

U.S. CONSUMER PRODUCT SAFETY COMMISSION



FINAL REPORT STUDY OF AVERSIVE AGENTS

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EXECUTIVE SUMMARY

The Consumer Product Safety Commission (CPSC) was directed by Congress in section 204 of the Consumer Product Safety Improvement Act of 1990 (Improvement Act) to conduct a study of aversive agents.

The CPSC defined the term aversive for the purpose of this study as a substance added to a product with the intent of deterring or limiting its ingestion. In July 1991, the CPSC requested information on aversive agents including bittering and pungent agents from the public in a Federal Register notice. The response to the request for information and the results of a literature review demonstrate that there is a lack of information available on aversive agents other than one bittering agent, denatonium benzoate. The information available on several additional bittering agents, including sucrose octaacetate, quercetin, naringen, quassin, and brucine was reviewed and is included in the report. Capsaicin, the most common pungent agent, was also reviewed for this study.

Acute toxicity of the aversive agents does not appear to be a major issue. Many of the bittering agents, including sucrose octaacetate and denatonium benzoate, have low toxicity at the levels used for aversion. However, none of the agents reviewed, including denatonium benzoate, have a complete toxicity profile. There is limited information on chronic human exposure and a lack of carcinogenicity and teratogenicity data on denatonium benzoate.

The environmental impact of widespread use of extremely bitter compounds such as denatonium benzoate was expressed as a concern by the commenters. The limited data suggest that denatonium benzoate does not totally biodegrade. The environmental impact of this is unknown.

Effectiveness of aversive agents is the primary issue. None of the compounds reviewed totally deter ingestion; therefore, a child will drink some of the product before the bitter or hot taste can be detected. This restricts the utility of aversive agents. Aversive agents are unlikely to protect children from being harmed after ingesting highly toxic or corrosive substances that can injure or kill after one or two swallows.

Inclusion of aversive agents is not recommended in oral drugs, hydrocarbon-containing products, topical products, products with low toxicity, high toxicity, or corrosive products.

Non-drug products that require child-resistant packaging and have moderate toxicity may benefit from the addition of an aversive. Products that will not kill or severely injure in the one to three mouthful range, but are associated with toxicity at higher levels, are the most appropriate products for aversive addition.

Aversives are not an alternative to child-resistant packaging. Aversives may be an additional protective measure if found to be effective. However, there is no evidence that

denatonium benzoate or any other possible aversive agent is actually effective at limiting ingestions of consumer products.

Consumer products containing aversive agents should not be labeled or promoted as being safer than products not containing aversive agents.

The CPSC recommends that the use of aversives should not be considered for regulation until the effectiveness of these substances to limit ingestions is demonstrated.

FINAL REPORT STUDY OF AVERSIVE AGENTS

I. INTRODUCTION

Section 204 of the Consumer Product Safety Improvement Act of 1990 (Pub. L. 101-608, 104 Stat. 3110) (Improvement Act), directs the Consumer Product Safety Commission (CPSC) to:

"...conduct a study of requiring manufacturers of consumer products to include aversive agents, as appropriate, in products which present a hazard if ingested to determine the potential effectiveness of the aversive agents in deterring ingestions".

The study was to be completed no later than two years after the enactment date. The Commission reported the status of the study to Congress in November 1991. The status report described the study design.

The CPSC staff designed a study to address the issues outlined by Congress; appropriateness, effectiveness, and the need for regulatory action.

The Improvement Act directed the CPSC to consult with appropriate consumer, health, and business organizations and government agencies to obtain information to conduct the study of the use of aversives. On July 1, 1991, the Commission published a Federal Register notice to inform the general public about the study and to solicit information. The comments received in response to the Federal Register request for information focused on one particular bittering agent, denatonium benzoate. This bittering agent is promoted as an aversive agent in the United States and Europe. The commenters raised the following issues about the use of aversives.

- Definition of aversive
- Effects of chronic exposure to aversives
- Environmental impact of widespread aversive use
- Feasibility of adding aversive agents to products
- Measurement of aversive
- Cost of aversive use
- Labeling products that contain aversives
- Impact of regulating aversive agents

This report addresses the issues outlined above by presenting the current state of knowledge on the use of aversive agents.

II. SAFETY OF AVERSIVE AGENTS

The CPSC defines the term aversive agent as a substance which is added to a product with the intent of deterring or limiting its ingestion. The chemical properties of an aversive agent determine the types of products the aversive can be added to. Chemical stability and solubility partially determine aversive-product compatibility. It is important that aversive agents not add to the toxicity of a product. The following section provides information on the chemistry and toxicity of several compounds from two major aversive agent categories; bittering agents and pungent agents.

A. BITTERING AGENTS

Bittering agents are a group of chemically dissimilar compounds that have a common trait of adding a bitter taste to substances. Chemicals considered to be bittering agents include: denatonium salts, sucrose octaacetate, quinine, flavonoids, and quassinoids. Many of these chemicals or classes of chemicals are approved as alcohol denaturants (making ethyl alcohol unfit for consumption) in the United States.

The optimal aversive agent should have a margin of safety between the amount used to bitter a product and the toxic level. Table 1 compares the taste threshold, the relative bitterness, and acute toxicity of these substances. The taste threshold is defined as the amount of chemical perceived as bitter by humans. The amount of the bittering agent needed to make a substance unpalatable is higher than the threshold amount. The relative bitterness compares the bitterness between the chemicals.

The denatonium salts are the most bitter compounds known. The concentration of denatonium benzoate used as an aversive agent is much lower than the level associated with toxic effects. This is not the case for brucine, a quassinoid; this compound has a narrow safety margin at bittering concentrations.

The following sections outline the chemistry and toxicity of several bittering agents.

1. Denatonium (benzoate, saccharide, chloride)

As stated previously, most of the responses to the Federal Register request for information provided comment and information on the bittering agent, denatonium benzoate. The part of the molecule responsible for the bitterness is the denatonium cation. Several other derivatives including the saccharide and the chloride salts are also bitter.

a. Uses

Denatonium benzoate is approved as an alcohol denaturant in many countries. In the United States, this compound is present as an additive in two approved formulations of specially denatured alcohol (SDA), SDA-1 and SDA-40B. SDA-1 and SDA-40B contain

Table 1. Relative Taste and Toxicity of Bittering Agents

Substances	Threshold ¹ (ppm)	Relative ² Bitterness	Oral LD ₅₀ ³ (mg/kg)
Denatonium Saccharide	0.01	1000.00	1430
Denatonium Benzoate	0.05	500.00	612
Denatonium Chloride	0.10	100.00	820
Sucrose Octaacetate	10.00	1.00	5000 ⁴
Quassinoids:			
Quassin	16.70	0.67	800
Brucine	4.50	2.20	1
Flavonoids:			
Quercetin	50.00	0.20	2000 ⁵
Naringen	65.00	0.15	NA ⁶

¹ Relative bitterness is the bitterness of the substance as compared to sucrose octaacetate.

² Threshold is the concentration detected by 50% of the adult human subjects tested.

³ Oral LD₅₀ is the median lethal dose for albino rats.

⁴ No animals died at the highest testable concentration of 5000 mg/kg.

⁵ No animals died after oral doses of 2000 mg/kg/day for nine days.

⁶ No data available.

denatonium benzoate at a final level of 11 parts per million (ppm) and 6 ppm respectively. These alcohols are used as solvents in many cosmetics and consumer products.

Denatonium benzoate is used as a flavoring in placebo medicines. Until recently, this bittering agent was an active ingredient in nail biting and thumb sucking deterrents. The Food and Drug Administration (FDA), citing a lack of efficacy data, removed approval for these products.

Denatonium benzoate is used as an active ingredient in animal repellents. The denatonium salts are used to control cannibalism in pigs.

This bittering agent is widely promoted as an aversive agent. One firm manufactures and markets denatonium benzoate as an ingestion deterrent using a registered trade name. Several manufacturers of cosmetic, automotive, and cleaning products are adding denatonium benzoate to products. The amount of denatonium benzoate added to products as an aversive

is usually between 20 and 50 ppm. This is greater than the level used to denature alcohol in the United States. Other countries, such as Norway, require denaturing levels of denatonium benzoate in the 50 ppm range.

The U.S. Environmental Protection Agency (EPA) allows the addition of denatonium benzoate as an inert ingredient for pesticides intended for indoor, non-food use.

b. Solubility and Stability

Denatonium benzoate is soluble in water, alcohols, and chloroform. The solubility of denatonium benzoate is extremely low in hydrocarbons; however, a new formulation of denatonium benzoate and a blend of surface active agents will dissolve in hydrocarbon solvents containing 12% aromatics, such as mineral spirits.

Denatonium benzoate is stable over a wide range of pHs. At alkaline pHs, the benzoate salt may be converted to the hydroxide salt, which may be less stable. Degradation of denatonium benzoate occurs at pH 11.5 or greater when present at temperatures of 50 °C. The solid is stable at temperatures up to 140 °C. Denatonium benzoate is unstable in strong oxidizing agents such as chlorine bleach and hydrogen peroxide.

c. Acute Toxicity

Several toxicity studies were sponsored by the Department of Housing and Urban Development (HUD). Their interest in this compound stems from the use of denatonium benzoate to bitter paint to prevent paint pica (eating of paint chips).

The studies included determining the acute median lethal dose (LD_{50}) studies in adult and neonatal rats and rabbits. The denatonium benzoate was given orally and the animals were observed for 14 days following oral administration. There were no gross lesions found after necropsy of the rats which died following administration of the higher doses of denatonium benzoate. During necropsy, many of the rabbits had lung, thymic, and tracheal congestion and hemorrhage. Similar studies were performed by others with denatonium saccharide. The LD_{50} values for various species are listed in Table 2. The LD_{50} values range from 600 to 1400 mg/kg depending on the salt and the species tested.

d. Chronic Animal Studies

Chronic one year and two year studies were performed using monkeys and rats, respectively. In the monkey study, animals were dosed orally with 1.6, 8, or 16 mg/kg/day denatonium benzoate for one year. No changes related to the compound were seen in general behavior and appearance. No gross pathologic lesions considered to be compound related were observed in the animals which were sacrificed at 3, 6, or 12 months or which died during the course of the study. Several deaths that occurred to animals receiving the higher dosage levels may have been attributed to effects related to the compound, according to the

Table 2. Acute Oral Toxicity of Denatonium Salts

Species	LD ₅₀ (mg/kg) ¹	
	Denatonium Saccharide	Denatonium Benzoate
Mice	1232	865
Rats	1430	612
Neonatal Rats	23	NA
Rabbits	1390	593
Guinea Pigs	1300	805
Shrimp	600 ²	400 ²
Rainbow Trout	1500 ²	1000 ²

¹ LD₅₀ is the median oral lethal dose.

² These values are LC₅₀s, the median lethal concentration in mg/l.

results of the study. A cause of death could not be established for five of the nine monkeys that died during the course of the study. In the absence of a cause of death unrelated to the compound (intratracheal intubation, or injury), the deaths are considered to be compound related although no compound related gross lesions were seen.

In the two year toxicity study, rats were given denatonium benzoate orally at dosages of 1.6, 8, or 16 mg/kg/day. No gross or microscopic pathologic lesions considered to be related to the compound were seen.

e. Mutagenicity

Denatonium benzoate was not mutagenic in the Ames test (concentration to 5000 ug/plate), the fluctuation test (1000 ug/ml), or the yeast gene conversion assay (5000 ug/ml). This bittering agent also was non-mutagenic in the mouse micronucleus test.

f. Irritation and Sensitivity

Denatonium benzoate is not irritating to rabbit ocular mucosa at concentrations of 0.005 to 0.05 percent. The skin sensitizing potential of denatonium benzoate is considered to be low. No contact allergenicity was seen in guinea pigs following repeated dermal applications of 10% denatonium benzoate.

In a human forearm irritation patch test conducted at the Toho University in Japan, solutions of 0.05 % or 0.005 % denatonium benzoate were applied to the forearm of 30 subjects. Although details of this study were not given, the authors stated that irritation due to denatonium benzoate is unlikely.

The medical literature reported a case of asthma and urticaria from exposure to denatonium benzoate. A 30 year-old male experienced contact urticaria when exposed to an insecticidal spray and a skin disinfectant containing denatonium benzoate. The subject had a positive reaction to concentration of denatonium benzoate as low as 2×10^{-6} mg/l. This is the only confirmed case of hypersensitivity to denatonium benzoate.

g. Summary

Denatonium salts are extremely bitter. Denatonium benzoate is used as an alcohol denaturant and has been present in many household products for years. This bittering agent is soluble in alcohols, ethylene glycol, and water, making it compatible with many household products. Denatonium benzoate is not stable in chlorine bleach and hydrogen peroxide. Acute toxicity does not occur at the suggested aversive level of between 20 and 50 ppm. There is one documented case report of human sensitivity to denatonium benzoate. No data is available on inhalation toxicity and teratogenicity of this compound. The effects of chronic human exposure to denatonium benzoate has not been studied directly.

2. Sucrose Octaacetate

Sucrose octaacetate (SOA) is a crystalline sucrose derivative with a very bitter taste. SOA has limited solubility in water, but is highly soluble in alcohols. SOA is used commercially as an alcohol denaturant and a component of adhesives, plastics, and lacquers. This bittering agent is an active ingredient in nail biting and thumb sucking deterrents.

a. Toxicity

SOA is detected as bitter at 10 ppm (Table 1). A concentration of 600 ppm will render a substance inedible. Although higher concentrations of SOA are needed for bitterness than the denatonium salts, the toxicity of SOA is very low. Acute toxicity studies conducted with rats and rabbits failed to estimate a lethal dose; oral doses as high as 45 g/kg produced no compound-related adverse effects. In addition, no effects or pathologies were noted after feeding rats and rabbits 4 g/kg/day for a three month period.

Sucrose octaacetate has little or no activity as a skin or eye irritant. SOA is an active ingredient in nail biting deterrents. In one study, 90 volunteers painted their fingernails with a mixture of denatonium benzoate (.15%) and SOA (6%). Nails were licked at four hour intervals, and nails, mouth, and tongue were checked for signs of irritation. No irritation was noted when the mixture was applied to the nails and tested for 30 days. The FDA has preliminarily ruled that SOA is safe in concentrations up to six percent. Because of a lack of

data to establish the effectiveness of SOA as a nail biting deterrent, the FDA has not finalized the status of this compound in nail biting preparations.

b. Summary

SOA is less bitter than denatonium benzoate; however, the margin of safety is larger. SOA has little acute toxicity. There is limited information available on chronic toxicity and mutagenic, carcinogenic, and teratogenic potential of this compound. This compound has limited solubility in water, making it incompatible with many household products.

3. **Flavonoids**

The flavonoids are a group of structurally similar compounds that are found in various plants, food products, and dyes of natural origin. The daily diet of individuals in the United States contains an estimated one gram of these substances. Quercetin, a yellow crystalline solid with a bitter taste, is the prototype for this class. This compound is practically insoluble in water, but soluble in alcohol. A related flavonoid, naringen, is responsible for the bitter taste of grapefruit. It is soluble in acetone and alcohol. These compounds are the least bitter of the bittering agents reviewed (Table 1).

a. Toxicity

The oral LD₅₀ of quercetin exceeds 2 g/kg in rats and mice. The symptoms of toxicity in these species include somnolence, muscle weakness, and respiratory depression. Rapid metabolism may account for the low toxicity of quercetin.

Humans tolerate an acute oral dose of 4 g and an intravenous dose of 100 mg of quercetin. Concentrated dietary supplements containing at least 250 mg of quercetin and other flavonoids are available commercially; no serious effects are linked to their use.

A diet of four percent quercetin for two years produces no ill effects in golden hamsters. No compound-related histopathologic lesions or changes in body weight develop in rats fed daily doses of up to 650 ppm quercetin for 410 days.

b. Mutagenicity

Quercetin exhibits the strongest mutagenic activity of the flavonoids. This compound induces base substitutions and frameshift mutations in the Ames Test. In addition, chromosomal aberrations and sister chromatid exchanges occur in mammalian cell cultures. Although quercetin is consistently positive in short-term genotoxicity tests, in vivo tests tend to be negative. Quercetin (1,000 mg/kg) does not induce micronuclei in bone marrow erythrocytes of mice. Adding quercetin in the diet for eight days does not induce micronuclei in mice.

c. Summary

There is limited information available on this class of bittering agent. The taste threshold is much greater for this class than denatonium benzoate. The limited solubility in water also limits the usefulness of these compounds. Further toxicity studies are required. At this time, there is no benefit for using these compounds as aversive agents instead of denatonium benzoate.

4. **Quassinoids**

The quassinoids are obtained from a variety of natural sources. The more common members of this class include brucine and quassin. These compounds are soluble in benzene, alcohol, acetone, chloroform, and acetic acids, but are poorly soluble in ether. Solubility in water depends on the particular compound and its salt formulation, but is usually about 1 g/1,000 ml. As a group they are susceptible to alkaline degradation.

Most quassinoids are bitter in the range of 10-20 ppm. The threshold values for quassin and brucine are 16.7 and 4.5 ppm, respectively (Table 1). Quassin and brucine are used commercially as alcohol denaturants. Some of the formulations of SDA in the United States contain 11 ppm of quassin or brucine.

a. Toxicity

The acute oral LD₅₀ values for quassin in the rat and mouse are 800 and 1,200 mg/kg respectively. In contrast, brucine (2,3-methoxystrychnine) is a very toxic central nervous system stimulant. Exposure to this agent produces muscle spasms and rigidity, convulsions, and death. The acute oral LD₅₀ of brucine in rats is 1 mg/kg. Ingestion of 80 mg by an adult human can produce profuse sweating, weakness, convulsions, respiratory failure, and death.

b. Summary

While quassin may have a role as an aversive agent, limited information on chronic toxicity is available. Brucine is highly toxic and should not be used as an aversive agent. Denatonium benzoate replaced this compound as a denaturant in alcohol in many countries.

B. PUNGENT AGENTS

Pungent agents or irritants are used as medicinal and flavoring agents. These compounds produce a sharp biting taste and a burning sensation when topically applied to mucosal and skin surfaces. Common pungent agents include:

Capsaicin (red chile peppers)
piperine (black pepper)
allyl isothiocyanate (oil of mustard)
resiniferatoxin

The relative pungency and the threshold level for taste are listed in Table 3. Resiniferatoxin is the most potent pungent agent. The irritation produced by this compound is delayed and prolonged; a response can last for several hours. This limits the usefulness of resiniferatoxin as an ingestion aversive. Allyl isothiocyanate is volatile and has been proposed as an aversive agent in glues and related products with inhalation abuse potential. The volatile nature of this compound limits the usefulness as an aversive agent in consumer products. Piperine, the pungent agent in black pepper, is 70 times less active than capsaicin as a pungent agent. There is no benefit of using this compound over capsaicin as an aversive agent. Capsaicin, a common pungent agent will be described in the following section.

Table 3. Potency of Pungent Agents

Substances	Threshold ¹ (ppm)	Relative ² Pungency
Resiniferatoxin	0.001	10000.00
Capsaicin	0.020	1000.00
Piperine	1.350	151.00
Allyl Isothiocyanate	4.100	4.00

¹ Threshold is the concentration detected by 50% of the adult human subjects tested.

² Relative pungency is the pungency of the substance as compared to capsaicin = 1000.

1. Capsaicin

Capsaicin is the major pungent ingredient in red chile peppers of the genus capsicum. It is a common part of the diet in the United States. The pungency threshold of capsaicin is 0.02 ppm (Table 3). Capsaicin imparts a pungent taste to water even when diluted to one part in eleven million parts water.

Pungency is due to the 3-methoxy-4-hydroxy-benzyl residue in the capsaicin molecule. The hydroxyl group at the C-4 position of the aromatic ring is required for the perception of pungency and pain. The pungency is not destroyed by heating with sodium hydroxide solution but is destroyed by oxidation with other chemicals.

Capsaicin is sparingly soluble in cold water and is more soluble in boiling water. It is readily soluble in organic solvents such as petroleum benzene, alcohol, ether, glacial acetic acid, hot carbon disulfide, and fatty oils.

a. Uses

Capsaicin is a component of anti-mugging spray because of the irritant effects.

Repeated exposures of high doses of capsaicin desensitize the area to pain. This activity of capsaicin is more interesting to medical practitioners. Current clinical trials are using capsaicin to provide relief from the chronic pain associated with such ailments as Herpes zoster and diabetic neuropathy. Chili extracts are used in liniments, plasters, and salves to relieve muscular and rheumatic pains and inflammation.

b. Sensation

The pungency of capsaicin also can be influenced by parameters other than concentration and repeated exposure. Capsaicin mouth-burn is masked by increasing concentrations of sucrose and citric acid but not by salt. The capsaicin burn can be suppressed by cooling. The burn intensifies when solutions are warmed.

c. Toxicity

The acute toxicity of capsaicin varies with the route of administration. The LD₅₀ value following intravenous administration is 0.56 mg/kg compared to an LD₅₀ value of 512 mg/kg after dermal administration. Systemic administration of capsaicin results in degeneration of nerve cells. Mixtures of capsaicinoids can produce hepatic necrosis following repeated oral administration to rats and rabbits.

d. Sensitivity

Topical application of capsaicin to the skin or mucosal surfaces causes no permanent damage at lower levels. Long term (ten weeks) topical capsaicin in the rat does not destroy the sensory fibers innervating the treated skin or cause permanent functional impairment. Treated rats show no distress or behavioral changes.

Topical application of high concentrations of capsaicin to mucosal and skin surfaces causes irritation and pain. In humans, one percent capsaicin solutions produce strong burning sensations and cause a severe dermatitis. This concentration also causes severe pain and conjunctival inflammation in the eye. Capsaicin irritates the membranes of the nose, causing prolonged sneezing and coughing as well as allergic reactions. Capsaicin can also cause a severe irritant bronchospasm (constriction of the bronchi). However, long-term chronic exposures produce no serious side effects or permanent damage to the skin or to the pulmonary system.

e. Summary

There is limited information available on the chronic toxicity of capsaicin. The levels of capsaicin that would be used as an aversive agent do not seem to pose any acute toxicity, other than those expected from the irritant effects. The use of capsaicin as an aversive would have limited application because of the limited solubility in aqueous solutions and the irritant nature.

III. ENVIRONMENTAL IMPACT

One area of concern voiced by commenters was the environmental impact of widespread aversive use. The focus is on denatonium benzoate since this agent is extremely bitter at low levels and is widely promoted as an aversive agent.

A. AQUATIC TOXICITY

The toxicity of denatonium benzoate in aquatic species was reported to be low. The LD₅₀ values of shrimp and rainbow trout are 400 mg/l and 1000 mg/l after 96 hours, respectively.

A study was carried out using activated sludge, a common type of wastewater treatment, to determine acute toxicity to aquatic microorganisms. Bacteria use oxygen during the breakdown of organic materials. Toxic chemicals can inhibit the utilization of oxygen and thus lower the dissolved oxygen. Denatonium chloride (1-150 ppm) did not affect the oxygen utilization when compared with glucose, a non-toxic, highly biodegradable substance.

B. BIODEGRADATION

Quaternary compounds tend to be slowly biodegraded. The denatonium cation is a quaternary ammonium compound which is permanently charged. Such charged compounds tend to be impermeable to cell membranes and therefore less accessible to microbial systems. Manufacturers of denatonium benzoate and ethylene glycol antifreeze sponsored testing to determine the environmental fate of denatonium. The contractors used several different assays based on protocols accepted by the Chemical Testing Program of the Organization for Economic Co-operation and Development (OECD) to determine biodegradability. One of these (OECD 301D) showed no chemical deterioration of denatonium benzoate; a second, the Zahn-Wellens test (OECD 302B), showed a 36 percent breakdown after 28 days.

In addition, a carbon dioxide production test, sponsored by the ethylene glycol manufacturers, was conducted to determine the rate and extent of the ultimate biodegradation of denatonium chloride. The ultimate degradation product of carbon-based molecules is carbon dioxide. Results showed that solutions of 10-20 ppm denatonium chloride were poorly metabolized (4.5 percent) as compared with the glucose control (74.6 percent) after 28 days.

The daily rate of degradation could not be determined for denatonium chloride since the rate was so low.

Several tests were conducted to test the removability of denatonium benzoate. Approximately 70 percent of the carbon in denatonium remained after 28 days. The testing laboratory also measured the soluble organic carbon in a Semi-Continuous Activated Sludge (SCAS) test. The test substance is added to the sludge solution incrementally on a daily basis until the final test concentration of 20 ppm is reached, and the samples are withdrawn daily over the next 7 days. Little or no soluble organic carbon from denatonium chloride disappeared over this period. It is not known whether the soluble organic carbon is associated with denatonium salt or a partially degraded product.

C. SUMMARY

The information suggests that denatonium has low toxicity to aquatic organisms; however, this substance is poorly biodegraded. Chlorination performed at water treatment facilities would destroy denatonium benzoate since this compound is unstable in oxidizing solutions. The effect of denatonium benzoate on the ground water is not known. Denatonium benzoate is reportedly adsorbed onto common soil types. No further information is available concerning the potential environmental impact of denatonium salts.

IV. EFFECTIVENESS OF AVERSIVE AGENTS

The CPSC protects children from serious personal injury or illness resulting from handling, using, or ingesting hazardous substances through issuing and enforcing the regulations of the Poison Prevention Packaging Act (PPPA) of 1970. The PPPA requires hazardous household chemicals be contained in child-resistant packages. Deaths of children under five years of age from poisoning by household chemicals have decreased significantly from 216 in 1972 to 55 in 1989. However, there are still many documented ingestion incidents: poison control centers reported over one million ingestions by children under five years of age in 1990. Therefore, the study focuses specifically on the efficacy of aversive agents in deterring or limiting ingestions by children.

Aversive agents are substances which are added to a product with the intent of deterring or limiting its ingestion. Several categories of compounds are identified as having potential aversive characteristics: odorants, bittering agents, and irritants. The intended purpose of adding any of the potential aversive compounds is to make the product less appealing (smell or taste bad). These agents involve either the two chemical senses of taste and smell or the sensation of pain. In order to address the question of effectiveness of aversive agents in deterring ingestions by children, it is necessary to assess the development of the senses and the types of sensory inputs children respond to, both positively and negatively.

Anatomical evidence suggests that young children have the same capacity to taste and smell as adults. The taste buds, taste receptors, and olfactory receptors are present in a functional form at birth. It is unclear, however, if children have the same preferences for odors and taste as adults. An overview of the senses of smell and taste and the results of experiments conducted to determine preferences for odors and tastes are presented below.

A. SENSE OF SMELL

The receptors responsible for the sense of smell are located in the nose and are linked by nerves to the brain. Smell occurs in cycles with respiration. Each breath presents the nasal tissue responsible for smell with a new odor sample. The receptors adapt very quickly and perception of a strong smell may almost vanish after one minute. Although humans have a fairly sensitive sense of smell, there are great differences between people in the ability to detect odors and to respond hedonically to various smells.

1. Odor Preferences

Infants and children have the ability to discriminate odors and distinguish between intensities of odors. Studies examining the comparison of odor preferences and aversions between children and adults, however, have produced conflicting results. Young children (2-4 years) showed fewer preferences for strong odorants, compared to older children (4-7 years) who responded more similar to adults. In these early studies, the young children showed strong biases; more children liked the smell when asked if it smelled "pretty" than when asked if it smelled "ugly". More recent studies have used forced-choice paradigms, where a child is asked which of two odors he prefers. Preschool children three years-old had similar odor preferences and aversions as adults in studies conducted in this manner. Additional well-controlled studies are required to firmly establish that children possess the same aversion to odors as adults.

2. Summary

The argument could be made that an odorant may have the potential to deter ingestions because an odor may be detected before swallowing; the effectiveness of an odorant to do so, however, is unknown. While the addition of odorants to natural gas and propane for purposes of detection has been successful, it is unknown if odorants will play a major role as ingestion deterrents. Further study is required to discern the effectiveness of odorants as ingestion deterrents.

B. SENSE OF TASTE

The taste receptors are present in taste buds on the tongue, soft palate, and other areas of the mouth and throat. Taste buds develop and mature by the 13th to 15th week of gestation in the human fetus. The newborn responds to taste stimuli from birth. The sense of taste is divided into four primary sensations: sweet, sour, bitter, and salty. The various

areas of the tongue and throat exhibit differences in sensitivity for these tastes. The tip of the tongue is sensitive to all four tastes, but especially to sweet and salt. The sides of the tongue are most sensitive to sour or acid but may also respond to salt. The back of the tongue and throat is sensitive to bitter flavors.

The taste threshold for bitter is lower than the thresholds for the other primary sensations in adults in general. However, there is a wide variability among the bitter concentrations that will be tolerated by humans. Some of this difference may be due to genetics. The ability to detect the bitter taste of certain propylthiourea derivatives is a genetic trait. Between 15-30% of the adult population are unable to detect the bitter taste of this class of compounds. Psychophysical studies have shown that nontasters may also be unable to detect other bitter molecules, including saccharin and denatonium benzoate.

1. Taste Preferences

Studies were conducted to discern patterns of taste preference in children compared to adults. Although responses to taste are present at birth, it is more difficult to determine parameters such as fine taste discrimination and taste preference in very young children. In one study, four flavors were used to represent sweet (cherry), hot (cinnamon), spicy (peppermint), and bitter (horehound). Children disliked the spicy taste most, with the bitter taste second most disliked. In contrast, the adult participants most disliked the bitter taste. The authors noted that the children tended to respond more quickly than adults. They speculated that there may be a latency for activation of the bitter receptors, which are located towards the back of the mouth. Thus, the quick responses by children would tend to lead to a choice of spicy or hot over bitter as the most distasteful flavor.

2. Bitterness

Studies have been designed to study the taste reactivity of children to bitterness. The motivation of children who have ingested household products is unknown. The oral exploratory drive is high in some children. In one study, sucrose octaacetate (SOA) was added in varying concentrations to lollipops, to measure the effects of bittering agents on the mouthing times of children with and without prior histories of accidental ingestions. This study included groups of adults as well as children. Increasing the concentration of bittering agent related to the rejection of the lollipops by both adult and child populations; the mouthing times decreased as the concentration of SOA in the lollipop increased. Children with prior ingestion histories reacted similarly to those without prior ingestions. The author stated that adult taste panels could be used as an initial screen for bitterness due to the similarity of the responses between the toddlers and adults.

Another study was conducted to measure the amount of orange flavored potassium supplement that a child would consume. The potassium chloride in the supplement has a bitter, metallic taste. The children stopped eating the orange flavored, powdered potassium supplement before consuming an adult therapeutic dose. The children responded initially by

expressing a like for the powder, then changing the response to one of dislike. The authors concluded that the bitter, metallic after-taste appeared to deter them from eating a significant amount. The authors speculated that an unpleasant taste may act to limit a child from ingesting a toxic amount, at least when a product has a relatively low toxicity. It should be noted, however, that this product was in powdered form and the authors stated that the children were more interested in playing with the powder and required encouragement to eat it. The results of this study were considered by the Commission in the decision to exempt powdered potassium supplements from the child-resistant packaging requirements.

3. Denatonium Benzoate

The use of aversive agents to prevent paint pica was explored. The Department of Housing and Urban Development contracted several studies to examine the effect of denatonium benzoate as an aversive in paint. The mouthing times of young children (9-12 months) on dolls painted with paint containing either no denatonium benzoate or several different concentrations were measured. There were significant differences in the mean mouthing times between control groups and the experimental groups. No differences in mean mouthing times were measured between the groups with dolls painted with different concentrations of denatonium benzoate. The effects of age, children with pica, and repeated exposure in the home situation cannot be extrapolated from these preliminary studies.

Several studies were designed specifically to test the effectiveness of bittering agents as ingestion deterrents in liquid products with children. In one study, conducted by the Procter and Gamble Company, denatonium benzoate (11.4 ppm) was added to a dilute solution of dishwashing liquid. Two age groups of test and control children were recruited (18-23 months and 25-47 months). In both cases, the test groups ingested significantly less detergent solution. The majority of test children ingested less than the volume of one swallow (5 mls), and none of the children in the test group ingested more than three swallow volumes. In the control group, nine children out of 55 ingested more than the volume of three swallows. In the younger age group, none of the children retasted the denatonium benzoate containing detergent solution compared to 67% of controls who did retaste. The authors concluded that the addition of denatonium benzoate to liquid detergents will reduce the probability of large volume ingestions. The authors caution, however, that the environment of the experimental setting (supervised) is different from real life ingestion situations where the child is often alone and has a strong drive to explore. This curiosity could override the aversion to taste.

In another study, 10 ppm denatonium benzoate was added to orange juice as the test solution. The mean amount consumed by the 30 children offered the test juice was 5.75 g. The majority of children refused a second drink; however, seven children took additional tastes of the test solution. One child consumed 26 grams. In a videotaped segment of the experimental protocol, the children responded by wiping their tongues, making faces, and shivering. The author concludes that denatonium benzoate would be useful in preventing accidental poisoning from products with mild to moderate toxicity. It should be noted that the

children were tested with their mothers present and with a substance that is familiar to children. It is not known how these experimental results correlate to accidental ingestion. The authors speculate that since many household products are inherently noxious, the addition of denatonium benzoate will increase the unpalatability further and produce greater avoidance than demonstrated with palatable orange juice.

All of the studies discussed above and additional related studies have demonstrated that the addition of bittering agents can decrease the average amount of liquid ingested by children in a controlled situation. The children do consume some of the product, however, even in controlled situations. This is further demonstrated by an ingestion of a thumb sucking deterrent by a young child. A poison control center alerted the CPSC to a case of a 21 month-old male who accidentally ingested a thumb sucking deterrent containing denatonium benzoate. There is limited volume in these products (15 mls total) and the child ingested approximately one half of the contents, between one and two swallows.

Nail biting and thumb sucking deterrents containing denatonium benzoate are no longer available. The FDA removed OTC products containing denatonium benzoate from the market due to a lack of efficacy data.

4. Effectiveness of Bittering Agents in Commercial Products

Although there are products on the market in the United States and other foreign countries that contain bittering agents, there are limited data available on the effectiveness of aversive agents to limit ingestions of consumer products.

The CPSC is aware of one study that looked directly at the effects of an aversive to limit ingestions in marketed products. The Procter and Gamble Company adds denatonium benzoate to two of nine liquid laundry detergents. Denatonium benzoate is added at 11.4 ppm, the same amount found to limit the ingestion of dilute soap solutions by children in a controlled study.

Procter and Gamble evaluated the incidence of ingestion and the ingested volume of the products with denatonium benzoate compared with similar products without the bittering agent. The data were obtained from telephone calls received through the Procter and Gamble toll-free telephone numbers printed on the product labels. There were no differences in the frequency of calls received (the data were normalized to the volume sold). The rate was approximately three ingestions per million cases of product sold. To evaluate the comparison of ingested volume of the products with and without the bittering agent, the percent of ingestions that involved volumes greater than one fluid ounce were compared. The percentage of ingestions that were reported to involve volumes greater than one ounce was similar for products with or without the aversive (5.1% vs. 4.7% respectively). The number of calls received was not reported. The age range of the ingesters was not given. Procter and Gamble did not speculate on the reasons for the lack of effect, except to mention that the size of the data base may not be adequate to see an effect.

5. Pungent Agents

Limited data are available on the use of pungent agents or irritants as aversive agents. There has been much interest in the potential use of one compound, oil of mustard, to deter intentional inhalation or "sniffing". This discussion, however, is limited to effectiveness of pungents as ingestion deterrents. These compounds have a spicy or pungent taste. Food spiced with chilis is initially unpalatable to children and also to adults because of the burn-like sensation in the mouth and throat, flushing of the face and neck, and sweating of the forehead. After experiencing this reaction a few times, many people begin to prefer it and seek it out. Different cultures have different preferences for spicy and hot. In families where cooking is done with chilis, children may not respond to capsaicin in chemical products as an aversive.

At higher concentrations, the irritants produce burning and painful oral sensations. These agents, like bittering agents, would not be expected to deter total ingestions of products. The irritants are detected less rapidly than tastes or smells and therefore the product would be initially ingested. The result of the ingestion would be a lasting, burning pain. The irritants may elicit strong vocal and behavioral responses following ingestion that could alert the caregiver of the ingestion. Additional study is necessary to determine the effectiveness and usefulness of these compounds as ingestion aversives.

C. SUMMARY OF EFFECTIVENESS

There is a lack of data on the efficacy of aversives to reduce the amount of consumer product ingested. In addition, no post-marketing study has been designed specifically to evaluate the effectiveness of aversive agents in consumer products.

V. AVERSIVE-PRODUCT APPROPRIATENESS

What types of products would be appropriate for the addition of an aversive agent? An effective aversive agent will limit the amount of a substance that is ingested. The aversive compounds available today will not deter or prevent ingestions. Aversives are not a panacea and should only be used with other poison prevention methods (child-resistant packaging, parental education, etc.).

In order to assess what product types are appropriate for aversive addition, it is important to know what product types are accidentally ingested by children. The American Association of Poison Control Centers (AAPCC) evaluated 3.8 million pediatric poisoning incidents to assess the poisoning hazard of household products.

The AAPCC assigned a hazard factor to household products and drugs that were ingested by children under 6 years of age. The hazard factor for each product or chemical was determined by examining serious medical outcome of the ingestions and normalizing the

data to the overall rate of toxic effects. This approach takes into account the severity of the medical outcome and does not base the hazard on the number of poison exposures.

The AAPCC used the results of this analysis to suggest products that may be appropriate for the addition of an aversive agent. Various comments and opinions were voiced by other groups on the types of products that should contain aversives.

A. ACCEPTABLE USES

The AAPCC recommends that aversive agents be added to a few selected toxic substances. Prospective surveillance of poisonings should be conducted to determine the impact of aversive addition on the severity of ingestions. Substances suggested by the AAPCC include:

- ethylene glycol
- methanol
- paraquat
- selected pesticides
- acetonitrile-containing cosmetics
- bromate-containing cosmetics

The AAPCC states that the lack of efficacy and chronic toxicity data precludes recommending adding aversives to all household, garden, and personal care products. Many household products have low toxicity and are unlikely to result in serious toxicity if ingested. Therefore, adding aversive agents is unnecessary.

A major manufacturer of denatonium benzoate has a different approach to the choice of product for the use of aversive agents. The company stated in a written comment that any product that will cause harm to a 4 year old child when a cupful (250 mls) is swallowed should contain an aversive agent. The company believes that if aversives are effective, the benefits should be applied as widely as possible.

B. QUESTIONABLE USES

In addition to the use of aversive agents in mildly toxic substances, commenters expressed doubt about the use of aversives in several product categories.

The commenters agreed that aversives (most notably denatonium benzoate) have limited usefulness in extremely corrosive or toxic products. If one or two mouthfuls of a product can injure a child, the aversive would not prevent the injury. The ingestion of strong acid- or alkali-containing drain cleaners and oven cleaners may not be affected by adding bittering agents. The corrosive nature of these products cause intense pain following ingestion. It is doubtful that a bitter taste would limit the ingestion.

The AAPCC analysis of poisonings demonstrated the hazard of hydrocarbon-containing products. Furniture polish, lighter fluid, and paint solvents are examples of these products. The toxicity of hydrocarbon ingestion is usually not the result of gastrointestinal absorption, but rather the result of inhalation or aspiration. Products with low viscosity have a high aspiration potential. Aspiration of a few milliliters at the time of ingestion by small children can result in chemical pneumonia.

Children's responses after ingesting substances containing denatonium benzoate include wiping their tongues, crying, and shivering. They do not normally spit out the liquid. It is important to assess whether these activities will increase the likelihood of aspiration of hydrocarbon-based products. Aversive addition in this case may increase the possibility of toxicity rather than lowering it. Until this question can be addressed, care must be taken when discussing hydrocarbon-denatonium benzoate appropriateness.

C. UNACCEPTABLE USES

Pharmaceuticals are a product category that generated comments against aversive use. Several drug companies and trade associations cautioned against the addition of aversive agents to oral pharmaceuticals. Drug-aversive interactions and the potential for unknown toxicity is a major concern. The need for additional clinical testing to satisfy FDA requirements was also mentioned as a drawback. Drug products are meant to be ingested by the patient to prevent, eliminate, or ease the symptoms of a medical problem. Patient compliance is an important part of health care and may be affected by the addition of a bittering agent to oral pharmaceuticals.

Topical drugs, including ophthalmologic and otic preparations were also mentioned as a class of product that should not contain aversives. Hypersensitivity, absorption, and chronic exposure were raised as issues.

D. ODORANTS AND PUNGENTS

Although the focus of this report is bittering agents, limited information has been included on odorants and pungent agents. In addition to the limitations listed above, the odorants and pungent agents have limited usefulness as potential ingestion aversives in many product types due to the nature of their aversion. Odorants would not be appropriate for use in general household products that are intended to be used inside. The pungent agents exert an irritant effect on skin as well as oral tissues and therefore would not be useful in products that come in contact with skin.

VI. DEFINING AND MEASURING AVERSIVE

A firm which markets denatonium benzoate as an ingestion deterrent commented that most consumer products will be made aversive by the addition of 20-50 ppm denatonium

benzoate. The comment from this firm states that various factors affect the amount needed to render a product unpalatable. These include:

- viscosity
- existing taste
- existing perfume
- composition

Two other important issues that must be considered when using an aversive agent are:

1. How much aversive must be added to a product to render it unpalatable?
2. What means can be used to measure the appropriate aversive level in consumer products?

A study described previously determined that adult taste panels could be used as an initial screen for bitterness due to the similarity of the responses between the toddlers and adults to bitter lollipops. This is the approach used by the commenter.

The firm states that adult test panels are used to determine the appropriate level of denatonium benzoate in consumer products. As a service to customers interested in using the firm's trade name on their household product, the firm analyzes each ingredient of the product and reviews the toxicity. The supplier of denatonium benzoate states that in several cases, it required products to be reformulated in order to be marketed with the supplier's trade name.

The company suggests a standard tasting protocol. The one used by the company uses 20 male volunteers. The subjects are screened for the ability to recognize the bitter taste of caffeine. The product with and without the bittering agent is taste tested using a 10 microliter sample onto the back of the tongue.

The samples are rated for bitterness using an eight point scale:

- | | |
|---|------------------------|
| 1 | extremely tolerable |
| 2 | very tolerable |
| 3 | moderately tolerable |
| 4 | slightly tolerable |
| 5 | slightly intolerable |
| 6 | moderately intolerable |
| 7 | very intolerable |
| 8 | extremely intolerable |

A sample is considered unpalatable by the company if 75 percent of the subjects rate the product above the moderately intolerable range.

The approach of standardizing a method to determine the amount of aversive that should be added to a product has merit. Standardization becomes an issue when discussing the regulation of aversive agent use or defining a study of the efficacy of aversive agents. It is unknown whether use of the test panels described above is the best method for standardization assessment.

VII. COST OF ADDING AVERSIVE AGENTS TO CONSUMER PRODUCTS

The most obvious cost of adding an aversive agent in consumer products is the cost of the aversive agent itself. Other costs are incurred by testing the new formulation of the product with the aversive agent. Less obvious costs could arise from adverse impacts on worker health or the environment. In some cases, legal or licensing costs will be incurred to obtain the right to use an aversive.

A. COST OF AVERSIVE AGENT AND REFORMULATION

Aversive agents can be added to many consumer products at relatively low cost to the manufacturer or repackager on a per unit basis. Comments received from a supplier of denatonium benzoate and from manufacturers of consumer products indicate that the addition of an aversive agent may increase the manufacturer's cost by no more than a few cents per gallon of product.

Although the cost of adding the aversive is low for most products, additional costs may be incurred for adding aversive agents to certain products. According to a manufacturer with experience using denatonium benzoate as an aversive agent, the cost of adding an aversive agent to a consumer product is influenced by the complexity of the product's formulation. Products with complex formulations contain several ingredients and even minor changes in either the ingredients or the manufacturing process may affect the characteristics of the products. Adding an aversive agent to a product with a complex formulation may be more costly since the product may require more extensive testing and subsequent reformulation. In addition to stability testing, testing may be needed to ensure that the desirable attributes of the product have not been adversely affected (e.g., performance, toxicity, scent). The manufacturer will incur costs necessary to evaluate the probable consumer response to the addition of an aversive agent.

B. IMPACT ON WORKER HEALTH AND THE ENVIRONMENT

Some commenters suggested that widespread use of aversive agents may have negative impacts on worker safety and the environment. At the concentrations to which workers may be exposed, some aversive agents such as denatonium benzoate, are toxic. If the use of aversive agents is increased, the potential for worker exposure is also increased.

Some commenters expressed the fear that a significant increase in the use of aversive agents in common household products (cleaners and detergents) will increase the amount of aversive agents being discharged into the environment. The commenters stress that the impact of aversive agents in the environment is not known.

Although the potential exists for adverse effects on worker health or the environment, these concerns are speculative. Many workers are exposed to denatonium benzoate since it is widely used as a denaturant and an aversive agent without any documented problems, except one case of human sensitivity. CPSC is not aware of any incidents where denatonium benzoate has caused environmental damage.

VIII. LABELING AVERSIVE USE

One issue that stimulated much comment is labeling for the presence of aversive agents in household products. There are two types of labeling for aversive agents, ingredient labeling and promotional labeling.

A. INGREDIENT LABELING

The primary reason for labeling the presence of aversive agents is to identify products that contain an aversive. Ingredient labeling involves listing the aversive agent, such as denatonium benzoate, with the other product ingredients (i.e. alcohol, ethylene glycol, dyes, fragrances, etc.). This allows consumers to consciously purchase products that contain an aversive agent.

Is there a benefit in knowing that a product contains an aversive? The purpose of aversive addition is to limit the amount of household product that a child accidentally ingests. As discussed previously, aversive agents do not deter or prevent ingestions, and the effectiveness of aversive agents in limiting the volume of an ingested household product has not been demonstrated. An ingestion of a product by a young child requires action on the part of the parent or caregiver. Knowing that a product contains an aversive agent should not alter the response of a parent to the poisoning, such as calling a poison control center. Since the toxicity of a product does not change when an aversive is added, knowing that a product has an aversive plays little if any role in the handling of a poisoning situation.

B. PROMOTIONAL LABELING

Adding aversive agents and labeling the product as such has been used by some companies as a marketing tool. Labeling can imply value added to the product or extra responsibility on the part of the company. One manufacturer of denatonium benzoate has a set of requirements that must be met before a product can bear the firm's trade name. Safety, stability, compatibility, and taste testing are evaluated. Thus, the use of the trade name is associated with product testing and quality control.

Proponents of aversive labeling have suggested that labeling products will highlight the potential danger of a product and therefore increase parental vigilance. No supporting evidence is supplied. Those voicing an opinion against labeling state that the opposite is true; labeling a product as containing an aversive will decrease parental vigilance by giving the impression that the aversive will keep their children safe from poisoning by that product. No direct evidence for this position is provided.

The results of research have shown, however, that lowering the perceived hazardousness of a product may lead to incorrect handling of the product. This is the basis for regulations under the Federal Hazardous Substances Act (FHSA) that prohibit the use of disclaimers on hazardous household products which require cautionary labeling. Labeling products as safer or protected by an aversive is prohibited and negates the purpose of the warning label.

Aversive labeling advocates have stated that manufacturers do not use labeling or mention aversive agents because the presence of an aversive label highlights the dangerous nature of the product to the purchaser. This is contrary to the requirements of FHSA, which requires toxic substances to bear cautionary labeling. It is unlikely that the addition of an aversive label will point out the hazard more directly or clearly. Labeling the presence of an aversive adds one more piece of information to the container, which may detract from the warning and confuse or change the consumer's opinion about the hazard.

IX. REGULATING AVERSIVE USE

The Congress requested that the CPSC "conduct a study of requiring manufacturers of consumer products to include aversive agents, as appropriate, in products which present a hazard if ingested ...". Therefore, the issue of regulating the use of aversive agents is addressed below. The staff has been monitoring legislative activity concerning the use of aversive agents in consumer products in the United States. Many state governing bodies have bills pending. Two states, California and Oregon, however, have enacted legislation concerning the use of aversive agents. This section will detail the two state laws and present issues associated with regulating aversive use.

A. CALIFORNIA

The California Children's Poison Protection Act of 1990 requires toxic household substances identified in the Act to contain a nontoxic bittering agent, unless the product is packaged with child-resistant closures. In addition, the legislation required several chemicals with topical applications to be contained in child-resistant packaging "due to the lack of long-term testing results for dermal exposure of available bittering agents..". Many of the chemicals listed in the Children's Poison Protection Act of 1990 require child-resistant packaging under the PPPA.

Requiring either child-resistant packaging or aversive use is not recommended by the Commission or by the American Association of Poison Control Centers (AAPCC).

The Commission considered this issue previously during a rulemaking proceeding to require child-resistant packaging of home permanent neutralizers containing sodium bromate or potassium bromate (55 FR 51897 1990). A comment was received urging the Commission to allow the addition of the bittering agent, denatonium benzoate, to permanent-wave neutralizers as an alternative to requiring child-resistant packaging. After considering information about the use of denatonium benzoate, the Commission concluded that the addition of this bittering agent may not deter young children from initially swallowing small amounts of hair neutralizers and receiving a toxic amount of sodium or potassium bromate. The Commission concluded, "while bittering agents may provide an added measure of deterrence, the presently available evidence does not show that they should be used as an alternative to child-resistant packaging, at least for the extremely toxic substances subject to the proposed rules."

The AAPCC resolution from the Board of Directors includes the following section concerning the addition of aversive agents to products:

"..Be it further resolved that these actions be publicized as intended to augment but in no way replace those other proven poison prevention programs - e.g., use of child-resistant containers, appropriate packaging and labeling, parental education, etc."

B. OREGON

The Oregon legislation is very different from the law passed in the state of California. The Oregon legislation requires antifreeze containing ten percent or more ethylene glycol and windshield washer fluid containing four percent or more methyl alcohol to include an aversive agent approved by the Oregon Poison Prevention Task Force within the product in a concentration so as to render the product unpalatable. This legislation becomes effective on July 3, 1993.

The Poison Prevention Task Force consists of five members, including the medical director of the Oregon Poison Center, the Assistant Director for Health, a licensed pediatrician, an academic chemist, and a representative of industry. The task force function is to review and grant or deny requests for exemption or extension. In addition, the Task Force will evaluate statewide poisoning data for the purpose of making recommendations for addition or deletion of products from the requirements.

C. REGULATION CONCERNS

Neither of these state laws define aversive or unpalatable, or give guidelines to measure the aversiveness or unpalatability of the products. No guidelines are provided to help the manufacturer determine what concentration of aversive is required.

It is unclear how compliance to these laws will be measured. While ingredient labeling may help identify products that contain aversive agents, neither of these regulations deal with the issue of ingredient or promotional labeling.

Commenters voiced concern over different requirements in several states. One association urges "comprehensive Federal regulations be passed" in order to preempt conflicting state and local regulations.

X. CONCLUSIONS

The following section lists the conclusions regarding the use of aversive agents.

There is limited information available on aversive agents other than denatonium benzoate.

Acute toxicity is not expected at the low levels of denatonium benzoate used for aversion (20-50 ppm).

The toxicity profile of denatonium benzoate is not complete. There is limited information on chronic human exposure and no inhalation toxicity and teratogenicity data are available.

Denatonium benzoate does not appear to totally biodegrade. The environmental impact of widespread use of this bittering agent is unknown.

Although the results of laboratory tests indicate that the average amount of denatonium benzoate-containing solutions consumed by children is significantly less than control solutions, there is no direct evidence that denatonium benzoate or any other possible aversive agent is effective at limiting ingestions of consumer products in the home environment.

Aversive agents are not recommended as ingestion deterrents in highly toxic or corrosive products, oral drugs, hydrocarbon-based products, topical products, and products with low toxicity.

Aversive agents, if found to be effective, may be useful in non-drug products that require child-resistant packaging and have moderate toxicity. Products that will not kill or severely injure in the one to three mouthful range, but are associated with toxicity at higher levels, are the most appropriate products for aversive addition.

Aversives are not an alternative to child-resistant packaging. Aversives may be an additional protective measure if found to be effective.

Products containing aversive agents should not be labeled or promoted as being safer than products without aversive agents.

Mandating the use of aversive agents should not be considered until the effectiveness of these substances to limit ingestions has been demonstrated.

XI. RECOMMENDATIONS

The CPSC recommends that the use of aversive agents should not be required due to the lack of efficacy data. In addition, the CPSC recommends against the promotion and use of aversive agents as an alternative to child-resistant packaging and other proven effective means of reducing injuries and deaths from ingestion of hazardous products.

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