher adverse brain effects
(vacuolation in cerebral cortex and thalamus/hypothalamus) compared to both control and male rats (CA
EPA 2005 at Table 11), and female rabbits in a 90-day rabbit study had vacuolation of brain white matter.
[27] See Appendix C for further details about the brain effects caused by these 7 pesticides.

attention, cognitive speed, memory retrieval, visuopatial skills, and executive function are likely to be most sensitive to subtle white matter dysfunction… (p 249)."

Filley's book examines the disorders of white matter which are wide-ranging and are associated with multiple sclerosis, HIV dementia, lupus, migraine, hydrocephalus, to name a few. We brought Filley's book to the attention of OPP in previous submissions (Connett E et al. 2002, Connett P et al. 2002).

O.   Varner et al. (1998) reported damage to the brain of rats at levels as low as 1 ppm fluoride. The authors stated:

> "In summary, chronic administration of AlF3 and NaF in the drinking water of rats resulted in distinct morphological alterations in the brain, including effects on neurons and cerebrovasculature."

P. According to the NRC (2006), fluoride has the potential – at doses significantly lower than OPP's RfD for infants and children - to exacerbate the neural developmental effects (e.g. IQ deficits and mental retardation) of low iodine intake.

In summary, 1) since the brain has been the major target organ in Dow's studies on sulfuryl fluoride, 2) since sulfuryl fluoride appears to rapidly metabolize into fluoride ion, 3) since NRC has concluded that the fluoride ion can damage the brain, and 4) since no DNT has ever been performed for fluoride, it is imperative that an oral DNT study be conducted on fluoride before consideration of setting tolerances. OPP's action in waiving the DNT study was based on faulty reasoning and flawed science. As a result it was not protective of the public's health. It is also not consistent with the requirements set forth under FFDCA, as amended by FQPA.

IV. NO SAFE ROOM FOR ADDITIONAL FLUORIDE EXPOSURES

In determining whether a pesticide residue is safe, the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, directs OPP to consider the cumulative impact from all sources of exposure to the chemical for "which there is reliable information." Thus, in addition to the direct exposure from the residues, the OPP must consider the impact of the full "aggregate exposure" to the chemical. To quote:

> "[T]he term "safe", with respect to a tolerance for a pesticide chemical residue, means that the Administrator has determined 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." 7 U.S.C. § 346a(b)(2)(A)(ii)

Because people are now regularly exposed to many sources of fluoride – including dental products, fluoridated drinking water, processed foods, tea, pesticide residues (e.g. cryolite in grape juice & wines[28]), and certain fluorinated pharmaceuticals[29] – it is particularly important and appropriate to carefully consider the impact of the total aggregate exposure to fluoride.

In its risk assessment for sulfuryl fluoride, however, OPP significantly underestimated the full extent of aggregate fluoride exposure in the US. Whereas OPP concluded that aggregate exposures to fluoride do not exceed the reference dose for any age group, this conclusion can be readily shown to be false when correcting for several serious deficiencies in OPP's analysis.

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[28] Due to the use of cryolite (a fluoride-bearing pesticide) on vineyards, grape juices have been found to contain up to 6.8 ppm (Stannard 1991), and wines have been found to contain up to 12 ppm (Sawyer Ostrom 1996).

[29] A growing number of pharmaceuticals are fluorinated (i.e. organofluorine compounds). Several studies have indicated that at least some of these fluorinated compounds may metabolize into fluoride ion within the body and thereby contribute to ionic fluoride exposure (Rimoli 1991, Pradhan 1995). Considering the widespread use of these pharmaceuticals, this could prove to be a very significant source of fluoride - one which was not considered by EPA in its aggregate exposure analysis.

In agreement with Objectors, the New York State Attorney General's Office, after reviewing EPA's risk assessment, concluded that:

> "Aggregate and cumulative exposures have been drastically underestimated for subsets of the population under varying circumstances" (Kaufmann 2006).

Thus, even if one assumes that the reference dose used by OPP was safe and appropriate (a conclusion directly contradicted by NRC's review), it is nevertheless evident (as demonstrated below) many Americans are already exceeding it.

Moreover, since the NRC has concluded that severe dental fluorosis is a toxic effect, it is imperative to examine how close children are to exceeding the dose that causes this effect. As detailed below, OPP's own data shows that many children are exceeding the dose that OPP admits can cause severe dental fluorosis. Hence, because FFDCA, as amended by FQPA, directs OPP to issue tolerances which are protective of children's health, it is clear that there is no safe room for any additional fluoride exposures. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 4.1 OPP under-estimated average level of fluoride in US water

As part of its exposure analysis, OPP attempted to determine the average fluoride concentration of US water supplies. OPP's method for deriving an average fluoride concentration was incorrectly weighted[30] leading to an obvious error in OPP's exposure analysis. According to OPP's estimates, only 57 million or just 20% of Americans (60 million people) consume water with > 0.7 ppm fluoride (USEPA 2003a;

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[30] EPA's estimate was based on public water system reports of fluoride content. The error in EPA's analysis appears to lie in the characterization of these water systems into very broad population categories (e.g. <10,000, 10,000-100,000; 100,000-1,000,000, & >1 million). Since water fluoridation is much more common in cities than small towns, the use of these broad population categories appears to have incorrectly weighted the results.

Table c.33). This, of course, is incorrect since, according to the CDC (2005), 170 million

Americans drink fluoridated water (0.7-1.2 ppm). OPP's estimate, therefore, of the

number of Americans exposed to fluoridated water was off by a factor of 3. This, in turn,

led to an under-estimation of the average fluoride content of US water supplies.

According to OPP, the average fluoride content of US water is 0.4 ppm. Confirmation

that this is incorrect can be found in a recent national analysis of US water supplies by

USDA. According to USDA (2004), the average fluoride content of US water supplies

(municipal + well) is 0.71 ppm – almost twice as high as OPP's estimate. Accordingly,

OPP's risk assessment supporting the tolerances is scientifically, factually and legally

inadequate.

ISSUE 4.2 OPP under-estimated exposure to fluoride from water by failing to account for full range of water consumption

In addition to under-estimating the average level of fluoride in US water supplies,

there is another significant problem with OPP's drinking water exposure analysis. By

only using the chronic exposure model in the DEEM software, OPP was only able to

determine the *average* fluoride exposure from water based on the *average* daily intake of

water. By only accounting for the average water consumer, the OPP's exposure estimate

does not account for, or protect, people with above-average thirst. This is a limitation

inherent in the DEEM software.

In a recent OPP Dietary Exposure Assessment the output of DEEM-FCID 2.03 is

described:

> "For chronic exposure assessments, consumption data are averaged for the entire
> U.S. population and within population subgroups." [US EPA 2004b)

As FAN has verified using the DEEM software, the chronic exposure model computes only the average exposure for the entire US population and designated subpopulations. The subpopulations are based only on age and sex, not water consumption. Thus, the software and the underlying food consumption database do not allow for any breakdown of exposure by the varying percentiles of water intake. Hence, there is no way to determine the water fluoride intake among the top 25%, top 10%, top 5%, and top 1% of water consumers.

OPP's failure to obtain this vital information represents a major failure of due diligence, and probably the most glaring problem with its exposure analysis. After all, water is the most significant source of fluoride exposure in the US population, and – as highlighted by the Food and Nutrition Board (2004) - its consumption varies greatly across the spectrum of the population. To restrict, therefore, an analysis of water fluoride exposure to simply the average, or 50th percentile, water consumer, provided a fatal blow to OPP's ability to detect the true extent of fluoride exposure in the US among sizeable subsets of consumers.

As is amply documented, there exists a wide variability in both food and water consumption habits among the population. Therefore, the only way to obtain an accurate dietary exposure assessment is to determine the variability in consumption from individual to individual and use the resulting consumption distribution for the population. The FDA has found that, as a rule of thumb, the top 10% consumers of any food eat about twice as much as the average. The top 5% consume about four times as much as average (FDA 1995). The CFSII studies by USDA show that a similar difference in consumption patterns exists with tap water (NRC, Table B-4). According to USDA's

data, the top 10% of consumers drink about 2.5 times more water than the average, while the top 1% consumers drink about 5.5 times more water than the average (NRC, Table B-4).

By only considering the average water consumer, therefore, OPP has significantly under-estimated the fluoride exposures from water experienced by a sizeable percentage of the population. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 4.3 When accounting for the full range of water consumption, it is evident that many people are exceeding the RfD

Had OPP conducted an analysis that addressed the intake of high-end water consumers they would have found that many Americans are currently exceeding the RfD from water sources alone. To demonstrate this fact, we produce below the results of 2 sets of analyses we have recently conducted along with data from the NRC (2006) and a recent published study (Phipps 1998).

Our first set of analyses utilized the 1988-1994 NHANES water intake data as reproduced in Appendix D of the Food and Nutrition Board's 2004 report. Since the NHANES data is divided into percentiles of exposure, it was possible to estimate the water intake of the top 1%, top 5%, top 10%, and top 15% of water consumers. We then applied this water consumption data to US populations residing in areas with legally allowable levels of fluoride in water (2 to 4 ppm). In order to determine how many people live in such areas, we utilized the CDC's 1993 Fluoridation Census for data on

public water systems, and a recent national survey from the USGS for data on private wells (Focazio 2006)[31].

As can be seen in the following table, this analysis indicates that between 1 and 15% of individuals on water systems with 2-4 ppm fluoride in the US will exceed the reference dose just from their intake of water. (For further details about this analysis, see Appendix B of Connett E, 2005c).

Table 4-A. Americans exceeding RfD in 2-4 ppm areas				
Water Fluoride	No. of Americans on public water systems (CDC 1993)	No. of Americans on private wells (Focazio 2006)	% of People exceeding RfD (8 mg/day) based on NHANES water intake data	# of People exceeding RfD (8 mg/day)
2.0–2.4 ppm	~565,000	~405,000	≥1	≥9,700
2.5-2.9 ppm	~209,500	~315,000	≥5	≥26,225
3.0–3.4 ppm	~230,000	~135,000	≥10	≥36,500
3.5–3.9 ppm	~68,000	~135,000	≥15	≥30,450
≥ 4 ppm	~210,000	~360,000	≥15	≥85,500
Total:	~1,282,500	~1,350,000	>6%	≥188,375

For our second analysis we utilized the DEEM software. We sought to conduct an analysis that would correct three key problems with OPP's DEEM analysis, namely

- For all analyses we utilized USDA's (2004) data on the average fluoride level of US water supplies (0.71 ppm) for the non-tap water categories. We used this figure as a substitute for OPP's mistaken 0.4 ppm estimate.

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[31] The study by USGS (Focazio 2006) indicates that just as many Americans are exposed to elevated fluoride from private wells as from public water systems. In a sampling of 15,496 wells, the USGS found that 3% of the wells contained more than 2 ppm fluoride, while 0.8% contained more than 4 ppm fluoride. Since the EPA estimates that 15% of the American population (~45 million people) get their water from private wells, the USGS data indicates that about 1.3 million people are exposed to ≥2 ppm fluoride from their well water, which is roughly equivalent to the number of people exposed through public water systems.

- For the tap water categories, we didn't limit our analysis to only those individuals drinking 2 ppm fluoride in water. We also performed analyses for people drinking water with 1 ppm and at various intervals between 2 and 4 ppm.
- In order to get an indication of fluoride exposure among high-end water consumers, versus simply the average consumer, we utilized DEEM's acute model, rather than the chronic model. We predicated this decision on the assumption that the range of water consumption reported among individuals in the USDA's 2 day survey provides a rough surrogate for the spectrum of chronic water consumption across the population[32].

The results of our DEEM analyses are summarized in Table 4-B. As with the analysis above, the DEEM analyses show that many high-end water consumers living in 2 to 4 ppm areas will exceed the reference dose. Moreover, the DEEM analyses also indicate that a subset of individuals living in 1 ppm areas (about 0.25% to 0.5% of the population) will exceed the reference dose as well. With over 100 million Americans living in 1 ppm areas, a figure of 0.25-0.5% translates into hundreds of thousands of people. (For the full DEEM analyses, see Appendix C of Connett E, 2005c).

TABLE 4-B				
Fluoride Dosage (mg/kgday) by Water Consumption Percentile				
Tap Water F level	90th	95th	99th	99.9th
1.0 ppm	0.037	0.049	0.090	**0.171**
2.0 ppm	0.067	0.088	**0.157**	**0.338**
2.2 ppm	0.077	0.102	**0.186**	**0.370**
2.7 ppm	0.094	**0.125**	**0.228**	**0.452**
3.2 ppm	0.111	**0.147**	**0.270**	**0.538**
3.7 ppm	**0.128**	**0.170**	**0.316**	**0.622**
4.0 ppm	**0.138**	**0.183**	**0.330**	**0.671**
***Bold** indicates dosage exceeds OPP's reference dose.*				

Our estimates on the extent of fluoride intake from water gains further support from NRC's recent review (NRC 2006), and an empirical survey of fluoride intake from tap water (Phipps 1998).

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[32] The NRC review supports our use of the 2-day data for predicting high-end water consumption patterns. According to NRC: "given the size of the population sampled, the likelihood that the entire sample represents days of unusually high or unusually low water intake is small. Thus, these values are considered reasonable indicators both of typical water consumption and of the likely range of water consumption from various sources on a long-range basis" (NRC, p. 370).

Unlike the OPP, the NRC did not limit their analysis of fluoride intake from water to average water consumers. While NRC did conduct a DEEM analysis of average fluoride exposure from water, it also conducted an analysis which focused on fluoride exposures among high-end water consumers. In their analysis, NRC confirmed our estimates that 1% of adults living in 2 ppm areas will exceed the current RfD from water intake alone (NRC, Table B-14). NRC also confirmed our estimates that some susceptible subsets of consumers (e.g. diabetics) may exceed the RfD in 1 ppm areas just from water intake (NRC, Table 2.4). NRC also found – when considering all sources of intake[33] - that up to 1% of young adults (20-24 yr olds) will exceed the RfD in 1 ppm areas (NRC, Tables B.14, B.7, & 2.9).

A recent study of fluoride exposure from water, meanwhile, suggests that both our analysis, and NRC's analysis, may have under-estimated the full extent of fluoride exposure from water. The study, by Phipps et al 1998, assessed tap water consumption among older adults in 3 American communities in the northwest with varying levels of fluoride in the water (0.3, 0.7,and 2.5 ppm). In calculating tap water consumption, the study considered "tap water used to make coffee, tea, and other beverages plus water used in making soups and other concentrated foods." Among the 2.5 ppm community, the study found that approximately 33% of the people surveyed ingested more than 8 mg/day, with some ingesting as much as 14 mg/day (Phipps 1998, Figure). By way of comparison, our analyses – and NRC's analyses - have estimated that about 5% of people

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[33] In determining total fluoride exposure, NRC considered exposures from sulfuryl fluoride. However, it utilized OPP's January 2004 estimates, rather than OPP's revised estimates of July 2005. As a result, NRC under-estimated fluoride exposure from sulfuryl fluoride by about a factor of thirty (0.0003 mg/kg/day vs 0.0095 mg/kg/day).

living in 2.5 ppm areas would exceed the RfD. Thus, if Phipps' study is correct, then total tap water consumption may be significantly higher than typically assumed.

In any event, it is amply clear based on all of the analyses described above (our analyses, NRC's analyses, and the survey by Phipps) that many consumers – living in communities with fluoride levels currently considered 'safe' - are exceeding the reference dose from water consumption alone. This fact was obfuscated by OPP though its decision to focus strictly on the average consumer, and to limit its analysis to only 2 ppm fluoride in water. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 4.4 OPP has underestimated children's exposure to fluoride from toothpaste

As with its drinking water analysis, OPP has also underestimated fluoride exposure from toothpaste as well. According to OPP:

> "Despite the variability in the estimates of ingested toothpaste, maximum exposures to fluoride observed in those studies appear to converge to approximately 0.3 mg/day (assuming 2 brushings per day)... The exposure estimates range from 0.004 to 0.04 mg/kg/day and should be considered conservative in nature..." (US EPA 2004a, page 34).

OPP's assertion that 0.3 mg/day fluoride represents the "maximum" exposure from toothpaste is not supported by the scientific literature. Indeed, not only is 0.3 mg/day significantly lower than most reported maximum exposures from toothpaste, it is also lower than many of the reported *average* exposures!

For example, in 1999, Levy compiled data from studies which measured the quantity of toothpaste ingested by children (see Table 4-C). Levy compiled published data for 11 groupings of children ≤ 5 years old – the age range most susceptible to swallowing excess toothpaste. Of these 11 groups of children, data on maximum intake

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was presented for 4 groups. All 4 of these maximum intakes (range = 0.66 - 2.55 mg/day) exceed (by a factor of two to nine) OPP's purported "conservative" maximum.

Perhaps more notable, however, is the fact that the *average* fluoride exposures in 9 of these 11 groups also exceed OPP's purported *maximum* exposure (see table 4-C).

Based on this data, it is clear that OPP has made a significant underestimation of the fluoride exposure children receive from toothpaste.

TABLE 4-C: Comparison of Documented Fluoride Ingestion from Toothpaste with OPP's Purported Maximum Dose (0.3 mg/day)					
	Average F Intake from Toothpaste		Maximum F Intake from Toothpaste		
Age	Intake from 2 Brushings (1,100 ppm F)	% of OPP's Estimated "Max" Intake	Intake from 2 Brushings (1,100 ppm F)	% of OPP's Estimated "Max" Intake	Reference
2	0.73 mg	**243%**	n/a	n/a	Levy 1999 *(Naccahe '87)*
2-3	0.62 mg	**207%**	n/a	n/a	Levy 1999 *(Simard '84)*
2-4	0.66 mg	**220%**	1.61 mg *(90th percentile)*	**>537%**	Levy 1999 *(Barnhart '76)*
3-6	0.84 mg	**280%**	2.55 mg	**850%**	Levy 1999 *(Hargreaves '75)*
3	0.40 mg	**133%**	n/a	n/a	Levy 1999 *(Naccahe '85)*
4	0.48 mg	**160%**	n/a	n/a	Levy 1999 *(Naccahe '87)*
4	0.86 mg	**287%**	n/a	n/a	Levy 1999 *(Simard '84)*
4	0.29 mg	97%	0.66 mg	**220%**	Levy 1999 *(Ericsson '74)*
5	0.48 mg	**160%**	n/a	n/a	Levy 1999 *(Simard '84)*
5	0.24 mg	80%	n/a	n/a	Levy 1999 *(Naccahe '85)*
5-6	0.59 mg	**197%**	n/a	n/a	Levy 1999 *(Baxter '79)*

Another way that OPP underestimated fluoride exposure from toothpaste is to assume that the instructions on the labeling will "significantly limit" ingestion. According to OPP:

"Regarding exposure to fluoride via dental products, the Agency believes that warning labels on these products provide explicit direction on how to significantly limit dietary exposure to fluoride-containing dental products for children." (US EPA, 2002)

There are two problems with this assumption.

First, while the instructions warning children not to swallow toothpaste are available in the fine print on the back of the tube, toothpaste manufacturers continue to make child-friendly toothpastes with appealing flavors like bubble-gum and watermelon. Such flavors will undoubtedly tempt kids to use more, and swallow more, of the paste – a fact supported by published research (Levy 1992, as cited in Levy 1999).

Another problem with OPP's assumption is it does not take into consideration the millions of people who do not have the literacy skills to read the warning label on toothpaste. According to the National Institute for Literacy (NIFL),

"Almost all adults in Level 1 can read a little but not well enough to fill out an application, **read a food label**, or read a simple story to a child... Between 21 and 23 percent of the adult population or **approximately 44 million people**, according to the National Adult Literacy Survey (NALS), scored in Level 1" (emphasis added; NIFL, 2005)

Also, we are not aware of any toothpaste sold in the US that has warnings in any language other than English.

Thus, by A) misrepresenting published data on toothpaste ingestion and by B) assuming that ingestion of toothpaste will not be a problem due to the presence of instructions in fine print, OPP has underestimated the extent of childhood fluoride exposure from toothpaste. This fact becomes particularly significant when considering the narrow margin (as discussed below) that currently exists between OPP's estimates for

total fluoride exposure in children and the dose that – according to OPP's own estimates - can cause severe dental fluorosis. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 4.5 Children are exceeding the dose that causes severe dental fluorosis

As discussed earlier, the National Research Council has concluded that severe dental fluorosis is an adverse effect to human health. Thus, if OPP is to set an RfD that is protective of children's health (as required by FFDCA), it will need to set the RfD at a level that does not cause severe dental fluorosis.

According to OPP's health risk assessment, severe dental fluorosis may be caused at doses exceeding 2 mg/day[34]. Thus, if OPP is to follow the requirements of FFDCA, as amended by FQPA, and protect children's health, the allowable dose for children must not exceed 2 mg/day. *This is significant because OPP has acknowledged that some children have aggregate exposures to fluoride that exceed 2 mg/day* (USEPA 2006, Appendix II).

According to OPP, the aggregate exposure for 6-12 year olds is 2.2 mg/day, or 11% greater than the dose that can cause severe fluorosis. The aggregate exposure, meanwhile, of 3-5 year olds is estimated by OPP to be 1.9 mg/day -- just a sliver below 2 mg/day. While these estimates provide sufficient reason, in of themselves, to reject the tolerances, it is important to emphasize that OPP's estimates are based on a significant underestimation of fluoride exposure from toothpaste. As can be seen in Table 4-D, if one substitutes OPP's purported "maximum" daily exposure from toothpaste (0.3 mg/day)

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[34] EPA derived the 2 mg/day estimate from the Office of Drinking Water's SMCL (Secondary Maximum Contaminant Level). The SMCL, which is set at 2 mg/L, is designed to prevent moderate and severe dental fluorosis – both of which occur when the fluoride concentration in water exceeds 2 mg/L. A child drinking 1 liter of water with 2 mg/L fluoride will ingest 2 mg/day. Hence, EPA selected 2 mg/day as the dose of concern for severe dental fluorosis (USEPA 2006, Appendix II).

with the *average* daily toothpaste exposure from 7 peer-reviewed studies (0.56 mg/day), it can be seen that many children in the 3-5 year age-group will also exceed 2 mg/day from all sources.

Table 4-D. Risk Estimates for Severe Dental Fluorosis:			
Revising OPP's analysis with a corrected estimate[a] for toothpaste exposure			
Population Subgroup	Dose that may cause severe dental fluorosis (USEPA 2006)	OPP's Estimate of Total Exposure (% of fluorosis dose)	Total Fluoride Exposure with corrected toothpaste estimate (% of fluorosis dose)
All infants (<1 year)	2 mg/day	1.465 (73%)	1,465 (73%)
Children 1-2 years	2 mg/day	1.386 (69%)	1.645 (82%)
Children 3-5 years	2 mg/day	1.912 (96%)	**2.172 (109%)**
Children 6-12 years	2 mg/day	**2.218 (111%)**	**2.218 (111%)**
Bold = Exceeds OPP's estimate of dose (2 mg/day) that can cause severe dental fluorosis.			
(a) The corrected toothpaste estimate is based on the comprehensive data compiled by Levy (1999). Whereas OPP assumed a "maximum" intake of 0.3 mg/day fluoride from toothpaste, the corrected estimate (0.56 mg/day) is based on the <u>average</u> daily dose (assuming 2 brushings of toothpaste with 1100 ppm fluoride; the most common concentration in the US) reported in the 7 studies cited by Levy (see Table 3-C above) which assessed fluoride ingestion from toothpaste among 2 to 5 year olds. Since little data was available for <1 year olds or >6 year olds, and since it is probable that these age groups would ingest less toothpaste than 2-5 year olds, we have not revised OPP's estimate of 0.3 mg/day for these age groups.			

It is readily apparent that many children are exceeding the dose that OPP estimates can cause severe dental fluorosis. It is imperative, therefore, for OPP to rescind the tolerances, as there is no safe room for additional fluoride exposures. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 4.6 Many infants will exceed 2 mg/day if the fluoride content of formula is considered

In its exposure analysis, OPP appears to have overlooked a major source of fluoride intake among infants: infant formula. This is a significant omission because if the fluoride contribution from formula is accounted for, it becomes evident that some

infants – living in 1 ppm areas - will ingest more than 2 mg/day from water and formula alone.

According to recent studies, infant formulas – particularly soy-based formulas – can contain significant levels of fluoride. Levy (1995) notes that:

> "Soy-based formulas contain higher levels of fluoride than milk-based formulas. The fluoride level in five ready-to-feed soy-based formulas ranged from 0.17-0.38 ppm (mean = 0.30 ppm) in a recent study of infant formulas available in Iowa... When reconstituted with deionized water, fluoride levels of powder and liquid concentrates of soy- and milk-based formulas were similar to the ready-to-feed levels" (Levy 1995).

Of particular concern are powder-based soy formulas. As described by Levy, powdered soy formulas can add 0.38 ppm fluoride to water used in the reconstitution of the formula[35] (Levy 1995). Thus, if water with 1 ppm fluoride is used to reconstitute the formula, the resulting concentration would be as high as 1.38 ppm. The significance of this fact becomes evident when considering water consumption patterns for infants. According to USDA's CFSII database, one percent of 6–12 month old infants consume 1.529 liters of community water per day (NRC, Table B-4). If these infants live in a 1 ppm area, they would consume up to 2.1 mg/day from water and formula alone if they consumed the water in the form of formula -- which many babies do. Thus, without even taking into account fluoride exposure from baby foods or dental products, some infants can exceed OPP's threshold dose for severe dental fluorosis in 1 ppm areas.

In its health risk assessment, OPP dismissed concern about the risk for severe dental fluorrosis in infant populations by claiming that "fluorosis which occurs in the infant population subgroup will be to their deciduous [baby] teeth" and "does not pertain

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[35] Abstracts from other published studies on soy formulas – the full papers of which Objectors do not yet have - indicate that the fluoride contribution from powdered soy formulas may, in some instances, be significantly higher than 0.38 ppm, thus adding to the concerns stated above (see Van Winkle 1995; Buzalaf 2001).

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to fluorosis of the permanent teeth" (USEPA 2006, p. 37). OPP's contention, however, that fluoride exposure during the first year of life does not cause fluorosis on the permanent teeth has been directly contradicted by a new study published this year by Hong (2006). The study, one of the largest and most comprehensive of its kind, monitored the fluoride intake of about 500 children from birth to the age of 4. When the children turned 9, the authors examined the two permanent upper front teeth of each child for signs of fluorosis and assessed which of the child's first 4 years of exposure were most significant in predicting the presence of fluorosis. In doing this analysis, the authors found that the "first year" of life was the "most important" year in predicting the eventual development of permanent fluorosis on the upper front two teeth. According to Hong (2006), other previous studies have reported similar results. Thus, OPP's assumption that fluoride exposure during the first year of life does not affect fluorosis on the permanent teeth is incorrect.

Considering, therefore, that A) some babies in 1 ppm areas can ingest more than 2 mg/day of from water and formula alone, that B) 2 mg/day can cause severe dental fluorosis, and that C) fluoride exposure during the first year of life can cause fluorosis on the permanent teeth, there is no safe room for additional fluoride exposures among the infant population. Accordingly, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 4.7 Millions of more people will exceed RfD if OPP follows NRC's recommendation and lowers the MCLG

As detailed in Section I, OPP has derived its current RfD from ODW's 1985 MCLG. Since the NRC has now concluded that the MCLG is unsafe and "should be

lowered", OPP will eventually need to lower the RfD if it is to remain in accordance with the best available science.

Since many Americans are already exceeding the current RfD, any reduction in the RfD, would greatly increase the number of Americans exceeding the RfD. For example, the NRC estimates that approximately 5% of adults living in 1 ppm areas ingest about 4 mg/day from all sources (NRC, Table B-13 & Table 2.9). This represents over 5 million people. Hence, if the new allowable dose is less than, or equal to 4 mg/day -- as seems likely based on the NRC's findings – a huge number of Americans will exceed the RfD.

V. OPP's EVALUATION OF ACUTE TOXICITY FAILED TO ADEQUATELY EVALUATE RISK OF OF NON-LETHAL EFFECTS

In its health risk assessment, OPP concluded that it would not be possible for acute fluoride toxicity[36] to result from the tolerances. This assessment, however, was a result of OPP limiting its consideration to only those doses of fluoride that can cause "death." By restricting its consideration to only fatal, or potentially fatal, effects, OPP failed to consider the risk for non-fatal acute effects, such as vomiting and gastrointestinal pain. This omission was significant because – as we will demonstrate below – consumption of some foods fumigated with permissible levels of sulfuryl fluoride can produce doses of fluoride which exceed doses documented in peer-reviewed studies to produce sub-lethal symptoms of acute toxicity. This is particularly true for dried eggs which OPP allows to be fumigated at 900 ppm, a concentration that – if it were a toothpaste - would require a FDA-mandated poison that cautions parents to call a "poison control center" if their child swallows more than a "pea-sized amount."

ISSUE 5.1: OPP failed to identify dose that can cause sub-lethal toxicity

On March 4, 2005, OPP announced that DOW was petitioning for additional sulfuryl fluoride tolerances. In this "notice of filing", OPP acknowledged that fluoride can produce various sub-lethal acute lethals, including "nausea, vomiting, diarrhea, abdominal pain, and paresthesia" (USEPA 2005a). However, the lowest acute toxic dose that OPP cited was 5 mg/kg, a dose that may cause fatalities in children, and which requires "therapeutic intervention and hospitalization" (Whitford 1987).

In citing 5 mg/kg as the lowest dose of concern, OPP failed to identify that much lower doses can cause acute fluoride toxicity. For example, according to a 1991 review

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[36] The term "acute toxicity" refers to adverse effects which result from a single exposure to a substance.

from officials at a Colorado Poison Control Center, some children suffer acute toxic effects after ingesting doses of fluoride below 1 mg/kg (Augenstein 1991). According to a 1994 study in the New England Journal of Medicine, some people suffer acute toxic effects (e.g. vomiting, nausea, stomach pain) from doses as low as 0.3 mg/kg (Gessner 1994); while, according to a comprehensive review of published data, some people suffer acute toxic effects at doses as low as 0.1 mg/kg – a dose fifty times lower than the minimum dose considered by OPP (Akiniwa 1997).

In failing to cite acute effects that can occur at dosages lower than 5 mg/kg, OPP ignored a key recommendation from Whitford (the scientist who promulgated the 5 mg/kg standard). According to Whitford (1987), the fact that 5 mg/kg should trigger immediate medical intervention, "does *not* mean that doses lower than 5.0 mg F/kg should be regarded as innocuous" (emphasis in original).

Failure by OPP to evaluate fully and carefully the available data on acute fluoride toxicity constitutes a failure to observe the standards set by the FFDCA. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 5.2: OPP's summary of doses causing sub-lethal effects in fluoridation accidents is superficial and deeply misleading

The superficiality of OPP's review of acute toxicity is perhaps best reflected in the following -- demonstrably false -- statement from the health risk assessment:

> "The Agency is aware of cases of acute toxicity following exposure to extremely high concentrations of fluoride in drinking water. These incidents appear to be due to malfunctioning fluoridation equipment and fall far outside the realm of expected exposures. As such, HED has not tried to assess acute toxicity for fluoride" (USEPA 2006, p. 19).

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The fact that OPP actually made this statement is proof, in and of itself, that OPP

failed to carefully evaluate the published data on fluoride's acute toxicity. For example,

the studies on water fluoridation accidents have consistently found that doses below 1

mg/kg can cause symptoms of acute toxicity (Akiniwa 1997, see Table 5). According to

one of the most comprehensive studies on the subject, published in the New England

Journal of Medicine, acute toxicity was produced in some people at doses as low as 0.3

mg/kg (Gessner 1994). According to the authors:

> "The lowest estimated dose of fluoride that caused symptoms was 0.3 mg per
> kilogram; 16 percent of the case patients received an estimated dose of less than
> 1.0 mg per kilogram" (Gessner 1994).

The fact that acute toxicity has been documented in fluoridation accidents at doses

well below 1 mg/kg is extremely significant, because – as will be demonstrated below –

these doses are achievable by consumption of foods fumigated with sulfuryl fluoride.

Hence, OPP's claim that the fluoride exposures from fluoridation accidents "fall far

outside the realm of expected exposures" from the tolerances is completely incorrect.

Accordingly, the risk assessment supporting the tolerances is scientifically, factually and

legally inadequate.

ISSUE 5.3 Tolerances pose demonstrable risk of acute fluoride toxicity

To demonstrate the risk of acute fluoride toxicity from the tolerances, we shall

take the examples of dried eggs and wheat flour, both commonly consumed items in most

people's diets. The fluoride tolerance for dried eggs is 900 ppm and for wheat flour is

125 ppm.

ISSUE 5.3.1: Risk of acute fluoride toxicity from fumigated dried eggs

The consumption of dried eggs fumigated at the permissible limit of 900 ppm fluoride, presents a clear risk for acute fluoride toxicity. This can be readily demonstrated by 1) calculating how many milligrams of fluoride an individual would ingest when consuming fumigated dried eggs, 2) dividing the quantity of ingested fluoride by the individual's bodyweight, and 3) comparing this dosage to the published data on fluoride dosages which can produce acute toxicity.

To determine how much fluoride an individual may ingest from fumigated dried eggs, we used recipes and conversion factors from several sources, including the American Egg Board and the USDA to determine how many grams of dried egg is mixed with water to make one egg equivalent. Both sources gave conversions by weight, not by volume, so there was no possibility of errors when converting volumes and densities to weights. Using both of these independent conversion factors returned the same result which provides reassurance that the methods are correct. Table 5 documents and references all of our calculations.

Table 5. Calculations for acute fluoride dose from dried eggs	
Data on which calculations are based	
F residue level in dried eggs [a]	900 ppm or 900 mg/kg
Average weight of one large fresh egg:	50 g (American Egg Board 2005)
Conversion factor from dried egg to fresh egg:	1 part by weight dried egg to 3 parts by weight water (USDA 2003; American Egg Board 2005)
USDA standard serving size:	2 eggs
90th percentile large serving:	4 eggs (FDA 1995; 90th percentile is double the mean)
Calculations	
12.5 g dried egg mixed with 37.5 g water gives 50 g reconstituted egg 12.5 g X 900 mg/kg X 0.001 kg/g = 11.25 mg per fresh egg equivalent 2 egg equivalents X 11.25 mg/egg equivalent = **22.5 mg fluoride per serving** 4 egg equivalents X 11.25 mg/egg equivalent = **45 mg fluoride per serving**	
(a) Our calculation here is based on whole dried eggs. These are the types of eggs most likely to be used as a direct replacement for fresh eggs in recipes like scrambled eggs and omelets.	

As can be seen in the table, the consumption of 2 fumigated dried eggs can result in a dose of 22.5 mg of fluoride, while the consumption of 4 fumigated dried eggs can result in a dose of 45 mg/day. Both of these doses would be sufficient to produce acute symptoms in an average weighing adult (70 kg), as they would produce dosages (0.3-0.6 mg/kg) exceeding the threshold for acute fluoride toxicity (0.1-0.3 mg/kg). The risk would be even greater for children. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 5.3.2: FDA poison warning reinforces concern about risk of acute toxicity from fumigated dried eggs

The above calculations, which indicate a risk of acute fluoride toxicity from fumigated dried eggs, is supported by an independent assessment from the Food and Drug Administration (FDA).

Since 1997, the FDA has required a poison warning on all fluoride toothpastes sold in the US. As a result, all fluoride toothpastes must caution users that children under six should only "use a pea-sized amount" and that:

> "If you accidentally swallow more than used for brushing, seek professional help or contact a poison control center immediately."

FDA's warning underscores the negligence of OPP's tolerance for dried eggs because the concentration of fluoride in most fluoridated toothpastes (1000-1100) ppm is virtually the same as the concentration that OPP allows in dried eggs (900 ppm). Hence, based on FDA's warnings, it seems hard to fathom why children should ever be unknowingly exposed to more than a pea-sized amount of dried eggs fumigated at the permissible limit[37]. Unfortunately, however, a pea sized portion of dried eggs, or even several pea-sized portions of dried eggs, would not even represent a single mouthful of scrambled eggs. Thus, on this basis alone, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 5.3.3: OPP's estimate of fluoride exposure from dried eggs is incorrect

In their assessment of the risk from fumigated dried eggs, the OPP made a mistake in their calculations of how many milligrams of fluoride would be contained in one reconstituted dried egg made up from 900 ppm dried egg powder (US EPA 2005b). According to OPP, consumption of dried eggs with 900 ppm fluoride would only result in a dose of 3.1 mg per egg. This estimate, however, is contradicted by the facts detailed above.

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[37] According to the New York State Attorney General's Office: "The remarkably high tolerance for dried or powdered eggs – 900 ppm – results, EPA explains, from the propensity of this compound to accumulate in foods of high fat and protein content producing a high amount of residue under normal fumigation practices. Yet the FQPA requires tolerances be set at levels "safe" for human health, not safe for existing industry practices" (Kaufmann 2006).

Since OPP (unlike Objectors) did not reference how they reached their estimate of fluoride exposure from dried eggs, we do not know where their mistake arose. We note, however, that they used recipes supposedly based on teaspoons and may have confused these with tablespoons. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 5.3.4: OPP's has incorrectly assumed that an individual will only consume one dried egg per meal

In OPP's response to the issue of dried egg tolerances, OPP claims that it is highly unlikely for any individual to ever consume more than a single egg's worth of dried eggs (US EPA 2005b). They base this on their claim that dried eggs will only be used in mixes such as baking mixes. They apparently don't realize that dried eggs are a standard USDA food item supplied to schools, Indian Reservations, prisons, food banks, disaster relief agencies, and other low budget end-users where they may frequently be used instead of fresh eggs to prepare dishes such as scrambled eggs or omelets (USDA 2005). The USDA purchased 4 million pounds of dried eggs in 2003 (USDA 2004). Dried eggs are also commonly found in lightweight foods for campers. Approximately 1/3 of all eggs consumed in the US are dried eggs (American Egg Board 2005a).

Moreover, two eggs is considered a single serving of eggs by the USDA. Almost everyone would consume at least a single serving, and many would consume two servings worth or four eggs. As shown above, a four-egg meal prepared with 900 ppm residue dried eggs would give an acute dose of 45 mg F. Depending on the weight of the individual, this could range from 1.5 mg/kg for a 30 kg child to 0.5 mg/kg for a large adult weighing 90 kg. These dosages range from 2x to 15x greater than the dosages found to cause acute gastrointestinal symptoms including vomiting. Accordingly, OPP's

risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 5.3.5: Current status of dried egg tolerances remains a problem

In its final health risk assessment, OPP announced that dried eggs were being removed from the list of "Commodities That Can Be Fumigated" (USEPA 2006). However, in the same risk assessment, OPP stated that "Incidental treatment of dried eggs resulting from space fumigations may be permitted" and the Agency continued to list the "recommended tolerance" of 900 ppm F for dried eggs in its table titled "Tolerance Summary for Sulfuryl Fluoride."

It does not appear, therefore, that OPP has actually implemented any action that would legally prohibit either the use of sulfuryl fluoride on eggs or the contamination of eggs with residues of sulfuryl fluoride. Nothing short of cancellation or deletion of the use from all of the registrations and the revocation of the tolerance will be adequate to legally bar use and residues in food. Until these steps are taken, it impossible to exclude these risks from the assessment of risk and consideration in connection with this Motion. Thus, the population remains at risk of acute fluoride toxicity from consumption of dried eggs fumigated with sulfuryl fluoride. The fact that this risk remains renders OPP's risk assessment inadequate and contrary to law.

ISSUE 5.3.6: Risk of Acute Fluoride Toxicity from Fumigated Wheat Flour

The high tolerances for dried eggs are not the only tolerances which could lead to acute toxic exposures. Wheat is a staple of most diets and OPP has granted wheat flour the second highest tolerance of any food item of 125 ppm. For example, roughly three slices of bread (about 75 g wheat) would contain 9 mg of fluoride if fumigated at the

allowable tolerance. For a 25 kg child this would produce a dosage of 0.36 mg/kg which exceeds the dosage that can cause acute toxicity. Adults could also exceed an acute toxic dose when eating large servings of wheat-based foods which have been fumigated at the legal limit. The risk assessment supporting the tolerances is, therefore, scientifically, factually and legally inadequate.

ISSUE 5.4 OPP was remiss in failing to consider sub-lethal doses of fluoride resulting from the tolerances on other commonly consumed foods.

The above analyses considered fluoride exposure from only two commodities, dried eggs and wheat flour. At this time we are unable to expand the analysis to consider all foods which will be fumigated because the list includes all processed foods. Even using DEEM software, the ability to do a full assessment is hampered by the difficulty in defining every category of processed food and its individual exposure contribution. But difficulty in performing an analysis does not relieve OPP from the requirement to perform an acute toxicity analysis taking into account exposures from all food items with tolerances. A failure to do so indicates that they cannot sustain the claim that they are proceeding with "A reasonable certainty that no harm will result." The omitted analysis should have included all processed foods with tolerances of 70 ppm, other grains with tolerances from 40 ppm to 125 ppm, and a wide range of commonly consumed fruits, vegetables, nuts, dairy, and meat products. By failing to have done this analysis, the risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

VI. SIGNIFICANT PROBLEMS PERSIST WITH OPP'S ESTIMATE OF CHRONIC FLUORIDE EXPOSURE FROM TOLERANCES

As detailed in the following set of issues, OPP's estimates of the chronic fluoride exposure that will result from the tolerances is significantly hampered by a multitude of uncertainties and limitations in the data. The totality of these uncertainties and limitations has handicapped OPP's ability to estimate the full range of fluoride exposures that will result from the tolerances. These substantial uncertainties and limitations rendered OPP incapable of determining that there was a "reasonable certainty that no harm will result" from aggregate exposures in setting the tolerances.

ISSUE 6.1: OPP only considered individuals with average consumption of fumigated foods

In estimating the fluoride exposure that will result from the tolerances, OPP only considered the average consumption of food for fumigated commodities. By only considering average consumption patterns for a food item, OPP's exposure estimates have failed to take into account, and protect, individuals who consume larger amounts of particular food items[38]. It was particularly negligent for OPP not to have paid special attention to above-average consumption of wheat products. Wheat products, which are allowed to contain up to 130 ppm fluoride -- the second highest tolerance approved by OPP -- form a major part of the diet. Hence, above-average consumption of wheat could have an appreciable impact on some people's exposure. According to the FDA, there is usually a four-fold difference in consumption between the average consumer

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[38] In many other risk assessments, EPA has assessed the risk to individuals who eat more than the average amount of food. It is not, therefore, an unusual procedure.

(50th percentile) and the 95th percentile consumer for any given food product. This difference is likely to be considerably greater if the 99th and 99.9th percentile consumers are considered. Accordingly, OPP's risk assessment supporting the tolerances is scientifically, factually and legally inadequate.

ISSUE 6.2: OPP's estimate of expected fluoride residues from fumigations is based on insufficient data

When the actual data upon which OPP's tolerances were determined is examined, it can be seen that it is insufficient to assure that the limited data will adequately reflect real world fumigation practices and residues. For example, for the critical commodity wheat flour, the range of fluoride residues found was 15 ppm to 82 ppm and most of this data was not from fumigation at the approved application rate. All of this data, meanwhile, was from a single flour mill facility, so there is no way to know how residues will vary under the unique fumigation conditions found at each facility. According to the New York State Attorney General's Office, this "lack of monitoring data to adequately characterize fluoride levels and food may lead to underestimated exposures" (Kaufmann 2006).

Fumigation is a complicated process involving many variables of temperature, ventilation rates, building leakage rates, fumigant injection sites, outside wind shielding foods from exposure, etc. To base tolerances on data from only a single site is presumptuous. Indeed, even within this single facility the HRA reports there was "a fairly high degree of variability across treatment replicates" [EPA HRA Oct. 2004 p 13]. The HRA goes on to state there was even more variability due to the properties of the food commodities themselves.

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ISSUE 6.3: OPP has failed to consider potential for unexpectedly high fluoride accumulation in certain, unforeseen processed foods

OPP has granted tolerances for an incalculable large number of food items under the catch-all heading "all processed foods." Only a small fraction of current "processed foods", however, have had any actual residue tests conducted on them. Considering that the composition of each food item (e.g.its protein and fat content) is a major determining factor for how much fluoride it will retain, the absence of any test data on most processed foods raises the distinct possibility that – as with dried eggs - some processed foods may concentrate fluoride to higher than expected levels. The following statement from OPP underscores the basis for this possibility:

> "For a number of finished products; the residues of sulfuryl fluoride in the packaged configuration were greater than in the open configuration. In all such cases, the packaging contained a polymer film, either as a bag liner or as lined paper. The phenomena were not mirrored in the fluoride residue levels. HED does not have a satisfactory theory to explain these observations at this time. Method performance leaves a high degree of uncertainty surrounding residues of sulfuryl fluoride in Oreo ® cookies, powdered eggs, and baking soda; and for residues of fluoride in white cake mix, pet foods, parsley, and baking powder" (USEPA 2006, p. 22)

ISSUE 6.4: It is unclear if OPP's DEEM analysis assessed exposure from "processed foods"

The DEEM computer model used by OPP to assess exposure from food does not allow for estimation of exposure from "processed foods." Only residues in raw agricultural commodities may be used in DEEM. OPP has still not supplied Objectors with the full supporting documentation for the Final Health Risk Assessment, so it is impossible to determine how, or even whether, OPP

included "processed foods" in their exposure assessment. Failure to include this wide range of foods or improper methods of estimation could lead to significant underestimation of exposures.

ISSUE 6.5: Dow's testing methods may have underestimated the concentration of fluoride residues resulting from fumigation

OPP has repeatedly stated (USEPA 2004b, 2005b, 2006) that the testing methods used by Dow to measure the fluoride residues on fumigated foods may underestimate the level of total fluoride compounds present. The fact that all residue data has been collected using methods that may have underestimated the true fluoride content undermines OPP's ability to predict the true extent of fluoride exposure from the tolerances.

ISSUE 6.6: OPP has failed to define a monitoring structure that would enforce compliance with "incidental" treatment restrictions

While OPP is no longer permitting the direct fumigation of either dried eggs or edible oils, it still allows both items to be "incidentally" fumigated. OPP's use of the term "incidental" raises more questions, however, than it answers. Most notably, OPP has failed to quantifiably define how often such food items can or will be fumigated, and what, if any, monitoring structure will be in place to ensure compliance with OPP's vague "incidental use" policy.

ISSUE 6.7: OPP has inappropriately excluded dried eggs and edible oils from its dietary exposure assessment

While permitting the "incidental" treatment of both dried eggs and edible oils, OPP has excluded both products from its most recent dietary exposure and

risk estimates. OPP defended this decision on the basis that it expects neither product to be fumigated regularly. Such a decision, however, was non-protective in light of the agency's failure to define its use of the term "incidental", and its failure to describe the mechanisms in place to ensure that only "incidental" treatment occurs. OPP hasn't informed the public of the alternative fumigation chemicals that will be used to fumigate dried eggs.

ISSUE 6.8: OPP's dietary exposure assessment failed to consider indirect contribution from animal feed tolerances

In its January 2006 Health Risk Assessment, OPP "appears" to have approved a new tolerance for "Animal Feed," that was not included in the July 2005 final rule. OPP states that the "Animal Feed" tolerance will be covered under "All processed food commodities not otherwise listed." OPP approved the "Animal Feed" tolerance without any discussion or clarification on the extent to which this will increase human exposure to fluoride. Because animals readily accumulate fluoride in their bone, and because particles from animal bone readily enter certain meat products (e.g. mechanically deboned meat), it can be expected that the new feed tolerances will result in increased fluoride exposure among humans. OPP's failure to take this secondary route of exposure into account has impaired OPP's ability to fully assess the impact of the tolerances.

**VII. OPP's PROCEDURAL ERRORS HAVE RENDERED THE
ENTIRE PROCESS FLAWED AND IN VIOLATION OF THE
REQUIREMENTS OF THE ADMINISTRATIVE PROCEDURE ACT**

OPP's conduct throughout the entire process of establishing the tolerances at issue

has been in flagrant violation of the requirements of the APA.

FFDCA Section 408(g)(2)(c) provides that in a hearing on objections to

tolerances, the final decision should be based on "substantial evidence of record."

Administrative Procedure Act (APA) Section 706(2)(E), 5 U.S.C. § 706(2)(E), provides

guidance as to this strict standard and the statute provides in general for the fair conduct

of federal administrative agency proceedings.

In reviewing agency informal rulemaking under the substantial evidence test:

> [A court's] paramount objective is to see whether the agency, given an essentially
> legislative task to perform, has carried it out in a manner calculated to negate the
> dangers of arbitrariness and irrationality in the formulation of rules for general
> application in the future.

Industrial Union Department v. Hodgson, 499 F.2d 467, 475 (D.C. Cir. 1974),

citing Automotive Parts & Accessories Ass'n v. Boyd, 407 F.2d 330.336 (1968). In this

matter, rather than "negate the dangers of arbitrariness and irrationality" in the

rulemaking process, OPP, to the contrary, has effectively courted those very dangers.

Further, OPP's actions become particularly acute given the demanding standard of the

substantial evidence test and the dangers to public health posed. See, JEFFREY S.

LUBBERS, A GUIDE TO FEDERAL AGENCY RULEMAKING 347 (3rd ed. ABA

1998) (use of the more demanding "substantial evidence" standard in "hybrid" informal

rulemaking instead of the usual "arbitrary and capricious" standard reflects Congress's

"view that the more stringent test afforded the courts more leeway to monitor agency

actions in implementing …new regulatory programs.") As set forth these Objections,

the OPP has acted in violation of the APA.

An additional and pertinent APA requirement is the one in Section 553 (c) that, in

informal agency rulemaking, agencies "shall give interested persons an opportunity to

participate in the rulemaking." 5 U.S.C. § 553(c). As set forth in this section, OPP's

actions failed to afford this opportunity to Objectors in a meaningful way. Courts have

found that such participation can be particularly important in their review of "pre-

enforcement, complex, scientifically based agency rules." LUBBERS, supra, at 197.   In

Portland Cement Ass'n v. Ruckelshaus, 486 F.2d 375 (D.C. Cir. 1973), *cert. denied*, 417

U.S. 921 (1974), the D.C. Circuit reviewed EPA rulemaking under the Clear Air Act

wherein EPA relied on test results that had not been made available for public comment.

The court held as follows:

> [There was a] critical defect in the decision-making process in arriving at the
> standard … in the initial inability of petitioners to obtain—in timely fashion—the
> test results and procedures used …[in determining the standard]. … It is not
> consonant with the purpose of a rule-making proceeding to promulgate rules on
> the basis of inadequate data or on data that, [in] critical degree, is known only to
> the agency.

> *Id.* at 393. See also, *United States v. Nova Scotia Food Products Corp.,* 568 F.2d

240, 252 (2d Cir. 1977) (emphasizing the importance of full disclosure by the Food and

Drug Administration of scientific research being relied on in order to generate

meaningful public comment). Thus, the case law supports Objectors' contention that

EPA must provide a meaningful opportunity for participation as required by the APA.

Closely related to the citizen participation requirement is the requirement that

there be a proper and complete "record" in rulemaking proceedings. See, APA Section

553(c), 5 U.S.C. § 553(c). An adequate record in the proceedings promotes not only

public participation but also effectiveness in the rulemaking process and proper judicial

review. See, LUBBERS, supra, at 214-24. The caselaw strongly supports the need for

such a record even where a court may have ruled against some petitioners on the narrow

facts of the particular case. See, *National Coalition Against the Misuse of Pesticides v.*

Thomas, 809 F.2d 875, 884 n.10 (D.C. Cir. 1987) (petitioners were found to have had

adequate opportunity to comment, but the court observed that "clearly supplied

information [is] critical to informed comment on EPA's proposal to reestablish the 30

[ppb] tolerance, and, for that matter, to review by the court").

In this matter, as described throughout this document and in this section in

particular, OPP has repeatedly failed to include complete, timely information. This has

greatly harmed the prospects for a fair and informed proceeding leading to tolerances that

comport with the requirements of the FFDCA and the APA. Under APA Section 706(1),

a reviewing court may "compel agency action unlawfully withheld or unreasonably

delayed." 5 U.S.C. § 706(1)

ISSUE 7.1: OPP violated the APA by thwarting public participation during issuance of first-time tolerances

Objectors first submitted their Objections and Request for a Hearing in April 2002

on OPP's tolerances for an Experimental Use Permit. These objections were deemed

"moot" by OPP in its final rule of January 2004. OPP's explanation for this was

"[b]ecause the tolerances that were objected to have now been revoked, the objections are

moot and are denied on that ground." OPP offered this rationale at the exact time it

issued its first-time tolerances for fluoride and sulfuryl fluoride on January 23, 2004.

Thus, at the most critical juncture in setting tolerances, Objectors were locked out. OPP

has since failed to respond to the substantive Objections to the January 23, 2004 Final Rule. Here, even given the reasonable discretion accorded to agencies in this area, such a failure to act cannot be deemed acceptable under the APA. In *Public Citizen Health Research Group v. Food and Drug Administration,* 740 F.2d 21, 34 (D.C. Cir. 1984), the D.C. Circuit remanded the case to the district for a determination whether FDA had "unreasonably delayed" resolution of a challenge to health warnings on aspirin bottles. Noting particularly the underlying statute's concern for health and safety, the court observed that "[i] f the district court finds unreasonable delay, it must fashion an appropriate remedy." *Id.* at 35 The court stated further:

> In deciding whether the pace of decision is unreasonably delayed, the court should consider the nature and extent of the interests prejudiced by delay, the agency justification for the pace of decision, and the context of the statutory scheme out of which the dispute arises. *Id.*

Based on the egregious nature of OPP's refusal, and considering the factors set out by the D.C. Circuit, OPP is in violation of APA Section 706(1).

ISSUE 7.2: OPP violated the APA by failing to issue Health Risk Assessment in timely manner

OPP erred in attempting to unlawfully supplement the admittedly inadequate record of the tolerances after the tolerances had been promulgated. Both the June 2005 and January 2006 Health Risk Assessments (HRA) were not available to the public and were sent to the Objectors in February 2006, long after the tolerances were promulgated on July 15, 2005. The final HRA of January 2006 had not even been written on July 15, 2005. As set forth above, the APA requires that the full record of any rulemaking be made available to the public prior to promulgation of the rule. The courts have repeatedly struck down rules which violate this requirement. This procedural error had

the effect of impairing the ability of the general public and petitioners in particular to meaningfully comment on the rule. In addition, it also greatly delayed the process of challenging the rule by means of objections. The New York State Attorney General's Office strongly concurs with Objectors on this point. According to the Attorney General's Office:

> "EPA's decision to establish new tolerances prior to finalizing the underlying health risk assessment has deprived the public of any meaningful participation in the rulemaking, and inevitably fosters the public impression that this process has been driven by the needs of the petitioner rather than by concern for the safety of the public food supply" (Kaufmann 2006).

ISSUE 7.3: OPP violated the APA by failing to place many required documents in public dockets.

OPP did not put the overwhelming majority of documents that it relied on and cited in its decision making process, into the docket for the public to access. For example, the April 2004 waiver of the DNT study, all animal studies, as well as many other documents pertaining to sulfuryl fluoride fumigation issues, were not placed into the docket as of March 8, 2006. On March 13, 2006, the Objectors requested from OPP numerous documents, which, several of which it has yet to receive (see Appendix D). FFDCA Section 408(d)(2)(A)(iv) requires applicants to provide "full reports of tests and investigations made with respect to the safety of the pesticide chemical..." with their petition for a tolerance. Subsection (v) imposes the same requirement for residues in food. The agency is then compelled to consider these documents by 408(d)(4)(A): "The Administrator shall, after giving due consideration to a petition... and any other information available to the administrator...". Since these documents are mandatory components of the basis for the rule, they must in accordance with the APA, be included in the docket for comment.

ISSUE 7.4: OPP violated the APA by not waiting for NRC report before issuing Final Rule

OPP committed a fatal procedural error when it promulgated the rule without waiting for the expert advice of the NRC report. According to the New York State Attorney General's Office, OPP's failure to defer its decision until the release of the NRC report "seriously undermined" the "validity and credibility" of the risk assessement. According to the Attorney General's Office:

> "it was unreasonable to establish the tolerances at issue ahead of the March 2006 release of the [NRC report] which EPA itself sponsored pursuant to the Safe Drinking Water Act. EPA has offered no rationale for ignoring the expert review that it requested. The agency thus deprived its decisionmaking process of the most up-to-date expert authority on the health effects of fluoride exposure, authority that actually contradicted at least two of EPA's central assumptions" (Kaufmann 2006).

The Agency's behavior is particularly difficult to fathom in light of the fact that EPA's Office of Water had requested the NRC report because it recognized that important new research was available. Indeed, at the first public meeting of the NRC in August 2003, an OPP official told the Objectors (Ellen and Paul Connett) that the OPP would not issue tolerances until the NRC issued its report. When tolerances were first issued in January 2004, the Objectors stated in their submission of March 2004 that it "was unwise and undefendable" to do so before the NRC Report. Accordingly, the Agency failed to act based on "substantial evidence on the record" when it decided not to await crucial information and analyses before promulgating the tolerances and provided no justification in the record or the tolerance documents for its haste.

Objectors assert that these failures by OPP are fundamental to procedural fairness and therefore constitute a gross violation of the APA.

CONCLUSION

In these Objections, Objectors have challenged the Regulations issued by EPA as having failed to comply with the requirements of the FFDCA and the APA. In doing so, Objectors have detailed both procedural failings of the process for determining the tolerances and the factual and scientific inadequacies of the agency's decision-making process. Objectors are certain that at hearing, the substantial issues of fact raised herein will be resolved in their favor, thus justifying their position that the present tolerances should not be allowed to stand.

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APPENDIX A

Timeline of Developments on Sulfuryl Fluoride (2001-2006)	
June 15, 2001	Notice of Dow's request to OPP for an Experimental Use Permit (EUP) for sulfuryl fluoride. Dow petitions OPP to establish a temporary tolerance for fluoride in/on walnut and sulfuryl fluoride in/on raisins. Dow requests OPP to establish an exemption from the requirement of a tolerance for fluoride in/on raisins (US EPA, 2001a).
September 5, 2001	OPP denies Dow's request for a tolerance exemption for fluoride in/on raisins, and instead propose the following temporary tolerances: fluoride at 30 ppm in/on raisins and 12 ppm in/on walnut, and a tolerance for sulfuryl fluoride in/on walnut at 2 ppm and in/on raisins at 0.004 ppm (US EPA, 2001).
September 19, 2001	Comments submitted to OPP on Sept 5th proposed temporary tolerances (Connett E, 2001).
February 7, 2002	OPP approves temporary tolerances, proposed September 5, 2001, to support Dow's EUP (US EPA, 2002).
February 15, 2002	Dow petitions OPP for tolerances for more than 40 raw and processed food commodities (US EPA, 20002a).
March 18, 2002	FAN submits comments to OPP on Dow's petition of February 15, 2002 (Connett P, Connett E, 2002).
March 27, 2002	OPP approves Dow's request for an EUP (US EPA, 2002b).
April 8, 2002	FAN submits Objections and a Request for Hearing on OPP's February 7, 2002, temporary pesticide tolerances (Connett E, Connett P, 2002).
January 23, 2004	OPP establishes the first-time food tolerances for residues of sulfuryl luoride from post-harvest fumigation. OPP approves the highest food tolerances for fluoride residues in its history. OPP sets a precedent by allowing a dosage of fluoride for infants that is five times higher than for adults. OPP announces that Dow withdrew the EUP because "the California Department of Pesticide Regulation has not issued the necessary state authorization to allow the EUP to proceed..." OPP also states that because the EUP has been withdrawn by Dow, he Objections and Request for Hearing submitted by FAN are moot. However, OPP publishes 5 documents in response to FAN's objections (US EPA, 2004).
March 23, 2004	Objections and a Request for Hearing submitted to OPP on the January 2004 tolerances from FAN and Beyond Pesticides (Connett P et al., 2004).
March 4, 2005	Dow petitions OPP for tolerances for over 600 food commodities (US EPA 2005a).
April 19, 2005	FAN submits comments to OPP on Dow's March 4, 2005, petition for tolerances (Connett E, 2005).
June 2, 2005	OPP's first response to the March 2004 Objections and Request for Hearing submitted by FAN and Beyond Pesticides (Jones JJ, 2005).

June 2, 2005	Draft EPA Human Health Risk Assessment for sulfuryl fluoride and the fluoride anion. The HRA was performed for the July 15, 2006, rule. (Doherty 2005) OPP did not make this draft HRA available to the public in the July 15, 2005, rule. OPP sent this HRA to Objectors on February 13, 2006, along with the 1-18-06 final HRA for this same rule.
July 15, 2005	OPP issues new tolerances for 219 processed food commodities, and a 70 ppm fluoride tolerance for all processed food not specifically cited. At this time they issue the highest- ever tolerance for fluoride residues: 900 ppm in/on dried egg (US EPA, 2005).
September 11, 2005	Objections and Request for Hearing submitted to OPP on July 2005 tolerances from FAN, the Environmental Working Group (EWG), and Beyond Pesticides (Neurath et al., 2005).
December 16, 2005	Submission to US OPP on the issues for an evidentiary hearing to revoke the tolerances approved for the use of sulfuryl fluoride, from Objectors: FAN, EWG and Beyond Pesticides.
January 18, 2006	Final OPP Human Health Risk Assessment for sulfuryl fluoride and the fluoride anion. This HRA post-dates the Federal Register notice establishing tolerances for all processed foods of July 15, 2005. (Doherty 2006) OPP sent this HRA to Objectors on February 13, 2006. This HRA was used as the basis for setting tolerances in the July 15, 2005, rule.
February 13, 2006	Letter from Jim Jones, Director, OPP, to Objectors, granting request to "submit further issues upon OPP's risk assessment for the July 15, 2005, rulemaking. A copy of that risk assessment and a revised version of the risk assessment correcting various errors is attached. Any additional issues for hearing must be submitted within 90 days of your receipt of this letter." (Jones 2006) In response, Objectors request the need to obtain all animal studies performed with sulfuryl fluoride, and that upon their receipt, comments would be forthcoming. Request agreed to by OPP's legal counsel, Jonathan Fleuchaus.
March 22, 2006	Public release of the report of the National Research Council, "Fluoride in Drinking Water: A scientific review of OPP's standards."
June 2006	Objectors submit petition to US EPA to stay the tolerances sulfuryl fluoride. (Wallace 2006)
July 5, 2006	OPP makes available the Objectors June 2006 petition in the Federal Register and solicits public comment. (US EPA 2006)
August 4, 2006	New York State Attorney General's Office submits substantive comments to OPP in support of the June 2006 Objectors petition. (Kauffmann et al. 2006)
August 4, 2006	Lawyer for Dow AgroSciences submits substantive comments to OPP in opposition to the June 2006 Objectors petition. (Abramson 2006)
Do you want to mention the meeting you had with Jim Jones	First-time meeting with US EPA on Objectors petition and objections. In attendance: Representing Objectors: Michael Connett of FAN, Richard Wiles of EWG, Jay Feldman of Beyond Pesticides, and Perry Wallace of Zelle, Hofmann, Voelbel, Mason & Gette.

APPENDIX B

Table. Sulfuryl Fluoride: Brain Effects reported from Dow's animal studies.				
Majority excerpts from: Table 1.--Subchronic, Chronic, and Other Toxicity Ref: January 23, 2004. Sulfuryl Fluoride; Pesticide Tolerance. Final Rule. Federal Register				
Type of Study	Animal	NOAEL mg/kg/day	LOAEL mg/kg/day	Based on:
2-Year combined chronic/ carcinogenicity	RAT	3.5 for M 16 for F	14 for M 62 for F	histopathology in brain (vacuolation in cerebrum and thalmus/hypothalamus). [* See note at end]
2-Week inhalation (1985)	RABBIT	30/30 (M/F)	90/90 (M/F)	malacia (necrosis) in cerebrum, vacuolation of cerebrum At 180/180 mg/kg/day for M/F, malacia (necrosis) in cerebrum, vacuolation of cerebrum, convulsions, hyperactivity,
2-Week inhalation (1992 study)	MOUSE	30 ppm		5 mice/sex/group were dosed 6 hr/day, 5 days/wk, for 9 exposures at 0, 30, 100, and 300 ppm sulfuryl fluoride, 99.6% purity. "very slight" cerebral vacuolation in six of ten 100 ppm mice. All high dose mice, except for 2 with sufficient autolysis** to impede microscopic evaluation, showed cerebral vacuolation, usually of "moderate" degree. Five high dose mice had very slight vacuolation of the medulla (CA EPA 2005, page C-8)." Autolysis = The cells start to dissolve and melt when you die.
90-Day inhalation toxicity	RAT	24/25 (M/F)	90/90 (M/F)	malacia (necrosis) in cerebrum, vacuolation of cerebrum
90-Day inhalation toxicity	RAT	-	180/180 (M/F)	malacia (necrosis) in cerebrum, vacuolation of cerebrum
90-Day inhalation toxicity	RAT	-	240/250 (M/F)	vacuolation of caudate-putamen nucleus and white fiber tracts of the internal capsule of the brain
90-Day inhalation neurotoxicity study (special design)	RAT	24/25 (M/F)	80/83 (M/F)	Disturbances in electro-physiological parameters (slowing of VER and SER waveforms in F and ABR waveforms in M)
90-Day inhalation toxicity	MOUSE	38/36 (M/F)	125/121 (M/F)	miscroscopic lesions in caudate-putamen nucleus and external capsule of the brain All animals had vacuoles (CA EPA 2005, page D-1).

Table (cont.) Sulfuryl Fluoride: Brain Effects reported from Dow's animal studies.				
90-Day inhalation toxicity	DOG	25/26 (M/F)	50/51 (M/F	slight histopathology of the caudate nucleus of the basal ganglia, transient neurological signs (lateral recumbancy, tremors, incoordination, salivation, tetany, inactivity) starting at day 19 in one Male
90-Day inhalation toxicity	RABBIT	8.6/8.5 (M/F)	29/28 (M/F)	vacuolation of white matter of the brain (female only)
90-Day inhalation toxicity	RABBIT	-	86/85 (M/F)	malacia (necrosis) and vacuolation of putamen, globus pallidus and internal and external capsules in the brain. "At 300 ppm, common brain findings were vacuolation to severe malacia of cerebrum (both sexes, in the above regions) and gliosis and/or hypertrophy of vascular endothelial cells in some females in the same regions (CA EPA 2005, page C-7.)"
Chronic toxicity	RODENTS	3.5 for M 16 for F	14 for M 62 for F	histopathology in brain (vacuolation in cerebrum and thalmus/hypothalmus)
1-Year chronic inhalation toxicity	DOG	5.0/5.1 (M/F)	50/51 (M/F)	malacia (necrosis) in caudate nucleus of brain
18-Month carcinogenicity inhalation	MOUSE	25/25 (M/F)	101/101 (M/F)	cerebral vacuolation in brain
Note: no evidence of carcinogenicity. The average measured sulfuryl fluoride concentrations to rats were 0, 5.1, 20.2, or 79.6 ppm. There was increased mortality in the 80-ppm groups. By the end of the study, the mortality rates were 100% (the last animal died between day 701-707) for treated males and females, compared with 42% (males) and 50% (females) for controls. "Premature death in this group was caused by chronic progressive glomerulonephropathy and mineralization/atrophy in a variety of tissues (aorta, bone, eyes, heart, liver, mammary gland, mediastinal tissues, mesenteric tissues, parathyroid glands, pituitary glands, spleen, stomach, and tongue) (CA EPA 2005, page 48)."				

APPENDIX C

Table: Brain effects (<u>vacuolation</u> and <u>malacia</u>) noted in animal studies with pesticides approved for use in the U.S.		
8 PESTICIDES	FOOD USE	EFFECTS
Bromoathalin Rodenticide *(fluorinated)* CAS No. 63333-35-7	No.	• white matter spongiosis • intramyelinic vacuolization • myelin splitting at the intraperiod line* • optic nerve vacuolization
Chlorfenapyr Insecticide *(fluorinated)* CAS No. 122453-73-0	All foods at 0.01 ppm where food products are held, processed, and/or prepared as a result of application to crack, crevice and spot applications.	• vacuolation primarily in white matter of the corpus callosum, tapetum, hippocampus, and cerebellum. • spongyform myelopathy and/or vacuolation seen in the brain and spinal cord of treated rats and mice • vacuolation of the spinal cord and optic nerve
Fluazinam Fungicide *(fluorinated)* CAS No. 79622-59-6	Peanut – 0.02 ppm Potato – 0.02 ppm Wine grapes (imported) - 3.0 ppm	• vacuolation of the white matter in the brain and spinal cord
Indoxacarb Insecticide *(fluorinated)* CAS No. 173584-44-6	67 food commodities. Also: EUP: Cherry (sweet & tart) to May 2007 Peaches from May 2003 to May 2006 Time-limited tolerances: Collards to June 2006 Cranberry to Dec 2007	• vacuolation of the piriform cortex
Methyl methacrylate EPA List 2 Inert CAS 80-62-6	Unknown - List 2 Inert Inerts are considered Confidential Business Information and the public do not know what pesticides contain them.	• malacia and gliosis in 5/9 females exposed to 2000 ppm and 1/8 females exposed to 1000 ppm. (14-week rat study) [Note: we do not know if it produces liquefactive necrosis]
Propamocarb hydrochloride Fungicide CAS No. 25606-41-1	Potato - 0.06 ppm	• vacuolation choroid plexus ependymal cells in the brain
Propetamphos Insecticide CAS No. 31218-83-4	All foods at 0.01 ppm where food products are held, processed, and/or prepared as a result of application to crack, crevice and spot applications.	• brain vacuolation • myeloid hyperplasia and neural vacuolation

Table (cont): Brain effects (<u>vacuolation</u> and <u>malacia</u>) noted in animal studies with pesticides approved for use in the U.S.		
Sulfuryl fluoride Fumigant CAS No. 2699-79-8	Incalculable number of food commodities All processed food has a 70 ppm fluoride residue tolerance except foods with specific tolerances.	• malacia (necrosis) in cerebrum, vacuolation of cerebrum (Studies: 2-week rabbit, 90-day rat) • malacia (necrosis) and vacuolation of putamen, globus pallidus and internal and external capsules in the brain (90-day rabbit study) • malacia (necrosis) in caudate nucleus of brain (1-year dog study) • vacuolation to severe malacia of cerebrum (3-week rabbit study) • vacuolation of the myelinated caudate-putamen fiber tracts in the brain (2-generation reproduction mouse study) • vacuolation of the white matter of the brain (Females). (90-day rabbit study) • malacia to vacuolation of the internal and external capsules, putamen, and globus pallidus of the brain (90-day rabbit study) • vacuolation of the caudate-putamen nucleus and white fiber tracts of the internal capsule (90-day rat study) • gliosis and vacuolation of focal areas of the putamen (13-week dog study) • vacuolation in cerebral cortex and in thalamic and hypothalamic areas (2-year rat study). • vacuoles – severity not reported (13-week rat study) • very slight vacuolation of the medulla (2-week mouse study)

APPENDIX D
Documents requested from US EPA by FAN, but not received as of 11/01/06

Source for following documents:
January 18, 2006: Human health risk assessment for sulfuryl fluorde and fluoride nion addressing the secion 3 registrtion of sulfuryl fluoride as a fumigant for foods and food processing facilities. PP# 3F6573. PAGE 6. http://www.fluoridealert.org/pesticides/sf.hra-jan18.2006.pdf

Document Number	Title of Document
HED Doc. No. 078003	Memorandum by M. Lewis (SRRD) to V. Dutch (SRRD), 11/17/99

Source for following documents:
October 31, 2003. SULFURYL FLUORIDE - Second Report of the Hazard Identification Assessment Review Committee. TXR NO.:0052208. USEPA. http://www.fluorideaction.org/pesticides/sf.oct.31.2003.epa.docket.pdf

Document Number	Title of Document
MRID 00090015	Developmental toxicity study, rats, rabbits
TXR 0008392	Ref: page 29
TXR 014568	HIARC report, 5-22-01
TXR 2673	Ref: page 29

Source for following documents:
January 2, 2004. Human Health Risk Assessment for Sulfuryl Fluoride and Fluoride Anion Addressing the Section 3 Registration of Sulfuryl Fluoride Post-Harvest Fumigation of Stored Cereal Grains, Dried Fruits and Tree Nuts and Pest Control in Grain Processing Facilities. PP# 1F6312. http://www.fluorideaction.org/pesticides/sf.jan.20.2004.epa.docket.pdf

Document Number	Title of Document
D283007	Doherty, M. D283007. 1/13/04. PP#1F06312 – Sulfuryl Fluoride. Section 3 Registration for the Post-harvest Fumigation of Stored Cereal Grains, Dried Fruits, and Tree Nuts, and Fumigation of Grain Milling Establishments. Summary of Analytical Chemistry and Residue Data.
D283008	Doherty, M. D283008. 1/13/04. Chronic Dietary Exposure Assessments for Sulfuryl Fluoride and Fluoride Anion, Addressing the Section 3 Registration of Sulfuryl Fluoride on Stored Cereal Grains, Grain Processing Facilities, Dried Fruits, and Tree Nuts. PP# 1F6312.

Cited at: Table 4.2.1.3. Average Residue Values of Fluoride Anion Resulting from the Uses of Cryolite, and Percent Crop Treated Estimates Used in the Chronic Dietary Exposure Assessment.

MRID 00158001	MRID 41380607	MRID 43077601
MRID 40635601	MRID 41380608	MRID 43830201
MRID 40901303	MRID 41380609	MRID 43867501
MRID 41380601	MRID 41380610	MRID 44742401
MRID 41380602	MRID 41380611	MRID 44742402
MRID 41380603	MRID 42067901	MRID 45009001
MRID 41380604	MRID 42656901	MRID 45113801
MRID 41380605	MRID 42659301	MRID 45162301
MRID 41380606	MRID 42751710	MRID 470178022

Source for following documents:
Index of Cleared Science Reviews
Vikane (Sulfuryl Fluoride) (Pc Code 078003)
http://www.epa.gov/pesticides/foia/reviews/078003.htm
Tox review 002674.
D Baron. Toxicology Branch.
Trade name: Vikane Fumigant
(page 2) Acute Rat Oral, Acute Guinea Pig Oral,
Acute Rat Feeding, Acute Rat Inhalation, Subacute Inhalation
June 8, 1979. Memorandum. 7 Page(s).
Phylis Johnson. Science Support Branch.
Transmission of RS Chemical Sulfuryl Fluoride FINAL Index Entry.
July 2, 1984. Memorandum. 10 Page(s).
M.I. Dow. Science Support Branch.
Sulfuryl Fluoride Qualitative Use Assessment.
January 23, 1985. Memorandum. 3 Page(s).
Ken Clark. Ecological Effects Branch.
Registration Standard - Sulfuryl Fluoride
'Attached is a copy of EEB's Topical Summary, Disciplinary Review and a Data Evaluation
Record.'.
January 22, 1986. Memorandum. 4 Page(s).
Joseph Reinert. Exposure Assessment Branch.
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01 through -05, DEB No. 6426, HED Project No.
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Product Amendment Action for Sulfuryl Fluoride Fumigant
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April 13, 1992. Memorandum. 2 Page(s).
Henry Jacoby. Environmental Fate & Groundwater Branch. Discussion. EFGWB had concerns about two uses and their impact on the environment. These were 1.) fumigation of large ocean-going vessels in ports and 2.) fumigation that involved moistening the soil with water.'.
April 13, 1992. Memorandum. 13 Page(s).
Kathy Monk. Environmental Fate and Effects Division.
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May 6, 1992. Memorandum. 7 Page(s).
 Marion Copley. Health Effects Division.
 Updated Toxicology Review for the Reregistration
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July 28, 1992. Memorandum. 9 Page(s).
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 Evaluation of Preliminary Air Monitoring Data for
 Structural Fumigation with Sulfuryl Fluoride

July 31, 1992. Memorandum. 2 Page(s).
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September 14, 1992. Memorandum. 6 Page(s).
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We received the following under this identifier number 42856201:
Cage and flight pen evaluation of avian repellency and hazard associated with Imdacloprid-
treated rice seed.
Avery, decker, Fischer
March 31, 1993.
59 pages
Identifying number: 105030 {"When referring to this report use this number")
EPA Front Page: MRID Number: 428562-01

FAN requested the following document and MRID 428562-01

February 2, 1994. Memorandum. 10 Pages.
Linnea Hansen. Toxicology Branch.
ID# 078003. Sulfuryl Fluoride. Evaluation of Motor
Activity Validation and Functional Observational Battery
Proficiency Testing Studies Submitted by Dow Chemical Co for
Sulfuryl Fluoride Neurotoxicity Testing. **MRID 428562-01, 02**
Tox review 010757. Pages 7-10 removed, registrant data.

We received the following under this identifier number 42856202.
Avian Risk Assessment for GAUCHO 240 Flowable systemic seed treatment insecticide applied
to cotton seeds
Report Number: 105188 ("When referring to this report use this number")
Author: D.L. Fisher
July 14, 1993
16 pages
EPA Front Page: MRID Number: 428562-02

FAN requested the following document and MRID 428562-02

February 2, 1994. Memorandum. 10 Pages.
Linnea Hansen. Toxicology Branch.
ID# 078003. Sulfuryl Fluoride. Evaluation of Motor
Activity Validation and Functional Observational Battery
Proficiency Testing Studies Submitted by Dow Chemical Co for
Sulfuryl Fluoride Neurotoxicity Testing. **MRID 428562-01, 02**
Tox review 010757. Pages 7-10 removed, registrant data.

January 25, 1993. Memorandum. 2 Page(s).
 Linnea Hansen. Toxicology Branch.
 Sulfuryl Fluoride. ID #078003. Review of Study [protocol] for Evaluation of Short-Term Inhalation
 Neurotoxicity in Rats (to Fulfill Guideline 81-8 Requirement).

January 27, 1994. Memorandum. 2 Page(s). Linnea Hansen. Toxicology Branch. Sulfuryl Fluoride. ID 078003. Review of a Protocol for a rat 2-Year Chronic Toxicity/Oncogenicity Study, Including Neurotoxicity Testing to Satisfy Guideline 82-5 (Subchronic Neurotoxicity Testing in Rat)
June 8, 1994. Memorandum. 2 Page(s). Linnea Hansen. Toxicology Branch. Sulfuryl Fluoride. ID NO. 078003. Chronic Neurotoxicity Study in Rat. [6(a)(2) data, MRID 432167-02]. [FAN RECEIVED THIS MRIDs].
May 1, 1995. Memorandum. 2 Page(s). Linnea Hansen. Toxicology Branch. Sulfuryl Fluoride. ID 078003. Response to 6(a)(2) Submission for Chronic Toxicity/Neurotoxicity/Carcinogenicity Data. MRID 433549-01, 02, 03, 432167-02. [FAN RECEIVED THESE MRIDs]..
May 23, 1997. Review. 6 Page(s). David Jaquith. Chemical Exposure Branch II. Non-Dietary Exposure Review; Re-Validation of Air Monitoring for Sulfuryl Fluoride
October 29, 1997. Review. 20 Page(s). David Jaquith. Chemical Exposure Branch II. Non-Dietary Exposure Review; Evaluation of Miran & Interscan for Monitoring Air Concentrations of Sulfuryl Fluoride. MRID No. 43836-01.
MRID Nos. 413888- 01 through -05 MRID 43836-01 MRID 418177-01 [FAN RECEIVED THIS MRID].

Source for following documents: **Summary of Toxicology Data: Sulfuryl Fluoride (Updated 6/2/04)** **CA EPA, DPR, Medical Toxicology Branch** http://www.fluorideaction.org/pesticides/sulfuryl.f.ca.epa.2004.pdf NOTE: We do not know which of the studies listed below are duplicates of those listed above.

Report Number	Title
50223-042 161152 (Combined. Chronic and Oncogenicity, Rat)	U.S. EPA review of Record #125637, above.
50223-020 097246 (Combined. Chronic and Oncogenicity, Rat)	Nitschke, K. D. and Quast, J. F., "Sulfuryl fluoride: Two-week inhalation toxicity study in beagle dogs". The Sciences, Dow (Midland), 4/30/**91**.
50223-042 161152 (Oncogenicity, Mouse)	U.S. EPA review of Record #125636, above.
50223-018 095931 (Reproduction, Rat)	Draft protocol for 50223-022 112308, above.

007 051087 (Teratology, Rat)	Data supplemental to a rat teratology study 006:036089, above. (Toxicology Research Laboratory, Dow Chemical, 11/19/80).
007 050992 (Teratology, Rabbit)	Data supplemental to a rabbit teratology study in 006:036088. (Toxicology Research Laboratory, Dow Chemical, 11/19/80).
50223-031 126406 (Neurotoxicity)	Exact duplicate of Appendix IV of Record No. 130056.
50223-012 071485 (Subchronic, Inhalation)	Nitschke, K. D., Dittenber, D.A., and Eisenbrandt, D. L. "Sulfuryl Fluoride (Vikane Gas Fumigant): 13-Week Inhalation Toxicity Study with Rats" (Mammalian and Environmental Toxicology Research Laboratory, Dow Chem. Co., Project ID K-016399-025R, 11/16/87).
50223-055 186125 (Subchronic, Inhalation)	Nitschke, K. D. and J. F. Quast, "Sulfuryl fluoride: two-week inhalation toxicity study in CD-1 mice," The Dow Chemical Co., Midland, MI, 2/11/02. Laboratory Project Study # K-016399-029.
50223-036 131289	(2 pages of additional information related to 50223-034 128669, above).
50223-0067 210013 (Metabolism)	"Sulfuryl Fluoride: Pharmacokinetics and Metabolism in Fischer 344 Rats", (A. L. Mendrala, et.al., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Study ID 001166, 22 May 2002).

We request all documents related to the statements in bold:

Page 37: Treated Cookware. The non-stick coating of fluoropolymer-treated cookware represents a potential source of fluoride exposure. A 1975 study (Full and Parkins) reported an increase in the fluoride concentration of water boiled in a non-stick coated pan compared to stainless steel or Pyrex glass. Due to their experimental design and the manner in which final fluoride concentrations are expressed, it is not possible to discern whether or not the increased fluoride concentration was due to leaching of fluoride from the cookware surface or differential evaporation noted for the treated cookware versus other materials. **The EPA [Office of Pollution Prevention and Toxics (OPPT)], in conjunction with other governmental agencies [FDA and CPSC], has been working with the manufacturers of these coatings to test these commercial articles under conditions of regular and misuse conditions to determine any decomposition products and their amounts. HED will coordinate with OPPT and will review the results of the cookware testing when the data become available.**

Source:
January 2, 2004. Human Health Risk Assessment for Sulfuryl Fluoride and Fluoride Anion Addressing the Section 3 Registration of Sulfuryl Fluoride Post-Harvest Fumigation of Stored Cereal Grains, Dried Fruits and Tree Nuts and Pest Control in Grain Processing Facilities. PP# 1F6312.
http://www.fluorideaction.org/pesticides/sf.jan.20.2004.epa.docket.pdf