UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: September 30, 2007

MEMORANDUM

SUBJECT: **Sodium Fluoride Risk Assessment** for the Reregistration Eligibility Decision (RED) Document. PC Code: 075202 (active). Case No. 3132

Regulatory Action: Reregistration Eligibility Decision (RED) (Phase I)

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Attached is the Risk Assessment for Sodium Fluoride The disciplinary science chapters are also included as attachments and are listed on the following pages.

Supporting chapters discussed in this Risk assessment and are included as Appendices:

- Occupational and Residential/Bystander Assessment of the Antimicrobial Use (Remedial Wood Treatment) of Sodium Fluoride for the Reregistration Eligibility Decision (RED) Document. Timothy Leighton, Environmental Scientist, August 2007.

- Sodium Fluoride Product Chemistry Chapter for the Reregistration Eligibility Decision Document (RED). A. N. Shamim, August 2007.

Ecological Hazard and Environmental Risk Assessment Chapter for Sodium Fluoride RED. Richard C. Petrie, July 2007.

- Toxicology Chapter for Sodium Fluoride RED. Timothy F. McMahon, August 2007.

- Environmental Fate Science Chapter for Sodium Fluoride RED. A. Najm. Shamim. August 2007.

- Sodium Fluoride- Incident Report Summary. Jonathan Chen, Ph.D. August 2007.

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1.0 EXECUTIVE SUMMARY

Hazard Characterization

Sodium fluoride is registered for commercial use only as a wood preservative for utility poles and railroad ties. Sodium fluoride products are used as supplemental wood treatments and are not intended for primary wood preservative or pressure treated wood preservation.

Sodium Fluoride is an inorganic substance which does not undergo hydrolysis typically like an organic compound. Sodium fluoride is water soluble and dissociates in water.

The acute toxicity database for sodium fluoride is considered complete. Sodium fluoride has a high order of toxicity via the oral route of exposure (Toxicity Category II) and a moderate order of toxicity via the dermal and inhalation routes of exposure (Toxicity Category III). Primary eye irritation studies classify sodium fluoride as corrosive (Toxicity Category I) whereas dermal irritation studies classify sodium fluoride as a mild or slight irritant (Toxicity Category IV). Sodium fluoride is not a dermal sensitizer. Sodium fluoride does not appear to be a primary developmental or reproductive toxicant based on the available animal studies. Further data are needed in the neurotoxic and endocrine effects of sodium fluoride. Positive mutagenicity results have been reported in mouse lymphoma assays, in chromosome aberration assays, in unscheduled DNA synthesis assays, and in *in vitro* sister chromatid exchange assays. Sodium fluoride has been classified as a "Group D" (not classifiable as to carcinogenicity). The recent conclusion of the 2006 National Academy of Sciences report supports this classification, where the report concluded that
"on the basis of the committee's collective consideration of data from humans, genotoxicity assays, and studies of mechanism of action in cell systems…the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed."

The database for metabolism consists of one study from the open literature. In a study by Hall et al. 1977, 6 adult male New Zealand rabbits were administered sodium fluoride in the diet (15 ppm), water (1 ppm), and in a single oral dose injected (0.5 mg/kg) directly into stomach through nasal catheter. Urine excretion following oral administration of sodium fluoride was 5 and 13% for 60 and 600 minutes, respectively. Under steady state conditions approximately 15% of fluoride ingested in food and water was absorbed by the animals. 15% was excreted in urine and 85% of ingested fluoride was removed via fecal excretion.

Dose-Response Assessment

For acute and chronic dietary risk assessments, no appropriate endpoints were identified that represent a single dose effect. Hence these risk assessments are not required.

For short-term (1-30 days) dermal risk assessment, a LOAEL of 20 mg/kg/day was selected based on based on significant reductions in body weight gain and suppressed spontaneous motor activity in an oral subchronic toxicity study in the rat. An uncertainty factor of 300 is assigned (10x inter-species extrapolation, 10x intra-species variation, 3x for use of LOAEL) in this case.

For intermediate-term (30 days-6 months) dermal risk assessment, a NOAEL of 1.5 mg/kg/day was selected based on histopathology observed in bone with degeneration in tibias and femurs of animals in a 6-month oral toxicity study in the mouse. An uncertainty factor of 100 is applied (10x inter-species extrapolation, 10x intra-species variation) in this case.

For long-term (> 6months) dermal risk assessment, a LOAEL of 1.3 mg/kg/day was selected based on dentine dysplasia in males and females, and ameloblast degeneration in males in a 2 year chronic toxicity/carcinogenicity study in the rat. An uncertainty factor of 100 is assigned (10x inter-species extrapolation, 10x intra-species variation) in this case.

For short-term (1-30 days) inhalation risk assessment, a LOAEL of 20 mg/kg/day was selected based on significant reductions in body weight gain and suppressed spontaneous motor activity at a dose of 20 mg/kg/day, in an oral subchronic toxicity in the rat. An uncertainty factor of 300 is assigned (10x inter-species extrapolation, 10x intra-species variation, 3x for use of a LOAEL).

For intermediate-term (30 days-6 months) inhalation risk assessment, a NOAEL of 1.5 mg/kg/day was selected based on histopathology observed in bone with degeneration in tibias and femurs of animals, in a 6-month oral toxicity study in the mouse. An uncertainty factor of 100 is assigned (10x inter-species extrapolation, 10x intra-species variation, 10x route extrapolation).

For long-term (> 6months) inhalation risk assessment, a LOAEL of 1.3 mg/kg/day was selected based on dentine dysplasia in males and females, and ameloblast degeneration in males in a 2 year chronic toxicity/carcinogenicity study in the rat. An uncertainty factor of 300 is assigned (10x inter-species extrapolation, 10x intra-species variation, 3x for use of a LOAEL) in this case.

FQPA Considerations

FQPA considerations are not applicable to sodium fluoride. There are no food use tolerances for this chemical and indirect food contact is not expected from the current uses of this chemical.

Dietary Exposure and Risk

There are no antimicrobial uses for sodium fluoride which involve dietary exposure, and thus a dietary exposure and risk assessment are not needed for the antimicrobial uses of this chemical.

Drinking Water Exposure and Risk

The antimicrobial uses of sodium fluoride are not expected to pose a hazard to ground water or surface water. Therefore, a drinking water exposure and risk assessment is not needed.

Residential Post-application Exposure and Risk

Potential bystander risks to the remedial wood treatment uses of sodium fluoride were assessed. The potential bystander inhalation exposure to sodium fluoride is minimized by the extremely low vapor pressure. The potential for dermal exposure to bystanders (i.e., children playing in the vicinity of treated poles) is minimized by the enclosure of the application site (i.e., capping of pre-drilled holes and groundline applications covered with dirt).

Aggregate Exposure and Risk

An aggregate risk assessment is not required for sodium fluoride. Residential exposures are assumed to be minimal as noted above from the antimicrobial uses of sodium fluoride.

Occupational Exposure

The occupational and potential bystander risks to the remedial wood treatment uses of sodium fluoride were assessed. The remedial wood treatment is used to treat poles, crossties, structural timbers such as bridge pilings and posts, etc., against decay producing fungi. Based on label directions, two distinct application types were assessed including predrilled hole treatments as well as groundline treatments. The pre-drilled hole treatments are applied with pre-packaged insert products and also mechanical pressure pumps. Exposure to the pre-packaged insert products is expected to be negligible and is not assessed quantitatively. PPE should be required for these products to mitigate potential exposure for leaks, etc. The inhalation risks for the pre-drilled hole spray

applications using the mechanical pressure pumps are not of concern. However, dermal risks are triggered for this application scenario for the treatment of distribution and transmission poles. Additionally, all of the dermal MOEs are below the target MOE for the groundline brush-on treatments (MOEs less then or equal to 1). The brush-on treatment also represents the high-end exposures for the trowel-on and impregnated wraps. Inhalation exposure is expected to be minimal for the groundline treatments because of the viscosity of the product as well as its low vapor pressure.

Ecological/Environmental Risk

Sodium fluoride is registered for commercial use only as a wood preservative for utility poles and railroad ties. Sodium fluoride products are used as supplemental wood treatments and are not intended for primary wood preservative or pressure treated wood preservation.

Sodium fluoride can be rolled or brushed onto an external wood surface typically 3 inches above and 18 inches below the ground surface. The application is then wrapped with a water proof bandage. Another method of application is by drilling holes into the timber and inserting sodium fluoride rods that contain pellets or tablets into the drilled holes. The holes are then sealed with a plug or putty filler.

Sodium fluoride is an inorganic substance which does not undergo hydrolysis but is water soluble and dissociates in water to sodium and fluoride ions. Fluoride ions undergo hydrolysis to form hydrogen fluoride acid and hydroxide ions which can shift the pH to alkaline. Sodium fluoride does not adversely affect soil biomass, microflora and macro invertebrates, and is not expected to be bio-accumulative. A field monitoring study of sodium fluoride treated poles found that sodium fluoride ions occasionally exceed background levels and do not migrate outward from treated poles more than 10 cm or for more than 50 cm deep. Elevated levels returned to background by the end of the 18 month study. Sodium fluoride is not expected to pose a hazard to groundwater or surface waters.

Sodium fluoride use as a wood preservative is not expected to pose an adverse risk to terrestrial or aquatic animals or plants based on current use patterns unless a spill were to occur. The use of water proof wraps and sealed injections should serve to greatly reduce environmental exposure.

Endangered Species

This preliminary analysis indicates that current sodium fluoride wood treatment uses are not likely to enter the environment in sufficient quantities to adversely affect terrestrial or aquatic species, however, an endangered species effects determination will not be made at this time.

Incident Reports

There are only limited incidents associated with acute exposure to sodium fluoride used in wood preservatives. All the symptoms are classified as either minor or moderate. Historically, there are some fatal incidents associated with oral exposure to sodium fluoride, but this occurred at much higher concentrations.

Chronic fluoride intake has been shown to decrease the prevalence of dental caries. However, high levels of fluoride exposure, especially by the oral route, can cause dental fluorosis and can result in an increased prevalence of bone fractures in the elderly or skeletal fluorosis (ATSDR, 2003).

2.0 PHYSICAL AND CHEMICAL PROPERTIES

Table 2.1 Chemical Identity of Sodium Fluoride	
Parameter	**Sodium Fluoride**
PC Chemical Code	075202
CAS Number	7681-49-4
Molecular Formula	NaF
Chemical Name	Sodium Fluoride
Synonyms	Chemifluoro, Dentafluoro, Villiaumite
Structure	Na-F

Table 2.2 Physical/Chemical Properties for Sodium Fluoride	
Parameter	**Sodium Fluoride**
Molecular Weight	42.00
Melting Point	993 ^{o} C
Boiling Point	1704 ^{o} C
Solubility	Water: 4.10 g/100 ml; at 15°C, 4.3 g/ 100 ml at 25 ^{o} C. Alcohol: Insoluble
Vapor Pressure	5.43 x 10^{-26} mm Hg (25 ^{o} C)[1]
Log Kow	-0.77 [1]
Henry law Constant	5.04 x 10^{-33} atm m^3/mole[1]
Bulk Density	37 in^3/lb (95% technical grade)
Density	2.55 g/cm^3
pH	Slightly Alkaline

[1] The values have been taken form the US EPA's EPI Suite Modeling Program, developed by OPPT

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Acute Toxicity

Adequacy of database for Acute Toxicity: The acute toxicity database for sodium fluoride is considered complete. For the technical grade active ingredient, sodium fluoride has a high order of toxicity via the oral route of exposure (Toxicity Category II) and a moderate order of toxicity via the dermal and inhalation routes of exposure (Toxicity Category III). Primary eye irritation studies classify sodium fluoride as corrosive (Toxicity Category I) whereas dermal irritation studies classify sodium fluoride as a mild or slight irritant (Toxicity Category IV). Sodium fluoride is not a dermal sensitizer. The acute toxicity data for sodium fluoride is summarized below in Table 3.1.

Table 3.1. Acute toxicity data for sodium fluoride technical a.i.

Guideline Number	Study Type/Test substance (% a.i.)	MRID Number/ Citation	Results	Toxicity Category
870.1100 (§81-1)	Acute Oral – Rat Purity 95.6% - Sodium Fluoride	43778501	LD_{50} (combined) = 105 (93-119 CL) Male LD_{50} = 120 mg/kg Female LD_{50} = 89 mg/kg	II
870.1200 (§81-2)	Acute Dermal – Rat Purity 95.6% - Sodium Fluoride	43778502	LD_{50} > 2000 mg/kg	III
870.1300 (§81-3)	Acute Inhalation - Rat Purity 95.6% - Sodium Fluoride	43778503	LC_{50} = 1.00 mg/L	III
870.2400 (§81-4)	Primary Eye Irritation - Rabbit Purity 95.6% - Sodium Fluoride	43778504	Severely irritating to unwashed eyes	II
870.2500 (§81-5)	Primary Dermal Irritation- Rabbit purity 95.6% – Sodium Fluoride	43778505	Slightly Irritating	IV
870.2600 (§81-6)	Dermal Sensitization - Guinea pig purity 95.6 % - Sodium Fluoride	43778506	Buehler: Not a skin sensitizer	No
870.2600 (§81-6)	Dermal Sensitization - Guinea pig purity not reported	40866801	Not a dermal sensitizer	No

3.2 FQPA Considerations

FQPA considerations are not applicable to sodium fluoride. There are no food use tolerances for this chemical and indirect food contact is not expected from the current uses of this chemical.

3.3 Dose-Response Assessment

3.3.1 Summary of toxicology endpoint selection for sodium fluoride. Table 3.2

Table 3.2. Sodium Fluoride for Use in Human Risk Assessment

Exposure Scenario	Dose (mg/kg/day) used in risk assessment UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Dietary Risk Assessments			
Acute Dietary (general population and females 13-49)	No appropriate endpoints were identified that represent a single dose effect. Therefore, this risk assessment is not required.		
Chronic Dietary	No appropriate endpoints were identified that represent a single dose effect. Therefore, this risk assessment is not required.		
Non-Dietary Risk Assessments			
Short -Term Dermal (1 - 30 Days)	LOAEL = 20 mg/kg/day	**Target MOE**=300 (10x inter-species extrapolation, 10x intra-species variation, 3x for use of LOAEL)	Oral Subchronic Toxicity – Rat (Sodium Fluoride) LOAEL = 20 mg/kg/day, based on significant reductions in body weight gain and suppressed spontaneous motor activity.
Intermediate -Term Dermal (30 Days- 6 months)	NOAEL = 1.5 mg/kg/day	**Target MOE**=100 (10x inter-species extrapolation, 10x intra-species variation)	6-month NTP oral toxicity study-mouse LOAEL = 7.5 mg/kg/day based on histopathology observed in bone with degeneration in tibias and femurs of animals

Table 3.2. Sodium Fluoride for Use in Human Risk Assessment			
Exposure Scenario	**Dose (mg/kg/day) used in risk assessment UF**	**Special FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Long-Term Dermal (> 6 months)	LOAEL = 1.3 mg/kg/day	**TARGET MOE =** 300 (10x inter-species extrapolation, 10x intra-species variation and 3x for use of LOAEL)	2-year NTP chronic toxicity/carcinogenicity study in rats LOAEL = 1.3 mg/kg/day, based on dentine dysplasia in males and females, and ameloblast degeneration in males
Short-term Inhalation (1-30 days)	LOAEL = 20 mg/kg/day	**Target MOE**=300 (10x inter-species extrapolation, 10x intra-species variation, 3x for use of LOAEL) Note: 10x route extrapolation for confirmatory inhalation study.	Oral Subchronic Toxicity – Rat (Sodium Fluoride) LOAEL = 20 mg/kg/day, based on significant reductions in body weight gain and suppressed spontaneous motor activity.
Intermediate-term Inhalation	NOAEL = 1.5 mg/kg/day	**Target MOE**=100 (10x inter-species extrapolation, 10x intra-species variation) Note: 10x route extrapolation for confirmatory inhalation study.	6-month NTP oral toxicity study-mouse LOAEL = 7.5 mg/kg/day based on histopathology observed in bone with degeneration in tibias and femurs of animals
Long-term Inhalation	LOAEL = 1.3 mg/kg/day	**TARGET MOE =**300 (10x inter-species extrapolation, 10x intra-species variation, 3x for use of LOAEL) Note: 10x route extrapolation for	2-year NTP chronic toxicity/carcinogenicity study in rats LOAEL = 1.3 mg/kg/day, based on dentine dysplasia in males and females, and ameloblast degeneration

Table 3.2. Sodium Fluoride for Use in Human Risk Assessment			
Exposure Scenario	**Dose (mg/kg/day) used in risk assessment UF**	**Special FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
		confirmatory inhalation study.	in males
Cancer	Sodium fluoride has been classified as a "Group D" (not classifiable as to carcinogenicity). This conclusion is consistent with the recent report by the National Academy of Sciences which concluded that 'the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed.'		

3.3.2 Dermal Absorption

There are no dermal absorption studies for sodium fluoride. Thus, dermal absorption is conservatively assumed to be 100%.

3.3.3 Classification of Carcinogenic Potential

Sodium fluoride has been classified as a "Group D" (inadequate evidence of carcinogenicity). This conclusion is consistent with the recent report by the National Academy of Sciences which concluded that 'the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed.'

3.4 Endocrine Disruption

EPA is required under the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (FQPA), to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that EPA include evaluations of potential effects in wildlife. For pesticides, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, sodium fluoride may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Registered Antimicrobial Uses

Sodium fluoride is used as a remedial wood treatment for the protection against decay producing fungi. Table 7.1 summarizes the various sodium fluoride label parameters used in this assessment including EPA Reg. No., percent active ingredient, signal word, personal protective equipment, and use directions/application methods. Application techniques include a product-specific dispenser, grease/caulking guns, pressurized sprayers, preservative cartridges, brush-on and/or trowel-on applications. The personal protective equipment (PPE) listed on the label range from a minimum protection of goggles to a maximum protection of goggles, gloves, and respirators. Label PPE should be reviewed for accuracy and consistency.

4.2 Dietary Exposure and Risk

There are no antimicrobial uses for sodium fluoride which involve dietary exposure, and thus a dietary exposure and risk assessment are not needed for the antimicrobial uses of this chemical.

4.3 Drinking Water Exposure and Risk

The antimicrobial uses of sodium fluoride are not expected to pose a hazard to ground water or surface water. Therefore, a drinking water exposure and risk assessment is not needed.

4.4 Residential Exposure/Risk Pathway

In general, remedial wood treatment for poles and beams on bridges do not occur in high traffic areas for bystanders. However, distribution poles are numerous and often located in people's front yards. The vapor pressure of sodium fluoride is negligible (i.e., 5.43×10^{-26} mmHg at 25 C), and therefore, no vapor will be released in the vicinity of treated poles. Additionally, label directions to cap treated holes after application will minimize any potential for dermal contact. Likewise, groundline treatments are also covered (i.e., brush-on and wrap treatments are below the groundline and then covered with dirt) and will minimize potential dermal contact to children playing in areas of treated poles.

5.0 AGGREGATE RISK ASSESSMENT AND CHARACTERIZATION

In order for a pesticide registration to continue, it must be shown "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food and drinking water), residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation).

An aggregate risk assessment was not performed for sodium fluoride. There are no dietary exposures from the antimicrobial uses of sodium fluoride, and residential exposures are assumed to be minimal.

6.0 CUMULATIVE EXPOSURE AND RISK

Risks summarized in this document are those that result only from the antimicrobial uses of sodium fluoride. The Food Quality Protection Act (FQPA) requires that the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common toxic mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the substances individually. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for sodium fluoride. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0 OCCUPATIONAL EXPOSURE ASSESSMENT

7.1 Summary of Registered Uses

Sodium fluoride is used as a remedial wood treatment for the protection against decay producing fungi. Table 7.1 summarizes the various sodium fluoride label parameters used in this assessment including EPA Reg. No., percent active ingredient, signal word, personal protective equipment, and use directions/application methods. Application techniques include a product-specific dispenser, grease/caulking guns, pressurized sprayers, preservative cartridges, brush-on and/or trowel-on applications. The personal protective equipment (PPE) listed on the label range from a minimum

protection of goggles to a maximum protection of goggles, gloves, and respirators. Label PPE should be reviewed for accuracy and consistency.

Table 7.1. Summary of Sodium Fluoride Labels.

EPA Reg No.	% ai	Signal Word	PPE	Label Directions (e.g., application techniques, rates,etc)
3008-58	97.5	Danger	Respirator, goggles	Includes a non pesticide statement
75340-2	54.92	Warning	Gloves	TIE-GARD dispenser; grease gun; pressurized applicator; Apply to drilled holes to "fill" and cap; Used on rail road ties and structural timbers such as bridge pilings and posts.
75341-6	92.6	Danger	Gloves	FLURODS (i.e., preservative cartridges, solid sticks) placed into drilled holes and capped. For treating poles, posts, timbers, crossties, etc. Rate: 39.2 grams/cubic foot wood.
75341-4	70.6	Danger	Gloves, goggles	PoleWrap. Groundline treatment. Dig 20 inches around pole, wrap down to 18 inches below groundline to 2 inches above groundline and cover with dirt.
75341-5	44.4	Danger	Goggles	Used in combination with copper naphthenate. Brush-on, trowel-on, grease gun. 1/16th of an inch rate 18 inches below and 3 inches above groundline and covered with a wrap. Also used in drilled holes applied by a grease gun and capped (paste density 12 lbs/gallon).
75341-12	8.39	Danger	Gloves, goggles, respirator, and respirator when spraying for continued or prolonged use or frequent use	Used in combination with copper naphthenate. Mix 1 gallon of product with 1.5 gallons of water. Apply using air or mechanical pressure pump into prepared opening (assume pre-drilled). Rate: 1 gallon of treatment solution per cubic foot of wood.
75341-13	44.42	Warning	Goggles, face shield or safety glasses, protective clothing, and chemical resistant-gloves	Used in combination with copper naphthenate. Brush-on, trowel-on, grease gun. 1/16th of an inch rate 18 inches below and 3 inches above groundline and covered with a wrap. Also used in drilled holes applied by a grease gun and capped.

Chemical-specific exposure data were not submitted to support the remedial wood applications. Therefore, AD developed a screening-level assessment using surrogate data to determine the potential risks associated with remedial wood treatment. Based on the label review listed in Table 7.1 above, there are two basic remedial applications: (1) applying product into pre-drilled holes; and (2) applying product around the circumference of poles at or below the groundline. Each remedial application can be applied using various techniques. Surrogate exposure data are not available for all

application techniques specified on the label. Representative exposure scenarios (i.e., application techniques) are used to represent the potential worker short-, intermediate, and in some cases long-term durations of inhalation and dermal exposures. Table 7.2 presents the representative exposure scenarios used to assess the labeled remedial wood treatment uses.

Table 7.2. Representative Exposure Scenarios for Remedial Wood Treatments.

Remedial Applications	High-end Exposure Scenarios	Application Techniques Represented by the High-end Exposure Scenario
Pre-drilled holes	Closed systems (PPE mitigation)	TIE GARD dispenser for rail ties; FLURODS (solid sticks)
	Sprays	Grease/caulking gun; air or mechanical pressure pump
Groundline	Brush-on	Brush; Trowel; PoleWrap (dry wrap)

7.1.1 Pre-Drilled Hole Treatments

TIE-GARD and FLURODS:

TIE-GARD and FLURODS are sodium fluoride products that are inserted into pre-drilled holes and capped are expected to result in minimal inhalation and dermal handler exposure because the products are engineered to be closed systems. The FLURODS are solid sticks that are placed in the pre-drilled holes. TIE-GARD is a gel product containing sodium fluoride. The automated rail tie use is packaged in 30 gallon PVC closed head drums. It is applied from high capacity rubber track machinery that rides on railroads and automatically injects the gel product into rail ties. Any potential for exposure from leaks/spills from these products (i.e., TIE GARD and FLURODS) is believed to be best mitigated by the label requirement of PPE such as chemical resistant gloves, goggles, long pants, and long sleeved-shirts. Therefore, the handler risks to pre-packaged products are not quantified.

Spray/Injection Applications:

Although EPA does not have a specific surrogate exposure scenario for injection of pesticides into wooden poles, similar exposure data for hand-held application equipment exist. The spray application is believed to represent the high end of exposure to the grease gun. The exposure data for hand-held applications that are available to EPA include data from the Pesticide Handlers Exposure Database (PHED) and the Outdoor Residential Exposure Task Force (ORETF). The data available from these sources are for garden hose-end sprayers, low pressure hand-wands, backpack sprayers, high pressure handwands, and rod shank termiticide applications. The most representative data available for an injection-type hand-held devise is the rod shank termiticide application from PHED. Other equipment types are not believed to be as representative because each one involves a spray and the injection into the pole will minimize spray.

The rod shank termiticide injection data in PHED are used to develop a screening-level assessment for the pole use. The dermal unit exposure (UE) for combined liquid pour and termiticide injection is based on 17 replicates with the test subjects wearing a single layer of clothing and chemical resistant gloves with AB grades (i.e., guideline recommendations for analytical quality). The dermal UE is 0.36 mg/lb ai. The inhalation UE is based on the same 17 replicates and the grades are also AB. The inhalation UE is 0.0022 mg/lb ai. Although not all of the labels currently specify the use of chemical resistant gloves (e.g., EPA Reg. No. 75341-5), the "gloved" clothing scenario is the only one available to assess risks.

7.1.2 Groundline Treatments

Groundline treatments consist of brush and trowel-on applications as well as impregnated wraps around poles. Once applied, the pole treatment is covered with dirt. The most representative surrogate exposure data available to assess the high-end of the exposure potential are for painting with a paint brush. The product is expected to have a much higher viscosity then paint. Because of the high viscosity and low vapor pressure, inhalation exposure is expected to be minimal. Dermal unit exposure values for paint brush applications from PHED were used (single layer of clothing). The dermal unit exposure is 24 mg/lb a.i. for the painting scenario for a test subject wearing long pants, long-sleeved shirt, and chemical resistant gloves.

7.2 Application Rates and Amounts Handled

Label directions indicate that sodium fluoride is applied into poles, timbers, etc, via four different formulations; paste, bandage or wrap, liquid and solid rods. The application for these formulations is very different from each other due to the physical properties and percentage of sodium fluoride present in each formulation. Typically paste formulations are applied by brush-on application around the groundline area of pole and then wrapped with a protective barrier before being backfilled with dirt. The dry impregnated wrap is applied around the groundline portion of the pole. Liquid formulations are normally applied to internal voids through means of pressurized injection and rods are applied by drilling application holes, inserting the rods into the holes and then plugging them.

Labeled application rates for pastes are to apply by brush to a thickness of 1/16th inch. The dry wrap is applied by cutting the wrap to match the circumference of the pole. Liquid application instructions include filling application holes to refusal and more specific instructions such as 1 gallon of diluted solution per cubic foot of wood. However, label directions are not provided to determine neither the number of holes per pole nor the number of cubic feet per pole to be treated with sodium fluoride. Therefore, for this assessment 1 cubic foot of wood per pole is assumed to be treated for the spray/injection application.

Specific amounts of sodium fluoride applied by workers daily are not available. Therefore, in addition to the number of cubic feet treated per pole, the number of poles treated per day (i.e., pre-drilled treatments, not groundline applications) with sodium fluoride was also estimated.

The amount of paste applied to each pole for groundline treatments is estimated to be 0.167 gallons/pole for distribution poles and 0.255 gallons per transmission pole (i.e., 21 inch wide treatment x up to 34 inch circumference for distribution poles and 50 inches for transmission poles x 1/16 inch thickness of product treatment).

- Distribution Poles - the smaller diameter wooden distribution poles (~140 million distribution poles in service) are treated at a high end rate of ~24 per day (for short-term duration). Workers treat these types of poles as their main work function, treating 5 days per week, on a yearly basis (i.e., 250 days/year). This scenario is represented by the short-, intermediate- and long-term exposure durations.

- Transmission Poles - the larger wooden transmission poles are treated at a rate of 30 per day. Workers treat these types of poles as their main work function, treating 5 days per week, on a yearly basis (i.e., 250 days/year). This scenario is represented by the short-, intermediate- and long-term exposure durations.

7.3 Exposure and Risk Estimates

Table 7.3 presents the potential dermal and inhalation short-, intermediate-, and long-term exposures and risks for the remedial pole treatment uses of sodium fluoride. The exposure and risks to handlers of the TIE-GARD product used in the automated rail tie treatment system and the solid stick FLURODS are expected to be minimal and are not quantified.

For the spray applications into pre-drilled holes for the transmission poles, the inhalation (all durations) and short-term dermal risks are not of concern. However, the short-, intermediate- and long-term dermal risks for the transmission poles are of concern. The short-, intermediate- and long-term dermal MOEs are 280, 21 and 18, respectively, with a target MOE of 300 for short-term and 100 for intermediate-term.

All of the dermal MOEs are below the target MOE for the groundline brush-on treatments (MOEs less then or equal to 1). The brush-on treatment also represents the high-end exposures for the trowel-on and impregnated wraps. Inhalation exposure is expected to be minimal for the groundline treatments because of the viscosity of the product as well as its low vapor pressure

Table 7.3. Dermal and Inhalation Exposure and Risks for Remedial Applications of Sodium Fluoride to Poles.

Application	Dermal UE (mg/lb a.i)	Inhalation UE (mg/lb a.i)	Rate (gal/pole)	Rate (lb a.i/gal)	# poles	Dermal dose (mg/kg/day)	Inhalation dose (mg/kg/day)	Dermal MOEs			Inhalation MOEs		
								ST (300)	IT (100)	LT (300)	ST (300)	IT (100)	LT (300)
Spray (Distribution Poles)	0.36	0.0022	1	0.47	24	0.058	0.00035	350	26	22	56,000	4200	3700
Spray (Transmission Poles)	0.36	0.0022	1	0.47	30	0.073	0.00044	280	21	18	45,000	3400	2900
Brush-on (Distribution Poles)	24	NA	0.225	5.33	24	5.17	NA	4	NA	NA	NA		
Brush-on (Transmission Poles)	24	NA	0.368	5.33	30	20.2	NA	1	NA	NA	NA		

UE are from PHED for termiticide MLAP, liquid pour, rod shank injection
Dermal UE is single layer of clothing and chemical resistant gloves.
Treatment solution for spray from EPA Reg. No. 75341-12 (i.e., 1 gal product x 8.34 lb/gal x 8.39% a.i / 1.5 gallons water = 0.47 lb a.i/gal treatment solution)
Brush-on rate EPA Reg No 75341-5 is 44.4% a.i; density of 12lb/gal = 5.33lb a.i./gallon
poles = registrant estimate during the reregistration phase 1 error comment period (Distribution is 24 poles per day and transmission is 30 poles per day
Dermal (mkd) = Dermal UE x rate x # poles x 1/70kg
Inhalation dose (mkd) = Inhalation UE x rate x #poles x 1/70kg
MOE ST Dermal & inhalation = LOAEL 20 mkd / dose; UF = 300
MOE IT Dermal & Inhalation = NOAEL 1.5 mkd / dose; UF = 100
MOE LT Dermal & Inhalation = LOAEL 1.3 mkd / dose; UF = 300

NA = Not applicable (e.g., short-term (ST) MOEs are only applicable for the high treatment frequency of poles).
ST = short-term; IT = intermediate-term; LT = long-term.

7.4 Data Limitations/Uncertainties

EPA has used the best available surrogate exposure data from PHED and CMA to develop a screening-level assessment for the handlers of sodium fluoride. The following uncertainties should be considered by the regulatory risk managers during the decision making process:

- Unit exposures are not available for the scenarios that are prescribed for remedial pole injection. Nonetheless, the data from PHED for combined mixing/loading/injecting a liquid termiticide is a reasonable surrogate for the pole treatment as the label for the remedial wood treatment indicates to apply a spray into predrilled holes with an air or mechanical pressure pump. The PHED termiticide scenario is considered to be of "high confidence" (i.e., 17 replicates of Grade AB data – indicating the analytical portion of the study meets EPA exposure test guidelines).

- Sodium fluoride is used to treat both poles and timbers. The assessment for the remedial wood treatments is based on applications to distribution and transmission poles as representative of all the remedial treatments. Although it is unknown how many timbers in a bridge or other structure are treated, the pole use is believed to be representative of the high end use.

- The use information for the remedial pole treatments is based on the registrant's response during the error comment period. The individuals contacted have experience in these operations and their estimates are believed to be the best available without undertaking a statistical survey of the uses.

8.0 ENVIRONMENTAL RISKS

8.1 Ecological Hazard

8.1.1 Toxicity to Terrestrial Animals

8.1.1.1 Birds, Acute

In order to establish the toxicity of sodium fluoride to avian species, the Agency requires an acute oral toxicity study using the technical grade active ingredient (TGAI). The preferred test species is either mallard duck (a waterfowl) or bobwhite quail (an upland game bird). The results of one acute oral toxicity study submitted for sodium fluoride are provided in the following table (Table 8.1).

Table 8.1. Acute Oral Toxicity of Sodium Fluoride to Birds

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/kg)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
Bobwhite quail (*Colinus virginianus*)	Sodium Fluoride 95%	LD_{50} = > 387 NOAEL = 45	Moderately toxic	Yes (core)	43611501

This acceptable acute oral toxicity study on the bobwhite quail indicates that sodium fluoride is moderately toxic on an acute oral basis. The guideline requirement OPPTS 850.2100 is satisfied.

8.1.1.2 Birds, Subacute

A subacute dietary study using the TGAI may be required on a case-by-case basis depending on the results of lower-tier ecological studies and pertinent environmental fate characteristics in order to establish the toxicity of a chemical to avian species. The preferred-test species are the mallard duck and bobwhite quail. The results of subacute dietary toxicity studies for sodium fluoride are provided in the following table (Table 8.2).

Table 8.2. Subacute Oral Toxicity of Sodium Fluoride to Birds

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (ppm)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
Bobwhite quail (*Colinus virginianus)*	Sodium Fluoride 95%	LC_{50} (diet) = >5620 NOAEC = 1000	Practically nontoxic	Yes (core) - 8-day test duration	43593102
Mallard duck (*Anas platyrhynchos)*	Sodium Fluoride 95%	LC_{50} (diet) = >5620 NOAEC = 5620	Practically nontoxic	Yes (core) - 8-day test duration	43593101

Sodium fluoride is practically nontoxic to avian species through subacute dietary exposure. These studies fulfill guideline requirements OPPTS 850.2200 (Bobwhite quail and Mallard duck).

8.1.1.3 Mammals, Acute and Chronic Toxicity

Wild mammal testing is not required by the Agency. In most cases, rat toxicity values obtained from studies conducted to support data requirements for human health risk assessments substitute for wild mammal testing. Refer to the human toxicology chapter for mammalian toxicity data.

8.1.1.4. Non-target Insects

Honeybees should not be exposed to sodium fluoride wood treatments due to the requirement to wrap the treated area with a waterproof barrier or the requirement to inject sodium fluoride into the wood and then seal the bore hole. Beehives should not be constructed from or treated with sodium fluoride. The product label(s) must state: "Sodium fluoride must not be used to treat wood intended for construction or maintenance of beehives." Otherwise, the following bee toxicity and honey residue studies are required: 850.3020, 850.3030 and 860.1500.

8.1.2 Toxicity to Aquatic Animals

8.1.2.1 Freshwater Fish, Acute

In order to establish the acute toxicity of sodium fluoride to freshwater fish, the Agency requires a freshwater fish toxicity studies using the TGAI. Preferred test species are rainbow trout (a cold water fish) and bluegill sunfish (a warm water fish). The results of two freshwater fish acute studies submitted for sodium fluoride are presented in Table 8.3.

Table 8.3. Acute Toxicity of Sodium Fluoride to Freshwater Fish

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
Bluegill Sunfish (*Lepomis macrochirus)*	Sodium fluoride 95%	LC_{50} = 830 NOAEC = 350	Practically nontoxic	Yes (core) - 96-hr test duration - static renewal test system	43648201

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
Rainbow Trout (*Oncorhynchus mykiss*)	Sodium fluoride 95%	LC_{50} = 317 NOAEC = < 26	Practically nontoxic	Yes (core) - 96-hr test duration - static test system	43648202

Freshwater acute toxicity tests indicate that sodium fluoride is practically nontoxic to fish on an acute basis. Study 43648201 fulfills the guideline requirement for the warm water species and study 43648202 fulfills the guideline requirement for the cold water fish species under OPPTS 850.1075.

8.1.2.2 Freshwater Invertebrates, Acute

The Agency requires a freshwater aquatic invertebrate study using the TGAI to establish the acute toxicity to freshwater invertebrates. The preferred test species is *Daphnia magna*. The result of one study submitted for sodium fluoride is provided in the following table (Table 8.4).

Table 8.4. Acute Toxicity of Sodium Fluoride to Freshwater Invertebrates

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
Waterflea (*Daphnia magna)*	Sodium Fluoride 95%	EC_{50} = > 120 NOAEC = 120	Practically nontoxic	Yes (core) - 48-hr test duration - static test system	43648203

The results of 43648203 indicate that sodium fluoride is practically nontoxic to freshwater invertebrates. This study fulfills guideline requirement OPPTS 850.1010.

8.1.2.3 Estuarine and Marine Organisms, Acute

Acute toxicity testing with estuarine and marine organisms using the TGAI is required when the end-use product is intended for direct application to the

marine/estuarine environment or effluent containing the active ingredient is expected to reach this environment. The preferred fish test species is the sheepshead minnow. The preferred invertebrate test species are mysid shrimp and eastern oysters. Sodium fluoride is not expected to reach the estuarine or marine environment, therefore, studies OPPTS 850.1075, OPPTS 850.1035, and OPPTS 850.1025 are not required for the current wood treatment use patterns.

8.1.2.4 Aquatic Organisms, Chronic

Chronic toxicity tests (fish early life stage and aquatic invertebrate life cycle) are required for pesticides when certain conditions of use and environmental fate apply. The preferred freshwater fish test species is the fathead minnow. The preferred freshwater invertebrate is *Daphnia magna*. Sodium fluoride is not expected to present a chronic aquatic toxicity concern, therefore, studies OPPTS 850.1300 and OPPTS 850.1400 are not required for the current wood treatment use patterns.

8.1.3 Toxicity to Plants

Non-target plant phytotoxicity tests are required for pesticides when certain conditions of use and environmental fate apply. Tests are conducted with one species of aquatic vascular plant (*Lemna gibba*) and four species of algae: (1) freshwater green alga, *Selenastrum capricornutum,* (2) marine diatom, *Skeletonema costatum,* (3) freshwater diatom, *Navicula pelliculosa,* and (4) bluegreen cyanobacteria, *Anabaena flos-aquae*. The rooted aquatic macrophyte rice (*Oryza sativa*) is also tested in seedling emergence and vegetative vigor tests.

Current sodium fluoride wood treatment use patterns are not expected to result in surface water or spray drift residues of sufficiently large quantities to adversely affect terrestrial or aquatic plant species. Therefore, non-target plant toxicity studies 850.4225, 850.4400, and 850.5400 are not required for the current wood treatment use patterns.

8.1.4 RISK QUOTIENTS

Risk characterization integrates the results of the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects. The means of this integration is called the quotient method. Risk quotients (RQs) are calculated by dividing exposure estimates by acute and chronic ecotoxicity values.

RQ = EXPOSURE/TOXICITY

RQs are then compared to OPP's levels of concern (LOCs). These LOCs are used by OPP to analyze potential risk to nontarget organisms and the need to consider regulatory action. The criteria indicate that a pesticide used as directed has the potential to cause adverse effects on nontarget organisms. LOCs currently address the following risk presumption categories: (1) **acute** -- potential for acute risk to non-target organisms which may warrant regulatory action in addition to restricted use classification, (2) **acute**

restricted use -- the potential for acute risk to non-target organisms, but may be mitigated through restricted use classification, (3) **acute endangered species** - endangered species may be adversely affected by use, (4) **chronic risk** - the potential for chronic risk may warrant regulatory action, endangered species may potentially be affected through chronic exposure, (5) **non-endangered plant risk** – potential for effects in non-target plants, and (6) **endangered plant risk** – potential for effects in endangered plants. Currently, OPP does not perform assessments for chronic risk to plants, acute or chronic risks to nontarget insects, or chronic risk from granular/bait formulations to birds or mammals.

The ecotoxicity test values (measurement endpoints) used in the acute and chronic risk quotients are derived from required studies. Examples of ecotoxicity values derived from short-term laboratory studies that assess acute effects are: (1) LC_{50} (fish and birds), (2) LD_{50} (birds and mammals), (3) EC_{50} (aquatic plants and aquatic invertebrates) and (4) EC_{25} (terrestrial plants). Examples of toxicity test effect levels derived from the results of long-term laboratory studies that assess chronic effects are: (1) LOAEC (birds, fish, and aquatic invertebrates), and (2) NOAEC (birds, fish and aquatic invertebrates). For birds and mammals, the NOAEC generally is used as the ecotoxicity test value in assessing chronic effects, although other values may be used when justified. However, the NOAEC is used if the measurement endpoint is production of offspring or survival.

Risk presumptions and the corresponding RQs and LOCs are tabulated below in Table 8.5.

Table 8.5. Risk Presumption Categories

Risk Presumption for Terrestrial Animals	**LOC**
Acute: Potential for acute risk for all non-target organisms	>0.5
Acute Restricted Use: Potential for acute risk for all non-target organisms, but may be mitigated through restricted use classification	>0.2
Acute Endangered Species: endangered species may be adversely affected by use	>0.1
Chronic Risk: potential for chronic risk may warrant regulatory action	>1
Risk Presumption for Aquatic Organisms	**LOC**
Acute: Potential for acute risk for all non-target organisms	>0.5
Acute Restricted Use: Potential for acute risk for all non-target organisms, but may be mitigated through restricted use classification	>0.1
Acute Endangered Species: endangered species may be adversely affected by use	>0.05
Chronic Risk: potential for chronic risk may warrant regulatory action	>1
Risk Presumption for Terrestrial and Aquatic Plants	**LOC**
Potential for risk for all non-endangered and endangered plants	>1

8.2 Environmental Fate Assessment

Sodium fluoride is an organic substance which does not undergo hydrolysis but is water soluble and dissociates in water to sodium and fluoride ions. Fluoride ions undergo hydrolysis to form hydrogen fluoride acid and hydroxide ions which can shift the pH to alkaline. Sodium fluoride does not adversely affect soil biomass, microflora and macro invertebrates, and is not expected to be bio-accumulative. A field monitoring study of sodium fluoride treated poles found that sodium fluoride ions occasionally exceed background levels and do not migrate outward from treated poles more than 10 cm or for more than 50 cm deep. Elevated levels returned to background by the end of the 18 month study. Sodium fluoride is not expected to pose a hazard to groundwater or surface waters. (Refer to the Environmental Fate Science Chapter for greater detail.)

8.3 Environmental Exposure and Ecological Risk Assessment

An environmental risk assessment was not conducted for sodium fluoride wood treatment uses because precautions are taken to prevent release into the terrestrial or aquatic environment. Some exposure to woodpeckers and wood boring insects may occur, however, sodium fluoride is practically nontoxic to avian and aquatic species tested. Any incidental exposure is not expected to be toxic to non-target species.

8.4 Endangered Species Considerations

Section 7 of the Endangered Species Act, 16 U.S.C. Section 1536(a)(2), requires all federal agencies to consult with the National Marine Fisheries Service (NMFS) for marine and anadromous listed species, or the United States Fish and Wildlife Services (FWS) for listed wildlife and freshwater organisms, if they are proposing an "action" that may affect listed species or their designated habitat. Each federal agency is required under the Act to insure that any action they authorize, fund, or carry out is not likely to jeopardize the continued existence of a listed species or result in the destruction or adverse modification of designated critical habitat. To jeopardize the continued existence of a listed species means "to engage in an action that reasonably would be expected, directly or indirectly, to reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of the species." 50 C.F.R. § 402.02.

To facilitate compliance with the requirements of the Endangered Species Act subsection (a) (2) the Environmental Protection Agency, Office of Pesticide Programs has established procedures to evaluate whether a proposed registration action may directly or indirectly reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of any listed species (U.S. EPA 2004). After the Agency's screening-level risk assessment is performed, if any of the Agency's Listed Species LOC Criteria are exceeded for either direct or indirect effects, a determination is made to identify if any listed or candidate species may co-occur in the area of the proposed pesticide use. If determined that listed or candidate species may be present in the proposed use areas, further biological assessment is undertaken. The extent to which listed species may be at risk then

determines the need for the development of a more comprehensive consultation package as required by the Endangered Species Act.

This preliminary analysis indicates that current sodium fluoride wood treatment uses are not likely to enter the environment in sufficient quantities to adversely affect terrestrial or aquatic species, however, an endangered species effects determination will not be made at this time.

9.0 INCIDENT REPORTS

The Agency reviewed the following information for human poisoning incidents related to sodium fluoride use: **(1) OPP Incident Data System (IDS)** – The Office of Pesticides Programs (OPP) **Incident Data System** contains reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992; **(2) California Department of Pesticide Regulation (1982-2004)** - The California Department of Pesticide Regulation pesticide poisoning surveillance program consists of reports from physicians of illness suspected of being related to pesticide exposure since 1982. **(3) National Pesticide Information Center (NPIC)** – NPIC is a toll-free information service supported by OPP that provides a ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991. **(4) National Poison Control Centers (PCC) (1993-1996)**. **(5) Incident Reports / Epidemiological Studies Published in Scientific Literature**

Between 1993 and 2003 there were 5 reported incidents in the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS). From 1993-1998 two cases involving oral exposure were reported with patients exhibiting symptoms such as blurred visions, chest and abdominal pain as a result of the exposure. These were considered to be moderate effects and were not life-threatening and the patients have returned to a pre-exposure state of well-being with no residual disability or disfigurement. From 1999-2003, three cases (two involving oral exposure and one involving aerosol inhalation exposure) were reported. For oral exposure, vomiting was the primary reported symptom while nausea and headache were the primary reported symptoms for inhalation exposure. These three cases were classified as minor effects as symptoms resolved rapidly and subjects returned to a pre-exposure state of well being with no residual disability or disfigurement.

The California Department of Pesticide Regulation has one reported incident involving sodium fluoride where a worker applying wood preservative to the base of a telephone pole, got some on his cheek. While wiping it off with his sleeve, he rubbed it into his left eye. He flushed the eye with a portable kit. The reported symptoms included pain, burning sensation, and marked conjunctival infection in the left eye. However, creosote and potassium dichromate may also have been involved in this incident.

There are some concerns associated with sodium fluoride exposure reported in the public literature.

Acute Effects

Direct contact with fluoride can result in tissue damage. At high concentrations, fluoride can cause irritation and damage to the respiratory tract, stomach, and skin following inhalation, oral, and dermal exposure, respectively (ATSDR, 2003). Dermal irritation and contact urticaria have been reported from dermal contact of sodium fluoride (Camarasa et al., 1993).

There are incidences associated with sodium fluoride through acute oral ingestion (Abukurah et al. 1972; Hayes, 1975; Eichler et al., 1982). As summarized by Dreisbach (1987), through oral exposure, soluble fluoride salts may cause salivation, nausea and vomiting, diarrhea, and abdominal pain. Later, weakness, tremors, shallow respiration, carpopedal spasm, and convulsions occur. Death is by respiratory paralysis. If death does not occur immediately, jaundice and oliguria may appear. Experience with oral fluoride supplements used to prevent tooth decay has been reassuring; no adverse effects occur unless enormous amounts are ingested. A variety of metabolic disorders may occur including hypocalcemia, hypomagnesemia, metabolic and/or respiratory acidosis and sometimes hyperkalemia, may also occur in acute fluoride poisoning (Gosselin, et al., 1984).

Cardiac effects have been reported associated with acute sodium fluoride through oral, dermal, and/or inhalation exposure routes. Approximately 2 hours after ingestion of 120 g of roach powder (97% sodium fluoride) in an unsuccessful suicide attempt, a 25-year-old male had severe toxic reactions that included tetany, multiple episodes of ventricular fibrillation, and esophageal stricture (Abukurah et al. 1972). Within 14 hours following exposure, the patient experienced 63 episodes of ventricular fibrillation. For example, a plasma fluoride level of 2,000 μg/L was reported in a case of severe oral poisoning with 53 g fluoride as sodium fluoride (Abukurah et al. 1972). The noticed cardiac symptoms may be associated with the metabolic disorder resulted from acute fluoride exposure.

Chronic Effects

Fluoride intake has been shown to decrease the prevalence of dental caries. However, chronic exposure to high levels of fluoride, especially through the oral route, can cause dental fluorosis and can result in an increased prevalence of bone fractures in the elderly or skeletal fluorosis (ATSDR, 2003).

Numerous epidemiological studies have examined the issue of a connection between fluoridated water and heart disease. There are studies indicating no significant differences between areas with different fluoride levels in mortality due to coronary disease, angina, and other heart disease (Leone et al. 1954; Heasman and Martin 1962). Although one study demonstrated a positive relationship between heart disease and water fluoridation (Hagan et al. 1954), this study was criticized for not properly age-adjusting the sample population (Jansen and Thomson, 1974). Other studies have suggested

fluoridation can decrease the incidence of cardiovascular disease (Bernstein et al. 1966; Luoma 1980; and Taves, 1978).

Numerous epidemiological studies have examined the issue of a connection between fluoridated water and cancer. Most studies have not found significant increases in cancer mortality (Erickson 1978; Hoover et al. 1976; Rogot et al. 1978; Taves 1977) or site-specific cancer incidence (Freni and Gaylor 1992; Gelberg et al. 1995; Hoover et al. 1976; Mahoney et al. 1991; McGuire et al. 1991). However, a couple of studies have reported significant fluoridation-related increases in cancer mortality**.** In order to address the cancer concern, the National Toxicology Program (NTP) conducted two chronic oral bioassays of fluoride administered as sodium fluoride (0, 25, 100, or175 ppm) in drinking water for 103 weeks, using F344/N rats and B6C3F1 mice (NTP, 1990). The estimated total fluoride intake (including fluoride in both water and diet) of control, low-, medium-, and high-dose male rats was 0.2, 0.8, 2.5, and 4.1 mg/kg/day, respectively. Similarly, the high doses for female rats, male mice, and female mice were 4.5, 8.1, and 9.1 mg/kg/day, respectively. The study found osteosarcomas in the bone of 1/50 male rats in the mid-dose group and 3/80 of the high dose male rats. An additional high-dose male had an extra skeletal osteosarcoma in subcutaneous tissue. Osteosarcomas were observed in one low-dose male mouse, one low-dose female mouse, and one control female mouse. There was also one osteoma in a control female mouse. No osteosarcomas were observed at mid- or high-dose levels in female rats or male or female mice.

In 1996, the EPA's Office of Prevention, Pesticides, and Toxic Substances classified sodium aluminofluoride (cryolite) as a "Group D" carcinogen (not classifiable as to carcinogenicity), citing the National Toxicology Program's carcinogenicity study of sodium fluoride (NTP, 1990). More recently, the National Academy of Sciences (NAS, 2006) at the request of the EPA conducted a review of the toxicologic, epidemiologic, and clinical data on fluoride since the 1993 NAS report. With respect to carcinogenicity, the 2006 NAS report concluded that "on the basis of the committee's collective consideration of data from humans, genotoxicity assays, and studies of mechanism of action in cell systems…the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed." This recent conclusion is consistent with the past conclusion of OPPTS regarding carcinogenic potential of fluoride.

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APPENDIX A

Toxicity Profile for Sodium Fluoride

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
870.3100 (§ 82-1) 90-Day oral toxicity in rodents Purity: 99%	Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). National Toxicology Program, Technical Report Series No. 393, NIH Publication No. 91-2848, December 1990, Pgs. 1-477. **Acceptable** Guideline 10 F344/N rats/sex/dose administered sodium fluoride at doses of 0, 10, 30, 100, or 300 ppm for 6 months	**NOAEL = 30 ppm** **LOAEL = 100 ppm**, based on the presence of hyperplasia in the glandular stomach There were no treatment-related effects on mortality. Treatment-related effects were noted in 300-ppm treated rats including clinical observations of dental fluorosis (chalk white appearance of teeth, overgrowth of upper incisors, occlusal surface of the lower incisor worn to the gum, unusual wear pattern of incisors) and rough hair coat, decreased food and water consumption, and reductions in mean body weight and body weight change. Measurement of fluoride content revealed a dose-dependent increase in fluoride concentration in bone and urine, while elevated levels of fluoride in plasma were only observed in 300-ppm treated rats. Treatment-related macroscopic effects were observed in the 300-ppm treated rats. A majority of the high-dose males exhibited thickened stomachs. Focal or multifocal punctate hemorrhages, perforated ulcer of the glandular stomach, and multiple, small, nonperforated ulcers were also observed in several 300-ppm males and/or females. These macroscopic changes were supported by microscopic evidence of pathology. Dose-dependent increases in incidence and severity of hyperplasia and necrosis of the glandular stomach was observed in rats treated with ≥100 ppm. Diffuse hyperplasia of the mucosal epithelium of the glandular stomach was noted in

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		5/10 males and 2/10 females treated with 100 ppm, and in 10/10 males and 9/10 females treated with 300 ppm. This effect was accompanied by minimal individual cell necrosis (apoptosis) in the pyloric region in 300-ppm treated rats, and by evidence of acute inflammation in several males at 300 ppm. Focal basal cell hyperplasia of the stratified squamous epithelium was located adjacent to the limiting ridge in nearly all 300-ppm treated rats. Microscopic evidence of the effects of the test article on the incisors included focal or multifocal degeneration of the enamel organ in 300-ppm males (5/10), localized in the maturation zone near the apical end of the tooth.
870.3100 (§ 82-1) 90-Day oral toxicity in rodents Purity: 99%	Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). National Toxicology Program, Technical Report Series No. 393, NIH Publication No. 91-2848, December 1990, Pgs. 1-477. **Acceptable** Guideline 8-12 B6C3F1 mice/sex/dose administered deionized water at doses of 0, 10, 50, 100, 200, 300 or 600 ppm for 6 months	**NOAEL = 50 ppm in female mice, and could not be determined in males** based on the observation of increased osteoid of the tibia in 5/10 males dosed at 50 ppm. **LOAEL = 50 ppm in male mice and 100 ppm in female mice** based on histopathology observed in bone. Premature deaths, including sacrifice due to moribundity, occurred at 300 ppm (1 male) and 600 ppm (4 males and 9 females) dose levels. Clinical signs of thin appearance, hunched posture and weakness were observed in several of the decedents prior to premature sacrifice. Clinical signs in surviving animals included chalky white incisors (≥100 ppm) and chipped teeth (≥300 ppm). The effects on the incisors correlated with microscopic findings, which

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		included focal or multifocal degeneration of the enamel organ. Mean body weight was significantly decreased in 600-ppm treated males and in 200- and 300-ppm treated females. Mean body weight gain was significantly decreased in ≥200-ppm males and in 200- and 300-ppm females. These parameters were also decreased in the 600-ppm females, but did not reach statistical significance, likely due to the reduced number of animals in this group as a result of premature deaths. Food consumption in 600-ppm males was approximately 77% of controls. Food consumption in the other treatment groups and water consumption in all treatment groups were within 20% of control values. There was a dose-dependent increase in fluoride content in bone and urine. Due to the pooling of plasma samples for sufficient volume for analysis, meaningful statistical analyses in this fluid could not be performed. The data indicate that there was generally a dose-dependent increase in fluoride concentration in the plasma. Animals that died prior to the termination of the study had noted histopathology in the kidney, liver, testes, and/or myocardium. Nephrosis in the kidneys and/or myocardial degeneration and mineral accumulation in degenerate myofibers were the likely causes of death in some of the decedents. Multifocal megalocytosis and syncytial alteration were observed primarily in the livers of 600-ppm treated mice. Necrosis, tubule degeneration, and the

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		presence of multinucleated giant cells in the seminiferous tubules were also noted in the males that died prior to terminal sacrifice; however, it could not be determined if these effects were due to treatment with sodium fluoride or secondary to the mice dying from other unrelated causes. Bone lesions, in the form of increased osteoid, were observed in the femurs of treated mice at ≥100 ppm, and in the tibias at 50 ppm. This histopathology is indicative of altered rates of bone deposition and remodeling as a result of treatment. Further, treatment with sodium fluoride induced degeneration of the incisors as evidenced by degeneration (dysplasia) in ≥300-ppm treated mice.
Non-Guideline Oral Subchronic (Rodent) Purity not reported	Bohatyrewicz, A. (1999). Effects of Fluoride on Mechanical Properties of Femoral Bone in Growing Rats. Fluoride 32:47-54. **Open Literature** 10 female 6-week-old Wistar rats/group administered NaF at levels of 0, 8, 30, and 60 mg of fluoride/L in drinking water for 6 weeks. Femoral bones from each rat were assayed for bending strength	High fluoride intake (30 and 60 mg/L) significantly decrease bone quality of the femoral shaft and neck of young rats. NaF administered in lower concentrations (8 mg/L) significantly increases the strength of the femoral neck from the control.
Non-Guideline Oral Subchronic (Rodent) Purity not reported	Paul, V. et al. (1998). Effects of Sodium Fluoride on Locomotor Behavior and a Few Biochemical Parameters in rats. Environmental Toxicol and Pharmacol 6:187-191. **Open literature**	Subchronic Toxicity: **NOAEL < 20 mg/kg/day (lowest dose tested)** **LOAEL ≤ 20 mg/kg/day** based on significant reductions in body weight gain and suppressed spontaneous motor activity. There were significant dose-

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	10 female Wistar rats/dose administered Sodium Fluoride via oral intubation at dose levels of 20 or 40 mg/kg/day for 60 days.	dependant decreases of 17 and 30% for food intake and 14 and 37% for body weight gain at the 20 and 40 mg/kg/day dose levels, respectively. Total protein concentrations in serum (low-dose, 13%; high-dose, 38%), liver (low-dose, 22%; high-dose, 42%), and skeletal muscle (low-dose, 15%; high-dose, 31%) were also significantly reduced in a dose-related manner in animals treated with sodium fluoride. Spontaneous motor activity was suppressed in a dose-dependant manner with decreases of 15 and 29% at the 20 and 40 mg/kg/day dose levels, respectively. However, motor co-ordination was not altered in treated animals. Total blood cholinesterase activity was reduced at the low- and high-dose, although there was no evidence of change in acetyl-cholinesterase activity of the cerebral cortex, brain stem, or cerebellum. Food intake reductions may account for the decrease in protein concentration of a direct deleterious action of fluoride on protein metabolism can also play a role in depleting protein in sensitive tissues. Thus, a decreased food intake together with a depletion of protein in soft tissues accounted for an inhibition of body growth in sodium fluoride-treated animals. Sodium fluoride deprived skeletal muscle of total protein and suppressed blood cholinesterase activity; although, these effects are unlikely to have a deteriorating action on neuromuscular function. However, similar sodium fluoride doses can produce neurobehavioral deficit resulting

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		in an inhibition of spontaneously occurring locomotor activity.
Non-Guideline Oral Subchronic (Rodent) Purity not reported	Pillai et al. (1988). Effect of Subacute Dosage of Fluoride on Male Mice. Toxicology Letters 44:21-29. **Open Literature** 5 Male Swiss albino mice administered 5.2 mg F/kg/day for 35 days.	**NOAEL ≤ 5.2 mg/kg/day (lowest dose tested)** **LOAEL ≤ 5.2 mg/kg/day**, based on significant decreases in body weight gain, and food and water consumption. There were significant changes in hematological analyses with decreases in red blood cells, lymphocytes, hemoglobin, albumin, total protein, cholesterol, glucose, and alkaline phosphatase. Statistically significant increases were observed in white blood cells, monocytes, basophils, and eosinophils. Food and water consumption was significantly decreased in treated animals compared to controls. There were significant treatment-related decreases from controls in body weight gain of sodium fluoride-treated mice after day 19 of the treatment period. A significant relationship between food and water consumption and the body weight was observed in the controls, but not in the treated animals. Significant increases in fluoride content were measured in the kidneys, stomach, brain, liver, and intestines of the sodium-fluoride-treated animals when compared to the controls. The increases were 3.5- and 1.5 fold greater than control in the kidneys and stomach, respectively, while the brain, intestines, and liver exhibited 2-fold increases over control. There was no evidence of sperm abnormalities following treatment with sodium fluoride.

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
Non-Guideline Oral Subchronic (Rodent) Purity: 99%	Chinoy and Patel. (2001). Effects of Sodium Fluoride and Aluminum Chloride on Ovary and Uterus of Mice and Their Reversal by Some Antidotes. Fluoride 1:9-20. **Open Literature** 20 Adult female albino mice administered 10 mg/kg/day NaF for 30 days.	Significant decline of ovarian protein and 3-beta- and 17-beta-hydroxysteroid dehydrogenase activities, which could be related to increased cholesterol levels in the ovary suggesting altered steroidogenesis.
Special Study Subchronic (subcutaneous injection) Toxicity Purity not reported	Shahshi et al. (1994). Effect of Long-term Administration of Fluoride on Levels of Protein, Free Amino Acids and RNA in Rabbit Brain. Fluoride 27.3:155-159. **Open Literature** Albino rabbits administered sodium fluoride via subcutaneous injection for 100 days at 0, 5, 10, 20, and 50 mg/kg/day. 12 animals/group	Fluoride treated rabbits showed a significant decline in soluble, basic, and total protein and free amino acid levels. RNA content rapidly decreased, except in male rabbits treated with 5 and 10 mg/kg/day sodium fluoride. Decreased body weight gain in the 20 and 50 mg/kg/day groups. Some animals in the 10, 20, and 50 mg/kg/day groups showed paralysis by day 35. No rabbits in the 50 mg/kg/day group survived the experiment.
870.3700a Developmental Toxicity (Rodent) Purity > 99%	Bates et al. (1994). Final report on the developmental toxicity of sodium fluoride (Cas No. 7681-49-4) in Sprague-Dawley rats. RTI, RTP NC, for NTP (PB95-110193). **Open Literature** Administered ad libitum in deionized/filtered drinking water to Sprague-Dawley-derived rats (26/group) on Gestation days 6-15 at levels 0, 50, 150, or 300 ppm. Rats killed on gestation by day 20 and	Maternal toxicity: NOAEL = 18 mg/kg/day LOAEL = 27 mg/kg/day, based on reduced maternal body weight. There were no treatment-related clinical signs, increases in mortality (100% survival), or decreases in body weight in rats dosed with sodium fluoride. The maternal body weight gain during the first two days of exposure (GD 6 to 8) was significantly reduced (55%) at 300 ppm (27 mg/kg/day) relative to controls. The mean maternal body weight

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	examined. Feed contained 12.4 ppm.	gain and water consumption during the treatment period was, also, significantly reduced, possibly due to a decrease in palatability. Reproductive toxicity: NOAEL ≥ 27 mg/kg/day (highest dose tested) LOAEL > 27 mg/kg/day (not established) There were no treatment-related effects on mean live fetal body weight /litter, and the number of live fetuses. A dose-related increase in the percent of litters with one or more externally malformed fetuses, the percent of externally malformed fetuses/litter, and the percent of skeletally malformed fetuses/litter occurred however was not statistically significant.
870.3700a Developmental Toxicity (Rodent) Purity not reported	Collins, T et al. (1995). Developmental Toxicity of Sodium Fluoride in Rats. Fd Chem Toxicol 33:951-960. **Open Literature** Female (CD:CRL: CD-BR, VAF+) rats were given drinking water containing 0, 10, 25, 100, 175, or 250 ppm Fluoride (0, 1.4, 3.9, 15.6, 24.7, or 25.1 mg/kg bw) 34, 35, 33, 33, 33, 35 female rats for each dose Caesarean sections were performed on gestation day 20.	Maternal Toxicity: NOAEL = 175 ppm (24.7 mg/kg/day) LOAEL = 250 ppm (25.1 mg/kg/day), based on significant reductions in body weight gain, and food and water consumption. There were no incidences of maternal mortality, changes in behavior, clinical signs, or mottled teeth in dams treated with sodium fluoride. In the 100 ppm dose group, there was 1 female rat that exhibited multiple, apparently random, clinical findings (exudate from the eye and nose, and overgrown teeth) that was not associated with treatment. The 250 ppm dose group experienced significant decreases in food and water consumption, and body weight gain that were 7, 30 and 11 % respectively, less than controls. A significant reduction (10.7%)

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		from control, in fluid consumption was observed in animals treated with 175 ppm sodium fluoride; however, there were no other treatment-related changes found at this dose level. Reproductive toxicity: NOAEL ≥ 250 ppm (25.1 mg/kg/day; highest dose tested) LOAEL > 250 ppm (25.1 mg/kg/day; not established) The pregnancy rate was greater than 90% for all groups. There was a significant decrease in the mean number of corpora lutea/female in dams of the 250 ppm dose group; however, because number of corpora lutea is determined at birth, this decrease is considered to be random. There were no significant changes in reproductive parameters in treated animals when compared to controls. Developmental toxicity: NOAEL ≥ 250 ppm (25.1 mg/kg/day; highest dose tested) LOAEL > 250 ppm (25.1 mg/kg/day; not established) There were no treatment-related effects in fetal body weight, litter sizes, or viable fetuses. Several external variations were observed in control and treated animas; however, there were no significant increases in the number of fetuses with at least 1, 2 or 3 variations, or in the number of litters with fetal sternebral variations. There was no evidence of teratogenicity observed in the rats following administration of phenol.

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
870.3700a Developmental Toxicity (Rodent) Purity > 99%	Heindel, J. et al. (1996). Developmental Toxicity Evaluation of Sodium Fluoride Administered to Rats and Rabbits in Drinking Water. Fund Applied Toxicol 30:162-177. **Open Literature** Administered ad libitum in deionized/filtered drinking water to Sprague-Dawley rats (26/group) on gestation days 6-15 at levels 0, 50, 150, or 300 ppm (0, 6.6, 18.3, or 27.1 mg/kg/day, respectively). Rats killed on gestation day 20 and examined. Feed contained 15.6 ppm.	Maternal toxicity: NOAEL = 18.3 mg/kg/day LOAEL = 27.1 mg/kg/day, based on reduced maternal body weight gain There were no treatment-related clinical signs, increases in mortality (100% survival), or decreases in body weights in rabbits dosed with sodium fluoride at the low- and mid-dose. The maternal body weight gain of the high dose group on GD 6-8 was 56% less than the controls. During the treatment period, as a whole, there was not a significant difference in mean body weight gain; however, a decreasing trend that approached statistical significance was observed. The water consumption during the treatment period was significantly reduced at the high-dose. The food consumption was decreased at the high-dose during GD 8-10, but was normal thereafter. Reproductive toxicity: NOAEL >= 27.1 mg/kg/day (highest dose tested) LOAEL > 27.1 mg/kg/day (not established). There were no changes in reproductive parameters in treated animals when compared to controls. Developmental toxicity: NOAEL >= 27.1 mg/kg/day (highest dose tested) LOAEL > 27.1 mg/kg/day (not established) There were no treatment-related effects on mean live fetal body weight/litter, live fetal number, and prevalence of malformations.

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
870.3700b Developmental Toxicity (Non- Rodent) Purity > 99%	Heindel, J. et al. (1996). Developmental Toxicity Evaluation of Sodium Fluoride Administered to Rats and Rabbits in Drinking Water. Fund Applied Toxicol 30:162-177. **Open Literature** Administered ad libitum in deionized/filtered drinking water to New Zealand White rabbits (26/group) on gestation days (6-19 at levels of 0, 50, 150, or 300 ppm. Rats killed on gestation day 30 and examined. Feed contained 15.6 ppm	Maternal toxicity: NOAEL = 18 mg/kg/day LOAEL = 29 mg/kg/day, based on reduced maternal body weight gain. There were no treatment-related clinical signs, increases in mortality (100% survival), or decreases in body weights in rabbits dosed with sodium fluoride at the low- and mid-dose. The high-dose (400 ppm) group, during GD 6 to 8, experienced a mean weight loss of 112 grams versus a mean weight gain of 14 grams for the control. During the GD 10 to 12, the 400 ppm group recovered with a mean weight gain of 71 grams versus 22 grams for the control. During the treatment period, as whole, there was not a significant difference in mean body weight gain. The water consumption during the treatment period was significantly reduced, possibly due to a decrease in palatability. The food consumption was decreased during the first four days of treatment, but was normal thereafter. Reproductive toxicity: NOAEL ≥ 29 mg/kg/day (highest dose tested) LOAEL > 29 mg/kg/day (not established) There were no changes in reproductive parameters in treated animals when compared to controls. Developmental toxicity: NOAEL ≥ 29 mg/kg/day (highest dose tested) LOAEL > 29 mg/kg/day (not established) There were no treatment-related

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		effects in mean live fetal body weight/litter, live fetal number, and prevalence of malformations.
Non-guideline Developmental Toxicity (Rodent) Purity not reported	Elbetieha, A et al. (2000). Fertility Effects of Sodium Fluoride in Male Mice. Fluoride 33:128-134. **Open Literature** 80 sexually mature Swiss mice exposed to 0, 100, 200, 300 ppm NaF via drinking water for 4 weeks (0, 12.35, 21.80, 39.19 mg/kg/day) and 10 weeks (0, 8.85, 15.64, 27.25 mg/kg/day) (10 mice/group/exposure period) Males mated after exposure periods to untreated female mice	2/10 and 3/10 mice died during 10 week exposure at 100 and 300 ppm, respectively. 200 and 300 ppm for 4 weeks caused significant increase in the relative weights of preputial glands. Mice tested for ten weeks showed no significant increase in any reproductive organ. Mice tested for 4 weeks ha d no effect on male fertility. 100, 200 and 300 ppm for 10 weeks caused a significant increase in resorptions, a decrease in implantations and pregnancies in untreated females mated with NaF treated males.
870.3800 Reproduction Purity not reported	Collins, T et al. (2001). Developmental Toxicity of Sodium Fluoride Measured During Multiple Generations. Fd Chem Toxicol 39:867-876. **Open Literature** Administered 0, 25, 100, 175, 250 mg of NaF in drinking water to (CD CRL: CD-BR) rats continuously for three generations. Parental generation (F0) was treated for ten weeks and mated within groups. On gestation day 20m caesarian sections were performed on 8 F0 females per group and their litters (F1) observed. The remaining F0 females were allowed to litter. Caesarian sections were performed on all of the F1 generation females (36/group) and were observed along with their litters.	Maternal toxicity: NOAEL ≥ 250 ppm (highest dose tested) LOAEL > 250 ppm (not established) There were no treatment-related effects on maternal mortality. A significant decrease from control in fluid consumption (30%) was observed at the 250 ppm dose level. There were no other changes in F0 maternal generation. There were significant decreases from control of 28 and 31% in fluid consumption in the F1 dams at the 175 and 250 ppm dose levels, respectively. The decreases in fluid consumption corresponded with decreased palatability of the solution. Food consumption was significantly reduced (11%) in F1 dams when compared to control in the 175 ppm dose group. There

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		was a 14% decrease from control in the body weight gain of F1 females (dams) treated with 175 ppm. These reductions at 175 ppm were considered random because of the lack of effect in the 150 pp, group. Gravid uterine weight measurements showed no doe-related differences. Reproductive toxicity: NOAEL ≥ 250 ppm (highest dose tested) LOAEL > 250 ppm (not established) There were no treatment-related effects in the mean number of corpora lutea, mean number of implantation sites, implantation efficiency, mean number of viable fetuses, and average percentage of early and late deaths per litter of dams. Offspring toxicity: NOAEL = 175 ppm LOAEL = 250 ppm, based on decreased ossification of the hyoid bone. Fetal body weight was not affected by treatment with sodium fluoride. There was no evidence of toxicity in fetuses or pups of the F1 generation. Similarly, the F2 generation fetuses and pups were unaffected by treatment with sodium fluoride with the exception of decreased ossification of the hyoid bone in the F2 fetuses at the 175 (not significant) and 250 ppm (significant) dose groups.
870.3800 Reproduction Purity not reported	Collins, T et al. (2001). Multigenerational Evaluation of Sodium Fluoride in Rats. Food and Chemical Toxicology 39.6:601-13.	The Maternal toxicity NOAEL is ≥ 250 ppm (highest dose tested). The Maternal toxicity LOAEL > 250 ppm (not established). Reproductive toxicity:

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	Open Literature Rats administered 0, 25, 100, 175, or 250 ppm NaF in drinking water throughout three generations.	NOAEL ≥ 250 ppm (highest dose tested). LOAEL > 250 ppm (not established). Rats were monitored daily during the 10 week growth period and only 2 animals died; 1 F0 male at 25 ppm and 1 F1 female of control dose groups. There were no dose-related clinical effects observed. No significant differences were observed in F0 female food consumption while there was a 5% decrease (significant) reduction in F0 males at 250 ppm (in the first 7 weeks, and week 9 of the 10 week growth period). F1 females exhibited an overall decrease in food consumption but never significantly different for control. Males of the F1 generation consumed less food than controls but in a dose-related or significant manner. Fluid consumption was significantly reduced from control levels in the 175 and 250 ppm dose groups with decreases of 11 and 20% for F0 females, 9 and 20% for F0 males, 19 and 29% for F1 females, and 15 and 25% for F1 males, respectively. F1 males in the 100 ppm dose group drank significantly less (9%) than control animals. The decrease in fluid consumption was attributed to a reduced palatability. Weight gain of F0 females and males showed a significant negative linear regression for the 10 weeks but only the individual weight gain of F0 males in 250 ppm dose group was statistically significantly less than controls. There was a 6% reduction from 367.0 to 345.9 g in first

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		generation females treated with the high-dose (250 ppm) of sodium fluoride. F0 female mating indices (mating and fertility) were over 90% in all groups, although these were slightly (but not significantly) decreased at the 250 ppm sodium fluoride dose level. Similarly, F1 female mating indices exceeded 90% with slight but not significant decreases in the 25 and 250 ppm groups; indicating a lack of compound-related effects. There were no significant or dose-related effects observed in implantation and reproductive parameters of any generation. Survival indices of the F2 generation (implantation, live-births, days 4, 7, 14, and 21 survival and lactation indices) were calculated for both male and female offspring. Neither significant nor dose-related effects were observed (data not shown in this study).
870.3800 Reproduction Purity not reported	Messer et al. Influence of Fluoride Intake on Reproduction in Mice. J. Nutr. 103:1319-1326. **Open Literature** Weaning female albino mice administered 0, 50, 100, and 200 ppm NaF via drinking water to 58, 55, 50, and 50 animals, respectively. Females mated and litters were normalized to 6 pups and a maximum of 4 litters were analyzed. Second generation mice from control and 50 ppm groups (38 and 44 animals, respectively)	Maternal Toxicity: Offspring toxicity: Retardation of growth in the 100 and 200 ppm F1 groups, with death in 50% of animals in the 200 ppm groups by 8 weeks of age. Reproductive toxicity: No litter production at the 200 ppm group and only 9 litters at the 100 ppm over a ten-week period. 50 ppm group had progressive decrease in litter production in both generations, but considered insignificant differences.

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	were mated and followed the same parameters as the parental group.	
Non-guideline Reproduction Purity not reported	Araibi et al. (1989). The Effect of High Fluoride on the Reproductive Performance of the Male Rat. J. Biol. Sc. Res. 20:19-20. **Open Literature** Male albino rats administered sodium fluoride in the diet for 60 days 15 mice/dose 100 or 200 ppm	Lesions on the teeth (mottling and erosion of enamel), a characteristic commonly associated with sodium fluoride exposure, were observed in animals at the end of the experiment. Males treated with sodium fluoride seemed to show less interest toward females when compared to those animals of the control group. The number of pregnant females were decreased 10 and 40% from controls in groups treated with 100 and 200 ppm, respectively. High-dose animals exhibited significant reductions in the number of pregnant females. The number of newborns produced by the 100 and 200 ppm dose groups were 30 and 57% (significant), respectively, less than controls. There was a decrease in average litter size for both dose levels, although neither reduction was significantly different from controls. Mean tubular diameters were significantly less than controls with 3 and 7% decreases in diameter for the 100 and 200 ppm dose levels, respectively. There were 94 and 93% (significant) increases in peritubular membrane thickness in the low- and high-dose groups, respectively. Treatment of animals with 200 ppm sodium fluoride resulted in significant decreases from control in percentage of seminiferous tubules containing spermatozoa. There were decreases in mean testosterone levels in the serum of treated animals with 29

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Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		(nonsignificant) and 71% (significant) reductions from controls observed in the 100 and 200 ppm dose groups, respectively There was a decrease in reproductive performance of male rats exposed to a high intake of sodium fluoride in spite of the absence (until the end of the experiment) of clinical signs in the teeth that are characteristic features of fluorosis. The testes of 200 ppm sodium fluoride-treated rates exhibited impairments of spermatogenesis based on changes in mean diameter of seminiferous tubules, the thickness of peritubular membranes, spermatozoa, and serum testosterone levels. The researchers suggested that sodium fluoride appears to be antispermatogenic and the decrease in testosterone may account for the decrease of mated females in sodium fluoride-treated groups.
Non-guideline Reproduction Purity not reported	Ream et al. (1983). Bone Morphology of Weaning Rats from Dams Subjected to Fluoride. Cell Tissue Res 233:689-691. **Open Literature** 0 or 150 ppm fluoride as NaF in drinking water administered to 12 female Sprague-Dawley rats for 10 weeks prior to breeding and during 3 successive pregnancy and lactation periods. Rebreeding periods commenced immediately following a 3 week lactation period and all litters were normalized to 8 pups were sacrificed and femur removed for analysis.	The amount of fluoride transferred to the offspring and incorporated into the skeleton is not sufficient to cause a visible structural alteration in the growth and development if the long bones.

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
Non-guideline Reproduction Purity not reported	Shivarajashankara et al. (2002). Histological Changes in the Brain of Young Fluoride-Intoxicated Rats. Fluoride 35:12-21. **Open Literature** 0.5 (control), 30 or 100 ppm fluoride (as NaF) in drinking water administered to female Wistar albino rats, respectively, during the last (3rd) week of pregnancy and throughout the lactation period. Litters exposed to same dose levels for up to ten weeks.	30 ppm fluoride did not show any notable alterations in brain histology, whereas rats exposed to 100 ppm fluoride showed significant neurodegenerative changes in the hippocampus, amygdale, motor cortex, and cerebellum. Changes included decrease in size and number of neurons in all regions, decrease in the number of Purkinje cells in the cerebellum, and signs of chromatolysis and gliosis in the motor cortex. These histological changes suggest a toxic effect of high-fluoride intake during the early developing stages of life on the growth, differentiation, and sub cellular organization of brain cells in rats.
Non-guideline Reproduction Purity not reported	Trabelsi, M et al. (2001). Effect of Fluoride on Thyroid Function and Cerebellar Development in Mice. Fluoride 34: 165-173. **Open Literature** 0 or 500 mg/L NaF in drinking water to pregnant and lactating mice, from the 15th day of pregnancy to the 14th day after delivery. Litter size was reduced to 8 pups for the control and tested group.	Tested group pups showed 35% decrease in body weight, a 75% decrease in the plasma free T4 level, a 27% decrease in cerebellar protein, and a 17% decrease in cerebral protein compared to the control. (Graphs missing in study).
870.4100a Chronic Toxicity (Rodent) Purity not reported	Varner, J.A. et al. (1998). Chronic Administration of Aluminum-Fluoride and Sodium Fluoride to Rats in Drinking Water: Alterations in Neuronal and Cerebrovascular Integrity. Brain Research 784:284-298. **Open Literature** Adult male Long-Evans rats received double deionized water (ddw) and 0.5 ppm Aluminum	No differences were found between the body weights of rats in the different treatment groups although more rats died in the aluminum fluoride (5) ad the NaF group (3) than the control group (1). All levels in samples of brain and kidney were higher in both the aluminum fluoride and NaF groups relative to controls. The effects of the two treatments on cerebrovascular and neuronal integrity were qualitatively and

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	Fluoride, or ddw and 2.1 ppm NaF for 52 weeks. 7 animals/group	quantitatively different. These alterations were greater in animals in the aluminum fluoride group than in the NaF group and greater in the NaF group than in controls.
Non-guideline Chronic Toxicity (Rodent) Purity not reported	Turner et al. (1995). Fluoride Reduced Bone Strength in Older Rats. J. Dent Res. 74:1475-1481. **Open Literature** Four groups of 64 to 66 rats administered 0, 5, 15, or 50 ppm of fluoride via drinking water for exposure periods of 3, 6, 12, or 18 months.	Femoral failure load was not significantly decreased in rats treated for 3 to 6 months , but was decreased as much as 23% in rats treated 12 to 18 months at 50 ppm fluoride.
870.4200a Oncogenicity (Rat) Purity not reported	Maurer et al. (1990). Two-Year Carcinogenicity Study of Sodium Fluoride in Rats. J. Natl. Cancer Inst. 82:1118-1126. **Open Literature** Sprague-Dawley rats fed a diet containing 0, 4, 10, or 25 mg/kg/day NaF added to a low-fluoride diet for up to 99 weeks 70 rats/group	There was no evidence of treatment-related incidence of carcinogenicity in Sprague-Dawley rats administered dietary sodium fluoride in concentrations up to 25 mg/kg/day for 2 years. All bone neoplasms observed were considered to be incidental and spontaneous and not related to sodium fluoride treatment, because of their low incidence and random distribution. The incidence of preneoplastic and neoplastic lesions at any site in rats of either sex was not altered by the administration of sodium fluoride. Sodium fluoride was not carcinogenic to rats within the confines of this study. At study termination, diet consumption for the 25 mg/kg/day (group 5) was significantly reduced when compared to the control (group 1), with decreases of approximately 20 and 18% for males and females, respectively. Body weight gain was significantly less than the control

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		for the 25 mg/kg/day dose group. Both male and female rats administered the high-dose of sodium fluoride experienced decreases of roughly 25% in mean body weight gain. Clear evidence of fluoride toxicity was seen in the teeth, bones, and stomach, the severity of which was related t dose and duration of treatment. At sodium fluoride concentrations of 4 mg/kg/day or greater, dental changes occurred including incisors malformations and fractures, and enamel hypoplasia. Treatment-related bone effects, mostly skull, were observed at concentrations of 10 mg/kg/day and greater, affected bones were white, thick, and found to have roughened surfaces and subperiostal hyperostosis. There was lack of bone marrow cavities in the new bone. There was an increase in incidence and severity of chronic inflammation of the gastric glandular mucosa in rats treated with sodium fluoride doses at or above 10 mg/kg/day.
870.4200b Oncogenicity (Mouse) Purity = 99%	Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). National Toxicology Program, Technical Report Series No. 393, NIH Publication No. 91-2848, December 1990, Pgs. 1-477. **Acceptable** Guideline 100, 70, 70, or 100 B6C3F1 mice/sex administered sodium fluoride in the drinking water at doses of 0, 25, 100, or 175 ppm (mice/sex) for 103 weeks.	Male: NOAEL = 9.6 mg/kg/day LOAEL = 16.7 mg/kg/day, based on the clinical chemistry changes in alkaline phosphatase and serum phosphorus (males) at 66 weeks and bone lesions (dentine dysplasia) Female: NOAEL = 11.3 mg/kg/day LOAEL = 18.8 mg/kg/day, based on the clinical chemistry changes in alkaline phosphatase and bone lesions (myelofibrosis) There were no compound-related effects on mortality, body weight,

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	(male: 0, 2.4, 9.6, or 16.7 mg/kg/day) (female: 0, 2.8, 11.3, or 18.8 mg/kg/day)	food consumption, water consumption, hematology, or organ weights. Treatment-related clinical findings included a dose-dependent increase in white discoloration of the teeth (27%, 39%, 80%, and 100% in males and 19%, 43%, 84%, and 100% in females, from control to high dose, respectively) which occurred as early as Day 74 in the high-dose animals compared to Day 508 in the control animals. Serum alkaline phosphatase was significantly increased in high-dose females at 24 (29%) and 66 weeks (88%) and in high dose-males at 66 weeks (11%). Serum phosphorus levels were significantly decreased (13%) in high-dose males at 66 weeks. There was a significant increase in incisor dentine dysplasia in high-dose males (78% in controls versus 91% at the high dose). There was an increase in the incidence of myelofibrosis (femoral, humerus, maxilla, and thoracic) in female mice at all doses.
870.4300 Chronic/Oncogenicity (Rodent) Purity = 99%	Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). National Toxicology Program, Technical Report Series No. 393, NIH Publication No. 91-2848, December 1990, Pgs. 1-477. **Acceptable** Guideline 100, 70, 70, or 100 F344/N rats/sex administered sodium fluoride in the drinking water at doses of 0, 25, 100, or 175 ppm (mice/sex) for 103 weeks. (male: 0, 1.3, 5.2, or 8.6	Three bone osteosarcomas were noted in high-dose males and one in a mid-dose male, with none in controls. A fourth osteosarcoma, not originating in the bone, was observed in an additional high-dose male. Dosing was considered adequate based on tooth deformities and discoloration; dentine dysplasia and degeneration in the ameloblasts and odontoblasts, bone osteosarcomas in males and osteosclerosis in females. Trend analyses revealed that, at the doses tested, there was a significant treatment-related increase in the incidence of bone osteosarcomas in males but the

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Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	mg/kg/day) (female: 0, 1.3, 5.5, or 9.5 mg/kg/day)	incidence was not significantly increased in the high-dose males as compared to controls when comparisons were made either within the animals scheduled for terminal sacrifice or all animals (including the interim sacrifice and concurrent control animals). In those animals scheduled for terminal sacrifice, statistical analysis of all organ osteosarcoma in dosed animals as compared to controls also failed to show significance. The study authors failed to perform the statistical analysis all osteosarcoma analysis among all animals. That analysis, done by the contractor, did reveal a significant difference between the high dose and control groups. Due to the fact that bone osteosarcoma incidence of the high-dose as compared to the control group was not significant, but displayed a significant positive trend, the occurrence of these rare tumors was considered equivocal evidence of carcinogenicity in male rats by the study authors. Such a conclusion was bolstered by the fact that bone osteosarcomas were not observed in treated females or in the parallel study in B6C3F1 mice (TR393). However, with the significant difference between high dose animals and controls in the all organ osteosarcoma incidence analysis when all animals are considered, the reviewer believes that the occurrence of osteosarcomas in the male rats should have been considered some evidence, if not clear evidence, of the carcinogenic activity of sodium fluoride. NOAEL < 1.3 mg/kg/day (lowest dose tested)

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Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		LOAEL = 1.3 mg/kg/day, based on dentine dysplasia in males and females, and ameloblast degeneration in males Mortality, body weight, body weight gain, food consumption, water consumption, hematology, and organ weights were not affected by exposure to NaF. Fluoride concentration increased with dose in blood (serum) at Weeks 27 and 66, and bone and urine at Weeks 27, 66, and 105. Analysis of bone fluoride revealed an increase with dose and age. Urinary calcium was observed to be significantly increased in high-dose females. Tooth discoloration (whitening and mottling) was noted in all treated animals with attrition, deformity, and occasional malocclusions noted in the high- and/or mid-dose males. Histopathology of the incisors noted dentine dysplasia (all dosed animals), degeneration of the ameloblasts (mid- and high-dose animals), and, to a lesser extent, degeneration of the odontoblasts (principally dosed males). Increases in the incidence and severity of osteosclerosis of the long bones were noted in the high-dose females (6/80 control; 18/81 high- dose, P=0.04).
870.5100 Bacterial reverse mutation test Purity not reported	Gocke et al. (1981). Mutagenicity of Cosmetics Ingredients Licensed by the European Communities. Mutation Research 90.2:91-109. **Open Literature** 5 Tester strains of Salmonella typhimurium in the presence and absence of metabolic activation.	**NEGATIVE** There was no evidence of induced mutant colonies over background following administration of sodium fluoride in the presence or absence of metabolic activation. The numbers of his+ revertants observed with treatment were not significantly different from

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		control with any of the study concentrations of sodium fluoride. Sodium fluoride was not mutagenic to any of the 5 Salmonella typhimurium bacterial strains in the presence or absence of metabolic activation.
870.5100 Bacterial reverse mutation test Purity not reported	Haworth et al. (1983). Salmonella Mutagenicity Test Results for 250 Chemicals. Env. Mutagenesis Supplement 1:3-142. **Open Literature** Incubation concentration up to 10 mg/plate	**NEGATIVE** There was no evidence of induce mutant colonies over background. Positive controls produced appropriate responses in corresponding strains of the bacterial reverse mutagenesis test. S. typhimurium did not show mutagenic activity in the presence or absence of metabolic activation following administration of sodium fluoride.
870.5100 Bacterial reverse mutation test Purity not reported	Li, Y., Dunipace, A., Stookey, G. (1987). Absence of Mutagenic and Antimutagenic Activities of Fluoride in Ames Salmonella Assays. Mutation Res 190:229-236. **Open Literature** Bacterial Tester Strains TA97a, TA98, TA100, TA102, and TA1535 (these 5 strains have a greater sensitivity) 0.44, 4.42, 44.2, 88.4m 221.1, 442.1, 1105.3, 2210.5, or 4421.0 µg/plate NaF. Cultures performed in triplicate in the presence and absence of metabolic activation.	**NEGATIVE** Sodium fluoride was not mutagenic in the Salmonella typhimurium bacterial strains in the presence or absence of metabolic activation. Toxic effects were first observed at concentrations ≥ 1100 µg/plate in various strains. The strains ranged from the most sensitive to least sensitive; 97a, 102, 100, 1535 and 98. The incorporation of metabolic activation increased the number of revertants, but did not significantly influence the toxic effects of sodium fluoride on the bacteria. There was no evidence of induced mutant colonies over background following administration of sodium fluoride in the presence or absence of metabolic activation. The numbers of his+ revertants observed with the

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		treatment were not significantly different from control with any of the study concentrations of sodium fluoride.
870.5100 Bacterial reverse mutation test Purity not reported	Martin, G. et al. (1979). Lack of Cytogenic Effects in Mice or Mutations in Salmonella Receiving Sodium Fluoride. Mutation Res 66:159-167. **Open Literature** Bacterial Tester Strains, Salmonella typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100 administered Sodium Fluoride. 0.1-500 µg/plate NaF Incubation time not reported	**NEGATIVE** There was no evidence of induce mutant colonies over background. Positive controls produced appropriate responses in corresponding strains of the bacterial reverse mutagenesis test. S. typhimurium did not show mutagenic activity in the presence or absence of metabolic activation following administration of sodium fluoride.
870.5100 Bacterial reverse mutation test Purity = 99.99%	Tong et al. (1988). The Lack of Genotoxicity of Sodium Fluoride in a Battery of Cellular Tests. Cell Biology and Toxicology 4.2:173-186. **Open Literature** Bacterial Tester Strains, Salmonella typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100 were incubated with sodium fluoride in the presence or absence of metabolic activation. 10, 20, 40, 80, 160, or 320 µg/plate	**NEGATIVE** Sodium fluoride was not mutagenic to any of the 5 Salmonella typhimurium bacterial strains in the presence or absence of metabolic activation. The higher doses (80-320 µg/plate) were slightly cytotoxic. However at all doses there was no evidence of induced mutant colonies over background following administration of sodium fluoride in the presence or absence of metabolic activation. The numbers of his+ revertants observed with treatment were not significantly different from control with any of the study concentrations of sodium fluoride.
870.5100 Bacterial reverse mutation test	Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS	**NEGATIVE**

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Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
Purity not reported	No. 7681-49-4) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). National Toxicology Program, Technical Report Series No. 393, NIH Publication No. 91-2848, December 1990, Pgs. 1-477. **Acceptable** Guideline Strains TA98, TA100, TA1535, and TA1537 of S. typhimurium exposed to sodium fluoride diluted in DMSO at concentrations of 0, 100, 333, 1000, 3333, and 10000 µg/plate in the presence and absence of mammalian metabolic activation, hamster or rat S9, using a pre-incubation procedure.	There was no clear evidence, or a concentration related positive response, of induced mutant colonies over background.
870.5300 In Vitro mammalian cell gene mutation test Purity = 99%	Caspary, W. et al. (1987). Mutagenic Activity of Fluorides in Mouse Lymphoma Cells. Mutation Res 187:165-180 **Open Literature** -S9 1-200, 300, 400, 500, 600, 0r 800 µg/mL Trial 2-50, 100, 200, 300, 400, 500, or 600 µg/mL +S9: Trial 1-100, 200, 300, 400, 500, or 600 µg/mL Trial 2-50, 100, 200, 300, 400, 500 or 600 400, 500, or 600 µg/mL Incubated for 4 hours with a 2-day expression period.	**POSITIVE** Sodium fluoride was mutagenic in L5179Y mouse lymphoma cells in the presence and absence of metabolic activation. There was evidence of general toxicity in the 300-500 µg/mL sodium fluoride concentration range and lethality usually occurred at higher concentrations (600-800 µg/mL). In the absence of metabolic activation, cytotoxicity was apparent at the 800 µg/mL sodium fluoride dose level in Trial 1. Cytotoxicity was observed in the presence of metabolic activation at 600 µg/mL. There were significant increases in mutation frequency following administration of sodium fluoride. Trial 1 (-S9) experienced 1.8-, 1.6-, 1.9-, and 2.9-fold increases at sodium fluoride concentrations of 300,

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		400, 500 and 600 µg/mL, respectively, while Trial 2 (-S9) exhibited a 1.6-fold increase at the 500 µg/mL dose. In the presence of metabolic activation, 1.5-, 3.1-, and 3.6- fold increases in Trial 1 and 1.6-, 1.9-, and 2.3-fold increases in Trial 2 occurred at sodium fluoride 400, 500, and 600 µg/mL and 300, 400, and 500 µg/mL, respectively. Sodium fluoride had a significant effect in gene mutations at the TK locus, although the addition of metabolic activation ha no apparent effect on either the toxicity or mutagenic activities of sodium fluoride. The measured mutant colony size was predominantly small.
870.5300 In Vitro mammalian cell gene mutation test Purity not reported.	Oberly et al. (1990). An Evaluation of the CHO/HGPRT Mutation Assay Involving Suspension Cultures and Soft Agar Cloning: Results for 33 Chemicals. Environmental and Molecular Mutagenesis 16:260-271. **Open Literature** Chinese Hamster Ovary (CHO)/HGPRT+ cells, Strain K1-BH4 were exposed to sodium fluoride for 9 days 250, 500, 600, 700, or 800 µg/mL in –S9 200, 400, 450, 500, 550, 600, or 700 µg/mL in +S9	**NEGATIVE** All doses greater than 450 µg/mL with and without activation were toxic, as is evident by the relative total growth of 38% or less. Sodium fluoride was not mutagenic at the HGPRT locus of Chinese hamster ovary cells.
870.5300 In Vitro mammalian cell gene mutation test Purity = 99.99%	Tong et al. (1988). The Lack of Genotoxicity of Sodium Fluoride in a Battery of Cellular Tests. Cell Biology and Toxicology 4.2:173-186. **Open Literature**	**NEGATIVE** The higher doses (80 and 160 µg/mL) were toxic and were not analyzed for gene mutatins. Sodium fluoride at doses up to 40 µg/mL did not result in any

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	ARL 1 (rat liver epithelial cell line) were exposed to sodium fluoride for 72 hours. 2, 10, 20, 40, 80, or 160 µg/mL	significant increase in TGR mutants above the control. Sodium fluoride was not mutagenic at the HGPRT locus.
870.5300 In Vitro mammalian cell gene mutation test Purity not reported	Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). National Toxicology Program, Technical Report Series No. 393, NIH Publication No. 91-2848, December 1990, Pgs. 1-477. **Acceptable** Guideline Trifluorothymidine (TFT)-resistant cells at the thymidine kinase (TK) locus exposed to sodium fluoride in lymphoma L5178Y cells cultured in vitro in either distilled water or culture medium for 4 hours at concentrations ranging from 50 to 600 µg/mL in the presence of mammalian metabolic activation (S9 derived from Aroclor 1254-induced Fischer 344 male rats) and from 50 to 1000 µg/mL in the absence of metabolic activation.	**POSITIVE** There was evidence of a concentration related positive response of induced mutant colonies over background. Sodium fluoride was tested up to cytotoxic concentrations (the maximum dose tested was 1000 µg/mL in one laboratory and 800 µg/mL in another). Mutant frequencies increased in a dose-related manner. Statistically significant ($p<0.05$) responses were observed in all trials, ±S9, at the high doses. Mutant fractions (vs. the solvent control response) at the highest doses tested in each trial were reported to be 83.0x10-6 vs. 29.5x10-6, 41.3x10-6 vs. 24.3x10-6, 134.0x10-6 vs. 58.0x10-6, and 195.5x10-6 vs. 51.0x10-6 in cultures tested in the absence of metabolic activation, and 94.0x10-6 vs. 25.8x10-6 and 75.7x10-6 vs. 33.0x10-6 in cells tested in the presence of metabolic activation.
870.5375 In Vitro mammalian chromosome aberration test Purity not reported	Aardema MJ, et al. (1989). Sodium Fluoride-Induced Chromosome Aberrations in Different Stages of the Cell Cycle: A Proposed Mechanism. Mutation Research 223:191-203. **Open Literature** Cells were exposed to 465, 650, 911, 1276, or 1786 ug/mL NaF for 4 hours, +/- S9 for 8 or 20	**POSITIVE** A high level of toxicity was observed at 1786 go/mL (high-dose) that limited chromosome aberration analysis to the lower dose groups. There was an increase in average cell generation time (AGT) as the concentration of sodium fluoride increased; indicating a treatment-related cell-cycle delay. At 20

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	hours of incubation. In separate experiments, cells were exposed to 100 ug/mL of sodium fluoride for 1 or 2 hours or concentrations of 0.1, 1.0, 10, 25, 50, 75, and 100 ug/mL for 3 hours	hours after treatment, greater than 50% of the cells were in their first mitosis at 911 and 1276 go/mL +/-S9 and at 465 and 650 go/mL +S9. Overall, there was a significant increase in the percentage of aberrant cells in sodium fluoride treated groups at the 8 and 20 hour post-treatment harvesting of cells. There were 4.5- and 3.5-fold increases in the percentage of aberrant cells, at the 8 hour harvest time, in the 465 and 911 go/mL dose group, respectively, in the absence of metabolic activation. In the presence of S9, the 465, 650, and 1276 go/mL dose groups exhibited 6.3-, 3.7-, and 5.0-fold increases, respectively, in the number of aberrant cells. In the 20 hour harvesting assay there was only one significant increase in the number aberrant cells; a 6.5-fold increase at the 1276 go/mL sodium fluoride in the presence of metabolic activation. In both harvest (8 or 20 hours) the aberrations were almost exclusively chromatid-type deletions and gaps. There was evidence of endoreduplicated cells observed in the chromosome aberration screening assay. At the 465, 650, 911, and 1276 go/mL dose levels, the percentages of endoreduplicated cells were 2, 3, 5, and 11% for -S9 and 4, 12, 15, and 14% for +S9, respectively. These cells all had an M0/M1 staining pattern indicating they had gone through 0 or 1 round of DNA synthesis. Endoreduplicated cells were also observed in the CHO 8 and 20 hour harvest time assays. At the 8 hour timepoint in the absence

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		of metabolic activation there was a 6% increase in endoreduplicated cells with the 1276 go/mL dose of sodium fluoride. There were endoreduplicated cell increases of 6, 16, and 22% in -S9 and 28, 26, and 34% in +S9 at the 20 hour harvest time point for the sodium fluoride concentrations of 650, 911, and 1276 go/mL, respectively. In separate experiments cells were exposed to 100 go/mL of sodium fluoride for 1 or 2 hours or concentrations of 0.1, 1.0, 10, 25, 50, 75, and 100 go/mL for 3 hours. There were no significant changes from control in chromosome aberrations until the 3 hour incubation assay. Sodium fluoride at doses greater than 10 go/mL induced increases in the percentage of aberrant cells that were significant at concentrations greater than or equal to 50 go/mL. The types of aberrations were chromatid deletions, isochromatid deletions, and a large number of gaps but not chromatid exchanges.In this CHO assay, cell-cycle kinetic studies indicated that aberrations were induced in cells exposed to sodium fluoride at the 20 hour harvest time (G1/S phase) but the increases in aberrant cells were greater at the 8 hour time point where most of the metaphases were from cells exposed to sodium fluoride in the G2 stage of the cell cycle. This sensitivity of the G2 cells was evident in the 3 hour exposure assay with increases in aberrant cells at concentrations greaterthan 10 go/mL; concentrations that are relatively much greater than levels present in water or dentifrices. The researchers

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		suggest that the level of sodium fluoride-induced mutagenicity is dependent on both the cell-cycle stage that cells are in during exposure and the length of time until harvest. Sodium fluoride induced positive mutagenic results in CHO cells at concentrations greater than or equal 50 go/mL when exposed for 3 hours in the presence and absence of metabolic activation. However, longer exposure times (8 or 20 hours) required greater concentrations of sodium fluoride (greater than or equal to 465 go/mL) to achieve mutagenic results.
870.5375 In Vitro mammalian chromosome aberration test Purity not reported	Albanese. (1987). Sodium Fluoride and Chromosome Damage (In Vitro Human Lymphocyte and In Vivo Micronucleus Assays). Mutagenesis 2:497-499. **Open Literature** Cells were exposed to 20 or 40 ug/mL NaF for 28 or 2 hours, +/- S9	**POSITIVE** Sodium fluoride was mutagenic in human peripheral blood lymphocytes in both the presence and absence of metabolic activation. However, mutagenicity appeared to be dependent on exposure time and concentration. There were significant dose-dependent increases in chromosome aberrations in the experiment without metabolic activation; with 6- and 18-fold increases in total number of damaged cells at the 20 and 40 go/mL dose levels, respectively, after 28 hours of incubation. In the presence of metabolic activation, there was a significant 2.5-fold increase in total number of damaged cells over control at the 40 go/mL dose level, after 2 hours of incubation. The chromosome aberrations observed following the administration of sodium fluoride were predominantly gaps, breaks, and fragments. No exchange-type aberrations (the type thought to correlate better with the

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		carcinogenic potential of chemicals) were found at any dose level or exposure period.
870.5375 In Vitro mammalian chromosome aberration test Purity not reported	Khalil. (1995). Chromosome Aberrations in Cultured Rat Bone Marrow Cells Treated with Inorganic Fluorides. Mutation Research 343:67-74. **Open Literature** Bone marrow cells of Sprague-Dawley rats 0.1, 1.0, 10 or 100 uM for 12, 24, or 36 hours of incubation experiments performed in quadruplicate/dose	**POSITIVE** Chromosomal aberrations in bone marrow cells increased following the administration of sodium fluoride in a dose- and time-dependent manner. Sodium fluoride was mutagenic in Sprague-Dawley rat bone marrow cells within the confines of this study. Overall, there was a significant increase in the percentage of aberrant cells in sodium fluoride treated groups for the 12-, 24-, and 36-hour exposures. Only the 0.1 uM treatment, 12-hour exposure cells did not have a significant increase in breaks/cell or in the percent of aberrant cells compared to controls. The increased aberrations at the other treatment levels mainly consisted of simple aberrations, such as breaks and fragments. Small number of complex aberrations, such as chromatid exchanges and rings, occurred sporadically, at doses 1.0, 10.0, and 100.0 uM. The number and percentage of aberrations increased with the increasing concentrations of sodium fluoride and with the prolongation of treatment. The only significant exposure time-related effects observed were between the 12- and 36-hour exposures at concentrations of 1.0, 10.0, and 100.0 uM.
870.5375 In Vitro mammalian chromosome aberration test	Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats	Chinese hamster ovary cells were exposed to sodium fluoride in culture medium at concentrations

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
Purity not reported	and B6C3F1 Mice (Drinking Water Studies). National Toxicology Program, Technical Report Series No. 393, NIH Publication No. 91-2848, December 1990, Pgs. 1-477. **Acceptable** Guideline	between 50 and 1600 µg/mL with metabolic activation (S9 from Aroclor 1254-induced male Sprague-Dawley rat livers) for 2 hours, or between 16 and 800 µg/mL without metabolic activation for 10 hours. **POSITIVE** There was evidence of a concentration related positive response of chromosome aberrations induced over background in one laboratory testing without metabolic activation; no other evidence of a positive response.
870.5375 In Vitro mammalian chromosome aberration test Purity not reported	Tsutsui T, et al. (1984). Sodium Fluoride-Induced Morphological and Neoplastic Transformation, Chromosome Aberrations, Sister Chromatid Exchanges, and Unscheduled DNA Synthesis in Cultured Syrian Hamster Embryo Cells. Cancer Research 44.3:938-941 **Open Literature** Syrian hamster embryo (SHE) cells were exposed to sodium fluoride for 16 and 28 hours 50 or 100 ug/mL for 16 hours 100 or 200 ug/mL for 28 hours	**POSITIVE** There was a dose- and time-dependent increase in chromosomal aberrations following administration of sodium fluoride in Syrian hamster embryo cells. Sodium fluoride was mutagenic in SHE cells within the confines of this study. Treatment-related effects on mortality were observed in SHE cells administered sodium fluoride. At sodium fluoride concentrations of 75, 100, and 125 go/mL, there were decreases in cell survival that were 10, 47, and 61%, respectively, less than control. There were significant dose-dependent increases in chromosome aberrations in the sodium fluoride-treated SHE cells. Sodium fluoride incubation of 16 hours exhibited increases in aberrant metaphases that were 9- and 24-fold greater than the control at the 50 and 100 go/mL/mL dose levels,

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		respectively. After 28 hours of exposure, the 100 and 200 go/mL/mL dose levels of sodium fluoride induced aberrant metaphases that were 19- and 29.5-fold greater than control, respectively. The chromosomal aberrations were predominantly gaps and some breaks.
870.5375 In Vitro mammalian chromosome aberration test	Tsutsui, T., N. Suzuki, et al. (1984). Cytotoxicity, Chromosome Aberrations and Unscheduled DNA Synthesis in Cultured Human Diploid Fibroblasts Induced by Sodium Fluoride. Mutation Research 139:193-198. **Open Literature** A separate cytotoxicity test was preformed with sodium fluoride administered to JHU-1 cells at concentrations of 50, 100, or 150 go/mL/mL for 1, 2, 6, 12, or 24 hours. Sodium fluoride was administered to JHU-1 cells in the mutagenicity assay at concentrations of 25, 50 or 75 go/mL/mL for 12 hours of exposure and 20 or 40 ug/mL for 24 hours exposure. Analyses for chromosome aberrations were performed in 100-500 metaphases.	**POSITIVE** There was a dose- and time-dependent increase in chromosomal aberrations following administration of sodium fluoride in cultured human diploid fibroblasts. Sodium fluoride was mutagenic in JHU-1 cells within the confines of this study. Treatment-related cytotoxic effects were observed in JHU-1 cells administered sodium fluoride. Cell survival decreased as the sodium fluoride concentration and duration of exposure increased. At sodium fluoride concentrations of 50, 100, and 150 go/mL, there were decreases in cell survival that were 100, 98, and 90% after 1 hour; 100, 75, and 65% after 2hours; 70, 48, and 40% after 6 hours; 55, 22, and 15% after 12 hours; and 17, 7, and 1% after 24 hours of exposure, respectively. Sodium fluoride was cytotoxic to JHU-1 cells and cell survival decreased linearly with increasing dose or exposure time. There were significant dose- and time-dependent increases in chromosome aberrations in the sodium fluoride-treated JHU-1 cells. The 12 hour sodium fluoride incubation exhibited increases in aberrant metaphases

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		that were 3.5- and 22.4-fold greater than the control at the 25 and 50 go/mL dose levels, respectively. Sodium fluoride at 75 go/mL provided few metaphases to analyze for chromosomal aberrations. After 24 hours of exposure, the 20 and 40 go/mL dose levels of sodium fluoride induced aberrant metaphases that were 7- and 47-fold greater than control, respectively. The chromosomal aberrations were predominantly gaps and some breaks.
870.5380 Mammalian Spermatogonial Chromosomal aberration test Purity not reported	Li, Dunipace, and Stookey. (1987). Effect of Fluoride on the Mouse Sperm Morphology Test. J. Dent. Res. 66:1509-1511. **Open Literature** B6C3F1 male mice were fed a low fluoride diet (<0.2 ppm) via stomach intubation at concentrations of 0.1, 1.0, 10, 20, 35, or 70 mg/kg. Treated daily for 5 days. 5 mice/group (except 70 mg/kg dose group with 9 mice)	**NEGATIVE** The frequency of abnormal sperm in NaF-treated groups was not significantly different from controls. NaF did not cause spermatogenic damage as determined by the frequency of sperm abnormalities and weights of testes. There was an increase in bone fluoride content with increasing dosage; concentrations less than or equal to 10 mg/kg exhibited significantly lower bone fluoride content than concentrations greater than or equal to 20 mg/kg. The increase in bone fluoride demonstrated that fluoride was adequately absorbed following intubation, and therefore, the route of administration of NaF used was justified. NaF was nonspermatogenic in male mice and supports the view point that Fl has no adverse mutagenic effects.
870.5380 Mammalian Spermatogonial Chromosomal aberration test Purity not reported	Mohamed and Chandler. (1982). Cytological Effects of Sodium Fluoride on Mice. Dept. of Biology and School of Medicine,	**POSITIVE** There were significant treatment-related increases from controls in

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	University of Kansas City, Missouri. Presented at the 12th I.S.F.R. Conference. **Open Literature** Male BALB/c mice were administered a low fluoride diet for 1 week and sodium fluoride in drinking water for 3 or 6 weeks 0.263 ppm fluoride in diet 1, 5, 10, 50, 100, or 200 ppm NaF in drinking water 4 mice/time period/dose	aberration rates among spermatocytes. There was evidence of cytogenetic damage found in animals administered sodium fluoride. Sodium fluoride within the parameters of this study was found to be mutagenic. In the three week study, all of the treatments demonstrated a significantly higher frequency of chromosomal aberrations compared to controls. A dose-related response occurred at doses 5 to 200 ppm, but the frequency of aberrations in the low dose (1 ppm) compared to the 5 ppm group did not express the same increasing trend. In the three week study, all of the treatments demonstrated a significantly higher frequency of chromosomal aberrations compared to controls. A dose-related response occurred at doses 5 to 100 ppm, but the frequency of aberrations in the low dose (1 ppm) compared to the 5 ppm group and the 100 ppm group compared to the 200 ppm group did not express the same increasing trend.
870.5380 Mammalian Spermatogonial Chromosomal aberration test Purity not reported	Pati and Bhunya. (1987). Genotoxic effect of an environmental pollutant, sodium fluoride, in mammalian in vivo test system. Carylogia 40:79-87. **Open Literature** Male Swiss mice were administered sodium fluoride as intraperitoneal injections of 5 equal parts of each dose of sodium fluoride over 5 days with 24 hours between each injection. 10, 20, or 40 mg/kg	**POSITIVE** Sodium fluoride was mutagenic to spermatogonial cells in Swiss mice within the confines of this study. There was a dose-related increased in the number of abnormal sperm that increased with increasing dose. The mean percentages of sperm abnormalities were 6.4, 6.8 and 7.6% for the 10, 20, and 40 mg/kg dose levels, respectively, of sodium fluoride. There were

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	Number of animals not reported	significant dose-dependent increases in the frequency of spermatogonial aberrations that were 3.1-, 3.3-, and 3.7-fold greater than the control at the sodium fluoride doses of 10, 20, and 40 mg/kg, respectively. The higher incidence of sperm abnormalities induced by sodium fluoride may be a measure of the genetic damage caused in the germline cells. There were significant increases over control in the number of spermatogonial aberrations in animals receiving sodium fluoride.
870.5385 Mammalian bone marrow chromosomal aberration test Purity not reported	Martin G, et al. (1979). Lack of Cytogenetic Effects in mice or mutations in salmonella receiving sodium fluoride. Mutation Res 66:159-167. **Open Literature** Male BALB/c mice were administered sodium fluoride in the diet and in drinking water for six weeks 0.5 ppm NaF in the diet 1,5, 10, 50, or 100 ppm NaF in drinking water Number of animals not reported	**NEGATIVE** There were no significant treatment-related differences observed in aberration rates among bone marrow cells. There was no evidence of cytogenetic damage found in animals administered sodium fluoride.
870.5385 Mammalian bone marrow chromosomal aberration test Purity not reported	Mohamed and Chandler. (1982). Cytological Effects of Sodium Fluoride on Mice. Dept. of Biology and School of Medicine, University of Kansas City, Missouri. Presented at the 12th I.S.F.R. Conference. **Open Literature** Male BALB/c mice were administered a low fluoride diet for 1 week and sodium fluoride in drinking water for 3 or 6 weeks	**POSITIVE** There were significant treatment-related differences observed in aberration rates among bone marrow cells. There was evidence of cytogenetic damage found in animals administered sodium fluoride. Sodium fluoride within the parameters of this study was found to be mutagenic. In the three week study, all of the treatments demonstrated a significantly higher frequency of

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	0.263 ppm fluoride in diet 1, 5, 10, 50, 100, or 200 ppm NaF in drinking water 4 mice/time period/dose	chromosomal aberrations compared to controls. A dose-related response occurred at doses 1 to 50 ppm, but the aberration frequencies in the higher doses were not significantly different from each other. In the six week study, all of the treatments demonstrated a significantly higher frequency of chromosomal aberrations compared to controls. A dose-related response occurred at doses 1 to 10 ppm, but the frequency of aberrations in the higher doses were not significantly different from each other.
870.5385 Mammalian bone marrow chromosomal aberration test Purity not reported	Pati and Bhunya. (1987). Genotoxic Effect of an Environmental Pollutant, Sodium Fluoride, in Mammalian In Vivo Test System. Carylogia 40:79-87. **Open Literature** Swiss mice were administered sodium fluoride orally, ip, or subcutaneously for 6, 24, or 48 hours 10 or 20 mg/kg intraperitoneally for 24 hours 40 mg/kg orally or subcutaneously for 24 hours 40 mg/kg intraperitoneally for 6, 24, or 48 hours 8 injections of 5 mg/kg intraperitoneally for 120 hours Number of animals not reported	**POSITIVE** Sodium fluoride was found to be mutagenic in Swiss mice bone marrow cells within the confines of this study. There were significant dose-related increases in chromosomal aberrations in the 24 hour experiment. Intraperitoneal injections of sodium fluoride at concentrations of 10, 20, and 40 mg/kg were 3.3-, 4.3-, and 5.2-fold greater than control, respectively. Similar and significant results were observed in the oral and subcutaneous experiments with 5.5- and 5.0-fold increases, respectively, over controls at the 40 mg/kg dose level. There were 1.9 and 3.3-fold increases over control at the 40 mg/kg dose levels of sodium fluoride administered intraperitoneally at 6 (not significant) and 48 hours (significant), respectively. The multiple, 5-time dosing of 8 mg/kg resulted in a significant 2.9-fold increase over control in

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		mouse chromosomal aberrations. There were treatment-related aberrations, including chromatid gaps and breaks, isochromatid gaps, fragments and exchanges in mouse bone marrow cells. Gaps were observed more frequently than breaks. Sodium fluoride induced dose- and time-dependent increases in the number of chromosomal aberrations, but there was no evidence of route-sensitivity. There was no practical difference observed at the same dose level in the 3 administration routes employed. Additionally, the chronic, repeated exposure of fractionated doses induced less aberrations than that of an equivalent dose treated once. The increases in chromosome aberrations were significantly greater than control in all experiments with one exception. Intraperitoneal injection of 40 mg/kg sodium fluoride over 6 hours failed to induce a significant number of chromosomal aberrations.
870.5385 Mammalian bone marrow chromosomal aberration test Purity not reported	Zeiger et al. (1994). Cytogenetic Studies of Sodium Fluoride in Mice. Mutagenesis 9:467-471. **Open Literature** Male B6C3F1 mice were administered fluoride in the diet for 1 week and sodium fluoride in drinking water for 7 days/week for 6 weeks 10-16 mice/dose 100, 200 or 400 ppm in drinking water	**NEGATIVE** There were no significant treatment-related differences observed in aberration rates among metaphase and anaphase bone marrow cells. There was no evidence of cytogenetic damage found in animals administered sodium fluoride. Three of sixteen mice from the 400 ppm group died during the sixteen-week treatment period. A decrease in body weight gain and water consumption occurred at the 200 and 400 ppm group. There were no other treatment-related signs.

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
870.5395 Mammalian erythrocyte micronucleus test Purity not reported	Albanese. (1987). Sodium Fluoride and Chromosome Damage (In Vitro Human Lymphocyte and In Vivo Micronucleus Assays). Mutagenesis 2:497-499. **Open Literature** Oral gavage of 500 or 1000 mg/kg NaF to Male Alpk:APF Sprague-Dawley rats, 5/group/sample time	**NEGATIVE** There were no significant increases in the frequency of micronucleated polychromatic erythrocytes in rat bone marrow cells at the concentrations of sodium fluoride used in this study. Sodium fluoride was not mutagenic in Alpk:APFSD rat bone marrow cells. There were no treatment-related effects on mortality in any of the low-dose (500 mg/kg) group; however, 4 of the 5 rats in the 1000 mg/kg group died prior to the 48 hour sampling period. No other abnormal signs were observed in the remaining animals in other dose/time groups. The ratio of normochromatic erythrocytes (NCEs) to PCEs was 1:1; which indicated that at the doses used sodium fluoride was not cytotoxic to the bone marrow cells.
870.5395 Mammalian erythrocyte micronucleus test Purity not reported	Gocke et al. (1981). Mutagenicity of Cosmetics Ingredients Licensed by the European Communities. Mutation Research 90.2:91-109 **Open Literature** Male and female NMRI mice and Sprague-Dawley rats	**NEGATIVE** There were no a significant increases in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow cells at the concentrations of sodium fluoride used in this study. Sodium fluoride was not mutagenic in NMRI mouse bone marrow cells. There were no treatment-related effects on mortality (100% survival) or MNPCEs in mice receiving administrations of phenol.
870.5395	Pati and Bhunya. (1987).	**POSITIVE**

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
Mammalian erythrocyte micronucleus test Purity not reported	Genotoxic effect of an environmental pollutant, sodium fluoride, in mammalian in vivo test system. Carylogia 40:79-87. **Open Literature** Swiss mice were administered intraperitoneal NaF 2 times over 24 hours 10, 20, or 40 mg/kg Number of animals not reported	There were treatment-related increases in MNPCEs in animals administered sodium fluoride, with 3-, 3.5-, and 5.15-fold increases over control at the 10, 20, and 40 mg/kg dose levels, respectively. These increases were significantly greater than the control with the exception of the low-dose (10 mg/kg). The induction of MN in bone marrow cells increased with sodium fluoride dose. MN frequency was at its highest in PCEs and least in immature white cells. There was evidence of mutagenicity in mouse bone marrow cells administered sodium fluoride within the confines of this study.
870.5395 Mammalian erythrocyte micronucleus test Purity not reported	Zeiger et al. (1994). Cytogenetic Studies of Sodium Fluoride in Mice. Mutagenesis 9:467-471. **Open Literature** Male B6C3F1 mice were administered fluoride in the diet for 1 week and sodium fluoride in drinking water for 7 days/week for 6 weeks. 10-16 mice/dose 100, 200, or 400 ppm	**NEGATIVE** There were no significant increases in the frequency of micronucleated polychromatic erythrocytes and normochromatic erythrocytes in B6C3F1 mice peripheral blood cells in the parameters of this study. Sodium fluoride was not mutagenic in B6C3F1 mice peripheral blood cells. Three of sixteen mice from the 400 ppm group died during the sixteen-week treatment period. A decrease in body weight gain and water consumption occurred at the 200 and 400 ppm group. There were no other treatment-related signs.
870.5500 Bacterial DNA damage or repair tests Purity = 99.99%	Tong et al. (1988). The Lack of Genotoxicity of Sodium Fluoride in a Battery of Cellular Tests. Cell Biology and Toxicology 4.2:173-186.	**NEGATIVE** There was no significant increase in net nuclear grain counts at sodium fluoride concentrations up to 160 go/mL. Sodium

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	Open Literature Male Fischer F-344 rat hepatocyte primary cultures (HPC) were administered sodium fluoride for 18 hours 20 cells/slide were scored 2, 10, 20, 40, 80, or 160 ug/mL Number of animals not reported	fluoride did not elicit DNA repair synthesis in the rat hepatocytes.
870.5550 Unscheduled DNA synthesis in mammalian cell culture Purity not reported	Tsutsui T, et al. (1984). Sodium Fluoride-Induced Morphological and Neoplastic Transformation, Chromosome Aberrations, Sister Chromatid Exchanges, and Unscheduled DNA Synthesis in Cultured Syrian Hamster Embryo Cells. Cancer Research 44.3:938-941 **Open Literature** Syrian hamster embryo (SHE) cells were exposed to sodium fluoride for 4, 8, 12, 24, or 33 hours. 10, 20, or 40 ug/mL	**POSITIVE** A dose- and time-dependent increase in unscheduled DNA synthesis was observed following administration of sodium fluoride in Syrian hamster embryo cells. Sodium fluoride was mutagenic in SHE cells within the confines of this study. Treatment-related effects on mortality were observed in SHE cells administered sodium fluoride. At sodium fluoride concentrations of 75, 100, and 125 go/mL, there were decreases in cell survival that were 10, 47, and 61%, respectively, less than control. There was no evidence of UDS at any dose of sodium fluoride in the 4 or 8 hour exposure time period. However, significant dose- and time-dependent increases in UDS were observed in the SHE cells treated with all three doses of sodium fluoride for 12 hours or greater. After 12 hours of exposure, the UDS (as measured by [3H]dThd cpm/culture well (x 10-2)) was at a level of 0.55 and 1.30 [3H]dThd cpm/culture well (x 10-2) for the 20 and 40 go/mL, respectively, dose groups. Sodium fluoride induced UDS levels of 0.75, 1.45, and 2.30 after 24 hours of

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		exposure and 0.45, 2.25, and 5.55 after 33 hours of exposure at concentrations of 10, 20, and 40 go/mL, respectively.
870.5550 Unscheduled DNA synthesis in mammalian cell culture	Tsutsui, T., N. Suzuki, et al. (1984). Cytotoxicity, Chromosome Aberrations and Unscheduled DNA Synthesis in Cultured Human Diploid Fibroblasts Induced by Sodium Fluoride. Mutation Research 139:193-198. **Open Literature** A separate cytotoxicity test was performed with sodium fluoride administered to JHU-1 cells at concentrations of 50, 100, or 150 go/mL for 1, 2, 6, 12, or 24 hours. Sodium fluoride was administered to JHU-1 cells in the mutagenicity assay at concentrations of 50, 70, 100, 150, 200, 300, or 400 go/mL for 4, 8, 12, 16, or 24 hours of exposure.	**POSITIVE** There was a significant dose-dependent increase in unscheduled DNA synthesis following administration of sodium fluoride in cultured human diploid fibroblasts. Sodium fluoride was mutagenic in JHU-1 cells within the confines of this study. Treatment-related cytotoxic effects were observed in JHU-1 cells administered sodium fluoride. Cell survival decreased as the sodium fluoride concentration and duration of exposure increased. At sodium fluoride concentrations of 50, 100, and 150 go/mL, there were decreases in cell survival that were 100, 98, and 90% after 1 hour; 100, 75, and 65% after 2hours; 70, 48, and 40% after 6 hours; 55, 22, and 15% after 12 hours; and 17, 7, and 1% after 24 hours of exposure, respectively. Sodium fluoride was cytotoxic to JHU-1 cells and cell survival decreased linearly with increasing dose or exposure time. UDS was not induced by sodium fluoride treatment over the dose range of 50-5000 go/mL for 1 hour. There were increases in the level of UDS after 4 hours of exposure; however, none exceeded 7 [3H]TdR cpm/culture well (x 10-2) and were not significantly different from untreated cells. No significant UDS was detected until the cells were treated for longer than 4

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
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		hours. The UDS levels were 9, 22, 29, and 41 for 8 hours and 3, 22, 44, and 52 for 12 hours of exposure at the sodium fluoride concentrations of 100, 150, 200, and 300 go/mL, respectively. The UDS levels increased with dose after 16 hours of exposure, with 15, 39, and 47 [3H]TdR cpm/culture well (x 10-2) at 150, 200, and 300 go/mL sodium fluoride, respectively. The inducibility was markedly decreased in cells treated for 24 hours; most likely a result of cytotoxicity.
870.5900 In Vitro sister chromatid exchange assay Purity not reported	Khalil A, Da'Dara A. (1994). The Genotoxic and Cytotoxic Activities of Inorganic Fluoride in Cultured Rat Bone Marrow Cells. Arch Environ Contam Toxicol 26:60-63. **Open Literature** Bone marrow cells of Sprague-Dawley rats from tibia and femurs 0.1, 1, 10, 100, 1,000 and 10,000 uM for 12, 24, and 36 hours	**NEGATIVE** Cell survival and cell division was significantly reduced at the high-doses (1,000 and 10,000 uM). However, Sodium fluoride did not induce a SCE increase in bone marrow cells; there was no evidence of mutagenicity.
870.5900 In Vitro sister chromatid exchange assay Purity not reported	Li Y, et al. (1987). Genotoxic Effects of Fluoride Evaluated by Sister-Chromatid Exchange. Mutation Res 192:191-201. **Open Literature** Male CHO cells 0.05, 0.5, 1.0, 2.10, 4.20, 5.30, or 6.30 mM, performed in triplicate in the presence and 1.2, 2.4, 6.0, or 12.0 mM for 24 hours of incubation	**NEGATIVE** The 5.30 and 6.30 mM dose levels of sodium fluoride were toxic and were not evaluated. There were no significant increases from controls in SCEs in CHO cells exposed to 0.05 to 4.20 mM sodium fluoride. Sodium fluoride did not induce a SCE increase in CHO cells; there was no evidence of mutagenicity.

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
870.5900 In Vitro sister chromatid exchange assay Purity = 99.99%	Tong et al. (1988). The Lack of Genotoxicity of Sodium Fluoride in a Battery of Cellular Tests. Cell Biology and Toxicology 4.2:173-186. **Open Literature** Human peripheral blood lymphocytes (HPBL) were exposed to sodium fluoride for 72 hours 2, 10, 20, 40, 80, or 160 ug/mL	**NEGATIVE** The 160 go/mL dose of sodium fluoride was toxic as indicated by total lack of cell entering the mitotic cycle. SCEs of cells exposed to sodium fluoride concentrations of 80 go/mL or lower did not differ significantly from the control. Sodium fluoride did not induce an increase in SCEs in HPBL cells; there was no evidence of mutagenicity.
870.5900 In Vitro sister chromatid exchange assay Purity = 99.99%	Tong et al. (1988). The Lack of Genotoxicity of Sodium Fluoride in a Battery of Cellular Tests. Cell Biology and Toxicology 4.2:173-186. **Open Literature** Chinese hamster cells (CHO) were exposed to sodium fluoride for 24-27 hours 2, 10, 20, 40, 80, or 160 ug/mL	**NEGATIVE** The 80 and 160 go/mL dose levels of sodium fluoride were toxic. There were no significant increases from control in SCEs in CHO cells exposed to 2-40 go/mL sodium fluoride. Sodium fluoride did not induce a SCE increase in CHO cells; there was no evidence of mutagenicity.
870.5900 In Vitro sister chromatid exchange assay **?????**	Toxicology and Carcinogenesis Studies of Sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). National Toxicology Program, Technical Report Series No. 393, NIH Publication No. 91-2848, December 1990, Pgs. 1-477. **Acceptable** Guideline **??????**	**POSITIVE** There was evidence of a concentration related positive response in SCEs induced over background in one of two studies performed, while the second did not find any evidence of a positive response.
870.5900 In Vitro sister chromatid exchange assay Purity not reported	Tsutsui T, et al. (1984). Sodium Fluoride-Induced Morphological and Neoplastic Transformation, Chromosome Aberrations, Sister Chromatid Exchanges, and	**POSITIVE** A dose-dependent increase in sister chromatid exchanges was observed following

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Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
	Unscheduled DNA Synthesis in Cultured Syrian Hamster Embryo Cells. Cancer Research 44.3:938-941 **Open Literature** Syrian hamster embryo (SHE) cells were exposed to sodium fluoride for 24 hours 20, 40, or 80 ug/mL	administration of sodium fluoride in Syrian hamster embryo cells. Sodium fluoride was mutagenic in SHE cells within the confines of this study. Treatment-related effects on mortality were observed in SHE cells administered sodium fluoride. At sodium fluoride concentrations of 75, 100, and 125 go/mL, there were decreases in cell survival that were 10, 47, and 61%, respectively, less than control. There were significant dose-dependent increases in SCE frequency in the sodium fluoride-treated SHE cells. After 24 hours of exposure, the frequency of SCEs increased 1.4-, 1.6-, and 2.1-fold over control at the 20, 40, and 80 go/mL dose levels of sodium fluoride, respectively.
870.5915 In Vivo sister chromatid exchange assay Purity not reported	Li Y, et al. (1987). Genotoxic Effects of Fluoride Evaluated by Sister-Chromatid Exchange. Mutation Res 192:191-201. **Open Literature** Male Chinese hamsters 0.1, 1, 10, 60 or 130 mg/kg 3 animals/dose (except for the 130 mg/kg dose group in which 8 animals were used)	**NEGATIVE** Sodium fluoride did not induce a SCE increase in CHBM cells; there was no evidence of mutagenicity. Death occurred in three out of the eight hamsters in the 130 mg/kg/day group. Although toxic effects were seen in the high dose group, there were no treatment-related increases in SCE.
Special Study Developmental Neurotoxicity Purity not reported	Mullenix et al. (1995). Neurotoxicity of Sodium Fluoride in Rats. Neurotoxicology and Teratology 17:169-177. **Open Literature** Sprague-Dawley rats	No maternal or offspring toxicity was indicated by reduced body weight in dams during prenatal treatment or in their pups soon after birth. However, prenatal exposure to sodium fluoride altered the behavioral outcome in male offspring when exposure

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	administered NaF via subcutaneous injection during the prenatal period on gestation periods 14-18 and 17-19. Weanlings received drinking water containing 0, 75, 100, or 125 ppm F for 6 to 20 weeks. 3-month old adults received 100 ppm for 6 weeks.	occurred on GD 17-19 and consisted of time structure changes in eleven behaviors and behavioral sequences. The behavioral differences did not coincide with the plasma fluoride levels. Body-weight was significantly reduced from the control group in 3-week old rats administered 125 ppm fluoride. Concentrations below 125 ppm did not affect body weight gain during 6-week exposures. Plasma fluoride levels were significantly increased in all test groups compared to control groups. The same direction of behavioral change (initiation and total time) occurred in treated animals when compared to controls. This change was independent and unrelated to sex of the animal, exposure time (6 or 16 weeks), or dose level (100 or 125 ppm). The act of standing and the related attention cluster tended to increase in total time, while the other acts consistently decreased in initiations and total times. The adult exposure to 100 ppm sodium fluoride had a significant effect on female behavior consistent with the behavioral change in the 3-week old rats. Similar behavioral time structure effects occurred when adult and weanling exposed rats approached 5 months of age. The effect on behavior varied with the timing of exposure during CNS development. There were differences between behavioral changes in weanling and adult exposure when compared to prenatal exposures. Prenatally induced behavioral effects were unaccompanied by changes in body weight or elevated plasma fluoride levels.

Table 5. Subchronic, Chronic, and other Toxicity Profiles for Sodium Fluoride		
Guideline Number/ Study Type/ Test Substance (% a.i.)	**MRID Number (Year)/ Citation/ Classification/ Doses**	**Results**
		The behavioral effects induced by weanling and adult exposures were accompanied often by weigh reduction and always by elevated plasma fluoride levels. Rats were exposed to sodium fluoride at concentrations ranging from 75-125 ppm for 6 or 20 weeks. Plasma fluoride levels reached 0.059-0.640 ppm and after 6 weeks of consuming 75 and 100 ppm of sodium fluoride animals exhibited greater plasma fluoride levels than animals treated with 125 ppm. The researchers suggest that there was a taste aversion that limited the water consumption at the 125 ppm level; prolonging the period needed to attain plasma levels that were achieved in 6 weeks by the two lower exposure levels. The levels of fluoride in plasma best predicted effects on behavior.
870.7485 General Metabolism	Hall et al. (1977). Kinetic Model of Fluoride Metabolism in the Rabbit. Environmental Research 13:285-302. **Open Literature** Adult male New Zealand rabbits were administered sodium fluoride in the diet, water, and in a single oral dose injected directly into stomach through nasal catheter 15 ppm in the diet 1 ppm in the water 0.5 mg/kg oral 6 rabbits	Urine excretion following oral administration of NaF was 5 and 13% for 60 and 600 minutes, respectively. Under steady state conditions approximately 15% of fluoride ingested in food and water was absorbed by animal. 15% was excreted in urine and 85% of ingested fluoride was involved in fecal excretion.