UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

RESPONSE TO PUBLIC COMMENTS CONCERNING THE USE OF SULFURYL FLUORIDE AS A POST-HARVEST FUMIGANT

January 16, 2004

The Agency received a pesticide petition (1F6312) from DowAgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268 proposing, pursuant to section 408(d) of the FFDCA, 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of sulfuryl fluoride and fluoride anion in or on certain raw agricultural commodities. The Agency published the Notice of Filing and Dow's risk assessment in the Federal Register (67 FR 7156, February 15, 2002) as required by the Food Quality Protection Act. The Agency subsequently received seventeen sets of written comments (including five sets of late comments) on this notice of filing. The Agency had previously received comments on prior Federal Register tolerance documents related to the establishment of tolerances for sulfuryl fluoride and fluoride anion, including two sets of comments on the notice of filing of a pesticide petition to establish temporary tolerances for residues of fluoride and sulfuryl fluoride in or on walnuts and sulfuryl fluoride (SF) in or on raisins and to establish an exemption from the requirement of a tolerance for inorganic fluoride in or on raisins published on June 15, 2001 (66 FR 32618), and 89 sets of comments (including 10 late comments) on the proposed rule to establish temporary tolerances for sulfuryl fluoride and inorganic fluoride residues resulting from application of sulfuryl fluoride in or on walnuts and raisins published on September 5, 2001 (66 FR 46415). In addition, an objection and request for hearing was submitted by the Fluoride Action Network (FAN) in response to the establishment of temporary tolerances for sulfuryl fluoride and inorganic fluoride residues resulting from application of sulfuryl fluoride in or on walnuts and raisins published on February 7, 2002 (67 FR 5735). The temporary tolerances for sulfuryl fluoride and inorganic fluoride were established in conjunction with the issuance of Experimental Use Permit 62719-EUP-45 that involved testing sulfuryl fluoride as a possible alternative to methyl bromide in the post-harvest fumigation of stored walnuts and raisins in California. This experimental use has not been conducted.

In general almost all the comments relate to fluoride exposure, fluoride toxicology and issues related to the exposure to fluorides from fluoridated water. The debate on water fluoridation has a long history and the Agency's Office of Water has commissioned the National Academy of Science (NAS) to review the current regulatory limits for fluoride in drinking water, i.e., MCLG/MCL of 4 ppm and a secondary MCL of 2 ppm. The previous NAS review of fluoride was published in 1993 (NRC 1993).

The comments are grouped into basic areas of concern and each section below contains a summary of the commenter's concerns grouped by general topic and/or particular argument. The Agency is including a discussion of all public comments including previous comments made concerning the tolerances for walnuts and raisins related to the Experimental Use Permit involving the post-harvest fumigation of stored walnut and raisins in California using sulfuryl fluoride. For that reason, the Agency will address below in a comprehensive manner all the concerns raised in comments on the proposed EUP and for these final tolerances. Almost all these comments relate to fluoride and not sulfuryl fluoride; however, a few comments were made concerning sulfuryl fluoride's acute toxicity and toxicity to the brain and worker/bystander exposure from its use as a fumigant.

In general, the comments addressed either procedural issues concerning the process of establishing tolerance levels for sulfuryl fluoride and total fluoride or technical issues concerning the human health and other consequences that would result from the use of sulfuryl fluoride and increased human exposure to fluorides. These issues are addressed separately in the following.

I Procedural Issues.

I(A) Notified parties

Comment: The list of potentially affected parties identified in the Federal Register notice is too limited and does not include the consumers of the food who will be exposed to increased levels of sulfuryl fluoride and total fluorides.

Agency Response: The Notice of Filing (EPA 2002b) lists industrial categories that may be affected and states "Potentially affected categories and entities may include, but are not limited to: .... This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in the table could also be affected." There was no intent to impose a limit on the parties who can respond to this notice, and in fact all comments are being considered.

I(B) Use of current studies

Comment: The Agency has not considered the most recent studies, and the CDC report on fluoridation and dental health is out of date.

Agency Response: The Agency's Office of Water, under the Safe Drinking Water Act, establishes drinking water standards to control the level of fluoride in the nation's public drinking water systems. The rationale for setting the MCL and SMCL are described in the following Office of Water documents: Proposed Rule dated May 14, 1985 (50 FR 20164) and the Final Rule dated November 14, 1985 (50 FR 47144). The Safe Drinking Water Act (SDWA) requires the Agency to review each National Primary Drinking Water Regulation (NPDWR) at least once every six years and revise them, if appropriate. As part of this review process, the Office of Water has requested the National Academy of Science (NAS) to review the current drinking water standards for fluoride. The project scope from the NAS website states "A subcommittee of the National Research Council's (NRC) Committee on Toxicology (COT) will review toxicologic, epidemiologic, and clinical data, particularly data published since 1993, and exposure data on orally ingested fluoride from drinking water and other sources (e.g., food, toothpaste, dental rinses). Based on those reviews the subcommittee will evaluate independently the scientific basis of the U.S. Environmental [Protection] Agency's (EPA) maximum contaminant level goal (MCLG/MCL) of 4 milligram per liter (mg/L) and secondary maximum contaminant level (SMCL) of 2 mg/L in drinking water. The subcommittee will advise EPA on the adequacy of its fluoride MCLG/MCL and SMCL to protect children and others from adverse effects. The subcommittee will consider the relative contribution of various fluoride sources (e.g., food, dental-hygiene products) to total exposure. The subcommittee will also identify data gaps and make recommendations for future research relevant to setting the MCLG/MCL and SMCL for fluoride. The subcommittee will not address questions of economics, risk-benefit assessment, or water-treatment technology." The previous NAS review of fluoride that was published in 1993 (NRC 1993) served as the basis for the retention of the 4 mg/L MCLG/MCL and 2 mg/L SMCL by the Agency in 1993 (EPA 1993). This scientific review process has begun, and two public meetings have been held with the Fluoride Action Network in attendance. The updated NRC assessment of the health impacts of fluoride exposure is expected to be completed in 2005. In the meantime, the Agency has carefully considered all of the recent data that was referenced in the comments to determine whether there are any new data that substantially change the weight of the evidence that supports the conclusions reported in the 1993 NRC review.

I(C) Timing of DOW's Section 3 request

Comment: The DOW submission of Section 3 request was within 8 days of getting the

EUP for the use of sulfuryl fluoride of walnuts and raisins.

Agency Response: Registrants are allowed to set their own time tables for submissions to the Agency. However, the Agency sets the time table for acting on the submissions as required to assure thorough consideration of all of the health and environmental issues.

I(D) Consideration of DOW's exposure assessment.

The Agency received a pesticide petition (1F6312) from DowAgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268 proposing, pursuant to section 408(d) of the FFDCA, 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of sulfuryl fluoride and fluoride anion in or on certain raw agricultural commodities. The Agency published the Notice of Filing and Dow's risk assessment (EPA 2002b) as required by section 408(d)(3) of the Food Quality Protection Act. The Agency subsequently conducted its own independent risk assessment.

I(D)(1) Comment: DOW used the Dietary Exposure Evaluation Model (DEEM), version 7.73, of Novigen Sciences, Inc. to estimate the dietary exposure to the U.S. population and critical sub-populations resulting from the use of sulfuryl fluoride under the conditions proposed.

Agency Response: At the time the comments were made, the DEEM software was not generally available. It is now available for fee of $100. Although the DEEM model is not available to the general public at no cost at this time, the underlying data and assumptions and the model's calculation formulas and algorithms are fully available. The principles employed by the model have been thoroughly discussed via the science policy papers produced during the advisory proceedings of the Tolerance Reassessment Advisory Committee and the Committee to Advise on Reassessment and Transition (EPA 2003). Furthermore, the DEEM model in particular was thoroughly reviewed by the FIFRA Scientific Advisory Panel (EPA 2000a). The SAP review included a document prepared by the developers of the DEEM model, Novigen Sciences, that explained the scientific rationale and operation of the model in detail, to the extent of appendices that provided the computer code for the computational portions of the DEEM model. A study of these documents provides interested parties with the background information necessary to properly evaluate reports of aggregate exposure calculated by data submiters or by the Agency. In addition, the Agency has published a User's Guide that explains the general approach taken in performing exposure assessments and lists many of the underlying technical documents (EPA 2000b).

I(D)(2) Comment: The way that DOW presents this data is not helpful for the general public which does not have access to the DEEM model of Novigen Sciences, Inc.

Agency Response: The method used by Dow to report the results of the model, total dietary exposure for the most highly exposed population subgroup, is typical of such reports and is easily understood. The Agency's risk assessment for sulfuryl fluoride and fluoride ion reports exposure in mg/kg bw/day units and as a percentage of the cPAD or MCLG as shown in Tables 1 and 2.

I(D)(3) Comment: No toxicological endpoint attributable to a single exposure was identified in the available toxicology studies on sulfuryl fluoride or inorganic fluoride that would be applicable for an acute dietary exposure.

Agency Response: Risk is a function of exposure and hazard. For sulfuryl fluoride, an acute toxicity endpoint is not appropriate for the oral route of exposure. For the oral route of exposure, a chronic toxicity endpoint is appropriate.

I(D)(4) Comment: Unless the US EPA is prepared to leave these matters in the hands of private consultants or some other priesthood, they should insist that DOW make the raw data available so that their calculations may be checked.

Agency Response: Agency scientists have reviewed the raw data used by Dow and have conducted an independent risk assessment of the proposed uses. The acceptability of the uses are based on the Agency's risk assessment, not Dow's.

I(D)(5) Comment: In our view what was needed was a table of the range of daily or yearly consumption of the 40 foodstuffs in question for the various age ranges in the population, or at least a reference to where such a table can be easily located and accessed.

Agency Response: The exposure estimate provided in the February 15, 2002 Federal Register (EPA 2002b) reports *total* exposure to *all* sources of sulfuryl fluoride residues on foods and the resulting fluoride ion levels. A table of consumptions of the 40 foodstuffs in question would not add to an understanding of dietary exposure to sulfuryl fluoride and fluoride ion residues. The food consumption raw data used for the Agency's fluoride risk assessment was developed by the US Department of Agriculture (USDA 2000).

I(D)(6) Comment: DOW's reporting the data as a dose in terms of mg per kg bodyweight per day is not helpful without specifying the bodyweights for the ages involved.

Agency Response: Body weight data used in Dow's assessment reported in the Notice of Filing is included in the USDA database (USDA 2000). Likewise, the assessment

conducted by the EPA used the body weights data collected as part of the USDA food consumption survey. For converting the MCL to a mg/kg bw/day basis, the Agency used body weights derived from data reported in the "Third National Health and Nutrition Examination Survey" (CDC 2003). Reporting of estimated exposure in terms of mg/kg BW/day is standard practice and should be readily understandable by interested parties. The Agency sees no valid reason to change accepted practice at this time.

I(D)(7) Comment: We request that the US EPA insists that DOW present their data in the following clear and easily checkable steps:

Step 1. How many mg per kg in each food stuff, i.e., the tolerances.

Step 2 How many kg of each foodstuff consumed per age group (this should be reported as a range)

Step 3 The range of total mg per day consumed for each age range

Step 4 The average bodyweight for each age group

Step 5 The range of total dose in terms of mg per kg bodyweight per day for each age group.

Agency Response: The proposed tolerances are listed in February 15, 2002 Federal Register notice (commenter's Step 1). The DEEM model incorporates food consumption information from the USDA Continuing Surveys of Food Intakes by Individuals, including *all* consumption of the foods of interest. The DEEM software is built upon a food consumption database that incorporates the hierarchical recipe structure developed by the USDA to translate foods as eaten (e.g. apple pie) to the constituent crop commodities (e.g., apples, wheat, beet sugar, and so on), as well as their processed forms that might be ingredients in foods as eaten. This treatment of the data is well suited to calculating total dietary exposure to a chemical contaminant because it is designed to capture all the commodities that comprise foods as eaten. Listing the consumption for all of these individual commodities in their various forms would add no new information, and might in fact make it more difficult to interpret the information (commenter's Step 2). The exposure assessment submitted by Dow included estimated exposure to 23 population groups; the February 15, 2002 Federal Register notice reports only the population group with the highest estimated dietary exposure (commenter's Steps 3 and 5). Presumably, the other information would be available via an FOIA request. However, the exposure estimates would be lower than what was reported, and having them would provide no additional useful information. As per standard practice, estimated exposure is calculated in mg/kg BW/day, based upon the body weights reported in the USDA food consumption surveys. The food consumption data used in the DEEM model are provided in units of g/kg bw/day. Body weight is one of the data elements and is provided in the raw

USDA data file already cited. Body weights are reported for study participants, so that food consumption (and ultimately exposure) may be estimated using the actual consumption per kg bw for the consumption survey participants. Therefore, it is not necessary to provide average body weights (commenter's Step 4).

I(D)(8) Comment: We do not understand why DOW should restrict its concern here to children aged 0 to 9 months. Exposure to older children is also of concern especially young boys whose bones are growing very fast.

Agency Response: Rather than restricting concern to very young children less than 1 year of age, Dow is addressing a population group highlighted as being of interest in previous reports by other parties.

I(D)(9) Comment: Nor do we understand why the exposure is restricted to exposure from water. Regrettably pediatricians are still prescribing fluoride drops to babies and older children are exposed to fluoride through dental products, especially those who can't control their swallowing reflex.

Agency Response: Water is a potential source of exposure and Dow included this information in their submission, although the exposure assessment in the submission primarily addressed residues in food. The Agency's risk assessment addresses fluoride residues from sulfuryl fluoride, cryolite, background levels in food, concentrations in water, concentrations in air, and topical dental applications (e.g., dentifrices).

I(D)(10) Comment: However, DOW's statement that the fluoride exposure to young children up to 9 months, ranged up to 1.73 mg was not converted (unlike the mean values) to mg/kg/day. Had they done so using the same bodyweight of 10 kg, they would have found that the dose ranged up to 0.173 mg/kg/day. This figure of 0.173 mg/kg/day is OVER the EPA's MCG for fluoride (i.e., 0.114 mg/kg/day).

Agency Response: The USDA food consumption database emphasizes consumption of various foods, so the Agency decided that an assessment of exposure to residues in water was best accomplished using standard water consumption estimates. In an independent risk assessment for fluoride in water, the Agency employed standard estimates for water consumption and body weights. The results of this independent risk assessment show that age-group exposures to fluoride in water, although they greatly exceed exposures attributable to sulfuryl fluoride applications, do not exceed established safety standards. The exposure levels reported by the Dow and the Agency risk assessments are summarized in Tables 1 and 2. The MCLG of 0.114 mg/kg/day is based on an adult body weight of 70 kg. The body

weights for children are lower so that the MCLG adjusted for children's body weight is higher.

I(D)(11) Comment: In other words even taking the EPA's lax standards at their face value, DOW's own data indicate that some infants up to the age of 9 months are already being overexposed to fluoride. This should clearly rule out any further addition of fluoride to foodstuffs that might be fed to babies up to 9 months, which includes a number of the foodstuffs for which DOW is seeking tolerances.

Agency Response: The Agency's risk assessment indicates that the total exposures including that from the proposed uses of sulfuryl fluoride are within current guidelines. The exposure levels for fluoride and sulfuryl fluoride are summarized in Tables 1 and 2.

I(D)(12) Comment: DOW makes the classic mistake of dividing incremental exposure to fluoride (from their proposed action) to the existing background exposure, when what they should be doing is ADDING the incremental exposure (for various age groups) to the existing background exposure. What is of interest here is the TOTAL exposure to fluoride. This is what should be compared with the EPA's MCG of 0.114 mg/KGB/day (8 mg per day for a 70 kg adult or 1.14 mg/day for a 10 kg infant), as lax as that may be.

Agency Response: The Agency's risk assessment accounted additively for fluoride exposures from all sources for which there is reasonably reliable data, including sulfuryl fluoride pesticide applications, cryolite pesticide applications, naturally occurring levels in food, water, and air, and fluoride in dentifrices. The assessment qualitatively addressed other potential sources of fluoride exposure.

Table 1: SUMMARY OF FLUORIDE EXPOSURE AND RISK AS CALCULATED BY DOW AGROSCIENCES AND THE EPA IN mg/kg bw/day

	EPA				DOW
Population Group	Children <1	Children 1-2	Children 3-5	Children 6-12	Children 1-6
From Sulfuryl Fluoride	0.0005	0.0013	0.0012	0.0007	
From Cryolite	0.0009	0.0031	0.0020	0.0008	
Food Background	0.0093	0.0175	0.0149	0.0094	
Water	0.1424	0.0407	0.0338	0.0227	
Total Dietary	0.1532*	0.0626	0.0520*	0.0337*	0.002149
Tooth paste	0.0429	0.0231	0.0136	0.0075	
Air	0.0019	0.0020	0.0012	0.0007	
Total Non-Dietary	0.0448	0.0251	0.0148	0.0082	
Total	0.1980*	0.0877	0.0668*	0.0419*	0.002149
Weight adjusted MCLG in mg/KG/day	0.571	0.308	0.182	0.1	
Total % MCLG	35	28	37	42	2 **

* Slight difference in total due to rounding errors.
** MCLG converted to 0.1 mg/kg bw/day, the lowest value for the Children 1-2, 3-5, or 6-12. The Dow assessment reported exposure and risk for Children 1-6 only, but the EPA assessment reported for the three groups indicated. Therefore, a direct comparison is not possible, but it is not expected that exposure and risk for the overall group would exceed that for the sub-groups shown in this table.

Table 2: SUMMARY OF SULFURYL FLUORIDE EXPOSURE AND RISK AS CALCULATED BY DOW AGROSCIENCES AND THE EPA FOR A cPAD OF 0.003 mg/kg bw/day

	EPA				DOW
Population Group	Children <1	Children 1-2	Children 3-5	Children 6-12	Children 1-6
Exposure mg/kg bw/day	0.000002	0.000004	0.000004	0.000003	0.000106
% cPAD	<1	<1	<1	<1	4

The Dow assessment reported exposure and risk for Children 1-6 only, but the EPA assessment reported for the three groups indicated. Therefore, a direct comparison is not possible, but it is not expected that exposure and risk for the overall group would exceed that for the sub-groups shown in this table.

I(E) Lack of FDA approval

Comment: The US Food and Drug Administration has not approved the use of sulfuryl fluoride on walnuts and raisins.

Agency Response: FDA and EPA share authority for the implementation of the Federal Food, Drug, and Cosmetic Act (FFDCA). However, Congress explicitly delegated to EPA the authority to establish tolerances for pesticide residues in food. FDA does not approve or evaluate pesticide uses. FDA does have responsibility for monitoring the level of pesticides in the food supply.

I(F) Rationale for tolerances on raisins

Comment: The public has been offered no information for the basis of the four-fold increase of inorganic fluoride in or on raisins. Because of this, the public has been denied the right to submit relevant comments. The existing tolerance is expressed in terms of cryolite, not fluoride.

Agency Response: The Agency addressed the tolerance for fluoride on raisins in the proposed rule for sulfuryl fluoride (EPA 2001b). This proposed rule also explained the effect of cryolite residues on fluoride tolerances. The existing tolerance for cryolite on grapes (40CFR180.145) is in fact a tolerance for fluoride, because the approved analytical method for enforcement tests only for fluoride, and not cryolite. There is no analytical method for distinguishing between cryolite and sulfuryl fluoride as the source of inorganic fluoride in or on grapes or raisins, nor is there any toxicological reason to distinguish between such residues.

In order to assess compliance with the tolerances in 40CFR180.145, measured levels of fluoride in grapes are converted to cryolite equivalents by multiplying the concentration (in parts per million) of fluoride by a factor of 1.84 (molecular weight of cryolite divided by molecular weight of fluoride, divided by the number of fluoride atoms in cryolite; (210 amu) / (19 amu x 6) = 1.84). A tolerance for fluoride (55 ppm expressed as Cryolite) residue in or on raisins was proposed but has not yet been finalized (EPA 1997). The Agency is proposing a 30 ppm tolerance for fluoride (55 ppm cryolite divided by 1.84 conversion factor) that would adequately address residues from cryolite use on grapes, sulfuryl fluoride use on raisins, and background levels.

I(G) Warning labels on toothpaste

Comment: The Agency has previously stated “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." We find [this] response ... particularly unsatisfactory....There are significant populations in the US who are at risk from fluoride exposure simply because they do not have the ability to read the "explicit direction" on toothpaste products. The National Literacy Survey reported that approximately 44 million people scored in Level 1; 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. We are not aware of any toothpaste sold in the US that has warnings in any language other than English.

Agency Response: The US Food and Drug Administration is responsible for regulating fluoride in drugs and other products such as tooth paste to assure their safety. The FDA mandated warnings on fluoride toothpaste in 1997. The Agency's exposure assessment included exposures from fluoridated tooth paste based on data on actual exposures measured before the warning labels were instituted in 1997. To the extent that the warning labels are effective, the exposure assessment may overestimate the exposures resulting from the use of fluoridated tooth paste.

I(H) Government opinions other than EPA's

Comment: The Agency has not given enough consideration to the stated position against the fluoridation of water by the Union that represents EPA scientists considering that they are government employees who are directly involved with assessing the health effects of chemicals, and the Agency has given too much consideration to the statements by the Surgeon General in support of the fluoridation of water.

Agency Response: The issues raised by the spokespersons for the Agency union are being considered on their technical merits. The regulatory authority for making the policy decisions has been assigned to the Agency, and while the policy opinions of dissenting Agency scientists are respected, the union scientists do not speak for the Agency. The Agency cited the Surgeon General's position as background information. The Agency conducted its own risk assessment of the proposed tolerances for sulfuryl fluoride and fluoride residues and did not rely solely on the Surgeon General's position on water fluoridation.

II Potential Toxic Effects from Exposure to Sulfuryl Fluoride

II(A) Effect on the thyroid gland

Comment: EPA published its risk assessment on sulfuryl fluoride in a September 5, 2001, Federal Register [OPP-301166; FRL-6799-6] and noted: chronic (1-2 year) inhalation studies follicular cell hypertrophy in the thyroid gland were observed in dogs and mice. In subchronic (90-day) inhalation studies follicular cell hypertrophy was noted in the thyroid gland

of mice. In 2-week inhalation studies intermittent tremors and tetany was noted in dogs. Hypoparathyroidism is one of the known causes of tetany.

Agency Response: The Agency agrees that in many animals studies, toxic effects were seen in other organs such as the thyroid, lung and kidney. However, the major site of toxicity is the brain and nervous system. The relationship between thyroid hypertrophy in the sulfuryl fluoride studies and effects on the parathyroid mentioned by the commenter are not clear.

II(B) Effect on white matter in the brain

Comment: Sulfuryl fluoride has impacts on the brain, particularly vacuolation of the white matter. Young children may be particularly susceptible to the toxic effects of fluoride on developing white matter. EPA's risk assessment of sulfuryl fluoride (EPA 2001b) discussed adverse effect on the brain and other organs. EPA noted that brain white matter was a major target in several of the animal studies (rats, dogs, rabbits, mice). EPA noted in its Sulfuryl fluoride RED document of 1992 (EPA 1992): "Very young children may be more susceptible than adults to sulfuryl fluoride neurotoxicity because the developing brain may be more vulnerable to chemical injury (p. 15)." According to Filley (2001) white matter development in young children differs "significantly" from gray matter: "Gray matter and white matter differ significantly in their patterns of development. Nerve cells begin to develop early in gestation, and the entire complement of central nervous system neurons is formed before birth (Nolte, 1999). The embryonic development of gray matter involves continual pruning of inessential neurons by programmed cell death and the simultaneous establishment of synaptic contacts between the ones that remain (Kandel, et al., 2000). In contrast, the white matter does not begin to form until the middle trimester of gestation (Nolte, 1999). The process is only partially completed at birth, and even by 2 years of age, it is still just 90% complete (Byrd, et al., 1993). The remainder of myelination then requires many years (Yakovlev and Lecours, 1967; Klingberg, et al., 1999, Fig. 3-1). The exact duration of this process is unclear, but recent evidence from a series of normal brains studied postmortem suggests that myelination proceeds throughout the end of the 6th decade (Benes, et al., 1994; p 33)." Of some concern is the fact that when the mottling of the teeth was observed (a known effect of the free fluoride ion) in sulfuryl fluoride animal experiments, vacuolation of the white matter of the brain was found also. For example: RED Facts (1992). "Administration of sulfuryl fluoride by inhalation for 6 hours/day for 90 days to rabbits at doses of 30, 100, or 300 ppm (11, 38, or 114 mg/kg/day) resulted in similar signs of toxicity although brain lesions occurred at lower levels. The NOEL was 30 ppm. The LEL was 100 ppm based on decreased body weights, decreased liver weight and mottling of the teeth (M,F), and microscopic vacuolation of the white matter of

the brain (F). In addition, at 300 ppm (M,F) there was alveolar histiocytosis, histologic changes in the nasal epithelium, and microscopic malacia to vacuolation of the internal and external capsules, putamen, and globus pallidus of the brain (MRID 408909-01)." In a search for "white matter" at the EPA Office of Pesticide Programs search site (http://www.epa.gov/pesticides/search.htm) only six pesticides were cited, four of these were fluorinated: Sulfuryl fluoride, Fluazinam (an organofluorine pesticide); Bromethalin (an organofluorine rodenticide); and Chlorfenapyr (an organofluorine pesticide). The other two were Hexachlorophene and Bensulfide. For Sulfuryl fluoride and the organofluorine pesticides cited above (Fluazinam, Bromethalin, Chlorfenapyr) animal studies reveal a disruption of the myelin. According to Filley (2001): "The clinical significance of the sequence of brain myelination has long been debated. Flechsig (1901) first speculated that myelination reflected functional maturity of the cerebral areas involved, and the observations of Yakovlev and Lecours (1967) supported this idea. However, the relative importance of white matter versus gray matter development has not been entirely clear. More recently, neuroadiologists have increasingly interpreted delayed myelination on MRI as indicating a neurologic abnormality (Byrd, et al., 1993). In clinical studies, there have been many suggestions that intact white matter contributes to cognitive development. In MRI studies of children with congenital hydrocephalus, for example, cognitive impairment has been correlated with delayed myelination (van der Knapp, et al., 1991) and with reduced size of the corpus callosum and other cerebral white matter tracts (Fletcher, et al., 1992). "One of the intriguing notions to arise from study of this area is the possibility that the acquisition of the mature personality in young adulthood depends to a substantial extent on frontal lobe myelination (Filey, 1998). Normal personality development requires the acquisition of traits such as reasoning, impulse control, and judgement that are traditionally associated with frontal lobe function. Because myelination of the frontal lobe occurs quite late in development - at a time when gray matter is relatively stable - the arrival of the adult personality may require the completion of this myelogenetic phase. Moreover, subtle modifications in personality with later adulthood may conceivably relate to continuing myelination in the 5th and 6th decades (Benes, et al., 1994). The understanding of these potential correlations could help establish a foundation for considering the neural organization of personality throughout the life span (pp. 33-34). "A wide range of syndromes involving both cognitive decline and emotional dysfunction has been linked with structural involvement of the brain white matter. Clinical observations of patients with white matter disorders generate the essential data to support this claim. Much additional information has been gathered with the help of magnetic resonance imaging (MRI), a powerful neuroimaging technique that has provided unprecedented views of the white matter and permitted correlations with neurobehavioural syndromes. These syndromes may equal or surpass in clinical importance the various deficits in motor and sensory function of white matter

lesions well known from classical neurology. Whereas caution is still appropriate in assessing the neurobehavioural importance of white matter changes, it is no longer possible to ignore them. (pp. 3-4). “Early clinical features of cerebral white matter involvement typically include confusion, inattention, memory dysfunction, and personality change. Measures of attention, cognitive speed, memory retrieval, visuospatial skills, and executive function are likely to be most sensitive to subtle white matter dysfunction. In contrast to disorders primarily involving the cortex, higher cerebral functions such as language, praxis, and perception are uncommonly affected; the usual preservation of language is an important point because affected individuals may display normal language and thus appear cognitively intact, when in fact they have significant deficits in other neurobehavioral domains (p 249).” If we take into consideration both Varner, et al. (1998) and the impacts on white matter discussed above a simple hypothesis suggests itself. Fluorine is particularly threatening to the brain, if it can be carried there, either in the form of a metal fluoride complex (e.g. AlF3) or as a fluorinated substance (e.g., sulfuryl fluoride or one of the organofluorines noted above). It might turn out that it is the intact complex or the intact molecule which causes the problem. But it also might turn out that it is the release of the free fluoride ion once the substance has got into the brain that causes the problem. Or both. Clearly a much more thoughtful and comprehensive analysis of this issue demands the attention of the regulatory agencies before they approve the use of sulfuryl fluoride in or on foodstuffs which could be consumed by humans, especially by young children. With so much uncertainty in this area it would be cavalier in our view to ascribe a tolerance which is considered “safe” or acceptable. At this stage in our knowledge the only appropriate approach is to assume a safety level of zero for sulfuryl fluoride on any foodstuff that is going to be consumed by infants or young children. The value of zero can be assured by not permitting the use of sulfuryl fluoride as a fumigant on these foodstuffs.

Agency Response: The Agency agrees that sulfuryl fluoride (SF) is a neurotoxic pesticide. The chronic reference dose or RFD is based on a NOAEL of 30 ppm or 8.5 mg/kg/day in a 90 day rabbit inhalation study. The next highest dose of 100 ppm or 28 mg/kg/day caused vacuolation of the white matter in the brains of the females and decreased body weights, decreased liver weights and dental fluorosis in males and females. The RFD is based on the NOAEL of 8.5 mg/kg with the usual 100X uncertainty factor, another 3X uncertainty factor for the use of a subchronic study to calculate a chronic reference dose, and an additional factor of 10X FQPA safety factor because a developmental neurotoxicity study is needed because of the known neurotoxic effects found in adult animal studies. Thus the total composite uncertainty factor is 3000X. In many animals studies, toxic effects were seen in other organs such as the thyroid, lung and kidney. However, the major site of toxicity is the brain and nervous system. The relationship between thyroid hypertrophy in the SF studies and effects on the parathyroid mentioned by the Petitioner are not clear. The only currently

available studies characterizing white matter lesions in the central nervous system resulting from exposure to sulfuryl fluoride are in adult organisms. To take into consideration the absence of data on which to assess the relative susceptibility of the developing organism, the additional uncertainty factor of 10 has been included in the calculation of the reference dose. The Agency agrees that lesions of the white matter of the central nervous system, such as those observed in mature organisms exposed to sulfuryl fluoride, are adverse effects and the level of exposure associated with such adverse effects has been taken into consideration in the selection of a critical effect for the reference dose for sulfuryl fluoride. However, there is no currently available data supporting the validity of the proposed hypothesis that exposure to sulfuryl fluoride increases the concentration of metal fluoride complexes in the brain, or that exposure to such metal fluoride complexes or free fluoride is selectively associated with lesions of the white matter. Moreover, there is no evidence available to indicate that developmental exposure to sulfuryl fluoride or metal fluoride complexes alters brain development. The absence of adequate data on development neurotoxicity is taken into consideration by including an additional uncertainty factor of 10 in the calculation of the reference dose for sulfuryl fluoride. The Agency establishes pesticide residue tolerances in accordance with the statutory requirements of the FFDCA which provides that tolerances are to be established using a standard of reasonable certainty of no human harm, not a standard of absolute certainty.

II(C) Acute toxicity to workers and bystanders.

Comment: Sulfuryl fluoride is acutely toxic and could pose problems for fumigators and those who live near the warehouses where the fumigant is used. Dow AgroSciences states that, based on the results of the existing developmental toxicity data and the low exposure potential that the sulfuryl fluoride use patterns represent, Dow AgroSciences does not agree that additional developmental toxicity data is needed for sulfuryl fluoride.

Agency Response: The Agency's risk assessment evaluated the safety to these groups and concluded that there is an adequate margin of safety (Dellarco 2004). As a condition of registration, DOW will be required to conduct and submit a developmental neurotoxicity study.

III Toxic Effects from Exposure to Fluoride

III(A) Adequacy of dental fluorosis as an end point for fluoride safety assessments.

Comment: Frequently fluoridation promoters dismiss fluorosis as merely a "cosmetic" effect. In our view, this is simply a political maneuver to protect the fluoridation program at all

costs. Paraphrasing what one commentator said about this, it is like describing the blue line that appears on the gum in some cases of lead poisoning as a merely a “cosmetic effect.” For a scientist, both the blue line on the gum in the case of lead poisoning and the white or colored specks on the tooth enamel in the case of fluoride exposure, is the first visible sign that the toxic substance in question has had its first visible toxic effect on the body.

Agency Response: In establishing the current MCL and SMCL for fluoride, the Agency stated that it does not consider moderate to severe dental fluorosis (also known as objectionally dental fluorosis) to be an adverse health effect. The Agency believes that the current evidence indicating that dental fluorosis is more than a cosmetic effect is not sufficiently persuasive to warrant regulation as an adverse health effect under the Federal Food, Drug, and Cosmetic Act. Therefore, at this time, based on the information available to the Agency, EPA is not concluding that the dental fluorosis associated with fluoride exposure is an adverse health effect under the FFDCA. However, the Agency does believe that dental fluorosis is an effect that should be considered under the unreasonable adverse effects standard of the Federal Insecticide, Fungicide, and Rodenticide Act. As a result, in reaching its regulatory decision for this action, the Agency has considered the risks of dental fluorosis along with the benefits of registering sulfuryl fluoride as an alternative to methyl bromide, a compound that is known to deplete the ozone layer.

III(B) Toxicology end points other than dental fluorosis.

Comment: In stating that the only organs of interest are the bone and teeth, the Agency has overlooked studies showing the effects of fluoride on the pineal gland, the thyroid gland, the central nervous system, bone fractures, and g-proteins. The EPA cites the following agencies to support their claim that the only two organs of interest are the bone and the teeth: “there have been numerous independent evaluations of the toxicity of fluoride: U.S. Public Health Service (DHHS 1991), Environmental Protection Agency (EPA 1985), National Academy of Science (NRC 1977, NRC 1993) and Agency for Toxic Substances and Disease Registry (ATSDR 1993). All of these reviews have indicated that the critical adverse effects, i.e., the endpoints to regulate, from fluoride ingestion are the effects on the bone and teeth.” FAN states that all the above cited reviews are outdated with respect to health issues. All these reviews have overlooked key studies on the pineal gland, thyroid gland, the central nervous system, bone fracture and G-proteins that FAN has cited in their EUP Hearing request. There is no evidence of safety regarding fluoride in the body in terms of long term effects.

Agency Response: The Agency has reviewed the papers cited by FAN and each of these organ systems is discussed below.

III(B)(1) Thyroid

Comment: Fluoride has adverse effects on the thyroid. Several authors have postulated that goitrous states may be attributed to fluoride intake and conversely that this element can be used in the treatment of hyperthyroidism. In addition, fluorine could have a mass-action effect on the uptake of iodine. In the past sodium fluoride tablets have actually been given to patients to relieve the symptoms of hyperthyroidism (Galletti and Joyet, 1958). Independent observers have argued that if fluoride can lower the activity of the thyroid gland of someone suffering from an over active thyroid gland, it might also reduce the activity of a normal thyroid gland and thus produce symptoms of hypo-thyroidism, or it might also reduce the activity of a normal thyroid gland. Millions of people suffer from hypothyroidism. According to the DHHS the range of doses adults receive who live in optimally fluoridated areas is 1.6 to 6.6 mg/day (DHHS 1991). This range overlaps the range of doses used in the Galletti and Joyet (1958) treatment regime for hyperthyroidism (2.3 - 4.5 mg/day). Bachinskii, et al. (1985) treated 123 people with elevated levels of fluoride (2.3 ppm) in their drinking water. He found that this treatment elevated TSH production, decreased T3 levels, and increased the uptake of radioactive iodide into the thyroid gland. Of the 123 people examined, 47 had normal thyroid function, 43 were hyperthyroid, and 33 were hypothyroid. One comment from a 51 year old man claimed that overexposure to fluoride in bottled water caused his thyroid to stop functioning and that TSH levels were 4 to 5 times normal levels. He claimed that allowing the proposed uses of sulfuryl fluoride would cause an epidemic of fluoride poisoning. Fluoride based drugs are currently given to patients to relieve hyperthyroid conditions. Scientists believe that fluoride can depress thyroid functions with levels as low as 2.5 mg/day. In the recently released book Thyroid Power (Shames 2002) the authors state that a major environmental trigger of low thyroid (now at epidemic levels in the US) is likely to be the fluoride added to municipal water supplies. Is it your wish that more people should be plagued with chronic fatigue syndrome?

Agency Response: The Agency has reviewed the papers cited by the Fluoride Action Network that deal with the effects of fluoride on thyroid functioning. The papers submitted by FAN do not convince EPA that fluoride produces significant effects on the thyroid because of study design and report deficiencies (Baetcke, et al. 2003).

III(B)(2) Endocrine disruptor. Impact on g-proteins.

Comment: Fluoride is a hormone disruptor. Fluoride mimics the action of many water-soluble hormones by interacting with G-proteins, which transmit hormonal messages across cell membranes. Fluoride in the presence of trace amounts of aluminum is capable of switching on the G-protein signaling mechanism used for the transmission of signals which

arrive at the outside of cells and result in changed activity inside the cell. These messengers include many water soluble hormones, some neurotransmitters, and some growth factors. It would appear that AlF_4^- can sit in the pocket on the G-protein that is normally occupied by the third phosphate of guanosine triphosphate (GTP). Normally the G-protein is in the "off" position when guanosine diphosphate (GDP) occupies the site; and in the "on" position when GTP occupies the site. However, when the site is occupied by GDP and AlF_4^- , it looks to the G-protein as if GTP is present, and is thus switched "on." The GDP (off) - GTP (on) switch is normally triggered when a messenger arrives at the receptor on the outside of the membrane. With AlF_4^- present the G-protein is switched on without the messenger. It is thus activated without the arrival of the normal messenger. The activated G-protein in turn activates the enzyme (adenyl cyclase) which converts ATP to cyclic AMP, which in turn excites a cascade mechanism resulting in changes inside the cell. Fluoride could interfere with many other hormones. As this G-protein signal is a key step in the mechanism of action of many water soluble hormones, a number of neurotransmitters and growth factors, this interference by fluoride, in the presence of a trace amount of aluminum, is very worrying indeed. If one goes to the PubMed web and enters fluoride and G-proteins one gets about 800 hits. An important review of this issue and a good starting point for many of these references is provided by Strunecka and Patocka (1999). It is surprising to us that Dow is unaware of this serious biochemical role of fluoride. Drs. Richard and Karilee Shames, authors of Thyroid Power (Shames 2002) suggest that in a misguided attempt to help curb cavities in young children, we may be unwittingly poisoning our collective endocrine systems.

Agency Response: The effects of Aluminum-fluoride complexes on G-protein and the enzymes associated with G-protein activation have only been demonstrated in vitro or when injected directly into the brain of laboratory animals. Thus, many significant questions still need to be addressed regarding biological availability and relative affinity for cellular and subcellular sites following human exposure (Baetcke, et al. 2003). The Agency has considered the new information on fluoride, and is not convinced that the data support the statement that fluoride is an endocrine disruptor. Dietary exposure to fluoride has not been shown conclusively to result in effects on reproduction, development or on hormones (Baetcke, et al. 2003)

III(B)(3) Fluoride affects the pineal gland

Comment: Fluoride accumulates in the pineal gland and may reduce melatonin production. The researcher Jennifer Luke discovered that the pineal gland is not protected by the blood brain barrier, has a high diffusion rate of blood and that it was also a calcifying tissue (it lays down the same crystals of calcium hydroxy apatite as are produced in the teeth and

bones). Eleven corpses of elderly people were analyzed and it was determined that the levels of fluoride in the crystals in the pineal gland were extremely high (a mean of about 9000 ppm). This research was a PhD thesis sent to EPA and published in Caries Research (Luke 2001). The four step process from tryptophan involves production of the neurotransmitter serotonin. It is conceivable that the production of this important substance is also lowered by the high concentration of fluoride – a well known enzyme inhibitor – in the pineal gland.

Agency Response: The effects of fluoride on the pineal gland have been reported only by one author in one study. The author states that the interpretation that depressed melatonin levels in the blood may hasten the onset of puberty is "conjectural". Because animal data on the effects of fluoride and the pineal gland comes from a single study with limited number of animals with only two dose levels, these findings should be confirmed by other laboratory studies. Also, the single report by the same author (J. Luke) on fluoride deposition in the aged human pineal gland from cadavers provides no data associating fluoride exposure with adverse effects in humans (Baetcke, et al. 2003).

III(B)(4) Neurotoxicity and effects on white matter of the brain

Comment: The Agency's own risk assessment discussed effects on the brain (EPA 2001b). FAN rejects the Agency's discussion of the Varner study in the EUP final rule. FAN maintains that the Agency has underestimated the significance of the Varner study as it relates to the neurotoxicity of fluoride. FAN cites the book "The Behavioral Neurology of White Matter" (Filley, 2001) and cites a paragraph from that book discussing the white matter in the brain. They state that the Agency has neglected to look into the impact of fluoride on G-proteins, especially fluoride in the presence of Al. Another commenter wrote "For many years I have been concerned about the growing presence of fluoride in our food supply as well as the other existing sources of fluoride that we are all exposed to daily. I feel that the US government has done little serious research on fluoride, and yet continues to blindly promote water fluoridation. I do not want to see yet another source added to this list, especially one that appears to be extremely toxic and causes brain damage in animals. The increasing prevalence of brain disorders in children such as ADD and ADHD is enough to question additional exposures to these types of chemicals."

Agency Response: The Agency's review of the data on the effect of fluoride on White Matter and G-proteins is summarized above in sections II(B) and III(B)(2). No data are available that suggest a direct causality between exposure to low levels of fluoride and brain disorders such as ADD, ADHD and seizures. The suggestion of an association made by the commenter is speculative and conjectural at this time.

III(B)(5) Fluoride, aluminum, and Alzheimer's disease.

Comment: Fluoride may cause or contribute to Alzheimer's disease by facilitating the movement of aluminum across the blood-brain barrier. Al and fluoride have adverse effects on the brain and fluoride enables the aluminum to move into the brain, across the blood-brain barrier. This increases the damage to the brain from aluminum. Rats fed either aluminum fluoride or sodium fluoride at a fluoride level of 1 ppm in their drinking water led to kidney damage, brain damage, a greater uptake of aluminum into the brain and the occurrence of beta amyloid plaques that are associated with Alzheimers disease. FAN rejects the Agency's discussion of the Varner study (Varner 1998) in the EUP final rule (EPA 2002a). FAN maintains that the Agency underestimated the significance of the Varner study as it relates to the neurotoxicity of fluoride. Fluoride facilitated aluminum crossing the blood brain barrier, and fluoride may contribute to Alzheimer's disease. More fluoride should not be added to the food supply, especially until the results of the Varner study are addressed. EPA should have listed all the pesticides that adversely affect the brain. FAN cites the book "The Behavioral Neurology of White Matter" (Filley 2001) and cites paragraphs from that book discussing the white matter in the brain. Since the middle 1990s there have been several important studies which have probed fluoride's possible impact on the brain. Mullenix (1995) demonstrated that rats treated prenatally with fluoride showed behavior patterns associated with hyperactivity and rats dosed after birth showed hypoactivity. Guan, et al. (1998) showed that membrane lipids in rat brain were impacted by chronic fluorosis. Several studies in China (Lee, et al. 1985; Zhao, et al. 1996; and Lu, et al. 2000) have shown the possible impact of high background fluoride (possibly in the presence of low iodide, Zhao 1998) on children's IQ. One of those that we have examined is the work by Zhao, et al. (1996) who found an approximate 5-10 point IQ deficit in children from a community with water containing 4 ppm natural fluoride compared to one containing 1 ppm. Since we fluoridate at 1 ppm, and the EPA's MCLG for fluoride is 4 ppm, this paper is of concern. Varner et al (1998) exposed rats to fluoride in their drinking water for one year. What was remarkable about this work is how low the concentrations were that caused damage. Both AlF_3 (aluminum fluoride) and NaF (sodium fluoride) given to the animals at the level of 1 ppm fluoride (the same level generally used in public drinking water) in their doubly distilled de-ionized drinking water caused both kidney and brain damage, an accumulation of aluminum into the brain and the formation of amyloid plagues which are associated with Alzheimer's disease. Apparently, this is the third time that Isaacson and his co-workers have found effects on the brain at these low levels. As a result of Varner's work aluminum fluoride was recently nominated by the Environmental Protection Agency and National Institute of Environmental Health Sciences for testing by the National Toxicology Program. According to the EPA and NIEHS, aluminum fluoride is a "drinking water

contaminant" with "known neurotoxicity" and a "high health research priority." If fluoride is added to water which contains aluminum, then aluminum fluoride complexes will form (BNA 2000, see http://www.fluoridealert.org/alum-fluoride.htm). We would add that if some of the fruits and vegetables with the fluoride residues proposed in DOW's application were cooked in aluminum saucepans, this too could lead to the formation of aluminum fluoride complexes.

Agency Response: The epidemiological and animal literature is insufficient to support a convincing association of fluoride exposure and Alzheimer's disease and impaired mental functioning. The Agency is not aware of any studies that provide a direct link between exposure to fluoride and Alzheimer's disease. In addition, one of the authors of the Varner (1998) study has indicated that the results of the study do not support a conclusion that aluminum or fluoride selectively damage the brain or that these compounds cause Alzheimer's Disease. The suggestion of an association made by the commenter is speculative and conjectural at this time (also see McDonagh 2000).

III(B)(6) Fertility and reproductive effects

Comment: Exposure to fluoride results in many fertility and reproductive effects in humans and animals including lowered fertility, lowered testosterone levels, lowered sperm quality, early puberty, and decreased birth weight. The Luke study including the second part of the Luke study needs to be considered, i.e., the production of melatonin in Mongolian gerbils. Fluoride lowers the production of melatonin in animal studies in a study conducted by Luke. Animals showed signs of reaching puberty earlier than controls. Luke cited a finding in the health study in the Newburgh-Kingston fluoridation trial (which was not thought significant at the time) that on average the girls in the Newburgh started menstruating 5 months earlier than the non-fluoridated Kingston girls (Schlessinger, et al. 1956). One of the risks we may be taking by exposing the whole population to fluoride is interfering with delicate regulatory timing processes, from the onset of puberty to the aging process. Animals showed signs of reaching puberty earlier than controls. Freni (1994) found lowered fertility in US counties which have fluoride levels at 3 ppm or higher. There has been some criticism of Freni's methodology, but we have not seen any of it which has been peer reviewed and published. Should Freni's finding be substantiated it would challenge the notion that 4 ppm is protective with respect to this serious outcome. Sushella and Jethanandani (1996) found lowered testosterone levels in patients with skeletal fluorosis in India. In a series of animal experiments both Sushella, Chinoy and others have found that fluoride lowers the testosterone levels and the production and quality of sperm (Chinoy and Sequeira, 1989; Chinoy, et al., 1991; Chinoy and Narayana, 1994; Kumar and Sushella, 1994).

Agency Response: The Agency has reviewed the papers cited by the Fluoride Action

Network that deal with the effects of fluoride on reproductive function, and considers the evidence to be insufficient to establish a causal link between fluoride exposure and effects on reproductive function in humans (Baetcke, et al. 2003). The human literature suffers from poorly designed studies and/or inadequate sampling. Although a few papers in the literature report adverse effects on reproduction in animal studies, these effects have not been reproduced by other laboratories, including well conducted reproductive studies in laboratory animals carried out by the US Food and Drug Administration (not cited by FAN). The Freni (1994) study is found to be of poor quality (Baetcke, et al. 2003). One comment cited the fluoridated water results in earlier menstruation in communities with fluoridated water (Newburgh-Kingston caries-fluoride study). However, the authors of the Newburgh-Kingston study concluded that "No differences of medical significance could be found between the two groups of children; thus further evidence was added to that already available on the safety of water fluoridation." The Newburgh studies (Ast and Chase, 1953; Ast, et al., 1956) were considered by the 1993 NAS review and thus do not provide new information on fluoride. Luke stated that fluoride may result in an early onset of puberty in treated gerbils but stressed that these findings were preliminary and this interpretation was conjectural. The Agency agrees with Luke that no firm conclusions should be drawn from this gerbil study. Furthermore, FDA did not observe an effect on puberty in their developmental and reproductive studies in rats (Collins, et al. 2001; Sprando 1997). The Agency has now considered the report by Susheela AK, Jethanandani P (1996). This is an epidemiological study comparing testosterone levels in 3 groups: fluorosis patients with 3.9 ppm F in their water, controls with high F in their water (4.5 ppm) and controls with low F in their water. (0.5 ppm). According to the authors, fluorosis patients had the lowest serum testosterone, with the high water F controls. However, confounding factors (e.g., age, diet, health status, exposure to other chemicals) were not accounted for that could affect testosterone levels. In the study by Chinoy, et al. (1991) direct injection into the vas deferens was used which is not a relevant route of human exposure, and thus should not be used for dose-effect extrapolation. The study by Chinoy and Narayana (1994) only provided in vitro data which can not be used for dose-effect extrapolation. The report by Kumar and Sushella (1994) did not demonstrate that oral exposure to fluoride at a relatively high dose (4.5 mg/kg bw) can lead to abnormalities in spermatids and epididymal spermatozoa of rabbits. Only one dose was used. Also, insufficient information on methods and lack of data on the treatment of controls are weaknesses in the report. It should be stressed that there are several studies conducted by other investigators that have not been able to reproduce the reproductive findings reported in these studies. The US Food and Administration conducted a multigeneration study in rats (Collins 2001). In this study, the effects of sodium fluoride ingestion at 0, 25, 100, 175 or 250 ppm in drinking water were measured in rats throughout three generations, and no cumulative effects on reproduction

were observed. FDA also reported (Sprando, et al. 1997) that sodium fluoride did not affect spermatogenesis and endocrine function (LH, FSH and serum testosterone were measured) in P and F1 generation male rats exposed in their drinking water at one of four concentrations (25, 100, 175, 250 ppm). Li, et al. (1987) did not find any spermatogenic influence of sodium fluoride (NaF) by means of the sperm morphology test when mice were intubated up to a maximally tolerated dose of NaF (70 mg/kg).

III(B)(7) Carcinogenicity

Comment: The likelihood of fluoride acting as a genetic cause of cancer must be considered. Although NTP found no increased cancers in the mice study, they found a dose related increase in bone cancer (osteosarcoma) in the male rats. They described this as "equivocal evidence of carcinogenicity." A national cancer survey (the SEER report [Ries et. al 2003]) found a greater increase in osteosarcomas in young males in fluoridated areas. However, Hoover, et al. (DHHS, 1991) from the National Cancer Institute downplayed these findings based on the fact that the cancer incidences were not related to the duration of exposure. In 1992 Cohn found an increase in osteosarcoma in fluoridated areas in NJ. In three counties he found nearly a seven fold incidence of osteosarcoma in young males in fluoridated towns compared to non-fluoridated ones. There was little difference in the rates for females. We would also note that the osteosarcomas found in the NTP study may not be the only cancers found in this study. Some cancers were removed in a controversial review process (Marcus, 1990).

Agency Response: The possibility that fluoride might increase the cancer risk was raised in a series of reports which were considered by the 1993 NRC. Additionally, the York Review has conducted a more recent evaluation of the literature and found that the epidemiologic literature falls short of establishing a causal association of increased cancer and exposure to fluoride in humans. The National Toxicology Program (1990) considered their own results as equivocal evidence of carcinogenicity. There is no new information that convinces EPA that there is a need to depart from OPP's use of the current Agency MCLG/MCL in pesticide risk assessments at this time.

III(B)(8) Effects of fluoride on bone

Comment: Some population subsets may be unusually susceptible to fluoride toxic effects such as nonvertebral fractures with postmenopausal osteoporosis. We are fortunate to have some data from high dose human experiments. One of the first was by Riggs, et al. (1990). There have been several others (Headlund & Gallagher, 1989; Gutteridge, et al. 2002; Bayley, et al., 1990; Riggs, et al. 1990) gave 34 mg of fluoride per day for 2-4 years to elderly

patients suffering from osteoporosis to see if the fluoride would reverse the loss of bone mineral density which characterizes this disease, and by so doing reduce the incidence of hip fracture. The authors did find an increase bone mineral density in the patients but at the same time, they found that the fluoride made the bones more brittle and more subject to breakage via torsional stress. That such treatments have led to an increase in hip fractures, not a decrease, as hoped and anticipated, provides a highly significant data point. It clearly raises the question that if relatively high doses over a short period of time makes bones more brittle to fracture, what about lower doses over much longer periods of time? Li, et al. (2001) looked at hip fracture rates in elderly residents in six Chinese villages with different levels of fluoride in their well water. They determined a relative risk ratio for each of six villages taking the level of hip fractures in the village with 1 ppm as their reference. While they found little difference in the hip fracture rates in the villages less than 1 ppm, they found that the rates almost doubled when the levels of fluoride went above 1.5 ppm and tripled when they went over 4.5 ppm. This apparent dose response adds a great deal of weight to this ecological study. The doubling of the hip fracture rates above 1.5 ppm and the tripling of the hip fracture rates at levels over 4.5 ppm, puts into serious question the safety of the US EPA MCLG of 4 ppm. Alarcon-Herrera, et al. (2001) in a study conducted in Mexico found a linear correlation between the severity of dental fluorosis in both children and adults and the incidence of bone fracture. What about 70 year exposure to a dose of 1.6-6.6 mg per day, that Americans living in optimally fluoridated communities may be exposed to according to the DHHS (1991). Since 1990 there have been about 20 investigations into a possible association between living in fluoridated communities and hip fracture in the elderly. Just over half have found a greater incidence of hip fracture in the fluoridated communities. And what about the US EPA's MCLG of 8 mg per day, deemed to provide “protection from any known or anticipated adverse health effects”? Would such a MCLG protect against increased hip fracture? The earliest clinical symptoms of skeletal fluorosis are identical to the early symptoms of oestoarthritis and other forms of arthritis. With over 40 million Americans suffering from various forms of arthritis, the possibility that fluoride may be causing osteoarthritis or exacerbating it, becomes a very important question. This is especially so since the cause of osteoarthritis has not been identified; it is usually explained as being part of the aging process. We have to ask whether part of this “aging process” is the steady accumulation of fluoride in our bones.

Agency Response: The Agency has now considered the new information on hip fractures since the 1993 NRC report (National Research Council, 1993) The Agency has found the results of the Li, et al. (2001) study cited by the Fluoride Action Network to be inconclusive due to inadequate exposure assessment, potential biases associated with misclassification of exposure, the failure to examine fractures other than hip separately, and limited statistical analysis found in this report. The Alarcon-Herrera, et al. (2001) paper was also found to be

inconclusive. The report shows some evidence of non-traumatic fractures in children associated with the two highest fluoride levels. But, the two highest levels occurred only in rural areas where children are likely to be more active out-of-doors where rough and tumble play might lead to fractures without any immediate cause being apparent. The authors do not mention this important confounder. It also appears likely that exposure to other sources of fluoride may have influenced the results of this study. In addition, mobility within the valley could have led to exposure misclassification. The occurrence of 7% fluorosis in the lowest exposure group strongly suggest this possibility. Therefore, it is not possible to determine, from this study, what the contribution of fluoride in drinking water is to increasing risk for non-traumatic fractures. Thus, the articles cited by FAN do not convince EPA that there is a need to depart from OPP's use of the current Agency MCLG/MCL in pesticide risk assessments at this time. When the NAS review is available, the Agency will revisit this conclusion. (Baetcke, et al. 2003)

III(B)(9) Juvenile arthritis

Comment: Juvenile arthritis is the number one acquired autoimmune disease for US children under the age of 17. They have clearly already absorbed too much fluoride from their food, air and water.

Agency Response: There is no data demonstrating a relationship between low levels of fluoride exposure and juvenile arthritis. The suggestion of an association made by the commenter is speculative and conjectural at this time**.**

III(B)(10) Renal toxicity

Comment: Varner, et al. (1998) exposed rats to fluoride in their drinking water for one year. What was remarkable about this work is how low the concentrations were that caused damage. Both AlF_3 (aluminum fluoride) and NaF (sodium fluoride) given to the animals at the level of 1 ppm fluoride (the same level generally used in public drinking water) in their doubly distilled de-ionized drinking water caused both kidney and brain damage....

Agency Response: Water containing high concentrations of fluoride has been shown to be acutely toxic to the kidneys in animal studies. However, several large community-based epidemiological studies have been conducted and report no increased renal disease in humans after long term exposure to drinking water with fluoride levels up to 8 mg/L (National Research Council 1993). The Varner et al. (1998) study found subtle morphological changes in the rat kidney after a 52 week exposure of nine rats to double distilled water containing 2.1 ppm fluoride anion from sodium fluoride. It should be noted that normal aging in the rat leads to an increase in kidney pathology. Thus, before such rat data are extrapolated to estimate

human risk, it is important to distinguish the renal effects caused by fluoride exposure from those that occur during the normal aging process. Furthermore, the exposure conditions in the Varner et al. study make it difficult to relate the observed effects to specific exposure levels to fluoride anion or aluminum trifluoride. The levels of fluoride and aluminum in the diet were not accounted for in this study and therefore the total exposure levels are not known.

III(B)(11) Allergen

Comment: One individual claimed to be allergic to fluoride.

Agency Response: No description of symptoms, scientific argument or documentation accompanied this claim. NRC (1993) reviewed the limited animal and human data in the literature on sodium fluoride-related hypersensitivity reactions and concluded that "the findings should be disregarded for the following reasons: (1) insufficient clinical and laboratory evidence of allergy or intolerance to fluorides used in fluoridation of community water, and (2) no evidence of immunologically mediated reactions in a review of the reported allergic reactions. One additional undocumented claim does not significantly challenge the validity of the NRC conclusion.

III(B)(12) Premature aging

Comment: One comment stated: "Water at 0.3 ppm causes me skin problems. I proved this by drinking [reverse osmosis] water until longstanding skin problems cleared up. When later I resumed drinking 0.3 ppm fluoride water the skin problems returned." A second comment claimed that fluoride causes premature aging and wrinkling.

Agency Response: Reverse osmosis removes many different impurities from water. It is not clear from this comment that the reduction in fluoride was related to the change in skin problems. The suggestion of an association between fluoride and premature aging and wrinkling made by the commenter is speculative and conjectural at this time.

III(B)(13) Fluoride is an enzyme poison

Comment: DenBesten (1997) [sic] provides some evidence that dental fluorosis is caused by the inhibition of an enzyme (a protease) which removes the last little bit of protein from between the mineral (i.e. calcium hydroxy apatite) prisms before they fuse to form the smooth enamel surface. It is the failure to remove this protein which causes the gaps in the enamel surface. The important question to ask from the toxicological point of view is: if fluoride is able to poison this enzyme in the growing tooth what other enzymes in the body can it poison? For example, what enzymes in the bone may it poison? What enzymes in other tissues may it poison? In 1981 John Emsley threw more light on fluoride's mechanism of action

when he showed that fluoride forms a strong hydrogen bond with the amide function. This not only explains why fluoride inhibits many enzymes but also indicates why it may interfere with DNA whose structure and function hinges on hydrogen bonds (Emsley, 1981).

Agency Response: There are several scientific problems with the statements made about the hydrogen bonding potential of fluoride and its effects on enzymes. Hydrogen bonds are electrostatic interactions between partially positive hydrogen atoms in molecules and partially negative atoms in the same or neighboring molecules (Lehninger, et al., 1993). Partial positive and negative charges within a molecule are the product of differences in the affinity of covalently bonded atoms for electrons resulting in bond polarity. Hydrogen fluoride, the simplest hydrogen-containing inorganic fluorine compound, has a p*K*a of 3.5. This means that the molecule can only participate in hydrogen bond formation to any significant extent at pH values of less than about 4.5. The pH maintained in most mammalian cells is about 7 to 7.3, a pH range where only about one in 1,000 to one in 10,000 of the fluorines is present as hydrogen fluoride. The remainder of the fluorines are present as monovalent, negative fluoride ions. The acid secreting cells of the stomach are an exception to this generalization. The low pH of the gastric secretions would favor the presence of the undissociated hydrogen fluoride, and hydrogen fluoride is capable of hydrogen bonding. The primary interactions that would be displayed by the fluoride ion would be ion-ion interactions or ion-dipole interactions rather than hydrogen bond interactions.

The distinction made above regarding the types of interactions expected between fluoride and cellular constituents is more than simply semantic. For example, interactions of fluoride ions with the hydrogen bonds in DNA are very unlikely since the negative charges on the DNA phosphate-sugar backbone and the pi-bonds of the DNA bases would tend to repel fluoride anion preventing its disruption of the DNA hydrogen bonds. Interaction of the fluoride ion with the positively charged DNA-associated polyamines or histone proteins would be more likely. However, to the knowledge of the Agency, there has been no experimental investigation of fluoride ion interactions with DNA-polyamines or histone proteins.

The results from studies of fluoride's mutagenicity and genotoxicity are consistent with the hypothesis that the effects of fluoride on chromosomes and DNA are indirect rather than direct. Most of the mutagenicity studies, particularly those using the Ames Assay, are negative (NAS, 1993). Although *in vitro* mouse lymphoma mutagenicity assays have some positive results, this assay detects chromosomal damage as well as gene mutations. The results from many of the *in vitro* studies of chromosomal effects are positive but the *in vivo* assays have approximately equal numbers of positive and negative results (National Academy of Sciences,

1993). Thus, the effects of fluoride on DNA appear to occur at the level of the chromosomes rather than the DNA bases.

Lack of hydrogen bonding potential of fluoride at physiological pH's would also determine the nature of its interaction with proteins. Fluoride ions could influence protein structure and, thus, enzyme activity by disrupting the electrostatic interactions between the acidic and basic amino acids, or by interrupting hydrogen bond interactions of polar amino acid side chains. Fluoride's ability to exert such an influence would be shared by other negative ions (i.e., chloride anions) and would be concentration and enzyme-specific. Fluoride would also have to compete with chloride and other intracellular negative ions for protein interaction sites. The small ionic radius of fluoride would be a factor favoring interaction with positively charged amino acid side chains that might not be accessible to larger ions.

It has been hypothesized (Spittle, 1994) that formation of relatively insoluble calcium or magnesium complexes might disrupt the activities of enzymes using these divalent cations as cofactors. This is a possible mechanism that might account for inhibition of some enzymes but divalent cation complex formation would be an enzyme-specific rather than a general effect.

To the knowledge of the Agency, there has been no systematic evaluation of the ability of fluoride to inhibit enzyme activities, or of the mechanism for such inhibition. Data on the specific enzymes inhibited and the dose-response for the effects would be required for the data to be used for quantitative risk assessment. A National Academy of Sciences (1993) report on the health effects of ingested fluoride endorsed conducting research on the mechanism by which fluoride interacted with cells and biomolecules, including enzymes, and research on specific mechanisms of enzyme inhibition would be beneficial.

III(B)(14) Exposure to fluoride reduces children's intelligence

Comment: Fluoride has neurological effects that result in a decrease in intelligence. EPA should have listed all the pesticides that adversely affect the brain. Since the middle 1990s there have been several important studies which have probed fluoride's possible impact on the brain. Mullenix (1995) demonstrated that rats treated prenatally with fluoride showed behavior patterns associated with hyperactivity and rats dosed after birth showed hypoactivity. Guan, et al. (1998) showed that membrane lipids in rat brain were impacted by chronic fluorosis. Several studies in China (Lee, et al. 1985; Zhao, et al. 1996; and Lu, et al. 2000) have shown the possible impact of high background fluoride (possibly in the presence of low iodide, (Zhao, 1998) on children's IQ. One of those that we have examined is the work by

Zhao, et al. (1996) who found an approximate 5-10 point IQ deficit in children from a community with water containing 4 ppm natural fluoride compared to one containing 1 ppm. Since we fluoridate at 1 ppm, and the EPA's MCLG for fluoride is 4 ppm, this paper is of considerable concern. Varner, et al. (1998) exposed rats to fluoride in their drinking water for one year. What was remarkable about this work is how low the concentrations were that caused damage. Both AlF_3 (aluminum fluoride) and NaF (sodium fluoride) given to the animals at the level of 1 ppm fluoride (the same level generally used in public drinking water) in their doubly distilled de-ionized drinking water caused both kidney and brain damage, an accumulation of aluminum into the brain and the formation of amyloid plagues which are associated with Alzheimer's disease. Apparently, this is the third time that Isaacson and his co-workers have found effects on the brain at these remarkably low levels. As a result of Varner's work aluminum fluoride was recently nominated by the Environmental Protection Agency and National Institute of Environmental Health Sciences for testing by the National Toxicology Program. According to the EPA and NIEHS, aluminum fluoride is a "drinking water contaminant" with "known neurotoxicity" and a "high health research priority." If fluoride is added to water which contains aluminum, than aluminum fluoride complexes will form (BNA, 2000, see http://www.fluoridealert.org/alum-fluoride.htm). We would add that if some of the fruits and vegetables with the fluoride residues proposed in DOW's application were cooked in aluminum saucepans, this too could lead to the formation of aluminum fluoride complexes.

Agency Response: The Agency has reviewed the papers cited by the Fluoride Action Network on the effects of fluoride on neurological effects in animals and on the reduction of children's intelligence, and find these papers to be inconclusive (Baetcke, et al. 2003). Those epidemiology papers reporting IQ effects in children are incomplete in their epidemiologic analysis to warrant any conclusion until other contributing factors, confounders, and biases are fully explored. The positive animal neurotoxicity studies cited by the Fluoride Action Network also contain study design deficiencies that do not permit scientifically supported conclusions. The Agency recognizes that some pesticides may potentially have an effect on the brain (e.g., organophosphate pesticides). But it is unclear how this information would add to the assessment of the potential hazards associated with exposure to fluoride. The conclusions reached by Mullenix, et al. (1995) are not supported due to a number of problems with their study. There have been no systematic studies comparing the Mullenix method for measuring neurobehavioral effects with the standard neurotoxicology battery, which has undergone extensive and international validation studies. There is no published record of validation of the Mullenix method. Also, the numerous T-Tests performed by these authors can lead to significance of results based on chance alone. Finally, there is no scientific basis to imply that motor changes are surrogate of cognitive deficits, as the authors do in this paper. In the Zhao, et al. (1996) and Li, et al. (1995) studies, the potential for exposures to chemicals e.g., lead

and methyl mercury which have a demonstrated effect on IQ was not assessed and the data were not corrected for possible confounding variables. Thus, conclusions regarding fluoride exposure and reduction in IQ can not be drawn. US EPA Office of Research and Development research efforts include characterization of the dissociation of fluoride complexes as part of an effort to determine if such complexes exist in drinking water. Knowing whether such complexes exist in drinking water is essential to determine if the Varner, et al. (1998) findings have implications for public health and whether additional health effects research is necessary to better characterize toxicity associated with exposure to such complexes. While the use of aluminum cookware is associated with small increases in aluminum content in the prepared food, the relative contribution of aluminum from cookware to total exposure is of equivocal significance relative to other sources of ingested aluminum. Insufficient data is available to draw conclusions on the form of aluminum in food prepared in aluminum cookware.

III(C) Bioaccumulation

Comment: There is no evidence of long term safety for fluoride. Due to bioaccumulation, 30 year effects need to be studied in a controlled experiment. The petition for experimental use permit tolerances is based on experience with fluoridation of the drinking water and the use of fluoride as a medication. The fluoride bone levels (asked) associated with the pre-clinical phase of skeletal fluorosis are in the range 3,500-5,500 ppm (DHHS, 1991, Table 23). It would be nice to know how close we are getting to these levels with lifetime exposure to fluoride from many sources. Unfortunately, despite its heavy promotion of water fluoridation and the millions of dollars spent on dental research, the US PHS has never sought fit to do the most elementary thing of preparing a comprehensive data base on fluoride bone levels in the US as a function of age, sex, race, location, fluoridation status, disease status, diet or anything else. According to the National Research Council (1993): “Crippling skeletal fluorosis might occur in people who have ingested 10-20 mg of fluoride per day for10-20 years” and according to the DHHS (1991) the range of adult daily dose in the US, in optimally fluoridated areas, is 1.6 - 6.6 mg per day. If we apply simple arithmetic to these figures (i.e. 1.6 to 6.6 mg per day) someone in the middle of the range might reach severe skeletal fluorosis in about 60 years. Furthermore, they might reach the milder symptoms, which are similar to the symptoms experienced in osteoarthritis -aching bones and joints - in less time than this. Someone receiving the 8 mg per day deemed protective by the US EPA would reach the early symptoms still earlier. The statement by the National Research Council (1993): “Crippling skeletal fluorosis might occur in people who have ingested 10-20 mg of fluoride per day for 10-20 years” refutes the claim by Dow [Section E.1] that “there is no directly applicable scientific documentation of adverse medical effects at levels of fluorine below 0.23 mg/kg/day.”

Since for a 70 kg adult 0.23 mg/kg/day translates to16 mg/day.

Agency Response: The Agency recently conducted a preliminary evaluation of 86 articles cited by the Fluoride Action Network in addition to other recent literature and did not find any new data that heighten the concern of the association of exposure to fluoride and adverse effects on human health. (Baetcke, et al. 2003).

III(D) Susceptible populations

Comment: There is a need for developmental, reproductive, and neurotoxicity data on fluoride for sensitive populations, including infants, children, the elderly, people over 55, and people with renal disorders, cardiovascular disease, vitamin C deficiency, magnesium deficiency, and calcium deficiency.

Agency Response: The Agency has now considered the new literature on the potential developmental, reproductive and neurotoxicity effects associated with fluoride exposure and the potential susceptibility of certain subpopulations. The Agency has reviewed the papers cited by the Fluoride Action Network that deal with the effects of fluoride on thyroid functioning. The papers submitted by FAN do not convince EPA that fluoride produces significant effects on the thyroid because of study design and report deficiencies (Baetcke, et al. 2003). The Agency has also reviewed the papers cited by the Fluoride Action Network that deal with the effects of fluoride on reproductive function, and considers the evidence to be insufficient to establish a causal link between fluoride exposure and effects on reproductive function in humans (Baetcke, et al. 2003). The human literature suffers from poorly designed studies and/or inadequate sampling. Although a few papers in the literature report adverse effects on reproduction in animal studies, these effects have not been not reproduced by other laboratories, including by well conducted reproductive studies in laboratory animals carried out by the US Food and Drug Administration (not cited by FAN). Finally, the Agency has reviewed the papers cited by the Fluoride Action Network on the effects of fluoride on neurological effects in animals and on the reduction of children's intelligence, and find these papers to be inconclusive (Baetcke, et al. 2003). Those epidemiology papers reporting IQ effects in children are incomplete in their epidemiologic analysis to warrant any conclusion until other contributing factors, confounders, and biases are fully explored. The positive animal neurotoxicity studies cited by the Fluoride Action Network also contain study design deficiencies that do not permit scientifically supported conclusions. Thus, the Agency can not find scientifically defensible data raising the issue of sensitive subpopulations and health effects associated with fluoride concerning reproduction, thyroid and neurological function. The Agency's risk assessment did consider the total fluoride exposure experienced by different subpopulations based on age, worker exposure, and proximity to the use of sulfuryl fluoride, and did not find that the total

fluoride exposure of any of these groups exceeded the level considered to be safe.

III(E) Total exposure to fluorides

Comment: EPA did not cover all routes of exposure. Americans are already over exposed to fluoride and dental fluorosis is a biomarker for that overexposure. A Canadian report indicates that children in North America are already over exposed to fluoride (Rose and Marier 1993, p. 55). This conclusion can be derived simply by calculating the various and multiple sources of fluoride a child is exposed to today. The clearest evidence that we are getting more fluoride today than we were in 1945, is the way that dental fluorosis figures have rocketed. The Agency should evaluate the range of exposures 0.023 to 0.094 mg/kg/day and not just the average exposure of 0.057 mg/kg/day. DOW states that the US EPA estimated in 1996 that the "high end dietary exposure to fluoride due to all sources and routes (including fluorination [sic] of water and the potential for fluoride residues resulting from the uses of cryolite) are approximately 0.085 mg/kg/bit/day." This would translate to a daily dose of 6 mg for fluoride for a 70 kg adult. In our view, this is far too close to the MCG of 8 mg per day. The Agency did not fully consider all of the sources of human exposure to fluoride.

Agency Response: The Agency's risk assessment quantitatively estimated fluoride exposure levels from water, air (background, worker exposure, and bystander exposure), toothpaste, and food (normal background, due to use of cryolite, and due to use of sulfuryl fluoride) for various subpopulations, and found that the total exposure was below the maximum level considered to be safe and that the use of sulfuryl fluoride accounted for less than two percent of the total fluoride exposure.

III(E)(1) Fluoride exposure from water

Comment: The Agency has not evaluated the exposure from water that is used for drinking and preparation of food is contaminated with fluoride both from natural sources and from the intentional addition of fluoride to drinking water. The DHHS estimates that an adult living in an optimally fluoridated area (0.7-1.2 ppm) gets between 1.6 and 6.6 mg per day (DHHS, 1991). The range of exposure for children in optimally fluoridated communities is 0.9 to 3.6 mg per day. A 20 kilogram child would have exposure of between 0.045 and 0.18 mg/kg/day. Children are above the MCL by 60%. Some schools in the US add 4.5 ppm of fluoride to their drinking water systems. For example, seventy-five (75) schools in Indiana fluoridate their drinking water systems at 4.5 ppm; sixty-one (61) schools (or communities) in North Carolina fluoridate their drinking water systems at 4.5 ppm; and sixty-four (64) schools in Kentucky fluoridate their drinking water systems at 4.0 ppm (DHHS, 1993).

Agency Response: The Agency's risk assessment quantified human fluoride exposure

from a number of dietary sources including both drinking (tap) water and other water such as bottled water and soft drinks. The U.S. Public Health Service published recommendations in 1995 for school fluoridation programs to obtain the benefits of fluoridation without increasing the risk for dental fluorosis (CDC 1995). The PHS recommends school water fluoridation only if: 1) The school has its own source of water, 2) The school is not connected to a community water system, 3) More than 25 percent of students are not served by a public water system that provides water at levels adequate to protect against dental caries, and 4) The students served are kindergarten age or greater.

III(E)(2) Fluoride exposure from processed food.

Comment: The Agency has not evaluated the exposure from processed food and beverage, particularly mechanically deboned chicken that is used to prepare children's food and beverages that are made with fluorinated water. Fein and Cerklewski (2001) reported that the fluoride content of certain children's food made with mechanically deboned chicken. They state: "Brand A pureed infant foods prepared from chicken contained 3.22 - 8.63 ppm F (mean 5.58); brand B contained 1.89 - 4.63 F [sic] (mean 2.82)... A significant correlation of calcium with the higher fluoride content of the chicken products suggests that mechanical deboning process was the source of the extra fluoride...."

Agency Response: The Agency's risk assessment considered the measured fluoride concentrations in many different foods in calculating the total dietary background exposures to fluoride for various subpopulations. With regard to mechanically deboned chicken, the mean residue of 5.58 ppm reported by Fein and Cerklewski for chicken was used for all poultry meat and meat-byproduct entries in the Agency's risk assessment. We further note that this residue level is approximately half of that reported in the 1980s and 1990s and reflects steps taken by the poultry industry to limit the amount of contamination that comes from the deboning process.

III(E)(3) Fluoride exposure from cooking in fluoridated water

Comment: The Agency has not evaluated the fluoride exposure that results from cooking in fluorinated water.

Agency Response: The background levels in food account for elevated fluoride levels due to the use of fluoridated processing water and preparation of foods with fluoridated water. The study by Taves (1983) used in the Agency's risk assessment describes residues of fluoride in foods prepared by a hospital in a fluoridated area; thus, it represents a worst-case set of residue values for background fluoride in foods. The assumption of 1 ppm fluoride in all non-tap water sources addresses the potential for fluoride residues in processed beverages.

The assumption of 1 ppm also extends to bottled water which, except for a few cases of fluoridated bottled water, is an extreme over-estimate of exposure from that source.

III(E)(4) Fluoride exposure from use of cryolite as a pesticide

Comment: The Agency has not evaluated the fluoride exposure resulting from exposure to cryolite residues in or on food.

Agency Response: The Agency's risk assessment specifically considered the fluoride residues on food resulting from the use of cryolite as a pesticide.

III(E)(5) Fluoride exposure from naturally occurring fluoride in food

Comment: The Agency has not evaluated the fluoride exposure from naturally occurring residues of fluoride in food.

Agency Response: The Agency's risk assessment specifically considered the naturally occurring presence of fluoride in food.

III(E)(6) Fluoride exposure from decomposition of non-stick coatings

Comment: The Agency has not evaluated the fluoride exposure from cooking in Teflon lined cookware. FAN cites the study by Full and Parkins (1975) where fluoride concentrations went from 1 ppm to 3 ppm when fluoridated water was boiled in a Teflon-lined pan until a one-third to one-half reduction in volume was attained. The report concluded "This result requires confirmation; but, if it is correct, then the release of fluoride into foods during cooking in plastic-coated wares requires investigation."

Agency Response: 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 the experimental design and the manner in which final fluoride concentrations were expressed, it is not possible to discern whether or not the increased fluoride concentration was due to leaching of fluoride from the coating or differential evaporation noted for the non-stick coated cookware versus other materials. Given that the boiling point of water is 100°C and fluorocarbon coatings have high thermal stability (thermal decomposition does not occur until approximately 400°C), it is unlikely that fluoride would be released in sufficient quantities to increase its concentration in the water by 3 fold. The EPA Office of Pollution Prevention and Toxics (OPPT) in conjunction with other governmental agencies including FDA and CPSC has been working with the manufacturers of fluorocarbon non-stick coatings to test commercial articles under conditions of regular and misuse conditions to characterize any decomposition products and their amounts. HED will coordinate with OPPT on this testing and will review the results of the cookware testing when the data

become available.

III(E)(7) Fluoride exposure from mothers' milk

Comment: The Agency has not evaluated the fluoride exposure from mother to infant exposure. Fluoride crosses the placenta from mother to fetus (Canada Report, 1993). There are also natural levels of fluoride in human milk estimated to be ca 0.01 ppm, approximately a hundred times less than baby formula reconstituted with fluoridated water.

Agency Response: Fetal Exposure: The Agency does not typically conduct an exposure assessment for unborn children. Rather, we address in utero effects via the mother. In the case of a developmental toxicant, we would either apply the toxicological endpoint to the mother through our assessment of the age group Females 13-49 (i.e., females of child-bearing age). Depending on the completeness of the toxicological database, the Agency may also apply a safety factor if there were concerns that the dose being used to assess women of child-bearing age was not being protective of potential developmental effects. To date, the Agency is not convinced that fluoride is a developmental toxicant. Exposure via Milk: The Agency's risk assessment has included fluoride levels of approximately 0.02 ppm in all milk (twice that estimated for human milk), and has assumed residues of 2 ppm in tap water and 1 ppm in all other water sources such as bottled water. Since it is this water that is used to reconstitute baby formula, the higher residues in formula are accounted for in the risk assessment.

III(E)(8) Fluoride exposure from fluoridated toothpaste

Comment: The Agency has not evaluated the fluoride exposure from exposure from fluorinated toothpastes, mouth rinses, other treatments for the prevention of dental caries. According to a 1999 Canadian report, a recent paper analyzed reports to the American Association of Poison Control Centers of suspected over-ingestion of fluoride from home-use dental products. Children under six accounted for 80% of the reports. Fluoridate toothpastes and mouth rinses can result in levels of fluoride that can be toxic by themselves.

Agency Response: The Agency's risk assessment specifically estimates the fluoride exposure resulting from the use of fluoridated toothpaste by various subpopulations.

III(E)(9) Fluoride exposure from pharmaceuticals

Comment: The Agency has not evaluated the fluoride exposure from fluorinated pharmaceuticals and vitamin tablets. For instance, Baycoll - a fluorinated drug - was recently recalled because of adverse health effects.

Agency Response: The Agency's risk assessment discusses the reasons why the

exposure to fluorides from pharmaceuticals is not considered to be significant.

III(E)(10) Fluoride exposure from air pollution

Comment: It is particularly important that when the US EPA re-estimates the total dose of fluoride for various age ranges of the US population that they include an estimate of fluoride exposure through inhalation and through food contaminated by air pollution. To this end we have included the TRI releases by state. However it should be remembered that not all industries or emissions are included in the TRI. HF is the number six in air pollutants in the US. Radioactive wastes from nukes are a source of environmental fluoride.

Agency Response: The Agency's risk assessment considered exposure to fluoride in air due both to ambient air levels of fluoride and increased air concentrations around various industrial facilities. The Agency has established emission restrictions to control the release of fluoride by a number of industries.

III(E)(11) Effect of caffeine on fluoride exposure

Comment: Caffeine in tea, coffee and sodas doubles the bio-availability of ingested fluorides. This must be considered in evaluating allowable human exposure to fluoride.

Agency Response: In 1990 Chan et al. (1990) reported that concomitant intragastric administration of sodium fluoride and coffee to rats resulted in a significantly higher plasma fluoride level than intake of the same amount of fluoride with water. However, subsequent research found that "...caffeinated coffee appeared to increase the initial absorption rate [of fluoride] but not the 4-hour bio-availability" (Chen and Whitford 1994). This short term transient effect of caffeine on the absorption rate of fluoride should have no effect on the chronic effects of fluoride exposure.

IV Other Effects Not Considered

IV(A) Greenhouse climate effects

Comment: There must be other fumigants that do not contribute to the greenhouse gas problem and don't result in fluoride exposure.

Agency Response: The expected contribution of fluoride from the use of sulfuryl fluoride on global warming is considered insignificant compared to the contribution of carbon dioxide and methane emissions.

IV(B) Economic impacts

Comment: The Agency has not evaluated the economic impacts of the proposed uses of sulfuryl fluoride. The economic impacts of the EUP on California export markets has neither been assessed or discussed. Over 40% of the California raisin crop is exported. The high tolerances for inorganic fluoride could result in adverse economic impacts for the US export markets to Europe and Japan. In addition, the European Community has established a tolerance of 1 ppm for fluoride residues in wine.

Agency Response: Except with regard to circumstances not present here [see 21USC346(b)(2)(B)], the FQPA of 1996 precludes the Agency from considering economic considerations when establishing tolerances. The European Community tolerance for fluoride in wine grapes relates to the effects of fluoride on the fermentation of wine, not human health effects. The Agency is not considering establishing a tolerance for the use of sulfuryl fluoride on wine grapes. The use proposed was for post-harvest treatment of raisins.

IV(C) Bioterrorism

Comment: The Agency has not evaluated the potential use of fluorides as a weapon of biochemical terrorism and the effect of the proposed increased exposure to fluoride on the susceptibility of people to this threat.

Agency Response: This is not an appropriate consideration for tolerance-setting under the FFDCA. In any event, fluoride is relatively non-toxic compared to other potential agents of bioterrorism, and the procurement and handling of significant quantities of fluoride present much greater problems than do other potential agents. For these reasons, fluoride is not considered to be a significant potential biochemical weapon.

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