UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
BETHESDA, MD 20814

This document has been electronically approved and signed.

BALLOT VOTE SHEET

DATE: January 11, 2012

TO: The Commission
Todd A. Stevenson, Secretary

THROUGH: Philip L. Chao, Assistant General Counsel
Kenneth R. Hinson, Executive Director

FROM: Mary A. House, Attorney, OGC

SUBJECT: Notice of Proposed Rulemaking: PPPA Rule Requiring Child-Resistant Packaging for Imidazolines

Ballot Vote Due - January 18, 2012

Staff forwarded a briefing package recommending that the Commission issue the attached draft proposed rule pursuant to the Poison Prevention Packaging Act of 1970 ("PPPA"). The proposed rule would require child-resistant ("CR") packaging for any over-the-counter or prescription drug product containing the equivalent of 0.08 milligrams or more of an imidazoline (tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline) in a single package. Imidazolines are a family of drugs that are vasoconstrictors indicated for nasal congestion and/or ophthalmic irritation. Imidazolines can cause serious adverse reactions, such as central nervous system ("CNS") depression, decreased heart rate, and depressed ventilation in children treated with these drugs or who accidentally ingest them.

Please indicate your vote on the following options.

I. Approve publication of the draft proposed rule in the *Federal Register*.

_____ _____
(Signature) (Date)

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II. Approve publication of the draft proposed rule in the *Federal Register*, with changes. (Please specify.)

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_____

_____ _____
(Signature) (Date)

III. Do not approve publication of the draft proposed rule in the *Federal Register*.

_____ _____
(Signature) (Date)

IV. Take other action. (Please specify.)

_____

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_____

_____ _____
(Signature) (Date)

Attachment: Draft *Federal Register* proposed rule: Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

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Billing Code 6355–01–P

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

[CPSC Docket No. CPSC-]

Products Containing Imidazolines Equivalent to 0.08 Milligrams or More

AGENCY: Consumer Product Safety Commission

ACTION: Notice of proposed rulemaking.

SUMMARY: The Consumer Product Safety Commission ("CPSC," "Commission," or "we") is proposing a rule to require child-resistant ("CR") packaging for any over-the-counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline, a class of drugs that includes tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline, in a single package. Imidazolines are a family of drugs that are vasoconstrictors indicated for nasal congestion and/or ophthalmic irritation. Products containing imidazolines can cause serious adverse reactions, such as central nervous system ("CNS") depression, decreased heart rate, and depressed ventilation in children treated with these drugs or who accidentally ingest them. Based on the scientific data, the Commission preliminarily finds that availability of 0.08 milligrams or more of an imidazoline in a single package, by reason of its packaging, is such that special packaging is required to protect children under 5 years old from serious personal injury or illness due to handling, using, or ingesting such a substance. We are taking this action under the Poison Prevention Packaging Act of 1970 ("PPPA").

DATES: Written comments must be received by [insert date that is 75 days after publication in the **FEDERAL REGISTER**].

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ADDRESSES: You may submit comments, identified by Docket No. CPSC–2011–XXXX, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments. To ensure timely processing of comments, the Commission is no longer accepting comments submitted by electronic mail (e-mail) except through *http://www.regulations.gov*.

Written Submissions

Submit written submissions in the following way:

Mail/Hand delivery/Courier (for paper, disk, or CD-ROM submissions), preferably in five copies, to: Office of the Secretary, Consumer Product Safety Commission, Room 802, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504-7923.

Instructions: All submissions received must include the agency name and docket number for this notice of proposed rulemaking. All comments received may be posted without change, including any personal identifiers, contact information, or other personal information provided, to *http://www.regulations.gov*. Do not submit confidential business information, trade secret information, or other sensitive or protected information electronically. Such information should be submitted in writing.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov*.

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FOR FURTHER INFORMATION CONTACT: Cheryl A. Osterhout Ph.D., Pharmacologist, Project Manager, Directorate for Health Sciences, Consumer Product Safety Commission, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504–7290; costerhout@cpsc.gov.

SUPPLEMENTARY INFORMATION:

I. Background

A. What is the purpose of the proposed rule?

To protect children younger than 5 years old from serious personal injury following ingestion, the proposed rule would require CR packaging for any over-the-counter ("OTC") or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline (including tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline) in a single package.

B. Why is CR packaging necessary for certain OTC or prescription products containing imidazolines?

Imidazolines are a family of drugs that are used as decongestants in eye drops and nasal products. Topical and nasal administration of imidazolines result in little absorption into the general circulation. Orally ingested, however, imidazolines are absorbed into the general circulation leading to systemic effects. Even though death from ingesting imidazolines is rare, ingestion can result in severe life-threatening consequences, such as central nervous system ("CNS") depression and cardiovascular effects. Specific symptoms of CNS depression upon ingestion of imidazolines range from drowsiness to coma, with a concurrent depression of the respiratory system. Other observed CNS side effects include: headache, lightheadedness, dizziness, tremor, insomnia, nervousness, restlessness, giddiness, psychological disturbances, prolonged psychosis, and weakness. Imidazolines have led to CNS depression and insomnia in different individuals. Prominent cardiovascular effects in response to overdose include low blood pressure and slowed heart rate. The medical literature and evidence from collected

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samples demonstrate that despite the danger of ingesting imidazolines, imidazoline products are not manufactured in CR packaging.

C. What statutory authority does CPSC have to regulate child resistant packaging?

The Poison Prevention Packaging Act of 1970 ("PPPA"), 15 U.S.C. 1471-1476, authorizes us to establish standards for the "special packaging" of any household substance if: (1) the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substance, and (2) the special packaging is technically feasible, practicable, and appropriate for such substance.

Special packaging, also referred to as "child-resistant (CR) packaging," is: (1) designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time, and (2) not difficult for "normal adults" to use properly. 15 U.S.C. 1471(4). Household substances for which we may require CR packaging include (among other categories) foods, drugs, or cosmetics, as these terms are defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321). 15 U.S.C. 1471(2)(B). We have performance requirements for special packaging. 16 CFR §§ 1700.15, 1700.20.

Section 4(a) of the PPPA, 15 U.S.C. 1473(a), allows the manufacturer or packer to package a nonprescription product subject to special packaging standards in one size of non-CR packaging only if the manufacturer (or packer) also supplies the substance in CR packages of a popular size, and the non-CR packages bear conspicuous labeling stating: "This package for households without young children." 15 U.S.C. 1473(a), 16 CFR § 1700.5.

II. Toxicity of Imidazolines

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Tab A of the CPSC staff's briefing package, available at **[insert link to CPSC staff briefing package]** contains the Directorate for Health Sciences' toxicity review for imidazolines, referred to hereinafter as "Tab A: Staff Briefing Package."

A. What medical conditions are imidazolines used to treat?

Imidazolines are used as topical decongestants because they produce vasoconstriction when administered to the eye or nasal mucosa. In the eye, the imidazolines relieve redness due to minor eye irritations by causing vasoconstriction of the blood vessels on the surface of the eye and eyelid (Facts and Comparisons, Ophthalmic Decongestants, Pharmacology, 2011). The onset of vasoconstriction after topical application is within minutes. As nasal decongestants, imidazolines temporarily relieve nasal congestion or stuffy nose due to the common cold, hay fever, or other upper respiratory allergies (Facts and Comparisons, Nasal Decongestants, Pharmacology 2011). The imidazolines cause vasoconstriction in mucous membranes, which decreases blood flow and leads to shrinking of swollen nasal mucosa and increased drainage of the sinuses.

B. What health risks are there for people who overdose on or orally ingest imidazolines?

The therapeutically effective dose of imidazolines occurs within a narrow dose range with toxic effects occurring at doses close to, or at, therapeutic levels. CNS depression (ranging from drowsiness to deep sedation) may occur after normal doses in infants. Overdoses (doses not specified) of these medications have caused initial spikes of high blood pressure leading to slowed heart rate, drowsiness, and rebound low blood pressure in adults. A shock-like syndrome with abnormally low blood pressure and slowed heart rate may also occur. Warnings on tetrahydrozoline- and naphazoline-containing OTC drugs state that use may cause CNS

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depression leading to coma in pediatric patients. Xylometazoline and oxymetazoline symptoms of overdose include: extreme tiredness, sweating, dizziness, a slowed heartbeat and coma.

When the drug is absorbed, it can act systemically within the body. Topical administration of imidazolines to the eye produces local effects to the blood vessels of the eye, but little is absorbed into the general circulation. (For purposes of this document, we interpret "absorption" as the passage of a drug from its site of administration into the blood plasma.)

Nasal administration of imidazolines causes an intense degree of vasoconstriction, and therefore, negligible absorption of the drug into the general circulation (POISINDEX®, 2011). However, with oral ingestion, imidazolines are absorbed into the general circulation, leading to systemic effects. These drugs are absorbed quickly, and symptoms can occur in as little as one hour, peaking at 8 hours, and resolving after 12–36 hours. Even though the symptoms resolve in a relatively short amount of time, ingestion of imidazolines can result in severe life-threatening consequences, including decreased breathing, decreased heart rate, and loss of consciousness, which require hospitalization to ensure recovery. Table 3, in section III.B of this preamble, summarizes relevant cases of imidazoline ingestion.

U.S. Food and Drug Administration ("FDA") regulations pertaining to "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use," at 21 CFR § 341.80(c)(2)(iv), require the product label for products containing naphazoline hydrochloride at a concentration of 0.05 percent to state: "Do not use this product in children under 12 years of age because it may cause sedation if swallowed." Specific symptoms of CNS depression upon ingestion of imidazolines range from drowsiness to coma, with a concurrent depression of the respiratory system. Other observed CNS side effects include: headache, lightheadedness, dizziness, tremor, insomnia, nervousness, restlessness, giddiness, psychological

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disturbances, prolonged psychosis, and weakness. Imidazolines have led to CNS depression and insomnia in different individuals. The insomnia, seen in a few cases, may be an unpredictable, idiosyncratic reaction (*i.e.*, a drug effect that occurs in a small number of people due to age, genetics, or disease state).

Prominent cardiovascular effects in response to overdose include rebound low blood pressure and slowed heart rate. Other reported cardiovascular adverse events include: palpitation (rapid heart rate), cardiac arrhythmia (variation from the normal rhythm of the heart), coronary occlusion (partial or complete obstruction of blood flow in a coronary artery), pulmonary embolism (lodging of mass in a lung), subarachnoid hemorrhage (bleeding between brain and surrounding tissues), myocardial infarction (interruption of blood supply to part of the heart, causing heart cells to die), stroke, and death associated with cardiac reactions in adults. Other systemic side effects can include: blanching (temporary whitening of the skin), sweating, nausea, gastric irritation, weakness, and high blood sugar (POISINDEX®, 2011).

C. What treatment options are available for imidazoline overexposure?

No specific treatment for imidazoline overexposure exists. Naloxone (an opioid blocker) has been used without consistent success. Gastric lavage is not recommended more than 1 hour after ingestion because the imidazolines are absorbed quickly after ingestion, leading to CNS depression and a greater risk of aspiration into the lungs. Activated charcoal may be used up to 1 hour after ingestion; but again, due to the CNS depression, there is a greater risk of aspiration into the lungs. Therefore, treatment of the clinical effects from imidazolines is supportive based on symptoms. For example, mechanical respiration would be administered to those with severe respiratory depression.

III. Ingestion and Injury Data

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A. What data on imidazoline poisonings is contained in the National Electronic Injury Surveillance System ("NEISS")?

The CPSC's Directorate for Health Sciences maintains the Children and Poisoning ("CAP") system, a subset of NEISS records containing additional information obtained through NEISS involving children under 5 years old (Boja, 2001). NEISS is a statistically valid injury surveillance and follow-back database that we maintain of consumer product-related injuries occurring in the United States. Injury data are gathered from the emergency departments (ED) of approximately 100 hospitals selected as a probability sample of all 5,000+ U.S. hospitals with emergency departments. The system's foundation rests on emergency department surveillance data, but the system also has the flexibility to gather additional data at either the surveillance or the investigation level. Surveillance data enable us to make timely national estimates of the number of injuries associated with (but not necessarily caused by) specific consumer products. This data also provides evidence of the need for further study of particular products. Subsequent follow-back studies yield important clues to the cause and likely prevention of injuries and deaths. For additional information on NEISS, see the CPSC's website at http://www.cpsc.gov/cpscpub/pubs/3002.html.

CAP includes data on each pediatric poisoning, chemical burn, or ingestion case reported from a NEISS hospital, as well as data on some ingestions that could lead to poisoning. Our review of data obtained from CAP is summarized in Tab B of the Staff's Briefing Package, hereinafter Tab B: Staff Briefing Package.

We searched the CAP database for incidents between January 1997 and December 2009, involving household products that typically contain imidazolines. During that time, there were an estimated 5,675 emergency room-treated injuries associated with household products containing imidazolines involving children under 5 years old. Table 1 below shows the injury

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estimates for each of the product groups involved in these incidents. Four-fifths of the estimated injuries (81 percent) involved eye drops.

Table 1: Estimated Imidazoline Product-Related Injuries to Children Under 5 Years Old, 1997–2009, by Product Group

Product	Estimated Injuries	Coefficient of Variation	Sample Size	95% Confidence Interval
Eye drops	4,571	0.19	138	2,831–6,311
Nose Sprays [1]	1,104	0.31	34	426–1,782
Total	**5,675**	**0.18**	**172**	**3,666–7,684**

Source: U.S. Consumer Product Safety Commission National Electronic Injury Surveillance System and Children and Poisoning System, 2011.

The following table of NEISS In-Depth Investigations qualitatively illustrates that children were able to obtain access to imidazoline packages.

Table 2: Selected In-Depth Investigation NEISS Reports Showing Child Access to Imidazoline Products

NEISS CASE #	Age	Imidazoline Product	How Accessed (from case narrative)
991018HEP9007	13-month-old	Eye drops	Eye drops were on counter. Bottle may have been partially open. Child found with open bottle of eye drops with cap in her mouth.
050525HEP9006	15-month-old	Eye drops	Parents saw child playing with bottle of eye drops. She had gotten cap off. Parents noted cap was broken on examination.
080714HEP9016	15-month-old	Eye drops	Child found playing with empty bottle of eye drops.
980430HEP9006	18-month-old	Eye drops	Older sibling opened bottle and gave to victim.
050907HEP9001	20-month-old	Eye drops	Eye drops on low dresser, child was able to reach with her hands. Parents say child can open "anything."
011023HEP9001	23-month-old	Eye drops	Child pulled eye drops off counter and removed lid.
000531HEP9005	2-year-old	Nasal Spray	Child came out of bathroom with empty bottle. Bottle had not been put away properly and was within victim's reach.
000601HEP9015	2-year-old	Eye drops	Mother left bottle on sink in bathroom after using it. Victim came out of

[1] The estimate for this category is highly variable due to small sample size and high coefficient of variation. These numbers should be interpreted with caution.

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NEISS CASE #	Age	Imidazoline Product	How Accessed (from case narrative)
			bathroom sucking on bottle. Not clear if child or mother took cap off.
011023HEP9003	2-year-old	Eye drops	Used chair to get to medicine cabinet in kitchen. Took out eye drops and opened them. Mother found child on kitchen counter with open eye drops in hand.
020130HEP9003	2-year-old	Eye drops	Took eye drops out of mother's purse and opened tightly closed cap.
970306HEP9001	2-year-old	Eye drops	Child found in bedroom with open bottle of eye drops. She opened bottle with her teeth.
990301HEP9015	2-year-old	Eye drops	Child took bottle of eye drops off of dresser and unscrewed top.
990416HEP9008	2-year-old	Nasal Spray	Child was in bedroom watching TV on bed. Took nasal spray off of nightstand next to bed. Open, empty bottle found on bed.
990419HEP9022	2-year-old	Eye drops	Bottle left on counter in bathroom was found empty in child's hand.
991018HEP9012	2-year-old	Eye drops	Child found holding bottle of eye drops; cap had been removed and was in his mouth.
020321HEP9004	3-year-old	Eye drops	Child found in bedroom with opened bottle of eye drops.
091009HEP9010	4-year-old	Eye drops	Bottle left on counter. Child was found with open bottle.

B. What data on imidazoline poisonings are contained in the FDA's Adverse Event Reporting System ("AERS")?

The AERS is a database of voluntary reports from health care professionals and consumers, and mandatory reports from manufacturers. AERS is maintained by the FDA and contains reports of adverse events and medication errors for all FDA-approved drugs and therapeutic biologic products. We asked the FDA for all AERS reports mentioning the imidazolines tetrahydrozoline, oxymetazoline, xylometazoline, or naphazoline. FDA provided 1,041 reports for 772 distinct cases involving both children and adults occurring between October 1968 and August 2010, for us to review. We checked for cases related to imidazolines,

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excluded the cases with concomitant drugs, and determined that 67 cases (with 115 total reports) were in scope for consideration in this rulemaking.

Reports through the AERS system show a wide variety of adverse events across all ages associated with the use of imidazolines. The top three system/organ classes with reported adverse events were psychiatric disorders (52 reports); nervous system disorders (47 reports); and respiratory, thoracic, and mediastinal disorders (38 reports). Sixty-two out of 67 in-scope cases (93 percent) reported an adverse event in one of the top three system/organ classes. (Reports can include more than one adverse event, so individual reports may be recorded in more than one system/organ class.) Our review of these cases is contained in Tab B: Staff Briefing Package.

C. What other information is available on the frequency, volume, and severity of ingestion of imidazolines?

The volumes of imidazoline ingestions in children (under the age of 5) that were reported from two sources, the FDA's AERS database ("MedWatch reports") and the medical literature, ranged from several drops to a high of 30 mL (2 tablespoons). The volume ingested was unknown in several imidazoline cases. Very serious adverse effects occurred in response to small oral doses of imidazolines; these are highlighted in Table 3 below, from highest to lowest dose in milligrams.

In MedWatch reports of adverse events occurring in response to ingestion of imidazolines, 43 cases occurred in children under 5 years old. Tetrahydrozoline ingestions constituted the majority of the cases (88 percent). There were no reported deaths related to imidazoline ingestion. *See* Tab A: Staff Briefing Package, Appendix A, for a complete list of cases.

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The most recent imidazoline ingestion case cites the lowest dose of ingestion of which we are aware that caused severe adverse symptoms in a child. The case involved a 25-day-old infant who suffered apnea after being treated with tetrahydrozoline nasal drops (0.05 percent). The mother inadvertently administered the nasal drops by the oral route three times per day with 0.5 ml/day (0.25 mg). The immature kidney and liver function of the newborn caused the drugs to clear the newborn's system slower than in an adult. CPSC staff reviewing this case report considered the three doses of nasal drops to be additive and calculated the total dose for this case to be 0.75 mg. After the second dose, the child was not feeding well and had low muscle tone. Two hours after the second dose, he developed apnea. After the third dose was administered, the child was brought to the hospital and admitted with a respiratory rate of four breaths per minute and a slowed heart rate. The infant was treated with naloxone, resolving the apnea and bradycardia. After two days, the child was in good condition and was discharged. After follow-up 10 days later, the child was in normal condition (Katar et.al. 2010).

Our review of the ingestion data is contained in Tab A: Staff Briefing Package.

Table 3: Relevant Cases of Imidazoline Ingestion

Estimated Dose	Onset/Symptoms	Age	Result	Reference
2.8-5.6 mg oxymetazoline	Within 5 minutes. Child passed out and stopped breathing. Given CPR and taken to ER.	18 mos.	Given fluids and admitted to ICU. Aroused from coma 8–10 hours later. Released later that day. Having headaches 3-4 times daily.	FDA MedWatch 439578450001 6/2004
3-4 mg naphazoline	"Soon" became "quite drowsy" for several hours	3 yrs.	Several hours.	Waring, 1945
3-4 mg naphazoline	One hour after ingestion. Became hypothermic, lethargic, irritable, pale, irregular gasping respirations,	22 mos.	Child warmed and treated with caffeine and oxygen. Symptoms resolved after 15 hrs.	Hainsworth, 1948

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Estimated Dose	Onset/Symptoms	Age	Result	Reference
	hypertension, bradycardia. Followed by unconsciousness and imperceptible respirations.			
2-2.5 mg tetrahydrozoline	90 minutes Lethargic, decreased heart rate, decreased blood pressure	17 mos.	Pediatric intensive care unit Recovered 24 hrs	Jensen et al. 1989
Up to 2 mg tetrahydrozoline	Sharp increase and then decrease of heart rate	22 mos.	Pediatric intensive care unit	FDA540321
1.25-2.5 mg tetrahydrozoline	Decreased heart rate Lethargic, difficult to arouse, depressed respiration	16 mos.	Admitted to hospital overnight	FDA671307
1.25-2.5 mg tetrahydrozoline	2 hrs. Ataxic, pale, drowsy, decreased heart rate, decreased respiration	1 yr.	Admitted to hospital Recovered 24 hrs	Mindlin 1966
1.3 mg tetrahydrozoline	30 min. Lethargic, difficulty breathing, vomiting, loss of consciousness	2 yrs.	Admitted to hospital, treated with charcoal. Released from hospital same day, symptoms resolved.	FDA 43222810001
1-1.5 mg tetrahydrozoline	2–3 hrs Lethargy, decreased blood pressure, decreased respiration	2 yrs.	Pediatric intensive care unit Mechanical respiration for 18 hrs Recovered 48 hrs	Tobias 1996
*0.25 mg x 3 or 0.75** tetrahydrozoline	2 hrs. Apnea, decreased respirations, slowed heart rate	25 days	Admitted to hospital Naloxone, Continuous positive airway pressure, oxygen Recovered 2 days	Katar et.al. 2010

**Due to diminished clearance of drugs by the liver and kidney of the newborn, the three doses are considered additive.*

IV. Level for Regulation

Absorption of imidazolines after oral ingestion can lead to unpredictable and profound CNS depression, including depressed respiration and cardiovascular events. It has been shown that children under 5 years old are accidentally ingesting imidazoline-containing products. The first cases of imidazoline toxicity in children after accidental ingestion occurred in the mid-

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1940s, shortly after the release of naphazoline into the market; and the incidents have continued to occur for more than 50 years (Waring 1945, Greenblat 1947, Hainsworth 1948, Meeker 1948, Bucaretchi et al., 2003). Symptoms of imidazoline toxicity include CNS depression, ranging from drowsiness to coma, bradycardia, and hypoventilation. Even though death from imidazoline exposure is rare, many of these events result in serious life-threatening consequences requiring hospitalization and intensive care monitoring for recovery. *See* Table 3, section III.C of this preamble, for a summary of relevant cases of imidazoline ingestion.

Mindlin (1966) reported a case in which a 1-year-old girl ingested between ½ to 1 teaspoon (2.5–5 mL) of tetrahydrozoline eye drops and suffered CNS depression with slowed respiration and decreased heart rate. Based on this ingestion, recent publications define 2.5 mL tetrahydrozoline (0.05 percent, 1.25 mg) as the dose at which serious toxicity from imidazoline exposure can occur after ingestion (Holmes and Berman, 1999; Eddy and Howell 2000). In the preamble to the proposed FDA rule for OTC nasal decongestants, it was reported that the minimum oral dose of oxymetazoline in an adult causing measurable cardiovascular effects (on blood pressure and heart rate) was 1.8 mg of oxymetazoline (41 FR 38312, 38398 (September 9, 1976)). This minimum dose may be lower for children because they appear to be more sensitive to imidazoline effects than adults (Brainerd and Olmstead, 1956). Cases indicate that ingestion of as little as 0.75 mg of imidazolines can result in serious illness in children, requiring supportive therapy (Katar et al., 2010; Summary see Table 3). The most recent case of imidazoline ingestion is reviewed above in section III.C of this preamble. It involved a 25-day-old infant who suffered apnea after being treated with tetrahydrozoline nasal drops (0.05 percent). CPSC staff reviewing this case report calculated the total dose for this case to be 0.75

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mg, which is the lowest dose of ingestion of which we are aware that caused severe adverse symptoms in a child.

Because serious effects on the heart and breathing rates occur with the ingestion of as little as 0.75 mg of tetrahydrozoline, we consider this the lowest observed adverse effect level ("LOAEL"). All of the imidazolines cause potent central and peripheral sympathetic effects, but tetrahydrozoline has the highest potency for CNS sedative/depressive effects and the lowest potency for cardiac effects. Oxymetazoline and naphazoline are the most potent imidazolines for peripheral cardiac effects and have an 8–10 times lower maximum daily dose than tetrahydrozoline (0.4 mg, 0.3 mg and 3.2 mg, respectively). Xylometazoline and oxymetazoline have a longer duration of action than tetrahydrozoline (12 hrs, 10 hrs, and 4–6 hrs, respectively).

Applying a safety factor of 10 to the LOAEL to derive a recommended regulated level of 0.08 mg for all imidazolines is appropriate in order to protect children from serious health effects following ingestion of this family of drugs. The level of 0.08 mg would require all known imidazolines (see Tables 1 and 2) currently on the market to be placed in CR packaging. (The assumptions underlying the use of safety factors are that by using these factors, both the public health and sensitive populations are protected. Further assumptions hold that humans are somewhere between 10 and 1,000 times more sensitive to some toxic agents than animals, and adults are less sensitive than children. Hence, a safety assessment can be conducted using the proper toxicological evaluation with different populations to establish the NOEL (no observable effect level) or its equivalent. We used a tenfold safety factor to divide the LOEL to reach a NOEL level.

V. Preliminary Findings Related to Child Resistant Packaging for Imidazolines

A. Do imidazolines in non-CR packaging pose a hazard to children?

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As noted above in sections II.B and III of this document, the toxicity data concerning children's oral ingestion of imidazolines demonstrate that they can cause serious illness and injury to children. Moreover, imidazolines are available to children in common household products, such as eye drops and nasal sprays. Products containing imidazolines currently do not use CR packaging. The Commission concludes preliminarily that a regulation is needed to ensure that products subject to the regulation will be placed in CR packaging by any current, as well as new manufacturers.

B. Is it technically feasible, practicable, and appropriate for the Commission to require special packaging for certain imidazoline-containing products?

Special packaging under the PPPA is designed to protect children from serious personal injury or illness. In addition to finding that special packaging is necessary to protect children, we must find that special packaging is technically feasible, practicable, and appropriate for these products (15 U.S.C. 1472 (a)(2)). For special packaging to be technically feasible, the technology must be available to produce packaging that conforms to established standards. A package is practicable if the special packaging is adaptable to modern mass production and assembly line techniques. Finally, packaging is appropriate if the packaging will protect the integrity of the substance adequately and will not interfere with its intended storage or use. All three of these conditions must be met before we can require special packaging for a product.

The definition of "packaging" is "the immediate package or wrapping in which any household substance is contained for consumption, use, or storage by individuals in or about the household." The PPPA defines "special packaging" as packaging that is designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of substance within a reasonable time and not difficult for normal adults to use properly.

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Section 2(4) of the PPPA. The child-resistance and adult-use-effectiveness of special packaging are measured by performance testing packaging with children and senior adults, respectively.

We evaluated packaging representative of OTC products that contain imidazolines. The specimens represent products from all four imidazoline families: naphazoline hydrochloride (HCL), oxymetazoline HCL, tetrahydrozoline HCL, xylometazoline, and a naphazoline HCL combination product. None of the samples used special packaging. The eye drops were packaged in squeeze-to-dispense plastic dropper bottles. The nasal spray was packaged in a plastic bottle with an attached metered pump sprayer, and the nasal drops were packaged in a squeeze-to-dispense plastic dropper bottle. *See* Tab C: Staff Briefing Package, for a more detailed discussion of the products.

With package size and/or type changes, ASTM Type IA, ASTM Type ID, and a CR metered pump sprayer design, are available to the market to replace the non-CR continuously threaded (NCRCT) and the non-CR (NCR) metered spray pump packages. Product packaging assembly line techniques used for the NCR packages can be adapted for some of the CR packages already in the marketplace. Other product manufacturers may use packages that could require changes in assembly- and filling-line techniques. New package sizes also may need to be designed. These new packages would require new tools to be produced. It could take up to 1 year from initiating tool design to final production of a new package, depending upon the complexity of the package.

Based on the foregoing, we preliminarily conclude that available data support the findings that CR packaging for household products containing imidazolines is technically feasible, practicable, and appropriate.

C. Has the Commission made any other findings related to special packaging?

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In establishing a special packaging standard under the PPPA, we must consider the following:

1. reasonableness of the standard;
2. available scientific, medical, and engineering data concerning special packaging and childhood accidental ingestions, illness, and injury caused by household substances;
3. manufacturing practices of industries affected by the PPPA; and
4. nature and use of the household substance. 15 U.S.C. 1472(b).

We have considered these factors with respect to the various determinations made in this notice, and preliminarily find no reason to conclude that the rule is unreasonable or otherwise inappropriate.

VI. Description of the Proposed Rule

The proposed rule would add a new paragraph 33 to 16 CFR § 1700.14(a), which contains a list of substances requiring special packaging. Pursuant to § 1700.14(a), all substances listed in § 1700.14 must meet the requirements for special packaging contained in § 1700.20(a) (on testing procedures for special packaging). Proposed § 1700.14(a)(33) would provide that any over-the-counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline (tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline) in a single package, must be packaged in accordance with the provisions of § 1700.15(a), (b), and (c). Section 1700.15(a) contains general requirements for special packaging, such as the special packaging must continue to function with the effectiveness specifications set forth in § 1700.15(b). Section 1700.15(b), on effectiveness specifications, provides criteria that special packaging tested pursuant to § 1700.20 must meet. Finally, § 1700.15(c) provides that special packaging subject to this paragraph (c) may not be reused.

VII. Request for Comments

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We invite interested persons to submit comments on any aspect of the proposed rule. Comments should be submitted in accordance with the instructions in the ADDRESSES section at the beginning of this notice.

VIII. Environmental Impact

Generally, our regulations are considered to have little or no potential for affecting the human environment, and environmental assessments and impact statements are not usually required. *See* 16 CFR 1021.5(a). More specifically, requiring CR packaging for certain imidazoline-containing products is not expected to have an adverse impact on the environment. Accordingly, the rule falls within the categorical exclusion in 16 CFR §1021.5(b)(2) for product certification rules and an environmental assessment or environmental impact statement is not required.

IX. Executive Order 12988 (Preemption)

According to Executive Order 12988 (February 5, 1996), agencies must state in clear language the preemptive effect, if any, of new regulations. Section 7 of the PPPA provides that, generally, when a special packaging standard issued under the PPPA is in effect, "no State or political subdivision thereof shall have any authority either to establish or continue in effect, with respect to such household substance, any standard for special packaging (and any exemption therefrom and requirement related thereto) which is not identical to the [PPPA] standard." 15 U.S.C. 1476(a). A state or local standard may be excepted from this preemptive effect if: (1) the state or local standard provides a higher degree of protection from the risk of injury or illness than the PPPA standard; and (2) the state or political subdivision applies to the Commission for an exemption from the PPPA's preemption clause and the Commission grants the exemption through a process specified at 16 CFR Part 1061. 15 U.S.C. 1476(c)(1). In addition, the federal

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government, or a state or local government, may establish and continue in effect a nonidentical special packaging requirement that provides a higher degree of protection than the PPPA requirement for a household substance for the federal, state or local government's own use. 15 U.S.C. 1476(b).

Thus, with the exceptions noted above, the proposed rule regarding CR packaging for household products containing an imidazoline above the regulated level would preempt non-identical state or local special packaging standards for such imidazoline containing products.

X. Regulatory Flexibility Act (Economic Analysis)

The Regulatory Flexibility Act ("RFA") generally requires that agencies review proposed rules for their potential economic impact on small entities, including small businesses. Section 603 of the RFA calls for agencies to prepare and make available for public comment an initial regulatory flexibility analysis describing the impact of the proposed rule on small entities and identifying impact-reducing alternatives. 5 U.S.C. 603. Section 605(b) of the RFA, however, states that this requirement does not apply if the head of the agency certifies that the rule, if promulgated, will not have a significant economic impact on a substantial number of small entities and the agency provides an explanation for that conclusion.

Nasal and ophthalmic products are classified within the NAICS 325412 *Pharmaceutical Preparation Manufacturing* industry. According to the U.S. Small Business Administration's Office of Advocacy, a firm classified within NAICS 325412 is considered a small business if the firm has fewer than 750 employees. Based on such classification, out of the approximately 45 firms that manufacture imidazoline-based eye drops and nasal sprays, approximately 20 firms are defined as "small businesses." There may be more manufacturers, in particular firms that manufacture under generic labels, that were not identified but that may be small businesses.

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Preliminary analysis shows the proposed rule would, if finalized, not have a significant impact on a substantial number of small businesses. First, the incremental costs of CR packaging for manufacturers are low, estimated at 1.5 cents per unit for imidazoline products. Manufacturers are likely to be able to pass on at least some of these costs to consumers. Second, most manufacturers of OTC drug products have diverse product lines that include other products that would not be covered by this possible regulation. Therefore, the products that would be affected by this proposed regulation may represent a small proportion of any one manufacturer's production. Finally, the requirements would apply only to products packaged after the effective date of the requirements. Therefore, businesses would have time to use up existing inventories of product and packaging. Based on the foregoing, we conclude preliminarily that the proposed rule regarding CR packaging for certain imidazoline products would not have a significant economic impact on a substantial number of small entities.

XI. Trade Secret or Proprietary Information

Any person responding to this notice who believes that any information submitted is trade secret or proprietary should specifically identify the exact portions of the document claimed to be confidential. We will receive and handle such information confidentially and in accordance with section 6(a) of the Consumer Product Safety Act (''CPSA''), 15 U.S.C. 2055(a). Such information will not be placed in a public file and will not be made available to the public simply upon request. If we receive a request for disclosure of the information or conclude that its disclosure is necessary to discharge our responsibilities, we will inform the person who submitted the information and provide that person an opportunity to present additional information and views concerning the confidential nature of the information. 16 CFR 1015.18(b).

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Thereafter, we will make a determination of whether the information is trade secret or proprietary information that cannot be released. The determination will be made in accordance with applicable provisions of the CPSA; the Freedom of Information Act (''FOIA''), 5 U.S.C. 552b; 18 U.S.C 1905; our procedural regulations at 16 CFR part 1015 governing protection and disclosure of information under provisions of FOIA; and relevant judicial interpretations. If we conclude that any part of information that has been submitted with a claim that the information is a trade secret or proprietary is disclosable, we will notify the person submitting the material in writing and provide at least 10 calendar days from the receipt of the letter for that person to seek judicial relief. 15 U.S.C. 2055(a)(5) and (6); 16 CFR 1015.19(b).

XII. Effective Date

The PPPA provides that no regulation shall take effect sooner than 180 days or later than 1 year from the date a final regulation is issued, except that, for good cause, we may establish an earlier effective date if we determine an earlier date to be in the public interest. 15 U.S.C. 1471n. Because it could take up to 1 year to produce a new package for some companies, we intend that any final rule become effective 1 year after the publication of a final rule in the *Federal Register*.

XIII. References

Please see all citing references in the staff's briefing package, available at [insert website address for briefing package].

List of Subjects in 16 CFR Part 1700

Consumer protection, Drugs, Infants and children, Packaging and containers, Poison prevention, Toxic substances.

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For the reasons given above, the Commission proposes to amend 16 CFR part 1700 as follows:

PART 1700--[AMENDED]

1. The authority citation for part 1700 continues to read as follows:

Authority: Pub. L. 91-601, secs. 1-9, 84 Stat. 1670-74, 15 U.S.C. 1471-76. Secs 1700.1 and 1700.14 also issued under Pub. L. 92-573, sec. 30(a), 88 Stat. 1231. 15 U.S.C. 2079(a).

2. Section 1700.14 is amended to add paragraph (a)(33) to read as follows:

§ 1700.14 Substances requiring special packaging.

(a) * * * * * * * *

(33) *Imidazolines.* Any over-the-counter or prescription product containing the equivalent of 0.08 milligrams or more of an imidazoline (tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline) in a single package, must be packaged in accordance with the provisions of § 1700.15(a), (b), and (c).

Dated: _____

_____
Todd A. Stevenson,
Secretary, Consumer Product Safety Commission

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Staff Briefing Package

Proposed PPPA Rule Requiring Child-Resistant Packaging for Imidazolines

January 11, 2012

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EXECUTIVE SUMMARY

Imidazolines, a class of drugs that include tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline, are decongestants used in eye drops and nasal products. Imidazoline products containing tetrahydrozoline have been available to consumers since 1954, and the first case study of adverse events in the literature occurred in 1955. The medical literature and evidence from collected samples demonstrate that imidazoline products are not manufactured in child-resistant (CR) packaging.

Topical administration of imidazolines to the eye produces local effects to the blood vessels of the eye, but little is absorbed into the general circulation. Nasal administration of imidazolines causes a significant vasoconstriction and therefore, negligible absorption of the drug into the general circulation. However, with oral ingestion, imidazolines are absorbed into the general circulation leading to systemic effects, such as central nervous system (CNS) depression and cardiovascular effects. Even though the symptoms resolve in a relatively short amount of time (24–48 hours), ingestion of imidazolines can result in severe life-threatening consequences, such as decreased breathing, decreased heart rate, and loss of consciousness, which require hospitalization to ensure recovery. Staff determined that imidazoline products containing more than 0.08 milligram (mg) imidazolines can cause serious personal injury and illness to children younger than 5 years old.

Staff's review of market information indicates approximately half the firms that manufacture imidazoline-based eye drops and nasal sprays are defined as "small businesses." However, a rule would not have a significant impact on the small businesses. First, the incremental costs of CR packaging for manufacturers are low; second, most manufacturers of over-the-counter (OTC) drug products have diverse product lines, so the impact of a CR requirement on imidazolines isn't expected to have a significant economic impact because their income isn't solely dependent on imidazoline sales. Staff analysis also indicates that a proposed rule for CR packaging is not expected to have an adverse impact on the environment.

Data support a conclusion that a special packaging standard for household products containing imidazolines is technically feasible (producible), practicable (adaptable to mass production techniques), and appropriate (chemically compatible with the product). Staff determined that CR packaging is available or can be developed within one year of publication of a final rule.

To protect children from serious personal injury following ingestion, staff recommends that the Commission vote to approve publication of a proposed rule that would require special packaging for OTC and prescription drug products containing the equivalent of 0.08 mg or more of naphazoline, tetrahydrozoline, oxymetazoline, or xylometazoline in a single package.

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Briefing Memo

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UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

Memorandum

This document has been electronically approved and signed.

Date: January 11, 2012

TO : The Commission
Todd A. Stevenson, Secretary

THROUGH: Cheryl A. Falvey, General Counsel
Kenneth R. Hinson, Executive Director
Robert J. Howell, Deputy Executive Director for Safety Operations

FROM : DeWane Ray, Assistant Executive Director
Office of Hazard Identification and Reduction

Cheryl A. Osterhout, Ph.D., Project Manager
Directorate for Health Sciences

SUBJECT : Proposed Special Packaging Rule for Imidazolines

I. Introduction

Imidazolines (naphazoline, tetrahydrozoline, oxymetazoline, and xylometazoline) cause contraction and narrowing of blood vessels or vasoconstriction and are indicated for nasal congestion and/or eye irritation. Currently there are prescription and OTC versions of naphazoline eye drops, and a prescription version of tetrahydrozoline nasal spray. Also available, are OTC nasal spray products with naphazoline, xylometazoline and oxymetazoline, as well as OTC eye drops products containing oxymetazoline and tetrahydrozoline (Facts and Comparisons, 2011).

Imidazolines have been shown to cause serious adverse reactions, such as central nervous system (CNS) depression, decreased heart rate, and decreased breathing in children treated with, or who accidentally ingest them. U.S. Consumer Product Safety Commission (CPSC) staff recommends that the Commission propose a rule under the Poison Prevention Packaging Act (PPPA) that would require child-resistant (CR) packaging for OTC and prescription drug products containing the equivalent of 0.08 milligram (mg) or more of the imidazolines naphazoline, tetrahydrozoline, oxymetazoline, or xylometazoline in a single package.

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II. Discussion

A. Toxicity (Tab A)

The Directorate for Health Sciences staff reviewed the toxicity of imidazolines (Tab A). This class of drugs (including tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline) are used as topical decongestants because they produce vasoconstriction when administered to the eye or nasal mucosa. In the eye, the imidazolines relieve redness due to minor eye irritations by causing vasoconstriction of the blood vessels on the surface of the eye and eyelid (Facts and Comparisons, 2011). The onset of vasoconstriction after topical application is within minutes. As nasal decongestants, imidazolines temporarily relieve nasal congestion or stuffy nose due to the common cold, hay fever, or other upper respiratory allergies (Facts and Comparisons, 2011). The imidazolines cause vasoconstriction in mucous membranes, which decreases blood flow and leads to shrinking of swollen nasal mucosa and increased drainage of the sinuses.

The therapeutically effective dose of imidazolines occurs within a narrow dose range with toxic effects occurring at doses close to, or at therapeutic levels. CNS depression (ranging from drowsiness to deep sedation) may occur after normal doses in infants. Overdoses (doses not specified) of these medications have caused initial spikes of high blood pressure leading to slowed heart rate, drowsiness, and rebound low blood pressure in adults. A shock-like syndrome with abnormally low blood pressure and slowed heart rate may also occur. Warnings on tetrahydrozoline- and naphazoline-containing OTC drugs state that use may cause CNS depression leading to coma in pediatric patients. Xylometazoline and oxymetazoline symptoms of overdose include: extreme tiredness, sweating, dizziness, a slowed heartbeat and coma.

"Absorption" is defined as the passage of a drug from its site of administration into the blood plasma. When the drug is absorbed, it can act systemically within the body. Topical administration of imidazolines to the eye produces local effects to the blood vessels of the eye, but little is absorbed into the general circulation. Nasal administration of imidazolines causes an intense degree of vasoconstriction, and therefore, negligible absorption of the drug into the general circulation (Posindex, 2011). However, with oral ingestion, imidazolines are absorbed into the general circulation, leading to systemic effects. These drugs are absorbed quickly, and symptoms can occur in as little as one hour, peaking at 8 hours, and resolving after 12–36 hours. Even though the symptoms resolve in a relatively short amount of time, ingestion of imidazolines can result in severe life-threatening consequences, including decreased breathing, decreased heart rate, and loss of consciousness, which require hospitalization to ensure recovery (see Table 3, this memo).

FDA regulations pertaining to "Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use" (21 CFR part 341) state, at 21 CFR 341.80(c)(2)(iv), require the product label for products containing naphazoline hydrochloride at a concentration of 0.05 percent to state: "Do not use this product in children under 12 years of age because it may cause sedation if swallowed." Specific symptoms of CNS depression upon ingestion of imidazolines range from drowsiness to coma, with a concurrent depression of the respiratory system. Other observed CNS side effects include: headache, lightheadedness, dizziness, tremor, insomnia, nervousness, restlessness, giddiness, psychological disturbances, prolonged psychosis, and weakness. Imidazolines have led to CNS depression and insomnia in different individuals.

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The insomnia, seen in a few cases, may be an unpredictable, idiosyncratic reaction (*i.e.*, a drug effect that occurs in a small number of people due to age, genetics, or disease state).

Prominent cardiovascular effects in response to overdose include low blood pressure and slowed heart rate. Other reported cardiovascular adverse events include: increased heart rate, palpitation,[1] cardiac arrhythmia,[2] coronary occlusion,[3] pulmonary embolism,[4] subarachnoid hemorrhage,[5] myocardial infarction,[6] stroke, and death associated with cardiac reactions in adults. Other systemic side effects can include: blanching,[7] sweating, nausea, gastric irritation, weakness, and high blood sugar (Poisindex, 2011).

There is no specific treatment for imidazoline overexposure; naloxone (an opioid blocker) has been used without consistent success. Gastric lavage is not recommended more than one hour after ingestion because the imidazolines are absorbed quickly after ingestion, leading to CNS depression and a greater risk of aspiration into the lungs. Activated charcoal may be used up to one hour after ingestion; but again, due to the CNS depression, there is a greater risk of aspiration into the lungs. Therefore, treatment of the clinical effects from imidazolines is supportive based on symptoms. For example, mechanical respiration would be administered to those with severe respiratory depression. All of the imidazolines cause potent central and peripheral sympathetic effects, but tetrahydrozoline has the highest potency for CNS sedative/depressive effects and lowest potency for cardiac effects. Oxymetazoline and naphazoline are the most potent imidazolines for peripheral cardiac effects and have an 8–10 times lower maximum daily dose than tetrahydrozoline (0.4 mg, 0.3 mg, and 3.2 mg, respectively). Xylometazoline and oxymetazoline have a longer duration of action than tetrahydrozoline (12 hours, 10 hours, and 4–6 hours, respectively).

B. Poisoning Data

1. National Electronic Injury Surveillance System (NEISS) (Tab B)

The CPSC's Directorate for Health Sciences maintains the Children and Poisoning (CAP) system, a subset of NEISS[8] records containing additional information obtained through NEISS involving children under 5 years old (Boja, 2001). CAP includes data on each pediatric poisoning, chemical burn, or ingestion case reported from a NEISS hospital, as well as data on some ingestions that could lead to poisoning.

Staff searched the CAP database for incidents between January 1997 and December 2009, involving household products that typically contain imidazolines. During that time, there were an estimated 5,675 emergency room-treated injuries associated with household products containing imidazolines involving children under 5 years old. Staff searched products commonly containing imidazolines. Table 1 shows the injury estimates for each of the product

[1] A rapid heart rate.
[2] Any variation from the normal rhythm of the heart beat.
[3] The partial or complete obstruction of blood flow in a coronary artery.
[4] The lodging of mass in lung.
[5] Bleeding between brain and tissues surrounding it.
[6] The interruption of blood supply to a part of the heart, causing heart cells to die.
[7] A temporary whitening of the skin.
[8] NEISS is a stratified statistical sample of emergency rooms in the United States from which product related injury estimates can be made.

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groups involved in these incidents. Four-fifths of the estimated injuries (81 percent) involved eye drops.

Table 1: Estimated Imidazoline Product-Related Injuries to Children Under 5 Years Old, 1997–2009, by Product Group

Product	Estimated Injuries	Coefficient of Variation	Sample Size	95% Confidence Interval
Eye drops	4,571	0.19	138	2,831–6,311
Nose Sprays[9]	1,104	0.31	34	426–1,782
Total	**5,675**	**0.18**	**172**	**3,666–7,684**

Source: U.S. Consumer Product Safety Commission National Electronic Injury Surveillance System and Children and Poisoning System, 2011.

The following table of NEISS In-Depth Investigations qualitatively illustrates that children were able to obtain access to imidazoline packages.

Table 2: Selected In-Depth Investigation NEISS Reports Showing Child Access to Imidazoline Products

NEISS CASE #	Age	Imidazoline Product	How Accessed (from case narrative)
991018HEP9007	13-month-old	Eye drops	Eye drops were on counter. Bottle may have been partially open. Child found with open bottle of eye drops with cap in her mouth.
050525HEP9006	15-month-old	Eye drops	Parents saw child playing with bottle of eye drops. She had gotten cap off. Parents noted cap was broken on examination.
080714HEP9016	15-month-old	Eye drops	Child found playing with empty bottle of eye drops.
980430HEP9006	18-month-old	Eye drops	Older sibling opened bottle and gave to victim.
050907HEP9001	20-month-old	Eye drops	Eye drops on low dresser, child was able to reach with her hands. Parents say child can open "anything."
011023HEP9001	23-month-old	Eye drops	Child pulled eye drops off counter and removed lid.
000531HEP9005	2-year-old	Nasal Spray	Child came out of bathroom with empty bottle. Bottle had not been put away properly and was within victim's reach.

[9] The estimate for this category is highly variable due to small sample size and high coefficient of variation. These numbers should be interpreted with caution.

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NEISS CASE #	Age	Imidazoline Product	How Accessed (from case narrative)
000601HEP9015	2-year-old	Eye drops	Mother left bottle on sink in bathroom after using it. Victim came out of bathroom sucking on bottle. Not clear if child or mother took cap off.
011023HEP9003	2-year-old	Eye drops	Used chair to get to medicine cabinet in kitchen. Took out eye drops and opened them. Mother found child on kitchen counter with open eye drops in hand.
020130HEP9003	2-year-old	Eye drops	Took eye drops out of mother's purse and opened tightly closed cap.
970306HEP9001	2-year-old	Eye drops	Child found in bedroom with open bottle of eye drops. She opened bottle with her teeth.
990301HEP9015	2-year-old	Eye drops	Child took bottle of eye drops off of dresser and unscrewed top.
990416HEP9008	2-year-old	Nasal Spray	Child was in bedroom watching TV on bed. Took nasal spray off of nightstand next to bed. Open, empty bottle found on bed.
990419HEP9022	2-year-old	Eye drops	Bottle left on counter in bathroom was found empty in child's hand.
991018HEP9012	2-year-old	Eye drops	Child found holding bottle of eye drops; cap had been removed and was in his mouth.
020321HEP9004	3-year-old	Eye drops	Child found in bedroom with opened bottle of eye drops.
091009HEP9010	4-year-old	Eye drops	Bottle left on counter. Child was found with open bottle.

2. FDA Adverse Event Reporting System (AERS) (Tab B)

The Adverse Event Reporting System (AERS) is a database of voluntary reports from health care professionals and consumers and mandatory reports from manufacturers. It is maintained by the U.S. Food and Drug Administration (FDA) and contains reports of adverse events and medication errors for all FDA-approved drugs and therapeutic biologic products. Adverse events in the AERS database are coded using terms from the Medical Dictionary for Regulatory Activities (MedDRA), which is maintained by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), acting as a trustee for the International Conference on Harmonization (ICH).

Health Sciences staff asked the FDA for all AERS reports mentioning the imidazolines tetrahydrozoline, oxymetazoline, xylometazoline, and naphazoline. FDA staff provided a total of 1,041 reports for 772 distinct cases occurring between October 1968 and August 2010, for Health Sciences staff to review. Staff checked for cases related to imidazolines, excluded the cases with concomitant drugs, and determined that 67 cases (with 115 total reports) were in-scope for this memo.

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Reports through the AERS system show a wide variety of adverse events across all ages associated with the use of imidazolines. The top three system/organ classes with reported adverse events were psychiatric disorders (52 reports); nervous system disorders (47 reports); and respiratory, thoracic, and mediastinal disorders (38 reports). Sixty-two out of 67 in-scope cases (93 percent) reported an adverse event in one of the top three system/organ classes.[10]

3. Ingestions (Tab A)

The volumes of imidazoline ingestions in children (under the age of 5) that were reported from two sources, the FDA's AERS database (MedWatch[11] reports) and the medical literature, ranged from several drops to a high of 30 mL (2 tablespoons). The volume ingested was unknown in several imidazoline cases. Very serious adverse effects occurred in response to small oral doses of imidazolines; these are highlighted in Table 3 from highest to lowest dose in milligrams.

In MedWatch case reports for adverse events occurring in response to ingestion of imidazolines, 43 cases occurred in children under 5 years old. Tetrahydrozoline ingestions constituted the majority of the cases (88 percent). There were no reported deaths related to imidazoline ingestion. See Tab A, Appendix A, for a complete list of cases.

The most recent imidazoline ingestion case cites the lowest dose of ingestion of which staff is aware that caused severe adverse symptoms in a child. The case involved a 25-day-old infant who suffered apnea after being treated with tetrahydrozoline nasal drops (0.05 percent). The mother inadvertently administered the nasal drops by the oral route three times per day with 0.5 ml/day (0.25 mg). The immature kidney and liver function of the newborn caused the drugs to clear the newborn's system slower than in an adult. Accordingly, staff considered the three doses of nasal drops to be additive. Therefore, staff calculated the total dose for this case to be 0.75 mg. After the second dose, the child was not feeding well and had low muscle tone. Two hours after the second dose, he developed apnea. After the third dose was administered, the child was brought to the hospital and admitted with a respiratory rate of four breaths per minute and a slowed heart rate. The infant was treated with naloxone, resolving the apnea and bradycardia. After two days, the child was in good condition and was discharged. After follow-up 10 days later, the child was in normal condition (Katar et.al. 2010).

[10] Reports can include more than one adverse event, so individual reports may be recorded in more than one system/organ class.

[11] FDA Medwatch Reports are one of several ways to make reports to the Adverse Event Reporting System. Not all Medwatch reports were included in the AERS database. Submission of a MedWatch report is voluntary. It is of note that Medwatch Adverse Event Reports have limitations. First, there is no certainty that the reported event was actually due to the product. The FDA does not require that a causal relationship between a product and event be proven; and reports do not always contain enough detail to evaluate an event properly. Further, the FDA does not receive all reports that may pertain to a product.

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Table 3: Relevant Cases of Imidazoline Ingestion

Estimated Dose	Onset/Symptoms	Age	Result	Reference
2.8-5.6 mg Oxymetazoline 0.3-0.5 mg/kg**	Within 5 minutes. Child passed out and stopped breathing. Given CPR and taken to ER.	18 mo.	Given fluids and admitted to ICU. Aroused from coma 8-10 hours later. Released later that day. Having headaches 3-4 times daily.	FDA MedWatch 439578450001 6/2004
3-4 mg Naphazoline 0.2-0.3 mg/kg**	"Soon" became "quite drowsy" for several hours	3 yrs.	Several hours.	Waring, 1945
3-4 mg Naphazoline 0.2-0.3 mg/kg	One hour after ingestion. Became hypothermic, lethargic, irritable, pale, irregular gasping respirations, hypertension, bradycardia. Followed by unconsciousness and imperceptible respirations.	22 mo.	Child warmed and treated with caffeine and oxygen. Symptoms resolved after 15 hrs.	Hainsworth, 1948
2-2.5 mg Tetrahydrozoline 0.2 mg/kg	90 minutes Lethargic, decreased heart rate, decreased blood pressure	17 mo.	Pediatric intensive care unit Recovered 24 hrs	Jensen et al. 1989
Up to 2 mg Tetrahydrozoline 0.2 mg/kg**	Sharp increase and then decrease of heart rate	22 mo.	Pediatric intensive care unit	FDA540321
1.25-2.5 mg Tetrahydrozoline 0.1-0.2 mg/kg**	Decreased heart rate Lethargic, difficult to arouse, depressed respiration	16 mo.	Admitted to hospital overnight	FDA671307
1.25-2.5 mg Tetrahydrozoline 0.1-0.3 mg/kg**	2 hrs. Ataxic, pale, drowsy, decreased heart rate, decreased respiration	1 yr.	Admitted to hospital Recovered 24 hrs	Mindlin 1966
1.3 mg Tetrahydrozoline 0.1 mg/kg**	30 min. Lethargic, difficulty breathing, vomiting, loss of consciousness	2 yr.	Admitted to hospital, treated with charcoal. Released from hospital same day, symptoms resolved.	FDA 43222810001
1-1.5 mg Tetrahydrozoline 0.1 mg/kg	2–3 hrs Lethargy, decreased blood pressure, decreased respiration	2 yr.	Pediatric intensive care unit Mechanical respiration for 18 hrs	Tobias 1996

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Estimated Dose	Onset/Symptoms	Age	Result	Reference
			Recovered 48 hrs	
*0.25 mg x 3 or 0.75** Tetrahydrozoline 0.2 mg/kg	2 hrs. Apnea, decreased respirations, slowed heart rate	25 days	Admitted to hospital Naloxone, Continuous positive airway pressure, oxygen Recovered 2 days	Katar et.al. 2010

*Due to diminished clearance of drugs by the liver and kidney of the newborn, the three doses are considered additive. **Weights estimated from www.cdc.gov/growthcharts by age, if no gender indicated assumed to be male, used 50th percentile.

C. Technical Feasibility, Practicability, and Appropriateness (Tab C)

Under the PPPA the CPSC may require special packaging for certain substances stored and used in the household to protect children from serious personal injury or illness.[12] In addition to finding that special packaging is necessary to protect children, the Commission must also find that special packaging is technically feasible, practicable, and appropriate for these products (15 U.S.C. 1472 (a)(1) - (2)). For special packaging to be technically feasible, the technology must be available to produce packaging that conforms to established standards. See S. Rep. 91-845, at 10 (1970). A package is practicable if the special packaging is adaptable to modern mass production and assembly line techniques. *Id*. Finally, packaging is appropriate if the packaging will adequately protect the integrity of the substance and will not interfere with its intended storage or use. All three of these conditions must be met before the Commission can require special packaging for a product.

Section 2(3) of the PPPA defines "package," in part, as "the immediate container or wrapping in which any household substance is contained for consumption, use, or storage by individuals in or about the household." Section 2(4) of the PPPA defines "special packaging" as packaging that is designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of substance within a reasonable time and not difficult for normal adults to use properly. The child-resistance and adult-use-effectiveness of special packaging are measured by performance testing packaging with children and senior adults, respectively.

Staff evaluated packaging representative of over-the-counter products that contain imidazolines. The specimens represent products from all four imidazoline families: naphazoline hydrochloride (HCL), oxymetazoline HCL, tetrahydrozoline HCL, and xylometazoline, and a naphazoline HCL combination product. None of the samples used special packaging. The eye drops were packaged in squeeze-to-dispense plastic dropper bottles. The nasal spray was packaged in a plastic bottle with an attached metered pump sprayer, and the nasal drops were packaged in a squeeze-to-dispense plastic dropper bottle.

Staff concludes that available data support the findings that CR packaging for household products containing imidazolines is technically feasible, practicable, and appropriate. With

[12] CPSC regulations at 16 CFR §§ 1700.15(b)(2)(i) and 1700.20 require special packaging to be both child-resistant and senior-friendly.

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package size and/or type changes, ASTM International (formerly American Society for Testing and Materials) Type IA, ASTM Type ID, and a CR metered pump sprayer design, are available to the market to replace the non-CR continuously threaded (NCRCT) and the non-CR (NCR) metered spray pump packages. Product packaging assembly line techniques used for the NCR packages can be adapted for some of the CR packages already in the marketplace. Other product manufacturers may use packages that could require changes in assembly- and filling-line techniques. New package sizes may also need to be designed. These new packages would require new tools to be produced. It could take up to one year from initiating tool design to final production of a new package, depending upon the complexity of the package.

D. Economic and Environmental Information (Tab D)

The Directorate for Economic Analysis staff prepared a description of the market and an evaluation of the possible economic effects of a draft proposed rule. This evaluation is summarized below and described in more detail at Tab D.

There are approximately 45 firms that produce eye drops and nasal sprays containing imidazolines. Based on available market information, sales of eye drops may amount to about 45 million units annually, and sales of nasal sprays may amount to about 38.8 million units annually.

Based on estimates of emergency department-treated injuries from NEISS during 1997 to 2009, augmented by estimates of medically attended injuries treated outside of hospital emergency departments using the CPSC's Injury Cost Model (ICM), there was an estimated *annual* average of 848 medically attended injuries involving imidazoline-containing eye drops and 204 medically attended injuries involving imidazoline-containing nasal sprays.

Available studies suggest that child-resistant packaging may reduce child poisonings by about 40 percent[13]. Thus, child-resistant packaging might be expected to prevent about 339 eye drop injuries (*i.e.,* 848 injuries x 0.40) and 82 nasal spray injuries (*i.e*., 204 x 0.40) annually. According to the Injury Cost Model, the societal costs of the injuries prevented might amount to about $5.3 million for eye drops and $1.3 million for nasal sprays annually. Given sales estimates described above, the reduction in societal costs, per unit of product sold, would amount to about 11.8 cents per container for eye drops (*i.e*., $5.3 million in societal costs prevented ÷ 45 million) and about 3.4 cents per container of nasal sprays (*i.e*., $1.3 million in societal costs prevented ÷ 38.8 million units).

The costs of using child-resistant packaging include the additional costs needed to manufacture child-resistant packages, as well as any additional time and effort needed to open and close child-resistant packaging. The added manufacturing costs may amount to about 1.5 cents per

[13] Rodgers, Gregory B. "The Safety Effects of Child-Resistant Packaging for Oral Prescription Drugs." *Journal of the American Medical Association*, Vol. 275, No. 21 (15 June 1996), pp. 1661–1665.
Rodgers, Gregory B. "The Effectiveness of Child-Resistant Packaging for Aspirin." *Archives of Pediatric and Adolescent Medicine*, Vol. 156, (September 2002), pp. 929–933.
Walton, William. "An Evaluation of the Poison Prevention Packaging Act." *Pediatrics*, Vol. 69, No. 3,(March 1982), pp. 363–370.

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container. The added time and effort needed to use child-resistant packaging is difficult to quantify; this is discussed at Tab D.

Small Business Considerations. Nasal and ophthalmic products are classified within the NAICS[14] 325412 *Pharmaceutical Preparation Manufacturing* industry. According to the U.S. Small Business Administration's Office of Advocacy, a firm classified within NAICS 325412 is considered a "small business" if the firm has fewer than 750 employees. Based on such a classification, out of the approximately 45 firms that manufacture imidazoline-based eye drops and nasal sprays, approximately 20 firms are defined as "small businesses." There may be more manufacturers, in particular, firms that manufacture under generic labels, which were not identified, and that may be small businesses.

There are several reasons to believe that a rule would not have a significant impact on a substantial number of small businesses. First, the incremental costs of CR packaging for manufacturers are low, estimated at 1.5 cents per unit for imidazolines products. Manufacturers are likely to be able to pass on at least some of these costs to consumers. Second, most manufacturers of over-the-counter pharmaceutical products have diverse product lines that include other products that would not be covered by a draft proposed rule. Therefore, the products that would be affected may represent a small proportion of any one business's production. Finally, the requirements would apply only to products packaged after the effective date of the requirements. Thus, businesses would have time to use up existing inventories of product and packaging.

Environmental Considerations. Requirements for CR packaging are not expected to have an adverse impact on the environment. CR packaging has virtually the same impact on the environment as non-CR packaging and is considered to be a "categorical exclusion" for purposes of the National Environmental Policy Act (16 CFR § 1021.5(c) (3)).

III. Staff Conclusions

Imidazolines are potent group of vasoconstrictors that cause CNS depression, as well as decreased respiration and cardiac adverse events if they are ingested. It has been shown from NEISS data (Table 2) that children under age 5 have been injured by accessing and accidentally ingesting imidazoline-containing products. A Poison Control Center specialist from the Children's Hospital in Philadelphia states that imidazoline toxicity is "profound," causing coma, bradycardia, and hypotension with small doses.[15]

Staff reviewed the medical literature to identify the types of adverse events that have been reported following ingestion of imidazolines and to determine the level at which health effects have occurred. Even though death from imidazoline exposure is rare, many of these events resulted in serious life-threatening consequences and required hospitalization and intensive care monitoring for recovery.

A case presented in this memorandum indicates that ingestion of as little as 0.75 mg of tetrahydrozoline can result in serious health effects in a child, requiring supportive therapy.

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[14] North American Industry Classification System.

[15] Bartlett D. (2003). Dangerous in small amounts: Ten nondrug substances that cause harm. J Em Nursing. 29(4):377–379.

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Since serious effects on the heart rate and breathing rate occur with the ingestion of as little as 0.75 mg of tetrahydrozoline, staff considers this the lowest observed adverse event level (LOAEL).

All of the imidazolines cause potent central and peripheral sympathetic effects: tetrahydrozoline has the highest potency for CNS sedative/depressive effects and lowest potency for cardiac effects; oxymetazoline and naphazoline are the most potent imidazolines for peripheral cardiac effects and have a lower maximum daily dose than tetrahydrozoline, while xylometazoline and oxymetazoline have a longer duration of action than tetrahydrozoline.

Because imidazolines, as a class of drugs, have been shown to cause serious health effects, staff recommends applying a safety factor[16] of 10 to the LOAEL to derive a regulated level of 0.08 mg for all imidazolines in order to protect children from serious health effects following ingestion.

Therefore, to prevent poisoning of children under 5 years old who might access these products, staff recommends that special packaging be required for products containing the equivalent of 0.08 mg or more of naphazoline, tetrahydrozoline, oxymetazoline, or xylometazoline in a single package. The level of 0.08 mg will require all known imidazolines currently on the market, including prescription and OTC products, to be placed in child-resistant packaging.

[16] The assumptions underlying the use of safety factors are that, by using these factors, the public health is protected, and special populations are also protected. Further assumptions hold that humans are somewhere between 10 and 1,000 times more sensitive to some toxic agents than animals, and adults are less sensitive than children. Hence, a safety assessment can be conducted using the proper toxicological evaluation with different populations to establish the NOEL (no observable effect level) or its equivalent. A tenfold safety factor was used to divide the LOEL in our case to reach a NOEL level.

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IV. Options

Option 1:

The Commission may propose a rule requiring special packaging for OTC and prescription products containing the equivalent of 0.08 mg or more of naphazoline, tetrahydrozoline, oxymetazoline, or xylometazoline in a single package if the Commission preliminarily finds that:

1) special packaging is required to protect young children from serious personal injury or illness from handling, using, or ingesting the product; and
2) special packaging is technically feasible, practicable, and appropriate.

Option 2:

The Commission may decline to propose a special packaging rule for imidazolines if it is unable to make the required findings.

V. Staff Recommendation

Staff recommends that the Commission vote to approve publication of a proposed rule that would require special packaging for OTC and prescription drug products containing the equivalent of 0.08 or more of naphazoline, tetrahydrozoline, oxymetazoline, or xylometazoline in a single package. Staff recommends a 1-year effective date because of the time that may be required for manufacturers to produce a new CR package.

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TAB A: Toxicity Review

TAB A

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UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

Memorandum

Date: January 11, 2012

TO : Mary Ann Danello Ph.D., Associate Executive Director
Directorate for Health Sciences

Lori E. Saltzman M.S., Division Director
Directorate for Health Sciences

FROM : Cheryl A. Osterhout Ph.D., Pharmacologist
Directorate for Health Sciences

SUBJECT : Imidazoline Toxicity Review

I. Background

Under the Poison Prevention Packaging Act (PPPA) of 1970, the U.S. Consumer Product Safety Commission (CPSC) can require a special packaging standard for hazardous household substances, including drugs. This action requires a finding by the Commission that the availability of any such substance, by reason of its packaging, is such that special packaging is required to protect children under 5 years old from serious personal injury or illness due to handling, using, or ingesting such a substance. Imidazolines are a class of drugs that include tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline. They are vasoconstrictors indicated for nasal congestion and/or ophthalmic irritation. Imidazoline decongestants can cause serious adverse reactions, such as central nervous system (CNS) depression, decreased heart rate, and depressed ventilation in children treated with these drugs or who accidentally ingest them. The potential for these injuries prompted CPSC staff to review the hazards of imidazolines to assess the need for child-resistant packaging under the PPPA. This memorandum will: (1) present available scientific data providing evidence of injury and illness caused by products containing tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline, emphasizing data relevant to childhood accidental ingestions; and (2) make a recommendation for a regulated level, should the Commission decide that a requirement for child-resistant packaging is needed to protect children from accidental ingestions or injuries from products containing imidazolines.

II. Available Formulations

The available formulations of imidazoline products are presented in Table 1. When the exact dose is not included in a clinical study, article, or Adverse Event Report, an estimated dose in milligrams (mg) was calculated using this table as a reference. This was completed by using drug concentration ranges of the available formulation concentration, total volume in the product

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(See Table 1), and the administration guidelines (See Table 2). Estimated doses are italicized throughout this memorandum whenever they are presented.

Table 1: Available Formulations of Ophthalmic Imidazoline-Containing Products.

Drug[a]	Available Dosage	Duration (hr)	Volume Available milliliter (mL)	Max Daily Dose milligrams (mg)	Total drug[a] milligrams (mg)	Availability
Naphazoline	0.012% 0.02% 0.03% 0.1%	4–6	15, 30	1.2	1.8–30	OTC OTC OTC Rx
Tetrahydrozoline	0.05%	4–6	15, 22.5, 30[c]	0.6	7.5–15[b]	OTC
Oxymetazoline	0.025%	up to 12	15, 30	0.08	3.8–7.5	OTC

Source: Facts and Comparisons 2000.
[a] Naphazoline and tetrahydrozoline ophthalmic preparations are also available in combination with the antihistamines pheniramine maleate and antazoline phosphate.
[b]Range of total drug contained in available packages.
[c]CPSC staff did find a 5 mL and 8 mL package in stores. Therefore, the total amount of tetrahydrozoline in the smallest package would be 2.5 mg.

Table 2: Formulations of Nasal Imidazoline-Containing Products.

Drug/ Availability**	Spray/ Drop	Conc.	Adult Directions	Age 6 < 12 years	Age2<6 years	Max Daily Dose*
Naphazoline OTC	Spray	0.05%	1–2 sprays in each nostril. No more than 4 doses/24 hours.	Not Recommended	Not Recommended	0.4 mg*
Oxymetazoline OTC	Spray	0.05%	2–3 sprays in each nostril. No more than 2 doses/24 hrs.	Same as Adult	Not Recommended	0.3 mg*
Tetrahydrozoline Rx	Spray	0.1%	3–4 sprays in each nostril. No more than 8 doses/24 hrs.	Same as Adult	Not Recommended	3.2 mg*
	Drops	0.1%	2–4 drops in each nostril. No more than 8 doses/24 hrs.	Same as Adult	0.05%: 2–3 drops in each nostril. No more than 8 doses/24 hrs.	Age 6 to adult = 3.2 mg. Age 2 to < 6yr = 0.6mg.
Xylometazoline OTC	Spray	0.1%	1–3 sprays in each nostril. No more than 3 doses/24 hrs.	0.05%: 1 spray in each nostril. No more than 3 doses/24 hrs	Same as children age 6<12.	0.9 mg*
	Drops	0.1%	2–3 drops in each nostril. No more than 3 doses/24 hrs.	0.05%: 2–3 drops in each nostril. No more than 3 doses/24 hrs.	Same as children age 6<12.	Age 12 to adult= 0.9 mg. Age 2 to 12 = 0.2 mg.

Source: Facts and Comparisons 2011. *Assuming a spray is a volume of ~50 microliters; ** OTC: over-the-counter, Rx: Prescription.

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III. Pharmacology

The class of drugs called imidazolines bind and activate imidazoline receptors. They also bind and activate alpha-adrenergic receptors. In the eye, imidazolines are indicated to relieve redness due to minor eye irritations by causing constriction of the blood vessels in the eyelid and on the eyeball (Poisindex 2011, Facts and Comparisons 2011). The onset of this vasoconstriction after applying the imidazoline to the eye occurs within minutes (Abelson 1984).

As nasal decongestants, imidazolines temporarily relieve nasal congestion or stuffy nose due to the common cold, hay fever, or other upper respiratory allergies. When applied to the nose, the imidazolines produce vasoconstriction in the nasal mucous membranes, causing decreased blood flow. This leads to shrinking of swollen nasal mucosa and increased drainage of the sinuses (Facts and Comparisons 2011).

Because imidazolines activate alpha-adrenergic receptors, there can be significant side effects if absorbed.[1] Also, because the therapeutic effects of imidazolines occur within a narrow dose range, adverse events occur at doses close to, or at, therapeutic levels. CNS depression (ranging from drowsiness to deep sedation) may occur after normal doses in infants. Overdoses (doses exceeding prescribed or recommended doses) of these medications have caused initial abnormally high blood pressure (hypertension), slow heartbeat (bradycardia), drowsiness, and rebound low blood pressure (hypotension) in adults. Also, a shock-like syndrome with hypotension and bradycardia may also occur. Warnings on over-the-counter drugs state that overdoses of tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline may cause CNS depression leading to coma in pediatric patients (Facts and Comparisons 2011, Poisindex 2011).

The elimination half-life (the time it takes for half of the drug dosage to be metabolized and cleared from the body) of tetrahydrozoline is 2–4 hours, and for oxymetazoline it is 5–6 hours. The half-lives for naphazoline and xylometazoline were unavailable. The duration of action of the imidazolines is as follows: tetrahydrozoline and naphazoline 4–6 hours, oxymetazoline 12 hours, and xylometazoline up to 10 hours. The potency of these drugs relative to one another is different, depending on the receptors activated (imidazoline vs. alpha-adrenergic) and whether it is a peripheral or central nervous system response. For eliciting CNS mediated sedation, the grading of potency is tetrahydrozoline > naphazoline > oxymetazoline (Delbarre and Schmitt 1971). The alpha-sympathetic mediated cardiac and blood pressure effect potency is as follows: oxymetazoline > naphazoline > xylometazoline > tetrahydrozoline (Autret et.al. 1971, Timmermans et.al. 1978).

Topical administration of imidazolines to the eye produces local effects to the blood vessels of the eye, but little is absorbed into the general circulation. Nasal administration of imidazolines causes an intense rapid vasoconstriction, and therefore, negligible absorption of the drug into the general circulation. However, there is the potential for absorption and systemic effects after nasal administration, if the liquid product drains down the throat and is swallowed. With oral ingestion, imidazolines are absorbed quickly into the general circulation and lead to systemic effects. Generally, symptoms can occur in as little as one hour, peaking at eight hours, and resolving after 12–36 hours (Poisindex 2011). Even though the symptoms resolve in a relatively short amount of time, ingestion of imidazolines can result in severe life-threatening consequences, such as decreased breathing, decreased heart rate, and loss of consciousness that require hospitalization to ensure recovery.

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When absorbed (from ingestion or drainage down the throat after intra-nasal administration) imidazolines interact with alpha–adrenergic receptors in the peripheral and central nervous systems, as well as imidazoline receptors in the CNS leading to adverse events (Brenner 2000). Specific symptoms of CNS depression, upon ingestion of imidazolines, range from drowsiness to coma, with a concurrent depression of the respiratory system. Other observed CNS side effects include: headache, lightheadedness, dizziness, tremor, insomnia, nervousness, restlessness, giddiness, psychological disturbances, prolonged psychosis, and weakness. Imidazolines can lead to CNS depression and insomnia in different individuals. The insomnia, seen in a few cases, may be an unpredictable idiosyncratic reaction (*i.e.*, a drug effect that occurs in a small number of people due to age, genetics, or disease state), or unexpected drug responses often seen in children (Facts and Comparisons 2011).

Prominent cardiovascular effects in response to an overdose of imidazolines include hypotension and bradycardia. However, imidazoline interaction with alpha-adrenergic receptors on the vasculature may also lead to vasoconstriction and hypertension. Other reported cardiovascular adverse events in adults include: tachycardia,[17] palpitation,[18] cardiac arrhythmia,[19] coronary occlusion, pulmonary embolism (lodging of a mass in the lung), subarachnoid hemorrhage (bleeding between the brain and the thin layers of tissues surrounding the brain), myocardial infarction, stroke, and death associated with cardiac reactions. Other systemic side effects include: blanching, sweating, nausea, gastric irritation, weakness, and hyperglycemia (high blood sugar) (Facts and Comparisons 2011, Poisindex 2011).

There is no specific treatment for imidazoline ingestion (Poisindex 2005). Gastric lavage is not recommended more than 1 hour after ingestion because the imidazolines are absorbed quickly, leading to CNS depression and a greater risk of aspiration. Activated charcoal may be used up to 1 hour after ingestion; but again, due to the CNS depression, there is a greater risk of aspiration. Therefore, treatment of the clinical effects from imidazoline ingestion is supportive care based on symptoms. For young children, this often necessitates admission to a pediatric intensive care unit. For example, mechanical respiration in an intensive care unit would be administered to those with severe respiratory depression (Bucaretchi et al. 2003).

IV. Toxicology

A. Clinical Studies

This memorandum focuses mainly on systemic effects; therefore, some clinical studies that focused on topical effects have not been included. In some clinical reports, doses were not included, so the administration guidelines and available product concentrations were used to estimate doses. Volume estimations were made for drops, assuming one drop is equivalent to 50 microliters (μL); however, estimates for spray volume were not made, due to the wide variation of spray volume released from different spray bottles.

[17] An increase in heart rate.
[18] A rapid heart rate.
[19] Any variation from the normal rhythm of the heart beat.

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Tetrahydrozoline

Clinical studies were performed on adult patients, as well as 13 children ranging from 2 to 12 years old. Test subjects were administered 0.1 percent intra-nasal tetrahydrozoline (three to four drops for adults and one to two drops for children in each nostril) every three to four hours, as needed, for nasal congestion (*this is calculated to be equivalent to an adult dose of 0.15–0.2 mg or 0.05-0.1 mg for children, assuming one drop is equivalent to 50 μL*). Adverse central stimulant side effects (insomnia, increased blood pressure, or irregular heart beat) were not observed with administration of tetrahydrozoline nasal drops over a period of two to three days (Parish 1954).

Early studies were also performed in infants under the age of 2 months. A therapeutic dose of 0.1 percent tetrahydrozoline nasal drops (one to four drops, equivalent to 0.05–0.2 mg tetrahydrozoline) was administered intra-nasally every four hours, and clinical signs were noted. One 6-week-old infant became markedly drowsy and was difficult to arouse four hours after administration of two drops of tetrahydrozoline nasal drops (approximately 0.1 mg tetrahydrozoline. With continued application of the drug, the infant remained extremely drowsy and exhibited decreased respirations. Out of 25 test periods, six infants (out of seven in the group) displayed moderate drowsiness, and four of these infants exhibited marked drowsiness. The authors concluded that "certain infants may exhibit alarming and unexpected toxic reactions" to tetrahydrozoline (Brainerd and Olmstead 1956).

Naphazoline

There were no published naphazoline clinical studies found.

Oxymetazoline

Ophthalmic studies were performed with 0.025 percent oxymetazoline (two drops/three times daily or 0.025 mg oxymetazoline per dose) in adults (n=23) over 10 days. No effects were seen on systemic blood pressure (Fox et al. 1979). In additional studies, 39 adult patients were treated with 0.025 percent oxymetazoline eye drops with a dose of 0.01 mg in each eye, twice a day, for seven days. Changes in blood pressure or heart rate were minimal and not significant between the treated and untreated groups (Duzman et.al. 1983, Duzman et.al. 1986).

Side effects were observed in several clinical nasal studies performed with oxymetazoline. These side effects included: rebound congestion, sneezing, bad taste in mouth, lacrimation,[20] rhinorrhea,[21] nasal burning, postnasal drainage, sore throat, nervousness, headache, as well as nonsignificant changes in blood pressure. It was noted that there were no instances of impaired sleeping, although some experienced improved sleep due to decongestion of the nasal passages (Kuhn 1966, Cowen 1966, Bailey 1969). Also, nasal instillation studies performed with pediatric patients 3 months to 10 years old did not show blood pressure changes or other side effects (0.025 percent or 0.025–0.1 mg oxymetazoline, depending on dose range of two to eight drops) (Neidorff 1966, Weimann and Heights 1967, Neffson 1968).

The preamble to the proposed FDA rule for the safety and effectiveness of over-the-counter nasal decongestants reports an unpublished double-blind study of orally administered oxymetazoline in adults. This study revealed that 3.6 mL of 0.05 percent oxymetazoline (1.8 mg) was the minimal

[20] The secretion and discharge of tears.
[21] The free discharge of a thin nasal mucus.

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oral dose producing a measurable effect on the cardiovascular system, including blood pressure and heart rate changes in adults. Nonspecific EKG changes were not observed (41 FR 38398).

Xylometazoline

A study was performed on 290 patients, including infants, children, and adults suffering from upper respiratory symptoms who were treated with 0.025 percent, 0.05 percent, or 0.1 percent nasal xylometazoline solutions, either twice or three times per day for approximately one week (three drops of 0.025 percent–0.1% xylometazoline for an approximate dose range of 0.0375 mg–0.15 mg per dose). Those patients with infections were treated with xylometazoline solutions also containing an antibiotic and steroid. There were no adverse effects on blood pressure in patients with normal blood pressure or those with a history of hypertension. Four patients reported adverse events, which included palpitations, insomnia, sneezing with burning, and rebound vasodilation (Jacques and Fuchs 1959).

A year later, a study was performed in 100 children and adults ranging from age 2 years to age 65 years, suffering from upper respiratory symptoms and treatment with 0.025 percent, 0.05%, and 0.1 percent nasal xylometazoline 2–3 drops in both nostrils, 3–4 times a day, for up to 9 days (the calculated dose per nostril is approximately 0.025–0.15 mg xylometazoline). Reported side effects included: slight burning, rebound vasodilation, headache, and throat dryness. Blood analyses were normal; there were no observed changes in urinalysis, and there were no observed alterations in blood pressure from a subset of randomly selected patients (not stated if child or adult) (Hagen and Trelles 1960).

Further clinical studies were performed in 44 children, ranging in age from 1 month to 16 years, and suffering from upper respiratory congestion. The children were treated with xylometazoline solutions at concentrations of 0.025 percent, 0.05 percent, or 0.1 percent (approximately 0.05–0.3 mg xylometazoline per dose). No local or systemic effects were observed (Sengelmann 1966).

An additional study treated 100 children (ranging in age from 1 month to 16 years) with

0.025 percent–0.05 percent xylometazoline nose drops for conditions ranging from otitis media,[22] respiratory allergies, acute upper respiratory infections, and nasal congestion from other disease states. The patients were treated with two to four drops in both nostrils of xylometazoline (*for a dose range per nostril of about 0.025 mg–0.10 mg*) for two to four days. There were no observed side reactions, systemic, or toxic effects. There were no instances of increased blood pressure (Bumbalo 1960).

B. Human Exposure

Published Case Reports Involving Topical Application

A summary of adverse events from topically applied imidazolines are included in this report to demonstrate toxicity. Individuals receiving topically applied imidazolines are typically suffering from other ailments and in some cases may be may be using other medications at the same time. When the information was available, the other medications were described in the case reports.

[22] Inflammation of the middle ear.

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Tetrahydrozoline

Topical exposure to tetrahydrozoline has caused serious illness in children. From 1955 to the present, there have been many reports in the medical literature describing adverse events in response to topically applied tetrahydrozoline. The first cases of adverse events to tetrahydrozoline were reported in 1955, after intranasal application in children. Dr. Friedman published a detailed report after his 22-month-old daughter suffered profound sedation after he applied levels of 0.1 percent tetrahydrozoline nose drops. She suffered vasomotor collapse with complete loss of consciousness, irregular respiration, weak pulse, and absence of reflexes one hour after application of the tetrahydrozoline nasal spray (approximately 1 mL or 1 mg tetrahydrozoline) for an upper respiratory infection. Treatment with epinephrine and caffeine produced wakefulness, but in less than one hour, a coma-like state reappeared. After seven hours, respiration and blood pressure increased, and by 12 hours, she had returned to normal (Friedman 1955).

Naphazoline

Topical exposure to naphazoline has also caused serious illness in children. Naphazoline was marketed in 1942, and as early as 1945, adverse events were noted. Sedation was recorded as an unexpected clinical observation in several children after nasal administration. A 7-year-old was given five drops of 0.1 percent naphazoline (0.25 mg) in each nostril, three times per day; and after each administration, the child felt drowsy for several hours. A 3-month-old infant was given a total of four drops of 0.05 percent naphazoline (0.1 mg) approximately every eight hours, and slept for about eight hours after administration. After receiving only two drops, the infant showed signs of drowsiness for 24 hours (Waring 1945).

Two years later, in 1947, there were several other reports of sedation and collapse in children following recommended doses of naphazoline. Some of the cases were described as a hypersensitivity reaction. A 2-month-old was given a total of six drops of 0.05 percent naphazoline (0.15 mg) for rhinitis. Thirty minutes later, the infant was pale, limp, and not arousable. Breathing was shallow with gasping respirations, and the infant's temperature was normal. The infant was hospitalized, treated with oxygen, epinephrine, and a central stimulant, and recovered fully after six hours (Greenblatt 1947).

A 1-month-old infant was brought to the hospital comatose, pale, and hypothermic after receiving naphazoline nasal drops. Examination revealed arterial hypertension, bradycardia, and apnea. She received intravenous support for nine hours when symptoms resolved. The conclusion was that naphazoline intoxication caused severe CNS depression and cardiovascular adverse effects. The authors discouraged the use of imidazoline derivatives in children younger than 7 years of age and recommended that they be kept out of children's reach (Claudet 1995).

Serious adverse events from naphazoline have also occurred in adults as a result of therapeutic doses and in two cases from administration of the drug during surgery. An 8-year-old and a 20-year-old were both treated with a naphazoline-soaked sponge for excessive bleeding after adenoidectomies and suffered complications of naphazoline intoxication. Within a few minutes, hypertension and reflex bradycardia occurred in both patients. After an hour and a half, the patients both suffered from pronounced hypotension, which was treated in the recovery area. Persistent CNS depression, including somnolence, hypothermia, and low respiration rate occurred. These symptoms resolved within 24 hours (Wenzel et. al., 2004).

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Oxymetazoline

Adverse events have occurred from topical nasal use of oxymetazoline in children under 5 years old, and in some cases from potential overdosing of the product. Soderman et al. (1984) reported on several cases of adverse events following the use of oxymetazoline nasal drops or spray in children under 5 years old. Included was the case of a 5-week-old girl who was given 0.1 mg/mL (0.01 percent, an approximate dose of 0.02–0.03 mg with four to six total drops) oxymetazoline nose drops, the recommended dose for a stuffy nose. The child became sedated and fell asleep; she was then admitted to the hospital. The dose was repeated, and she fell asleep again. On waking, the child was irritated, but returned to normal quickly. Another example was a 1-year-old who was treated with six drops of 0.25 mg/mL oxymetazoline (0.075 mg) twice a day for two days, along with penicillin for an ear infection. In the evening, the child became excited, could not sleep, and was not able to take his nap the next day. The insomnia resolved after treatment ended. The authors of this letter state that adverse events should be considered when prescribing oxymetazoline to infants and small children and also recommended warnings for overdoses in the labeling of the products (Soderman et.al. 1984).

Xylometazoline

All of the case reports of adverse events from xylometazoline resulted from nasal administration of the drug, at doses believed to be at therapeutic levels. For example, a 15-day-old infant was treated by her father with two total drops of 0.1 percent xylometazoline (0.1 mg) for nasal congestion. She ate and fell asleep. Two hours later, she awoke crying, and it was noted she was grey in color, had weak muscle tone, and was breathing irregularly. She was admitted into the hospital and treated with antibiotics. Within a few hours, she became comatose with a "cluster-type breathing pattern." She was transferred to the pediatric intensive care unit and was observed with prolonged weak tone and poor responsiveness but no significant cessation of breathing. Four to six hours after instillation of xylometazoline, her status improved, she regained consciousness, and breathing became more regular. After 12 hours, she was transferred from intensive care. The antibiotics were continued for 48 hours, and she remained in the hospital for six days under observation and further testing. She was released with no further symptoms. It was noted that the notion of the nose drops leading to such critical symptoms was dismissed by the medical team at first. The authors recommended that "imidazoline(s) [as a class] should be listed among the toxic products leading to coma in children" (Dunn et.al. 1993).

Published Case Reports Involving Ingestions

Because imidazolines are rapidly absorbed from the gastrointestinal tract, serious toxic symptoms have been reported due to ingestion of imidazoline-containing products. A summary of published reports of imidazoline ingestions is found in Table 3.

Tetrahydrozoline

The first reported case of ingestion of tetrahydrozoline in the United States occurred in 1966, when a 1-year-old ingested one-half to one teaspoon (tsp) of 0.05 percent tetrahydrozoline eye drops (approximately 1.25–2.5 mg). About two hours after ingestion, she became sluggish and fell without protecting herself. Upon examination three hours after ingestion, the child was drowsy, pale, and displayed slowed respiration and heart rate. She was admitted to the hospital, observed, and showed improvement over the next 24 hours (Mindlin 1966).

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Klein-Schwartz et al. reported a 20-month-old child who ingested 15 ml (1 tablespoon or tbsp) of 0.05 percent tetrahydrozoline eye drops (7.5 mg). After one hour, the child became progressively lethargic and difficult to arouse with tactile stimulation and exhibited semi-purposeful movement. The child was admitted to the hospital, and CNS status was monitored; 24 hours later, the child was awake and alert (Klein-Schwartz et al. 1984). This case initiated a review of data from the Maryland Poison Control Center from January 1979 to May 1982. In this 3 1/2- year time frame, there were 57 ingestions of products containing tetrahydrozoline by children under 2 years of age, all ingesting 15 ml (1 tbsp) or less. Twenty-six patients were treated with an emetic (*e.g.*, ipecac or salt water) to empty the gastrointestinal tract. The majority of patients were asymptomatic; however, five patients (9 percent) developed drowsiness. Nine patients were treated in an emergency room, and one was admitted. The detailed case report of the admitted patient was a 2-year-old who ingested 7.5 ml (1.5 tsp) of 0.05percent tetrahydrozoline eye drops (3.7 mg tetrahydrozoline). Four hours after ingestion, the child had symptoms of lethargy and was arousable only with a deep pain stimulus. The child's level of consciousness varied; but over the next 24 hours, gradually, he became responsive (Klein-Schwartz et al. 1984).

Jensen et al. reported a 17-month-old who ingested four to 5 mL (0.8 to 1 tsp) 0.05 percent tetrahydrozoline eye drops (2.0–2.5 mg). The child presented to the emergency room 90 minutes after ingestion, lethargic but arousable, with a slowed heart rate and decreased blood pressure. The patient was treated with charcoal and transferred to the pediatric intensive care unit for close observation of her neurologic and hemodynamic symptoms. The child recovered after 24 hours and was released (Jensen et al. 1989). Higgins et al. (1991) reported two cases of toxic symptoms in children who ingested tetrahydrozoline. In the first case, a 15-month-old ingested an unknown amount of 0.05 percent tetrahydrozoline and became lethargic, responding only to painful stimuli. On arrival at the hospital, the child was limp but suddenly became agitated with thrashing movements. The child was admitted to the intensive care unit because of periods of apnea and a slowed heart rate, was treated with charcoal and sorbitol, and observed overnight. The following morning, all vital signs returned to normal, and the child was released (Higgins et.al. 1991). In the second case, a 23-month-old child ingested approximately 6 mL (1.2 tsp) of 0.05 percent eye drops (3 mg). Several hours after ingestion, the child became increasingly lethargic, until she could be aroused only with vigorous physical stimulation. When awakened, the child was irritable and displayed uncoordinated movement. On arrival at the hospital, charcoal therapy was initiated, and the child was admitted for observation. After 20 hours, the patient's status was normal, and she was discharged (Higgins et al. 1991).

A 36-month-old child ingested a large volume of tetrahydrozoline eye drops, and became unconscious and required supportive treatment in intensive care. Ninety minutes after ingestion of 30 mL (2 tbsp or one ounce) of 0.05 percent tetrahydrozoline eye drops (15 mg), the child exhibited symptoms of lethargy only arousable with vigorous pain stimulation; the child also demonstrated decreased muscle tone, decreased blood pressure, slowed heart rate, and decreased respirations. Naloxone (an opioid receptor blocker, used to treat opiate overdose) was administered. The child awoke, but lethargy returned, and the heart rate decreased within 30 minutes. The child was admitted to the pediatric intensive care unit, underwent gradual improvement in the level of consciousness and was awake and alert within seven and one-half hours (Holmes and Berman 1999).

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A 2-year-old ingested a small volume (2 to 3 ml or 0.4 to 0.6 tsp) of 0.05 percent tetrahydrozoline eye drops (1.0–1.5 mg), resulting in serious adverse events. The initial symptoms were lethargy and decreased blood pressure 2–3 hours after ingestion. Progressive CNS depression and respiratory depression led to admission into the pediatric intensive care unit, and the child was placed on mechanical respiration. The patient was slowly weaned from respiratory support and removed completely after 18 hours. CNS status returned to baseline after 48 hours, and the child was discharged (Tobias 1996).

A 27-month-old male child (12 kg) with no significant medical history, presented to the emergency room with neurological and cardiovascular complications because of tetrahydrozoline ingestion. He was brought into the ER because he was "acting inappropriately." Three hours earlier, the child was found asleep on the carpet with an empty tetrahydrozoline eye drop container (15 mL (1 tbsp) or 7.5 mg tetrahydrozoline) nearby with the top chewed off. The child's eyes were rolled upward, and several attempts with noxious stimuli were required to awaken him. In the emergency department, the child was very drowsy to the point of being near sleep, had depressed respirations, and a slowed heart rate. He was transferred to the pediatric intensive care unit, given fluids, and monitored. The child's hemodynamic parameter and mental status normalized, and he was released the next day. Notably, the author of this case report, an emergency medicine resident, stated: "[A brand name tetrahydrozoline eye drop] is not marketed in childproof containers, despite the potential severity of an accidental ingestion. OTC medicines with potent pharmacological properties should be stored in areas out of reach of children, and manufacturers should package these products in childproof containers" (Daggy, 2003).

The most recent case, and with the lowest dose causing severe adverse symptoms, involved a 25-day-old infant who suffered apnea after being treated with tetrahydrozoline nasal drops (0.05 percent). The mother inadvertently administered the nasal drops by the oral route three times per day with 0.5 ml/day (0.25 mg). The immature kidney and liver function of the newborn caused the drugs to clear the newborn's system slower. Accordingly, staff considered the three doses of nasal drops to be additive. Therefore, staff calculated the total dose for this case to be 0.75 mg. After the second dose, the child was not feeding well and had low muscle tone. Two hours after the second dose, he developed apnea. After the third dose was administered, the child was brought to the hospital and admitted with a respiratory rate of four breaths per minute and a slowed heart rate. The infant was treated with naloxone, resolving the apnea and bradycardia. After two days, the child was in good condition and was discharged. After follow-up 10 days later, the child was in normal condition (Katar et.al. 2010).

There are three published cases of teens reporting serious illness after the ingestion of tetrahydrozoline. A 16-year-old unintentionally drank 15 mL (1 tbsp) of 0.05 percent tetrahydrozoline (7.5 mg) in adulterated milk. Two hours after ingestion, he displayed symptoms of CNS depression, constricted pupils, and decreased heart rate. Cardiac effects were also noted, including depressed heart rate and sinoatrial node arrest (irregular heart rate) five hours after ingestion. After 10 hours, a normal heart rhythm was observed, and the bradycardia resolved after 24 hours (Jones 1996).

A 17-year-old teen ingested a "mouthful" of 0.05 percent tetrahydrozoline eye drops, thinking they were a cough/cold remedy. The patient arrived to the emergency department about 25 minutes after drinking the eye drops; she was lethargic, disoriented, ataxic, and had slowed speech. She complained of dizziness, headache, and sinus congestion. The patient was admitted

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for observation and treated with intravenous (i.v.) fluids. Blood tests were negative for other drugs. Over the next 36 hours, the drowsiness, bradycardia, and orthostatic hypotension continued. The volume of ingestion was approximated by the authors to be 10–15 mL (two to three tsp), or 67–102 μg/kg tetrahydrozoline. The patient was discharged 38 hours later (Spiller et al. 2008).

Additionally, a 41-year-old male ingested 30 mL (2 tbsp or one ounce) of 0.05 percent tetrahydrozoline (15 mg) in an apparent suicide attempt and developed symptoms one hour after ingestion. On arrival to the hospital, he presented with CNS depression, chest pain, depressed heart rate, decreased blood pressure, hypothermia, dry mucous membranes, and diminished bowel sounds. The chest pain was hypothesized to be due to the patient's history of an enlarged heart, although damage to the heart due to a heart attack was ruled out. The patient was admitted into the intensive care unit, required supportive therapy to increase blood pressure and heart rate, and after 48 hours recovered fully (Lev and Clark 1995).

Naphazoline

There are also several cases of naphazoline ingestion in children. A 3-year-old ingested approximately 7 to 8 mL (1.4 to 1.6 tsp) of 0.05 percent naphazoline (3.5–4 mg) and became "quite drowsy" for several hours afterward (Waring 1945). Two years later, a case was reported in which a 14-month-old accidentally ingested 7.5 mL (1 ½ tsp) of 0.1 percent naphazoline (7.5 mg). He was hypothermic and fell asleep for 12 hours. He was treated supportively with caffeine and heat, and he recovered (Greenblatt 1947).

After ingesting approximately three to 4 mL (0.6 to 0.8 tsp) of 0.1 percent naphazoline (three to four mg), a 22-month-old boy suffered from hypothermia, lethargy, irritability, pallor, irregular gasping respirations, dilated pupils, hypertension, and bradycardia. The child became unconscious with almost imperceptible respirations. The child was warmed and treated with caffeine and oxygen. The duration of symptoms after ingestion lasted 15 hours, and the child recovered completely (Hainsworth 1948).

A 5-month-old was fed up to 15 mL (1 tbsp) of 0.1 percent naphazoline (15 mg) by an older sibling. Ten minutes later, he was admitted to the hospital in shock with pale, cold, and cyanotic skin. On exam, his pupils were fixed, no reflexes were present, there were no respirations, and he had a faint, regular slow pulse. Artificial respiration and oxygen were given, color improved, and the child began to take breaths. Pulse rate and blood pressure increased, and the child was moved to a warmed oxygen tent. Seven hours after admission, pulse rate and blood pressure returned to normal; and after 15 hours, the child recovered completely (Meeker 1948).

In the next case, a 2 1/2-year-old boy ingested an unknown amount of 0.05 percent naphazoline. After 30 minutes, the child became drowsy, pale, cold and unresponsive. On arrival to the hospital, he was unconscious, flaccid, lacking a pulse, and "apparently had expired." A dextrose infusion was administered and within minutes, the child improved. After four to six hours he recovered fully (Gillespie 1954).

A 19-month-old swallowed one ounce (2 tbsp) of 0.1 percent naphazoline nose drops (30 mg) was "later" brought to the hospital, and his stomach was washed out. Approximately four hours after ingestion, he went to his private physician for follow-up. The child presented with elevated blood pressure and was treated with heat to induce peripheral vasodilation. The child perspired profusely, turned red, and "waves of constriction of the peripheral blood vessels" recurred about

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every 15 minutes. Concurrently, the patient's eyes rolled upward, and he became somnolent, bordering on coma. Six hours after ingestion, the child could not be aroused and demonstrated sustained hypertension. Treatment with amyl nitrite caused a transitory drop in blood pressure. Therefore, the child was treated with a long-lasting peripheral vasodilator, magnesium sulfate, and the blood pressure steadily dropped to normal. The next day, except for a slight tremor, the child fully recovered (King 1950).

Naphazoline ingestions have also occurred in adults. A Japanese report describes three suicide attempts by ingesting a naphazoline-containing antiseptic first aid liquid. The patients presented with altered mental status, hypertension, bradycardia, and diaphoresis. Chest x-rays revealed acute pulmonary edema. Two cases required mechanical ventilation for resolution. All clinical effects resolved within 24 hours. In one case, the dose of naphazoline was calculated by the authors to be 225 mg (the patient ingested 3 bottles of 0.1 percent naphazoline). This patient (a 32-year-old male) was unconscious two hours after ingestion; he also had high blood pressure, a fast heart rate, and a respiration rate of eight breaths per minute. He was placed in the ICU on a ventilator and given nicardipine for high blood pressure. After 12 hours, he was breathing spontaneously, looking alert, and his blood pressure was within normal range (Fukushima et al., 2008)

Epidemiological Studies of Imidazoline Ingestion

Several epidemiological studies have been performed to examine imidazoline exposures. A retrospective study of imidazoline intoxications to the Belgian National Poison Center from 1986 to 1991, was done by Mahieu et al. Of 254 imidazoline exposures, 108 were from naphazoline. Seventy five percent of these were from ingestion, with 80 percent of naphazoline exposures occurring in children under the age of four. A more detailed study was performed on 19 cases with CNS depressive symptoms most frequent. Seventy-four percent of the 19 cases reported sleepiness, and greater than 50 percent reported pale/cold extremities, bradycardia, or respiratory depression. Hypertension and hypothermia were reported in 37 percent and 26 percent of the 19 cases, respectively. Coma was also reported in one case. In most cases, admission to the hospital for observation was required, and symptomatic treatment was given. In all cases, the symptoms resolved within 24 hours (Mahieu et. al., 1993).

A retrospective analysis was also performed by the German Poison Control Center. Of 108 cases of imidazoline intoxication, 80 percent of the patients were under age four. The method of intoxication was accidental oral ingestion of imidazoline nose drops in 70 percent of the cases, and 24 percent occurred after nasal instillation of naphazoline nose drops, specifically (Stamer et al., 2001).

In addition, a retrospective study was performed of children exposed to imidazolines from January 1994 to December 1999, and followed by the Poison Control Center at the Medical Sciences Faculty of UNICAMP in Brazil. There were 72 cases of exposure in children ranging in age from 20 months to 12 years old. Of these cases, 46 (64 percent) were from oral ingestion. It is of note that 98 percent of the patients exposed to naphazoline (n=47/48) had a greater risk of showing clinical adverse effects indicating intoxication than patients exposed to other imidazolines. The most frequently encountered clinical signs (the majority from naphazoline exposure) included near-sleep state, profuse sweating, pallor, decreased body temperature, and

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slowed heart rate. A 1-year-old consumed a bottle of 0.05 percent naphazoline (approximately 10–12.5 mg), required mechanical ventilation, yet recovered and was released from the hospital after three days. Most patients (68 percent) were asymptomatic 24 hours after exposure. Contact with the Poison Control Center was less than two hours after exposure in more than half of the cases, suggesting quick onset of clinical symptoms from the imidazolines (Bucaretchi et al. 2003).

A prospective study performed in the Netherlands from May 2002 to December 2004, collected data from poison centers in children younger than 6 years old involving xylometazoline ingestion. Follow-up was completed, and the frequency of severe symptoms was observed. From these observations, a systemic dose was calculated for poison control centers, with a low probability of severe symptoms occurring. Over the course of 32 months, 101 cases of xylometazoline exposure occurred, and 63 cases were followed up. Twenty cases were from nasal application, and 81 were from ingestion. In 78 cases, the children took the drugs, and in the remaining 23 cases, the parents exposed the child to the overdose (due to medication error). Symptoms reported at the first phone call were hypertension, swollen facial veins, dilated pupils, vomiting, fast heart rate, and decreased appetite; on follow-up, no additional symptoms were reported. There were no hospitalizations in the 61 cases in which a dose was calculated. The authors concluded that there were no severe symptoms observed after exposure of doses less than 0.4 mg/kg (95 percent CI) (VanVelzen et. al., 2007).

Table 3: Literature Reports: Summary of Imidazoline Ingestions with Known Doses, by Dose Level

DRUG	AGE	VOLUME/ CONC	DOSE (MG)	RESPONSE	REFERENCE
THZ*	25 Days	0.5 mL x 3 doses 0.05%	*0.75*	Not feeding well. Low muscle tone. Apnea. Decreased respirations to 4 breaths per minute. Slowed heart rate. Admitted to hospital, treated with naloxone. Released after 2 days.	Katar et. al., 2010
THZ	2 yrs	2–3 mL/ 0.05%	*1.0–1.5*	2–3 hrs later lethargy and ↓ blood pressure. Progressive CNS and respiratory depression led to admission to PICU and placement on mechanical respiration. 18 hrs later weaned off respirator. Discharged after 48 hrs.	Tobias, 1996
THZ	1 yr	½ to 1 teaspoon/ 0.05%	*1.25 – 2.5*	2 hrs later, sluggish and fell. 3 hrs later drowsy, pale, ↓ respirations and heart rate. Admitted to hospital. Improved 24 hrs later.	Mindlin, 1966
THZ	17 mo	5 mL/ 0.05%	*2.0-2.5*	90 mins. later lethargic, but arousable, slowed heart rate, ↓ blood pressure. Treated with charcoal and transferred to PICU for observation. Recovered 24 hrs later.	Jensen et. al., 1989
THZ	23 mo	6 mL/ 0.05%	*3*	Several hrs later lethargic and arousable only with vigorous physical stimulation; when awake, child irritable and uncoordinated.	Higgins et. al., 1991

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DRUG	AGE	VOLUME/ CONC	DOSE (MG)	RESPONSE	REFERENCE
				Treated with charcoal. Admitted for observation. 20 hrs later normal status.	
Naph**	22 mo	3–4 mL/ 0.1%	*3–4*	Hypothermic, lethargic, irritable, pale, irregular gasping respirations, dilated pupils, hypertension, bradycardia. Followed by unconsciousness and imperceptible respirations. Child warmed and treated with caffeine and oxygen. Symptoms resolved after 15 hrs.	Hainsworth, 1948
Naph	3 yrs	7–8 mL/ 0.05%	*3.5–4*	Became "quite drowsy" for several hrs.	Waring, 1945
THZ	2 yrs	7.5 mL/ 0.05%	*3.7*	4 hrs later lethargic and arousable only with deep pain stimulus. Level of consciousness varied, but responsive 24 hrs later.	Klein-Schwartz et. al., 1984
THZ	17 yrs	10–15 mL/ 0.05%	*5–7.5*	25 min. later lethargic, disoriented, ataxic, slowed speech, bradycardic, orthostaic hypotension. Treated with i.v. fluids. 38 hrs later, patient discharged.	Spiller et. al., 2008
Naph	14 mo	7.5 mL/ 0.1%	*7.5*	Hypothermic and fell asleep for 12 hrs. Recovered after supportive treatment with caffeine and heat.	Greenblatt, 1947
THZ	16 yrs	15 mL/ 0.05%	*7.5*	Symptoms 2 hrs later. CNS depression, constricted pupils, ↓ heart rate, irregular heart rate. Resolved after 24 hrs.	Jones, 1996
THZ	27 mo	15 mL/ 0.05%	*7.5*	Found next to empty eye drop bottle with top chewed off. Eyes rolled upward, difficult to awaken, not alert. In ER, child somnolent, bradycardic, ↓ respirations. Transferred to PICU, given fluids, and monitored. Symptoms resolved, and patient released next day.	Daggy, 2003
THZ	20 mo	15 mL 0.05%	*7.5*	After 1 hr, lethargic and difficult to arouse with semi-purposeful movement. Admitted to hospital and monitored. 24 hours later, awake and alert.	Klein-Schwartz et.al., 1984
Naph	1 yr	1 bottle/ 0.05%	*10-12.5*	Required mechanical ventilation. Recovered and released from hospital after 3 days.	Bucharetchi et. al., 2003
Naph	5 mo	15 mL/ 0.1%	*15*	10 minutes after exposure, admitted to hospital in shock with pale, cold, and cyanotic skin. Pupils fixed, no reflexes, no respirations, and pulse faint. Artificial respirations and oxygen given, color improved, and	Meeker, 1948

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DRUG	AGE	VOLUME/ CONC	DOSE (MG)	RESPONSE	REFERENCE
				child began to breathe. 7 hrs after admission, pulse rate and blood pressure returned to normal; 15 hrs later, child had completely recovered.	
THZ	41 yrs	30 mL/ 0.05%	*15*	Symptoms 1 hour later. CNS depression, chest pain, ↓ heart rate, ↓ blood pressure, hypothermia. Admitted into ICU 48 hrs for supportive therapy.	Lev and Clark, 1995
THZ	36 mo	30 mL/ 0.05%	*15*	90 min. later lethargic and arousable only with vigorous pain stimulation, ↓ muscle tone, ↓ blood pressure, ↓ heart rate, ↓ respirations. Treated with naloxone, child awoke but ↓ heart rate again within 30 minutes. Admitted to PICU, gradual improvement. 7.5 hrs later awake and alert.	Holmes and Berman, 1999
Naph	19 mo	1 fl. Oz./ 0.1%	*30*	4 hrs after ingestion child had elevated blood pressure and was somnolent, bordering on coma. 6 hrs after ingestion child unarousable with sustained hypertension. Treated to ↓ blood pressure. Next day, besides a tremor, child fully recovered.	King, 1950
Naph	32 yrs	3 bottles/ 0.1%	*225*	Found unconscious 2 hrs after ingestion. Hypertensive, tachycardic and ↓ respirations (8 breaths per minute). Placed in ICU, intubated, and placed on ventilator. Symptoms stabilized 12 hrs later.	Fukushima et.al., 2008

*Tetrahydrozoline, **Naphazoline

1. FDA MedWatch Reports of Imidazoline Ingestions

Table 4 lists the reports from the MedWatch Adverse Event Reporting System (AERS) for oral exposure to imidazolines leading to adverse events. The MedWatch AERS is a computerized information database maintained by the Food and Drug Administration (FDA). Submission of data to MedWatch is voluntary and has certain limitations. First, there is no certainty that the reported event was actually due to the product. The FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to evaluate an event properly. Further, the FDA does not receive all reports that occur with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity released about an event. Therefore, MedWatch cannot be used to calculate the occurrence instance of an adverse event in the U.S. population.[23]

[23] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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In case reports for adverse events occurring in response to ingestion of imidazolines, 43 cases occurred in children under 5 years old. Adults also suffered adverse events after ingesting imidazolines, due to inadvertent or intentional ingestions. Tetrahydrozoline ingestion was involved in the majority of cases. Ingestion of imidazolines did not lead to any cases of death.

In 43 Medwatch reports involving children (Table 4), the volume of ingestion ranged from several drops to 30 mL (2 tbsp) of imidazolines, although the volume of ingestion was unknown in several cases. Serious adverse effects occurred in response to small oral doses of imidazolines. A 22-month-old child was admitted into the pediatric intensive care unit with symptoms of vomiting and sharp rises and falls in heart rate after ingesting up to 4 mL (0.8 tsp) of 0.05 percent tetrahydrozoline (2 mg) (FDA540321). A 16-month-old child ingested 2.5–5 mL (½ to 1 tsp) of 0.05 percent tetrahydrozoline (1.25–2.5 mg) and displayed symptoms of slowed heart rate, lethargy with difficulty in arousal, paleness, and depressed respirations. The child was admitted to the hospital overnight, treated with activated charcoal lavage, laxative, and oxygen (FDA671307). The lowest recorded dose was a case with a 2-year-old ingesting ½ a teaspoon (1.3 mg) of tetrahydrozoline eye drops. The child showed symptoms of lethargy, difficulty breathing, increased heart rate, and loss of consciousness. The child was brought to the emergency room, the symptoms resolved, and the child was released later the same day (FDA432222810001).

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TABLE 4: FDA Medwatch Adverse Event Reports of Imidazoline Ingestions

ID #/ source / date	Product	Volume/ *Calculated Dose*	Age of Victim	Event
3260091 foreign, health care professional reported 05/05/99	Tetrahydrozoline (THZ) 0.05%	1 Bottle *7.5-3.8 mg*	12 mo	Drank tetrahydrozoline regular ophthalmic drops and was hospitalized. Patient responds to external stimuli Symptoms: Bradycardia, hypotension, somnolence, accidental overdose. Hospitalization.
3541586 foreign, health professional reported 7/25/00)	THZ 0.1%,	Unknown, ingestion	2 yr	Physician reports that his 2-yr-old daughter took tetrahydrozoline eye drops out of medicine cabinet in his home and ingested it. Unclear how much. Became drowsy, apneic, and unresponsive. Serum analysis revealed tetrahydrozoline. Child recovered completely. Symptoms: Hypoventilation, bradycardia, apnea, somnolence, delirium, miosis, pupillary disorder. Hospitalization.
69020200203301 10/1968	THZ	1/3 bottle *2.5 -5 mg*		Child with convulsive disorder of undetermined origin allegedly ingested 1/3 bottle of tetrahydrozoline eye drops with no visible side effects. Recovered
00081687 father of consumer 7/16/71975	THZ	0.5 oz 3 tsp *7.4 mg*	18 mo	Depressed respirations of 4 per minute. Treated with caffeine and sodium benzoate.
000115875 8/17/1979	THZ 0.05%	Unknown	5 yr	Poison Control Center received call that child ingested bottle of tetrahydrozoline eye drops. The child was given no medication. Symptoms: deep, but arousable sleep, slight hypothermia, low blood pressure, slow pulse. Kept in hospital overnight for observation and discharged. Fully recovered next day.
176135 313439 3/1/1983	THZ eye drops	7.5 mL ½ Tbsp *3.8 mg*	16 mo	Child played with a bottle of tetrahydrozoline eye drops, and one hour later he was very tired. She took him to bed and he fell asleep immediately. Symptoms: Somnolence, clouded state of mind, facial pallor, cold extremities, disturbance of peripheral circulation, bradycardia episodes, long respiratory pauses, hypothermia, hypoventilation, hypotension, apnea. Recovered.
316236 attorney 6/13/84	THZ eye drops	Drank contents bottle *7.5–15 mg*	19 mo	Child disassembled the dropper from a bottle of Visine and drank the contents. Child spent two days and one night in the hospital. Had stomach pumped, placed on i.v. fluids. Respiration and heart rate were monitored due to decrease in both. Hospitalized and recovered.
364092 reported 8/28/1985	THZ eye drops 0.05%	unspecified	21 mo	Ingestion. Infant received ICU care. Fully recovered.
465382 5/6/1986	THZ eye drops,	15 mL 1 Tbsp *7.5 mg*	1.5 yr	Ingestion leading to lethargy. Child recovered.
496909 07/06/1987	THZ eye drops	½ bottle *3.8–7.5 mg*	2 yr	Ingestion leading to symptoms of somnolence, skin discoloration, abnormal coordination. Hospitalization.
528958 health professional 4/10/1988	THZ eye drops	1 oz 6 tsp *15 mg*	1.5 yr	Ingestion leading to decreased blood pressure, heart rate, and respiration rate. Admitted to ICU. After 12 hrs

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ID #/ source / date	Product	Volume/ *Calculated Dose*	Age of Victim	Event
				supportive therapy, child stabilized and transferred out of ICU.
540321 consumer 8/19/1987	THZ eye drops	0–4 mL 0.8 tsp *0–2 mg*	1 yr	Ingestion leading to vomiting, sharp repeated rise and fall in heart rate. Admitted to PICU.
574417 health professional 4/10/1988	THZ eye drops	7.5 mL ½ Tbsp *3.75 mg*	1.5 yr	Ingestion. Pale lethargic, unresponsive, bradycardia, gasping respirations. Admitted into ICU. No tetrahydrozoline in blood samples.
589027 Consumer 12/07/1987	THZ eye drops	Unknown	2 yr	Ingestion leading to drowsiness. Child recovered.
590099 health professional 03/31/1989	THZ eye drops	Up to 15 mL 1 Tbsp *7.5 mg*	3 yr	Ingestion, hospitalized overnight for observation. Lethargic, ataxic. Resulted in inpatient hospitalization.
593993 consumer 1989	THX eye drops	Several drops	2 yr	Ingestion, hospitalized 24hrs. Decreased heart rate and respiration.
573994 consumer 5/5/1989	THZ eye drops	Unknown	1 2/3 yr	Ingestion in early morning. Lethargic, hypothermic, unconfirmed respiratory arrest in emergency room. Transferred to PICU for observation and released following day.
632171 health professional 11/3/1989	THZ eye drops	7.5 mL ½ Tbsp *3.75 mg*	1.5 yr	Ingestion, father (pharmacist) took to ER after turned pale and cold. Hypoventilation, bradycardia, pallor. Treated with i.v. fluids and manual stimulation. Condition resolved overnight.
633279 consumer 12/18/1989	THZ eye drops	Unknown	2 yr	Ingestion. Commented no major package warning and no child-proof cap. Near coma, severe hypotension, bradycardia.
639254 literature, health professional Reported 12/1989	THZ eye drops	4.5mL ~1 tsp *2.3 mg*	1.6 yr	Ingestion. Lethargic, bradycardia, hypotensive. Admitted to hospital, given activated charcoal, i.v. fluids, transferred to PICU, discharged after 24 hrs.
655923 666199 11/16/1988	THZ eye drops	Unknown	3 yr	Ingestion. Brought to ER, treated with charcoal and gastric lavage. Monitored 2 hrs and released.
671051 consumer 3/11/1990	THZ eye drops	0.5oz 3 tsp *7.4 mg*	2.8 yr	Ingestion. Admitted for observation and discharged after 24 hrs.
671307 consumer 5/10/1990	THZ eye drops	2.5-5 mL ½–1 tsp *1.3–2.5 mg*	1.4 yr	Ingestion. After 1 hr, showed symptoms, took to hospital. Lethargic, pale, difficult to arouse. Somnolence, bradycardia, hypoventilation. Treated with activated charcoal lavage and laxative. Administered oxygen. Admitted overnight, and discharged next morning.
680330 consumer (newsmedia) 7/19/1990	THZ eye drops	Unknown	1.5 yr	Tetrahydrozoline eye drops reported to cause coma and resultant hospitalization. Patient discharged next day. Reported child will see neurologist.
689288 consumer 8/6/1990	THZ eye drops	7-8 mL ~ ½ Tbsp *3.5–4 mg*	1 yr	Ingestion. 2 calls to Poison Control Center. Child became irritable and drowsy and brought to ER. Unresponsive on arrival at ER. I.V. started, treated with charcoal lavage. Admitted to ICU and discharged next day.

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ID #/ source / date	Product	Volume/ *Calculated Dose*	Age of Victim	Event
769105 consumer 12/27/1990	THZ eye drops	2.5–3.75 mL ½ – 3/4 tsp *1.3 – 1.9 mg*	1.5 yr	Ingestion. Treated in ER and kept overnight. Drug screen for aspirate negative.
774596 literature, health professional reported 7/28/1991	THZ eye drops	Unknown	1.3 yr	Ingestion of tetrahydrozoline eye drops. Lethargy/limpness. Blood pressure elevated, pupils miotic. Apnea, bradycardia, which responded to vigorous stimulation. Treated with activated charcoal and sorbitol.
1834745 foreign, health professional 10/07/1996	THZ nasal drops	All bottle contents, amount unknown	20 mo	Ingestion. Dizziness, short loss of consciousness, and apnea. Admitted to hospital, treated with i.v. fluids.
399350231101 Tobias Clin Ped 35(10):539-540, 1996 Reported 10/14/2002	THZ eye drops	2–3 mL ~1/2 tsp *1–1.5 mg*	2 yr	Child taken to ER, oxygen supplementation, glucose, to PICU, intubated, and put on mechanical respiration for 18 hrs. Symptoms resolved and child discharged.
399350350001 Klein-Schwartz, 1984,Am J Emerg Med 2(3):217-218 Reported 10/15/2002	THZ eye drops	15 mL 1 Tbsp *7.5 mg*	20 mo	Ingestion leading to CNS depression, somnolence, nervousness, vasodilation. Taken to ER 6 hrs after ingestion, monitored, symptoms resolved after 20 hrs, discharged.
399350470001 Klein-Schwartz, 1984,Am J Emerg Med 2(3):217-218 Reported 10/14/2002	THZ eye drops	7.5 mL ½ Tbsp *3.8 mg*	2 yr	Ingestion leading to CNS depression. Admitted to hospital. Level of consciousness varied from responding only to deep pain to non-purposeful agitation. Over first day, child became more responsive. Next day, he was awake and alert. Vital signs within normal limits. Pupils constricted.
4002573x0001 Holmes, Ped Emerg Care. 15:193-194 (1999) Reported 10/14/2002	THZ eye drops	30 mL 2 Tbsp *15 mg*	36 mo	One hour after ingestion became lethargic but still alert. Became lethargic and limp, decreased muscle tone, did not respond to voice commands. Given naloxone, child awoke, alert, and began to cry. Thirty minutes later child again became somnolent. Admitted to PICU, within 7.5 hrs after ingestion, infant awake, alert, and no manifestations of toxicity noted. Discharged
420841870001 Daggy et.al. Vet Hum Tox. (2003), 45:210-212 Reported 9/30/2003	THZ eye drops	Unspecified	27 mo	Found with eyes rolled upward, several attempts at arousing with noxious stimuli required to awaken, not responding in usual alert fashion. Brought to ER, became drowsier, but responsive. Transferred to PICU, treated with fluids, recovered next day, and discharged.
43222810001 3/6/2004	THZ eye drops	½ tsp *1.3 mg*	2 yr	Ingestion, within 30 min became lethargic, had difficulty breathing, vomited and periodically lost consciousness. Taken to ER and admitted. Treated with charcoal, increased heart rate. Released from hospital same day, symptoms resolved.
394511700001 2/12/2002	Oxymetazoline eye drops	0.5 ounces *11.25 mg*	3.5 yr	Ingestion. Child appeared sleepy and was taken to ER. Treated (unspecified) and transferred to PICU. Symptoms resolved, and sent home.
128468	Oxymetazoline Nasal Spray	15 mL	Child	Ingestion with symptom of somnolence.

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7/1981		1 tbsp *7.5 mg*		Child recovered.
439578450001 6/2004	Oxymetazoline eye drops	¾ of bottle ingested *2.8–5.6 mg*	18 mo	Child ingested oxymetazoline eye drops, within 5 minutes child passed out and stopped breathing. Child given CPR and taken to ER. Treated with meds to counteract barbiturate before eye drop ingestion known. Developed rash from those meds. Given fluids and antibiotic, spent night in ICU. Aroused from coma 8–10 hrs later. Released later that day. Having headaches 3–4 times daily. Other events have resolved.
367702210001 Reported 2/15/2001	Oxymetazoline no drip nasal spray	Unknown	19 mo	Child inadvertently accessed bottle of oxymetazoline nose spray. She took top off and may have ingested portion of the contents of the bottle. Contacted Poison Control Center, informed father this was medical emergency, advised him to rush daughter to ER. Child brought to hospital, treated with activated charcoal, and monitored for signs of toxicity. After several hours with no sign of effects, child released.
3269491-6-00-61	THZ eye drops	Unknown	12 mo	Drowsiness, bradycardia (slower than normal heart rate), and "moderate decrease on arterial pressure values."
3534556-7-00-01 physician	THZ 0.1%	Unknown	2 yr	Drowsiness, apnea (a period of time when breathing stops or is markedly reduced), unresponsive, constricted, and fixed pupils.
3867685-X-49-81 Grandparent 02/01/2002	THZ eye drops	½ bottle at once *3.8–7.5 mg*	2 yr	Slow heart rate, lethargic, red face, all events resolved within 24 hours.
4002673x0001 2002	THZ eye drops	30 ml 2 tbsp *15 mg*	36 mo	Lethargic, low respiration rate, bradycardia, hypotension, constricted pupils.
000005x8 Pharmacy	THZ eye drops	1/3 bottle *2.5–5 mg*	NA	Child with convulsive disorder of undetermined origin, no side effects.
00057471 Drug Manufacturer 01/18/1974	THZ nasal spray	12 mL 2.4 tsp *6 mg*	18 mo	Admitted to hospital.
3677022-1-00-01 Parent 02/15/2001	Oxymetazoline nasal spray	Unknown	19 mo	Child went to ER, given activated charcoal, monitored, and released.

V. Recommended Level for Regulation

Absorption of imidazolines after oral ingestion can lead to unpredictable and profound CNS depression, including depressed respiration and cardiovascular events. It has been shown that children under 5 years old are accidentally ingesting imidazoline-containing products. The first cases of imidazoline toxicity in children after accidental ingestion occurred in the mid-1940s, shortly after the release of naphazoline into the market; and the incidents have continued to occur for more than 50 years (Waring 1945, Greenblat 1947, Hainsworth 1948, Meeker 1948, Bucaretchi et al., 2003). Symptoms of imidazoline toxicity include CNS depression, ranging from drowsiness to coma, bradycardia, and hypoventilation. Even though death from

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imidazoline exposure is rare, many of these events result in serious life-threatening consequences requiring hospitalization and intensive care monitoring for recovery.

Mindlin (1966) reported a case in which a 1-year-old girl ingested between ½ to 1 teaspoon (2.5–5 mL) of tetrahydrozoline eye drops and suffered CNS depression with slowed respiration and decreased heart rate. Based on this ingestion, recent literature publications define 2.5 mL tetrahydrozoline (0.05 percent, 1.25 mg) as the dose at which serious toxicity from imidazoline exposure can occur after ingestion (Holmes and Berman, 1999; Eddy and Howell 2000). In the preamble to the proposed FDA rule for over-the-counter nasal decongestants, it was reported that the minimum oral dose of oxymetazoline in an adult causing measurable cardiovascular effects (on blood pressure and heart rate) was 1.8 mg of oxymetazoline (41 FR 38312, 38398 (September 9, 1976)). This minimum dose may be lower for children because they appear to be more sensitive to imidazoline effects than adults (Brainerd and Olmstead, 1956). Cases presented in this memorandum indicate that ingestion of as little as 0.75 mg of imidazolines can result in serious illness in children, requiring supportive therapy (Katar et al., 2010; Summary see Table 3).

Table 5: Relevant Cases of Imidazoline Ingestion

Estimated Dose	Onset/Symptoms	Age	Result	Reference
2.8-5.6 mg Oxymetazoline 0.3-0.5 mg/kg**	Within 5 minutes. Child passed out and stopped breathing. Given CPR and taken to ER.	18 mo.	Given fluids and admitted to ICU. Aroused from coma 8-10 hours later. Released later that day. Having headaches 3-4 times daily.	FDA MedWatch 439578450001 6/2004
3-4 mg Naphazoline 0.2-0.3 mg/kg**	"Soon" became "quite drowsy" for several hours	3 yrs.	Several hours.	Waring, 1945
3-4 mg Naphazoline 0.2-0.3 mg/kg	One hour after ingestion. Became hypothermic, lethargic, irritable, pale, irregular gasping respirations, hypertension, bradycardia. Followed by unconsciousness and imperceptible respirations.	22 mo.	Child warmed and treated with caffeine and oxygen. Symptoms resolved after 15 hrs.	Hainsworth, 1948
2-2.5 mg Tetrahydrozoline 0.2 mg/kg	90 minutes Lethargic, decreased heart rate, decreased blood pressure	17 mo.	Pediatric intensive care unit Recovered 24 hrs	Jensen et al. 1989
Up to 2 mg Tetrahydrozoline 0.2 mg/kg**	Sharp increase and decrease of heart rate	22 mo.	Pediatric intensive care unit	FDA540321
1.25-2.5 mg Tetrahydrozoline 0.1-0.2 mg/kg**	Decreased heart rate Lethargic, difficult to arouse, depressed	16 mo.	Admitted to hospital overnight	FDA671307

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Estimated Dose	Onset/Symptoms	Age	Result	Reference
	respiration			
1.25-2.5 mg Tetrahydrozoline 0.1-0.3 mg/kg**	2 hrs Ataxic, pale, drowsy, decreased heart rate, decreased respiration	1 yr.	Admitted to hospital Recovered 24 hrs	Mindlin 1966
1.3 mg Tetrahydrozoline 0.1 mg/kg**	30 min Lethargic, difficulty breathing, vomiting, loss of consciousness	2 yr.	Admitted to hospital, treated with charcoal. Released from hospital same day, symptoms resolved.	FDA 43222810001
1-1.5 mg Tetrahydrozoline 0.1 mg/kg	2–3 hrs Lethargy, decreased blood pressure, decreased respiration	2 yr.	Pediatric intensive care unit Mechanical Respiration for 18 hrs Recovered 48 hrs	Tobias 1996
*0.25 mg x 3 or 0.75** Tetrahydrozoline 0.2 mg/kg	2 hrs Apnea, decreased respirations, slowed heart rate	25 days	Admitted to hospital Naloxone, Continuous positive airway pressure, oxygen Recovered 2 days	Katar et.al., 2010

*Due to reduced clearance of drugs in the newborn, the three doses are considered additive. **Weights estimated from www.cdc.gov/growthcharts by age, if no gender indicated assumed to be male, used 50th percentile.

The most recent imidazoline ingestion case cites the lowest dose of ingestion of which staff is aware that caused severe adverse symptoms in a child. The case involved a 25-day-old infant who suffered apnea after being treated with tetrahydrozoline nasal drops (0.05 percent). The mother inadvertently administered the nasal drops by the oral route three times per day with 0.5 ml/day (0.25 mg). The immature kidney and liver function of the newborn caused the drugs to clear the newborn's system slower than in an adult. Accordingly, staff considered the three doses of nasal drops to be additive. Therefore, staff calculated the total dose for this case to be 0.75 mg. After the second dose, the child was not feeding well and had low muscle tone. Two hours after the second dose, he developed apnea. After the third dose was administered, the child was brought to the hospital and admitted with a respiratory rate of four breaths per minute and a slowed heart rate. The infant was treated with naloxone, resolving the apnea and bradycardia. After two days, the child was in good condition and was discharged. After follow-up 10 days later, the child was in normal condition (Katar et.al. 2010).

Because serious effects on the heart and breathing rates occur with the ingestion of as little as 0.75 mg of tetrahydrozoline, staff considers this the lowest observed adverse effect level (LOAEL). All of the imidazolines cause potent central and peripheral sympathetic effects, but tetrahydrozoline has the highest potency for CNS sedative/depressive effects and the lowest potency for cardiac effects. Oxymetazoline and naphazoline are the most potent imidazolines for peripheral cardiac effects and have an 8–10 times lower maximum daily dose than tetrahydrozoline (0.4 mg, 0.3 mg and 3.2 mg, respectively). Xylometazoline and oxymetazoline have a longer duration of action than tetrahydrozoline (12 hr, 10 hr, and 4–6 hrs, respectively).

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Thus, Health Sciences staff recommends applying a safety factor[24] of 10 to the LOAEL to derive a recommended regulated level of 0.08 mg for all imidazolines in order to protect children from serious health effects following ingestion of this family of drugs. The level of 0.08 mg would require all known imidazolines (see Tables 1 and 2) currently on the market to be placed in child-resistant packaging.

VI. Conclusion

Imidazolines are potent group of vasoconstrictors that cause CNS depression, as well as decreased respiration and cardiac adverse events if they are ingested. It has been shown from NEISS data (Table 2) that children under age 5 have been injured by accessing and accidentally ingesting imidazoline-containing products. A Poison Control Center specialist from the Children's Hospital in Philadelphia states that imidazoline toxicity is "profound," causing coma, bradycardia, and hypotension with small doses.[25]

Staff reviewed the medical literature to identify the types of adverse events that have been reported following ingestion of imidazolines and to determine the level at which health effects have occurred. Even though death from imidazoline exposure is rare, many of these events resulted in serious life-threatening consequences and required hospitalization and intensive care monitoring for recovery.

A case presented in this memorandum indicates that ingestion of as little as 0.75 mg of tetrahydrozoline can result in serious health effects in a child, requiring supportive therapy. Since serious effects on the heart rate and breathing rate occur with the ingestion of as little as 0.75 mg of tetrahydrozoline, staff considers this the lowest observed adverse event level (LOAEL).

All of the imidazolines cause potent central and peripheral sympathetic effects: tetrahydrozoline has the highest potency for CNS sedative/depressive effects and lowest potency for cardiac effects; oxymetazoline and naphazoline are the most potent imidazolines for peripheral cardiac effects and have a lower maximum daily dose than tetrahydrozoline, while xylometazoline and oxymetazoline have a longer duration of action than tetrahydrozoline.

Because imidazolines, as a class of drugs, have been shown to cause serious health effects, staff recommends applying a safety factor[26] of 10 to the LOAEL to derive a regulated level of 0.08

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[24] The assumptions underlying the use of safety factors are that by using these factors, both the public health and sensitive populations are protected. Further assumptions hold that humans are somewhere between 10 and 1,000 times more sensitive to some toxic agents than animals, and adults are less sensitive than children. Hence, a safety assessment can be conducted using the proper toxicological evaluation with different populations to establish the NOEL (no observable effect level) or its equivalent. A ten-fold safety factor was used to divide the LOEL, in our case, to reach a NOEL level.

[25] Bartlett D. (2003). Dangerous in small amounts: Ten nondrug substances that cause harm. J Em Nursing. 29(4):377–379.

[26] The assumptions underlying the use of safety factors are that, by using these factors, the public health is protected, and special populations are also protected. Further assumptions hold that humans are somewhere between 10 and 1,000 times more sensitive to some toxic agents than animals, and adults are less sensitive than children. Hence, a safety assessment can be conducted using the proper toxicological evaluation with different populations to establish the NOEL (no observable effect level) or its equivalent. A tenfold safety factor was used to divide the LOEL in our case to reach a NOEL level.

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mg for all imidazolines in order to protect children from serious health effects following ingestion.

Therefore, to prevent poisoning of children under 5 years old who might access these products, staff recommends that special packaging be required for products containing the equivalent of 0.08 mg or more of naphazoline, tetrahydrozoline, oxymetazoline, or xylometazoline in a single package. The level of 0.08 mg will require all known imidazolines currently on the market, including prescription and OTC products, to be placed in child-resistant packaging.

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TAB B: Analysis of Ingestion and Injury Data

TAB B

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UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

Memorandum

Date: February 2, 2011

TO : Cheryl A. Osterhout, Ph.D., Pharmacologist
Directorate for Health Sciences

THROUGH: Kathleen Stralka, M.S., Associate Executive Director
Directorate for Epidemiology

FROM : Craig O'Brien, M.S., Mathematical Statistician
Hazard Analysis Division

SUBJECT : Analysis of Data on Pediatric Ingestions and Injuries Involving Household Products Containing Imidazolines

I. Introduction

This memorandum gives results of an analysis of pediatric ingestions and injuries involving household products containing imidazolines. Data sources include the National Electronic Injury Surveillance System (NEISS), maintained by the U.S. Consumer Product Safety Commission (CPSC); the Children and Poisoning System (CAP), a subset of NEISS cases, maintained by CPSC's Directorate for Health Sciences; and the Adverse Event Reporting System (AERS), maintained by the U.S. Food and Drug Administration (FDA). Included here are statistics associated with data on children who have been treated in hospital emergency rooms from 1997 through 2009 as a result of injuries associated with imidazoline-containing products, and counts of adverse events reports associated with imidazoline-containing products to the FDA for all ages from October 1968 through August 2010.

II. Background

An imidazoline is a vasoconstrictor indicated for ophthalmic (eye) irritation or nasal congestion. The specific chemicals analyzed in this memo are tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline. All of these can cause cardiac, central nervous system, and respiratory adverse events when ingested. These adverse events can be serious in children (Dunn et. al., 1993). The Poison Prevention Packaging Act does not currently require child-resistant (CR) packaging for over-the-counter imidazolines.

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III. Injury Data

A. Methodology

NEISS is a probability sample of approximately 100 U.S. hospitals having 24-hour emergency departments (EDs) and more than six beds. Coders in each hospital code consumer product-related data from the ED record and the data is then transmitted electronically to the CPSC. Because NEISS is a probability sample, each case collected represents a number of cases (the case's *weight*) of the total estimate of injuries in the United States. Different hospitals carry different weights, based on stratification by their annual number of emergency department visits (Kessler and Schroeder, 1999).

The CPSC's Directorate for Health Sciences maintains the Children and Poisoning (CAP) system, a subset of NEISS records containing additional information obtained through NEISS involving children under 5 years old (Boja, 2001). CAP includes data on each pediatric poisoning, chemical burn, or ingestion case reported from a NEISS hospital, as well as some ingestions that could lead to poisoning. Staff searched the CAP database for incidents between January 1997 and December 2009 involving household products that typically contain imidazolines.

Hazard Analysis staff searched CAP for four product codes: NC1000 (decongestants/nose drops), NC1500 (nose sprays), NN2000 (eye drops), and NN2100 (Naphazoline eye drops). These product codes were then grouped into eye drops (NN2000 and NN2100) and nasal sprays (NC1000 and NC1500). The initial search found 1,303 cases. These cases were reviewed by Health Sciences staff for incidents involving imidazolines. A total of 172 relevant cases were identified.

Hazard Analysis staff used SAS® version 9 to compute estimates and the associated coefficients of variation for the number of injuries, as well as the estimated number of injuries with particular characteristics, such as age and gender. A coefficient of variation (C.V.) is the ratio of the standard error of the estimate (*i.e.*, variability) to the estimate itself. This is generally expressed as a percent. A C.V. of 10 percent means the standard error of the estimate equals 0.1 times the estimate. Large C.V.s alert the reader that the estimate has considerable variability. This is often due to a small sample size.[27] Estimates and confidence intervals are not reported unless the number of cases is 20 or more, the estimate is greater than 1,200, and the C.V. is less than 33 percent.

B. Results

An estimated 5,675 injuries associated with household products containing imidazolines and involving children under 5 years old were treated in U.S. hospital emergency rooms from 1997 through 2009. Four groups of products commonly containing imidazolines were searched. Table 1 (next page) shows the estimates for each of the product groups involved in these incidents. Four-fifths of the estimated injuries (81 percent) involved eye drops.

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[27] For a more detailed discussion of measures of variation associated with NEISS estimates, see Kessler E. and Schroeder T. *The NEISS Sample (Design and Implementation).* U.S. Consumer Product Safety Commission. October 1999. Pages 70–72.

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Table 1: Estimated Imidazoline Product-Related Injuries to Children Under Five Years Old, 1997–-2009, by Product Group.

Product	Estimated Injuries	Coefficient of Variation	Sample Size	95% Confidence Interval
Eye drops	4,571	0.19	138	2,831–6,311
Nose Sprays[28]	1,104	0.31	34	426–1,782
Total	**5,675**	**0.18**	**172**	**3,666–7,684**

Source: U.S. Consumer Product Safety Commission National Electronic Injury Surveillance System and Children and Poisoning System, 2011.

Table 1 presents the coefficients of variation for each estimate in order to illustrate the degree of uncertainty or sampling variation associated with the estimates. Estimates and confidence intervals are not normally reported, unless the number of cases is 20 or more, the estimate is greater than 1,200, and the C.V. is less than 33 percent. Given the small sample of imidazoline-related injuries, it is not possible to do a more detailed analysis of the injuries broken down by year, age, or other variables. The estimates for each year or each age fail to meet the above criteria. The vast majority of patients were treated and released.

IV. Adverse Event Data

A. Methodology

The Adverse Event Reporting System (AERS) is a database of voluntary reports from health care professionals and consumers and mandatory reports from manufacturers. It is maintained by the U.S. Food and Drug Administration (FDA) and contains reports of adverse events and medication errors for all FDA approved drugs and therapeutic biologic products. Adverse events in the AERS database are coded using terms from the Medical Dictionary for Regulatory Activities (MedDRA), which is maintained by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as a trustee for the International Conference on Harmonization (ICH).

The FDA strongly cautions that AERS data cannot be used to calculate rates of incidence for adverse events within the population. Many reports to AERS are voluntary; accordingly, it cannot be assumed that the voluntary reporting results in a statistically valid sample for making estimates for the general population. Furthermore, the adverse event reported may not have a causal link to the product in question. The FDA does not require a causal event to be proven, and reports do not always contain enough information to evaluate properly what occurred. The AERS data is not limited to pediatric users of imidazolines or to unintentional poisonings. AERS data includes all ages and usage types.

Health Sciences staff requested from the FDA all AERS reports mentioning the imidazolines tetrahydrozoline, oxymetazoline, xylometazoline and naphazoline. A total of 1,041 reports for 772 distinct cases occurring between October 1968 and August 2010 were provided to Health Sciences staff for review. Staff checked for cases related to imidazolines and the exclusion of cases with concomitant drugs. Heath Sciences staff determined that 67 cases (with 115 total

[28] The estimate for this category is highly variable due to small sample size and high coefficient of variation. These numbers should be interpreted with caution.

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reports) were in-scope for this memo. Hazard Analysis staff used SAS® version 9 and R version 2 to analyze the reports based on the MedDRA preferred terms, high level groups, and system/organ classes of the reported adverse events. A preferred term is a distinct descriptor (single medical concept) for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic. A high level group combines preferred terms by anatomy, pathology, physiology, etiology, or function. A system/organ class combines high level groups by etiology, manifestation site, or purpose.

Note that AERS cases can have multiple reports, and reports can have multiple adverse events. Staff analyzed the data so that no preferred term for an adverse event was counted more than once for each case. However, a case could be associated with multiple preferred terms in the same high level group or system/organ class, and thus, could be counted more than once in those combined counts.

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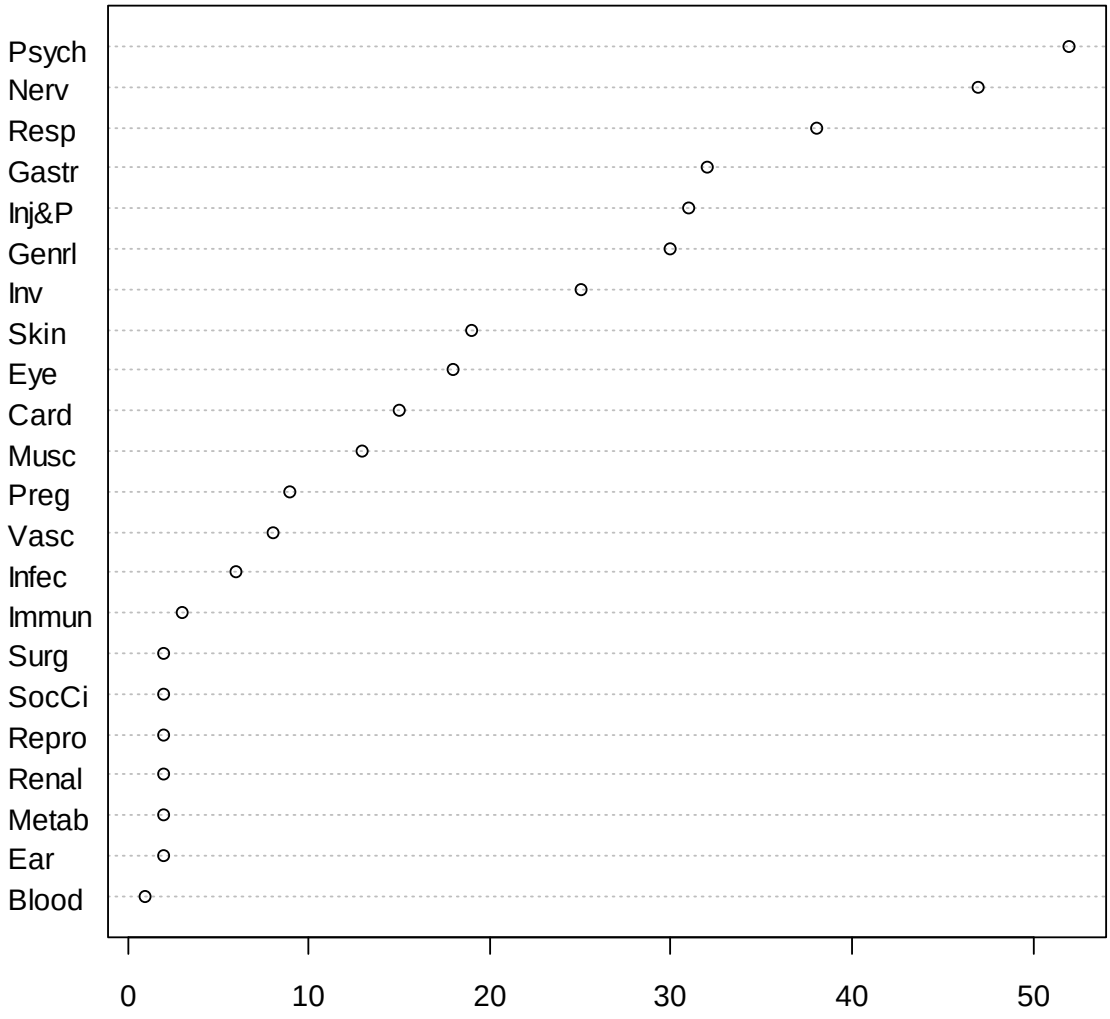
Figure 1: Reactions by System/Organ Class



Source: U.S. Food and Drug Administration's Adverse Event Reporting System.
All ages, October 1968 - August 2010.

Figure 1 shows the reported adverse events by system/organ class. The top three classes are psychiatric disorders (52 reports); nervous system disorders (47 reports); and respiratory, thoracic, and mediastinal disorders (38 reports). Sixty-two out of 67 in-scope cases (93 percent) reported an adverse event in one of the top three system/organ classes.

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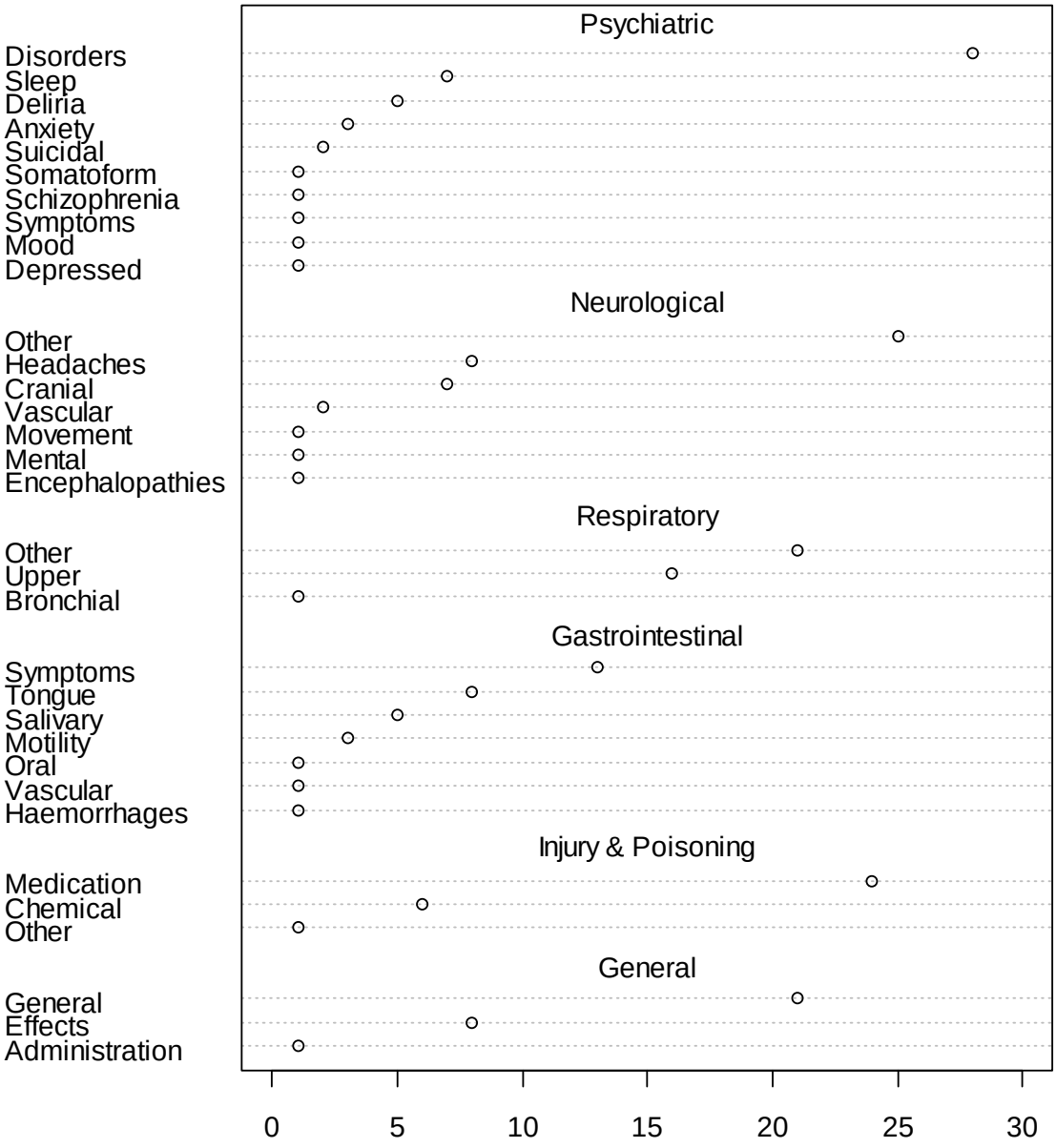
Figure 2: High Level Group Counts for Selected System/Organ Classes



Source: U.S. Food and Drug Administration's Adverse Event Reporting System.
All ages, October 1968 - August 2010.

Figure 2 shows the number of reports for each high level group in the top six reported system/organ classes. The "other" categories include too many preferred terms to enumerate in this report. For example, the respiratory/other high level group includes 125 preferred terms. Due to high counts and vague titles, counts of reported preferred terms for neurological/other and respiratory/other are shown in Figures 4 and 5, and counts of reported preferred terms for general/general are provided in Figure 6.

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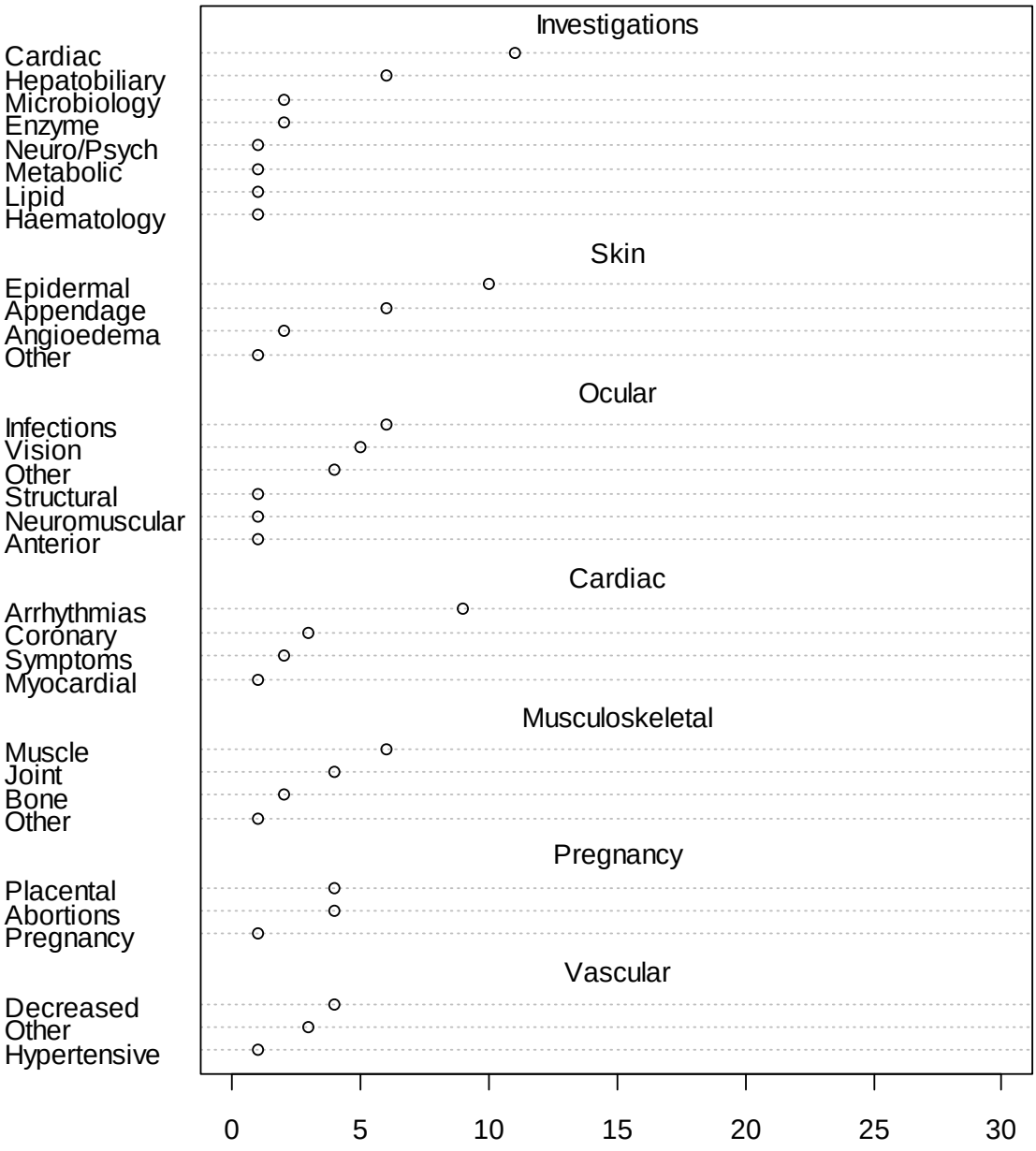
Figure 3: High Level Group Counts for Selected System/Organ Classes



Source: U.S. Food and Drug Administration's Adverse Event Reporting System.
All ages, October 1968 - August 2010.

Figure 3 shows the number of reports for each high level group in the 7th through 13th most reported system/organ classes. Counts for reported preferred terms in investigations/cardiac to assess the effect of imidazolines on heart rate and are presented in Figure 7.

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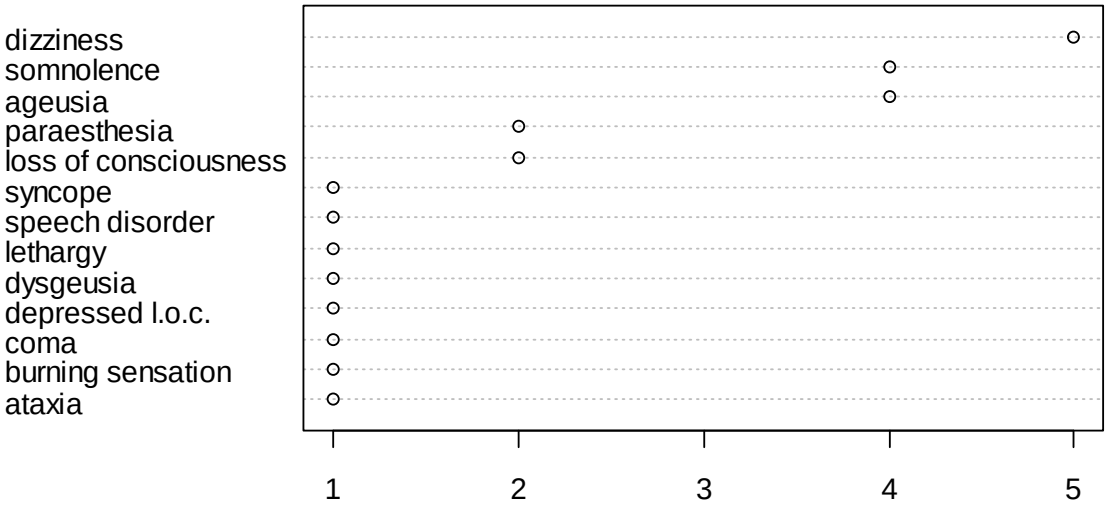
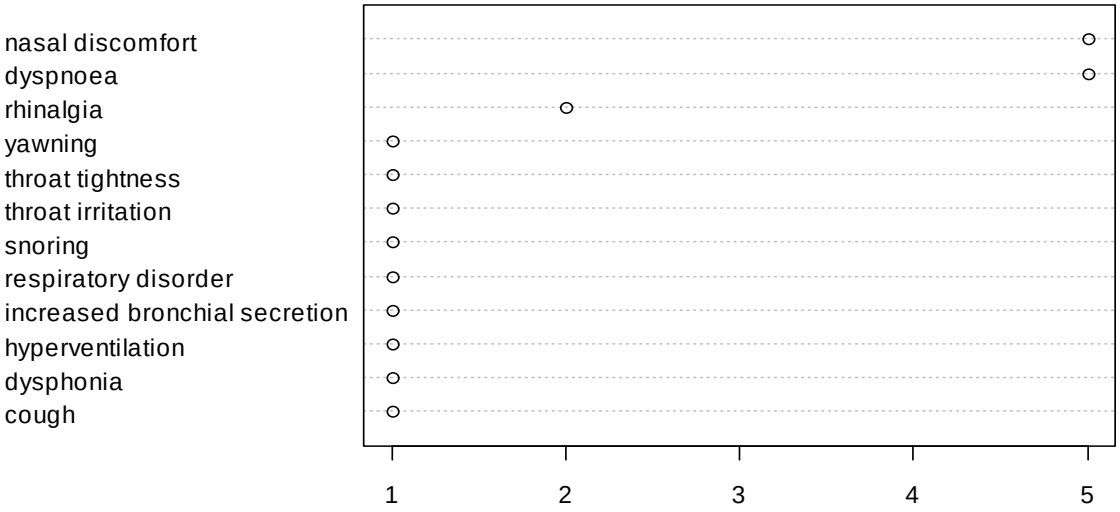
Figure 4: Adverse Reactions for Neurological/Other



Source: U.S. Food and Drug Administration's Adverse Event Reporting System.
All ages, October 1968 - August 2010.

Figure 4 shows the reported preferred terms in the neurological/other high level group. The most commonly reported preferred term in this high level group was dizziness with five reports. Somnolence and ageusia (loss of taste function) also had four reports each.

Figure 5: Adverse Reactions for Respiratory/Other



Source: U.S. Food and Drug Administration's Adverse Event Reporting System.
All ages, October 1968 - August 2010.

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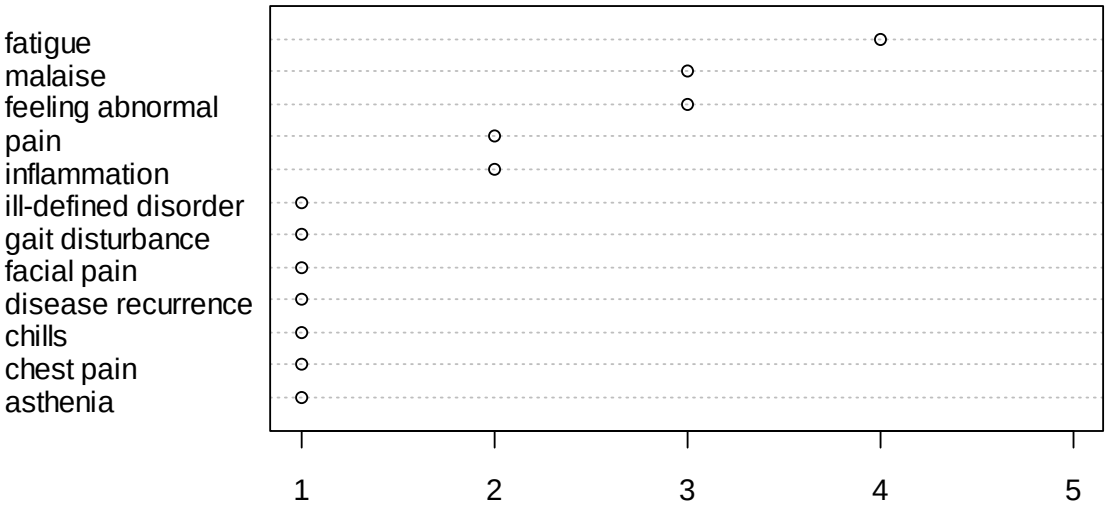
Figure 5 shows the reported preferred terms in the respiratory/other high level group. The two most commonly reported preferred terms in this high level group were nasal discomfort and dyspnoea (shortness of breath).

Figure 6: Adverse Reactions for General/General



Source: U.S. Food and Drug Administration's Adverse Event Reporting System.
All ages, October 1968 - August 2010.

Figure 6 shows the reported preferred terms in the general/general high level group. The most commonly reported preferred term in this high level group was fatigue with four reports. Malaise and feeling abnormal also had three reports each.

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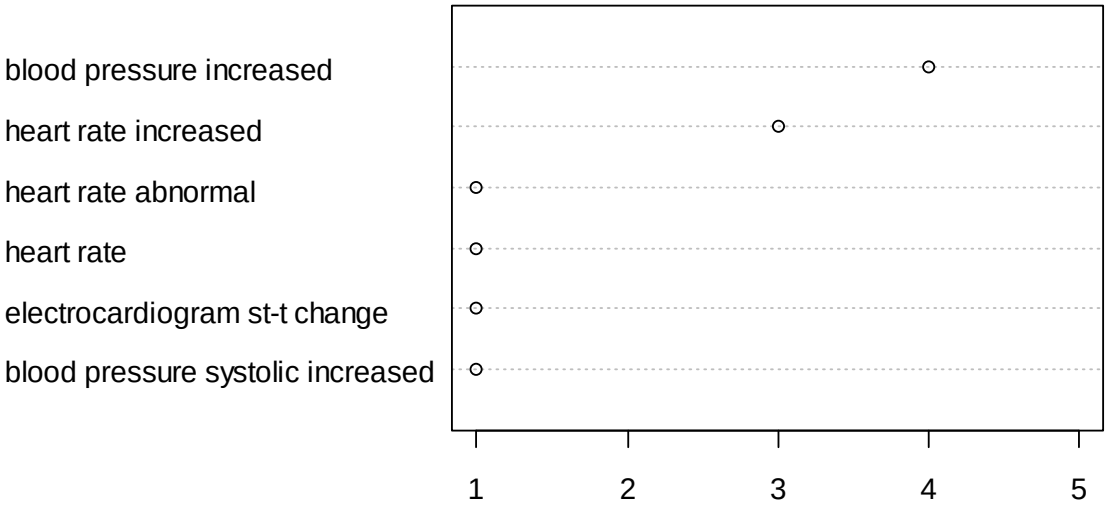
Figure 7: Adverse Reactions for Investigations/Cardiac



Source: U.S. Food and Drug Administration's Adverse Event Reporting System.
All ages, October 1968 - August 2010.

Figure 7 shows the reported preferred terms in the investigations/cardiac high level group. The most commonly reported preferred term in this high level group was increased blood pressure with four reports. Increased heart rate also had three reports.

Summary and Conclusion

Reports through the AERS system show a wide variety of adverse events across all ages associated with the use of imidazolines. In particular, 93 percent of cases reviewed showed adverse events in the psychiatric, neurological, and/or respiratory system/organ classes.

Searches using CAP reveal that young children are being exposed to and injured by household products containing imidazolines. The majority of injuries are associated with eye drops. For the 13 years between 1997 and 2009, an estimated 5,675 injuries to children under 5 years old treated in U.S. hospital emergency rooms were associated with these products, based on CAP data.

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TAB C: Technical Feasibilityof Special Packaging

TAB C

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UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

Memorandum

Date: January 11, 2012

TO: Cheryl A. Osterhout, PhD., Pharmacologist, Division of Health Sciences

THROUGH: Andrew Stadnik, P.E., Associate Executive Director
Laboratory Sciences Directorate

James C. Hyatt, P.E., Division Director
Division of Mechanical Engineering
Laboratory Sciences Directorate

FROM: Gregory K. Rea, Mechanical Engineer
Division of Mechanical Engineering
Laboratory Sciences Directorate

SUBJECT: Update of the technical feasibility, practicability, and appropriateness assessment of child-resistant and senior-friendly packages for imidazoline-containing household products.[29]

I. INTRODUCTION

Under the Poison Prevention Packaging Act (PPPA) of 1970, the U.S. Consumer Product Safety Commission (CPSC) may require special packaging that is child-resistant (CR) for certain substances stored and used in the household in order to protect children from serious personal injury or illness. In addition to finding that special packaging is necessary to protect children from serious personal injury or illness, the Commission must also find that special packaging is technically feasible, practicable, and appropriate for these products (15 U.S.C. 1472 (a)(1) - (2)). For special packaging to be technically feasible, the technology must be available to produce packaging that conforms to established standards. See S. Rep. 91-845, at 10 (1970). A package is practicable if the special packaging is adaptable to modern mass production and assembly line techniques. *Id*. Finally, packaging is appropriate if the

[29] Update of the January 10, 2005 CPSC Staff Memorandum from John W. Boja, Ph.D. titled, "Technical feasibility, practicability, and appropriateness assessment of child-resistant and senior-friendly packages for imidazoline containing household products." CPSC regulations at 16 CFR §§ 1700.15(b)(2)(i) and 1700.20 require special packaging to be both child-resistant and senior-friendly.

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packaging will adequately protect the integrity of the substance and will not interfere with its intended storage or use. All three of these conditions must be met before the Commission can require special packaging for a product.

The definition of "package" is "the immediate container or wrapping in which any household substance is contained for consumption, use, or storage by individuals in or about the household…" "Special packaging" is defined by the PPPA as packaging that is designed or constructed to be difficult for children under 5 years of age to open or obtain a toxic or harmful amount of substance within a reasonable time, and not difficult for normal adults to use properly (16 CFR §1700.1(4)). The child-resistance and adult-use-effectiveness of special packaging are measured by performance testing packaging with children and senior adults, respectively. 16 CFR §§ 1700.15(b) and 1700.20.

Staff evaluated the packaging of 12 representative examples (10 eyedrops, 1 nasal spray, and 1 nasal drop) of over-the-counter products that contain imidazolines. These packages are summarized in Table 1 and images of each are presented in Appendix A. The 12 specimens represent products from all five imidazoline families: naphazoline hydrochloride (HCL), naphazoline HCL combination products, oxymetazoline HCL, tetrahydrozoline HCL, and xylometazoline. None of the samples were packaged using special packaging. The 10 eyedrop samples were packaged in squeeze-to-dispense plastic dropper bottles. The nasal spray was packaged in a plastic bottle with an attached metered pump sprayer, and the nasal drop was packaged in a squeeze-to-dispense plastic dropper bottle.

A. Eye drops

Specimen 1 was packaged in a 0.16 fluid ounce (5 ml) translucent polyvinyl chloride (PVC) plastic squeeze dropper bottle. The bottle was finished with continuous threads, and the bottle opening was fitted with a plastic dropper plug with a 10mm-long nozzle. The closure on the bottle was a 15mm, non-child-resistant (NCR), continuously-threaded[30] (CT) plastic cap.

Specimen 2 was packaged in a 0.5 fluid ounce (15 ml), translucent PVC plastic, squeeze-dropper bottle finished with continuous threads. The bottle opening was fitted with a plastic dropper plug with a 10mm-long nozzle. The closure on the bottle was a 15mm NCRCT plastic cap.

Specimen 3 was packaged in a 1.0 fluid ounce (30 ml), translucent PVC plastic, squeeze-dropper bottle. The bottle opening was fitted with a plastic dropper plug with a 10mm-long nozzle and finished with continuous threads. The closure on the bottle was a 15mm NCRCT plastic cap.

Specimen 4 was packaged in a 0.5 fluid ounce (15 ml), translucent PVC plastic, squeeze-dropper bottle. The bottle was finished with continuous threads, and the bottle opening was fitted with a plastic dropper plug with a 10mm-long nozzle. The closure on the bottle was a 13mm NCRCT plastic cap.

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[30] Continuous threaded (CT) packages have matching spiral ridges on both the inside of a cap and on the outside of the corresponding bottle neck. The package is secured by rotating, screwing, or torquing the cap on the bottle, in a clockwise direction, without a downward force. A counterclockwise torque opens the package.

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Specimens 5, 6 and 7 were packaged in 0.5 fluid ounce (15 ml), opaque, high-density polyethylene (HDPE) plastic, squeeze-dropper bottles finished with continuous threads. The bottle openings were fitted with plastic dropper plugs with 10mm-long nozzles. The closures on the bottles were 15mm, non-child- resistant NCRCT plastic caps.

Specimen 8 was packaged in a 0.4 fluid ounce (13 ml), clear HDPE plastic, squeeze-dropper bottle. The bottle's 6.5mm diameter neck was finished with a 1mm thick, 3.5mm tall collar. Its opening was fitted with a plastic dropper plug with a 5mm-long nozzle. The closure on the bottle was a 10mm NCR plastic cap with buttresses that snapped onto the collar of the bottle neck.

Specimen 9 was packaged in a 0.5 fluid ounce (15 ml), translucent PVC plastic, squeeze-dropper bottle. The bottle was finished with continuous threads, and the bottle opening was fitted with a plastic dropper plug with a 10mm-long nozzle. The closure on the bottle was a 13mm NCRCT plastic cap.

Specimen 10 was packaged in a 0.5 fluid ounce (15 ml), translucent PVC plastic, squeeze-dropper bottle finished with continuous threads. The bottle's opening had a fitted plastic dropper plug that had a 10 mm-long nozzle. The closure on the bottle was a 15mm NCRCT plastic cap.

Table 1. Description of Packages for Products Containing Imidazoline
(Images of each package are presented in Appendix A.)

#	Imidazoline Family	Package Name			Closure		
		Product	Packaging	Dispenser	Size (mm)	Material	Type
1	Naphazoline HCL	Eye drops	0.16 fl.oz. (5 ml) Vinyl bottle	Dropper bottle	15	Plastic	NCRCT
2	Naphazoline HCL	Eye drops	0.5 fl.oz. (15 ml) Vinyl bottle	Dropper bottle	15	Plastic	NCRCT
3	Naphazoline HCL	Eye drops	1.0 fl.oz. (30 ml) Vinyl bottle	Dropper bottle	15	Plastic	NCRCT
4	Naphazoline HCL (combination)	Eye drops	0.5 fl.oz. (15 ml) Vinyl bottle	Dropper bottle	13	Plastic	NCRCT
5	Naphazoline HCL (combination)	Eye drops	0.5 fl.oz. (15 ml) HDPE bottle	Dropper bottle	15	Plastic	NCRCT
6	Naphazoline HCL (combination)	Eye drops	0.5 fl.oz. (15 ml) HDPE bottle	Dropper bottle	15	Plastic	NCRCT
7	Naphazoline HCL (combination)	Eye drops	0.5 fl.oz. (15 ml) HDPE bottle	Dropper bottle	15	Plastic	NCRCT
8	Tetrahydrozoline HCL	Eye drops	0.4 fl.oz. (13 ml) HDPE bottle	Dropper bottle	10	Plastic	NCR Snap
9	Tetrahydrozoline HCL	Eye drops	0.5 fl.oz. (15 ml) Vinyl bottle	Dropper bottle	13	Plastic	NCRCT
10	Tetrahydrozoline HCL	Eye drops	0.5 fl.oz. (15 ml) Vinyl bottle	Dropper bottle	15	Plastic	NCRCT
11	Oxymetazoline HCL	Nasal spray	0.5 fl.oz. (15 ml) HDPE bottle	Metered pump	18	Plastic	NCRCT*
12	Xylometazoline	Nasal drops	0.8 fl.oz. (25 ml) HDPE bottle	Dropper bottle	20	Plastic	NCRCT

*Attachment of the pump mechanism

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B. Nasal Spray

Specimen 11 was packaged in a 0.5 fluid ounce (15 ml) plastic bottle made of opaque HDPE. The bottle was finished with continuous threads onto which a metered pump dispenser was attached with an 18 mm NCRCT fitment. The pump mechanism was not child-resistant. A translucent PVC dust cover was included that slid over the tip of the metered pump.

C. Nasal Drops

Specimen 12 was packaged in a 0.8 fluid ounce (25 ml), opaque HDPE plastic, squeeze-dropper bottle. The bottle was finished with continuous threads, and the bottle opening was fitted with a translucent PVC plastic dropper plug with a 12mm-long nozzle. The bottle's closure was a 20mm NCRCT plastic cap.

II. TECHNICAL FEASABILITY

A. NCRCT Design Packages with a Dropper Dispenser

Specimens 1, 2, 3, 5, 6, 7, and 10 were packaged in plastic dropper bottles using a 15mm NCRCT closure; specimens 4 and 9 used a 13 mm NCRCT closure; and specimen 12 had a 20 mm NCRCT closure. Specimen 8 had the smallest closure reviewed for this work, a 10 mm snap-fit cap. Staff is not aware of 10 mm, 13 mm, 15 mm, or 20 mm ASTM[31] Type IA[32] CR closures available for a dropper dispenser. However, several alternatives exist for the packaging of these products. Staff is aware of three manufactures of ASTM Type IA child-resistant closures that integrate a bulb dropper into the closure.[33,34,35] This would differ from the existing package in that the dispenser would separate from the bottle (*i.e.*, integrated into the closure rather than into the bottle itself). The three ASTM Type IA closures will mate to a bottle with a 20 mm neck finish. Plastic or glass 1.0 fluid ounce bottles with a 20 mm neck finish are readily available. Smaller sized bottles with a 20 mm neck may have to be manufactured.

If an integrated bottle and dropper is desired, staff is aware of a bottle with a dropper dispenser that uses an ASTM Type ID[36] CR closure. The stock form of this package uses an oval,[37] 1.25 fluid ounce HDPE

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[31] ASTM, Standard Classification of Child-Resistant Packages, D-3475; ASTM, 100 Barr Harbor Drive, West Conshohocken, PA 19428–2959.
[32] An ASTM Type IA closure is a special CT closure that to open requires the user to push down on the closure while simultaneously rotating the closure in a counter-clockwise direction.
[33] Laboratory Report, Form 221, ASTM Type IA, 20mm closure, 99-590-0904, # 3705, CPSC, EHHS, June 7, 1999.
[34] Laboratory Report, Form 221, ASTM Type IA, 20mm closure, 99-820-6413, # 3750, CPSC, EHHS, August 30, 1999.
[35] Sample 10-810-5990, currently being evaluated by Laboratory Staff for a CPSC From 221 Laboratory Report.
[36] An ASTM Type ID closure is a special CT closure that to open, requires the user to lightly press a tab on a locking ring located below the closure while simultaneously rotating the closure in the counter-clockwise direction.
[37] The shape of the base of the container.

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bottle with an 18mm CRCT closure.[38] A dropper dispensing plug with a 9 mm-long nozzle has been fitted into the neck of the bottle. This ASTM Type ID package has been modified at a reasonable cost to a variety of other shapes and sizes. One manufacturer had the neck of a round, 4.0 fluid ounce HDPE bottle modified in order to accept this closure, while another manufacturer had the neck and shoulder of an oval, 4.0 fluid ounce PVC bottle modified to accept this closure.

The manufacturer of the above-mentioned closure has also manufactured a 13 mm, ASTM Type ID closure[39] that incorporates the same CR feature. This closure was mated to an aluminized plastic tube; however, the closure could be modified to fit a bottle. The smaller size of this closure would allow it to be used with smaller package sizes when the larger 20 mm closure may not be practical or aesthetically pleasing.

B. NCRCT Design Packages with a Metered Pump Dispenser

Specimen 11 was packaged in a 0.5 fluid ounce (15 ml) HDPE plastic bottle with a NCR metered pump dispenser attached to the bottle using a 20 mm NCRCT fitment. Staff is not aware of any CR metered pump nasal sprayers on the market; however, a metered pump dispenser for nasal spray has been designed but never produced[40]. The designer of this system anticipates that the CR metered pump sprayer would be mated to 1.5 and 2.0 fluid ounce bottles. However, they stated that the CR metered pump sprayer could be easily mated to a 0.5 or 1.0 fluid ounce bottle.

Staff concludes that the available data supports the finding that it is technically feasible to replace NCR packages with existing CR packages or to produce newly designed CR packaging for household products containing imidazoline.

III. PRACTICABILITY

A. NCRCT Design Packages with a Dropper Dispenser

For product manufacturers who choose to use commercially available ASTM Type IA products with a bulb dropper incorporated into the closure, new bottles with a different diameter opening would be required. The change in diameter size may also change the current assembly and filling line techniques.

For those product manufacturers who choose not to change the style of their package and wish to retain a dropper bottle that has the dropper nozzle dispenser, the current NCRCT packages would have to be replaced with redesigned CRCT packages. If those manufacturers wish to use the ASTM Type ID package that is available, the neck finishes of the bottle in current use would have to be modified to accommodate the new closure. The current assembly line techniques may also have to be modified because the outside diameter of a CR package is larger than the current NCRCT package. Changes to the

[38] Laboratory Report, Form 221, ASTM Type IA, 18mm closure, 05-450-7600, # 4108, CPSC, HS, April 28, 2005.
[39] Laboratory Report, Form 221, ASTM Type IA, 18mm closure, 05-450-7601, # 4109, CPSC, HS, April 28, 2005.
[40] Rea, G. K., Personal communication with a spray dispenser packaging manufacturer, August 8, 2011.

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filling line equipment may be necessary. However, if changes to the filling line are required, those changes are expected to be minimal.

B. NCRCT Design Packages with a Metered Pump Dispenser

Because there are currently no examples of CR-metered pump nasal sprayers on the market, it is difficult to ascertain the impact a change from an NCR metered-pump nasal sprayer to a CR-metered pump nasal sprayer would have. From the prototype design sketches available of the new product, the impact could be major or minor, depending on the final version that is produced. One of the proposed designs had the unit filled from the top, and it appeared to be similar in design and shape to the current NCR-metered pump sprayer. If this design was adopted, then minimal changes to the existing assembly and filling lines would have been required.

IV. APPROPRIATENESS

A. NCRCT Design Packages with a Dropper Dispenser

The current imidazoline products are packaged using either PVC or HDPE. Both of these materials, as well as glass bottles, are available for use with a CR bulb-type dropper closure. Because these materials currently are in use, or have been used in prior examples of imidazoline-containing products, no detrimental effects to the integrity or storage of the product are expected. The ASTM Type ID package is manufactured using HDPE and PVC plastics. Staff concludes that CR design packages would not interfere with the intended storage or use of household products containing imidazoline.

B. NCRCT Design Packages with a Metered Pump Dispenser

The current NCR package is manufactured using HDPE. The CR-metered pump dispenser was also anticipated to be manufactured in HDPE plastic. Since this plastic currently is in use and has been used in prior examples of imidazoline-containing products, no detrimental effects to the integrity or storage of the product are expected. Staff concludes that CR design packages would not interfere with the intended storage or use of household products containing imidazoline.

V. EFFECTIVE DATE

Section 8 of the PPPA specifies that the effective date shall not be sooner than 180 days or later than 1 year from the date such regulation is final, unless the Commission finds, for good cause, that an earlier date is in the public interest.

A. NCRCT Design Packages with a Dropper Dispenser

Product manufacturers who choose to use commercially available ASTM Type IA products with a bulb dropper incorporated into the closure would have to locate new suppliers, and modify the assembly and filling line machines. These changes could take anywhere from 6 months to 1 year to complete. Therefore, an effective date of 1 year is recommended.

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Manufacturers wishing to use the ASTM Type ID package would need to design changes to the current package, build new tooling, and modify the existing assembly line and filling machines to accommodate the new package. Alternately, manufacturers may choose to design a new package. This would also require new tooling and modifications to the assembly and filling lines. The changes could take up to a year to complete. Therefore, an effective date of 1 year is recommended.

B. NCRCT Design Packages with a Metered Pump Dispenser

Manufacturers who use the CR-metered pump dispenser may need to make changes to existing assembly lines. Changes to the filling line equipment would not be required. These changes could require 6 months to 1 year to complete. Therefore, an effective date of 1 year is recommended.

VI. CONCLUSION

Staff concludes that available data support the findings that CR packaging for household products containing imidazolines is technically feasible, practicable, and appropriate. With package size and/or ASTM package type changes, ASTM Type IA, ASTM Type ID, and a CR-metered pump sprayer design are available to the market to replace the NCRCT- and NCR-metered spray pump packages. Product packaging assembly line techniques used for the NCR packages can be adapted for some of the CR packages already in the marketplace. Other product manufacturers use many packages that could require changes in assembly and filling line techniques. New package sizes may also need to be designed. These new packages would require new tools to be produced. It could take up to 1 year from initiating tool design to final production of a new package, depending on the complexity of the package. Because of the potential changes, an effective date of 1 year is recommended.

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Appendix A: Images of Packages for Products Containing Imidazolines

Figure 1. NCRCT Dropper Bottle, 0.16 fl. oz. (5 ml) Vinyl bottle

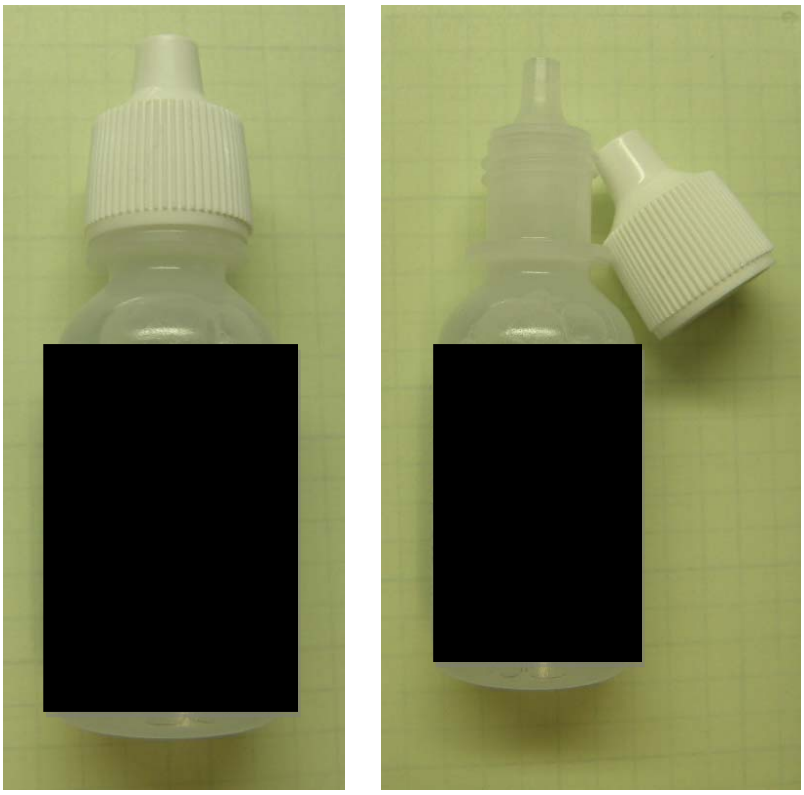

Figure 2. NCRCT Dropper Bottle, 0.5 fl. oz. (15 ml) Vinyl bottle

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Figure 3. NCRCT Dropper Bottle, 1.0 fl. oz. (30 ml) Vinyl bottle

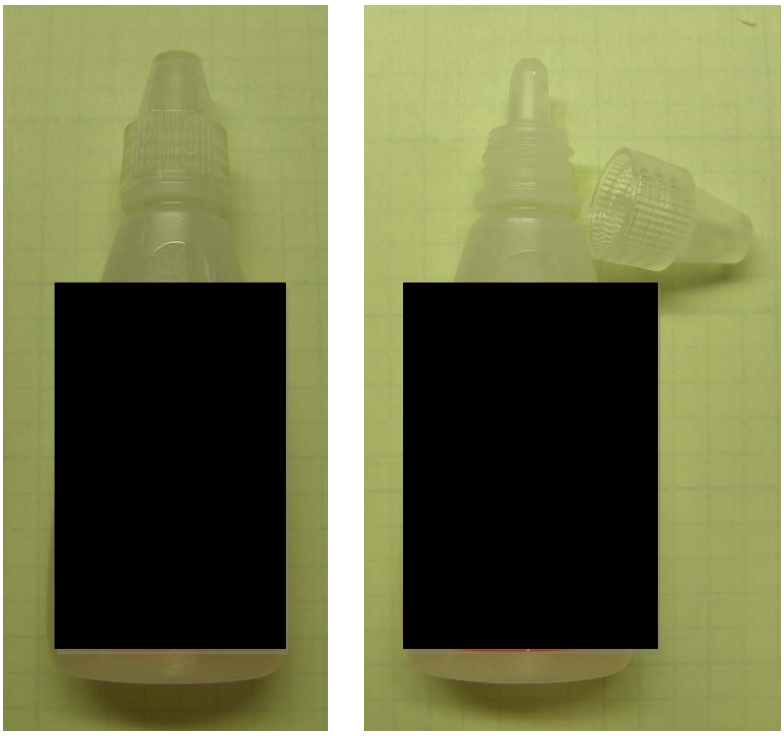

Figure 4. NCRCT Dropper Bottle, 0.5 fl. oz. (15 ml) Vinyl bottle

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Figure 5. NCRCT Dropper Bottle, 0.5 fl. oz. (15 ml) HDPE bottle

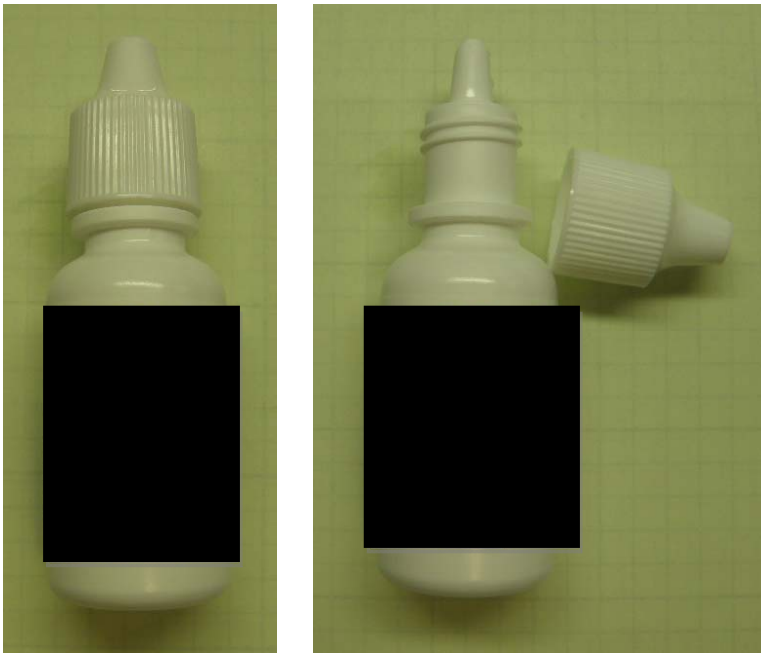

Figure 6. NCRCT Dropper Bottle, 0.5 fl. oz. (15 ml) HDPE bottle

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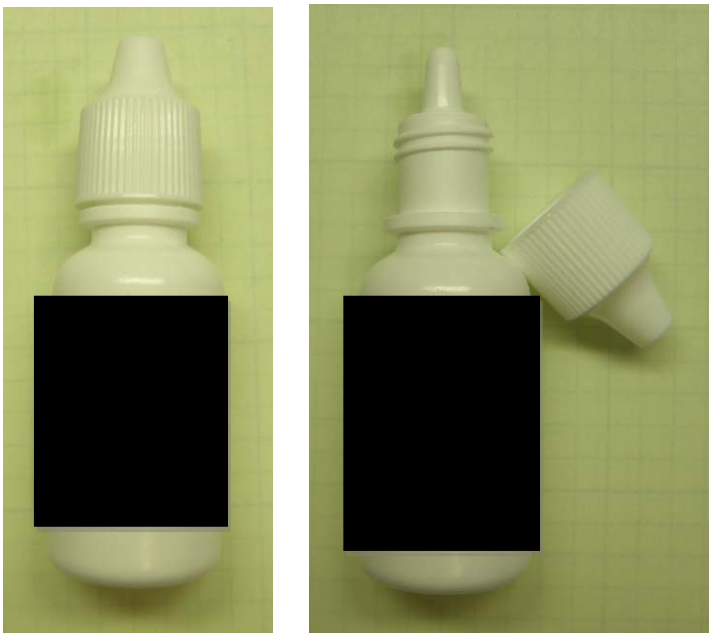

Figure 7. NCRCT Dropper Bottle, 0.5 fl. oz. (15 ml) HDPE bottle

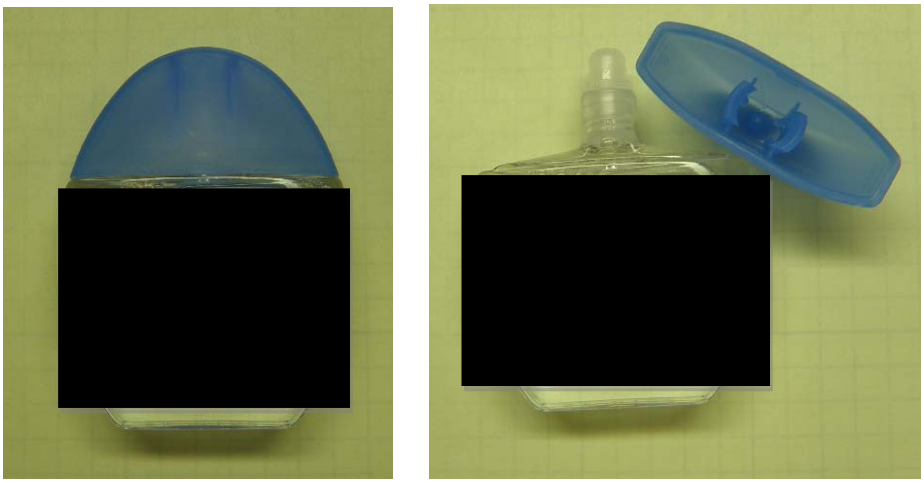

Figure 8. NCR Snap Dropper Bottle, 0.4 fl. oz. (13 ml) HDPE bottle

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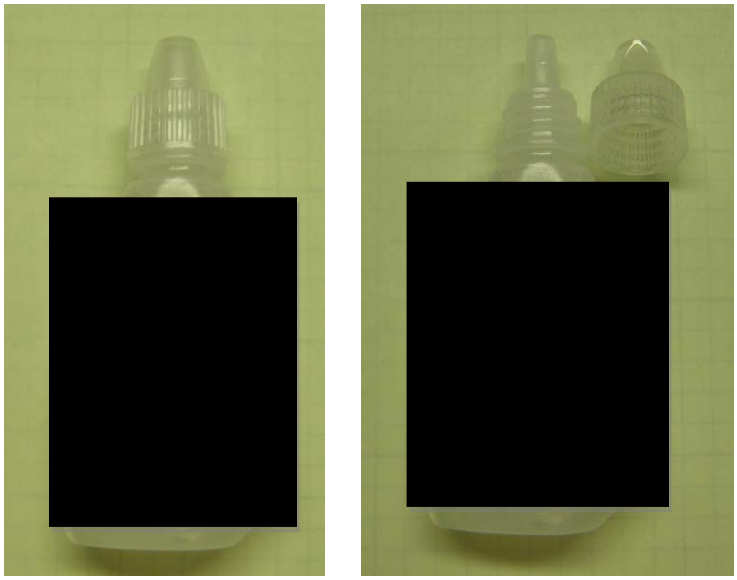

Figure 9. NCRCT Dropper Bottle, 0.5 fl. oz. (15 ml) Vinyl bottle

Figure 10. NCRCT Dropper Bottle, 0.5 fl. oz. (15 ml) Vinyl bottle

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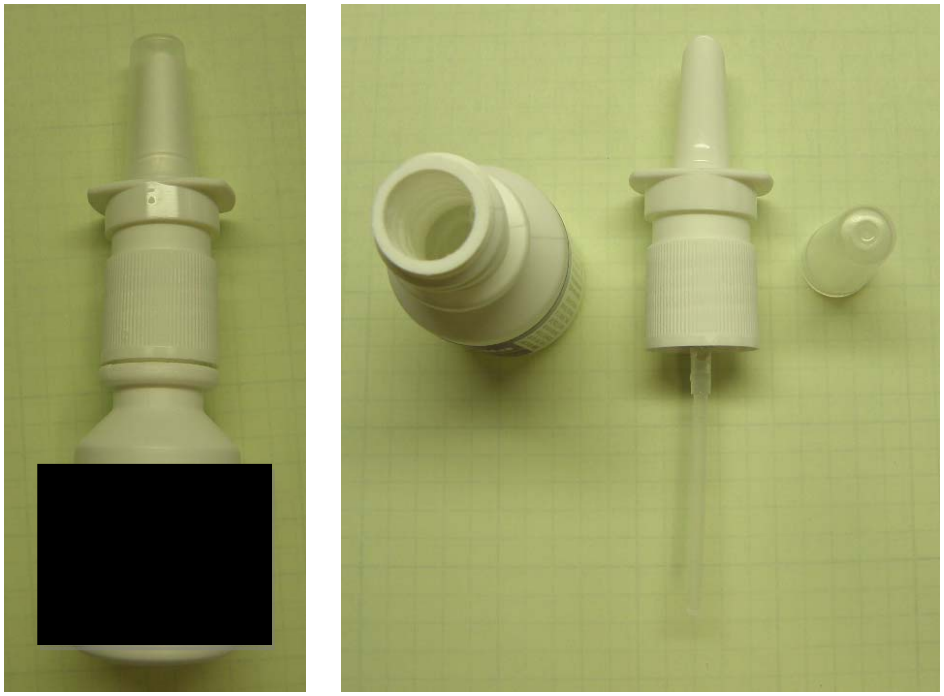

Figure 11. NCRCT Metered Pump, 0.5 fl. oz. (15 ml) HDPE bottle

Figure 12. NCRCT Dropper Bottle, 0.8 fl. oz. (25 ml) HDPE bottle

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TAB D: Economic Analysis

TAB D

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UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
BETHESDA, MD 20814

Memorandum

Date: January 11, 2011

TO : Cheryl A. Osterhout, Ph.D., Pharmacologist, Directorate for Health Sciences

FROM: Gregory B. Rodgers, Ph.D., Associate Executive Director, Directorate for Economic Analysis
Deborah V. Aiken, Ph.D., Senior Staff Coordinator, Directorate for Economic Analysis
John W. Peternel, Directorate for Economic Analysis

SUBJECT: Preliminary Economic Analysis: Eye drops and Nasal Sprays Containing Imidazoline

This memo provides information on the economic effects of requiring child-resistant packaging for imidazoline-containing products under the authority provided by the Poison Prevention Packaging Act. It contains:

1) a description of the market for imidazolines;
2) a description of the societal costs associated with unintentional pediatric exposure to imidazolines;
3) data on the cost to industry and consumers of requiring child-resistant (CR) packaging; and
4) information concerning small business and environmental considerations.

I. Market and Exposure Information

A. Type of Products

Imidazolines are a group of chemically related products that are vasoconstrictors. When applied topically to the eye, imidazolines constrict the small blood vessels in the eye, which reduces redness due to minor irritants, such as smoke, dust, or chlorine in swimming pools. When applied in the nasal passageway, imidazolines constrict the mucosal blood vessels, which decreases congestion in the nasal tissue. Imidazolines include the following chemicals: tetrahydrozoline, oxymetazoline, xylometazoline, and naphazoline. Imidazoline-based eye drops and nasal sprays are sold over-the-counter (OTC) and by prescription. This analysis is based solely on the OTC market since data on prescription sales is unavailable. The lack of information on prescription market has little impact on the analysis since the majority of sales are OTC.

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1. Ophthalmic Products (Eye drops)

Eye drops containing imidazolines are widely available at drug, grocery, and mass market retailers. Imidazoline eye drops generally come in small squeeze bottles. Based upon observations of shelf space devoted to these products at local retailers, the most common size is the 1/2-ounce (15 milliliters) bottle. The second most common size appears to be a 1-ounce bottle (30 milliliters). One-quarter ounce (8 milliliters) bottles are also available. Retail prices for the OTC drugs can range from as low as $3, to more than $9 per bottle, depending on the size of the bottle, the specific imidazoline used, the brand, and the retailer; however, most prices tend to be clustered toward the lower end of this range.

The number of doses per bottle varies by bottle size and instructions. For example, the label on a 1/2-ounce bottle of tetrahydrozoline eye drops instructs the consumer to use one to two drops per eye, up to four times a day. It also instructs the user to stop using the product and consult a doctor if the condition persists for more than 72 hours. Provided this bottle is used until exhausted, the 1/2-ounce bottle contains about 300 drops, or 75 to 150 doses.

2. Nasal Sprays

Nasal sprays containing imidazolines are widely available at drug, grocery, and mass market retailers. Some packages are used by rapidly squeezing the bottle to spray the product into a nostril. Other packages have a pump mechanism that activates the spray. As with eye drops, 1/2-ounce containers are the most common container size, and 1-ounce bottles are the second most common size. Other sizes are available, including 1.25-ounce sizes and 2-ounce sizes. Retail prices for the OTC drugs can range from about $4 to $9 a bottle, depending on the size of the bottle, the specific imidazoline used, the brand, and the retailer; however, based on a review of sales data, prices tend to average around $6 a bottle (Chain Drug Review, 2010a).

The number of doses per bottle varies by bottle size and use instructions. For example, the label on one national brand of nasal spray (oxymetazoline) instructed the user to use 2 or 3 sprays in each nostril every 10 to 12 hours without exceeding two doses in any 24-hour period. It also warned not to use the product for more than three days. A 1/2-ounce metered pump bottle contains enough product for 150 sprays or 25 to 38 doses.

B. Market Information

Imidazoline-based topical decongestants are sold under several brand names and are also available under generic labels. Table 1 (next page) provides industry data, including the number of manufacturers, annual dollar value of retail sales, and unit sales.

Based on an industry review, there are approximately 45 manufacturers that sell topical decongestant products under about 64 different labels (Facts and Comparison, 2007). Because some manufacturers produce both nasal and ophthalmic products, the number of manufacturers

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within the market for topical decongestants is not the sum of the manufacturers of ophthalmic products plus the manufacturers of nasal products.

For the 52-week period ending November 28, 2010, "Eye/Contact Lens Care Product" sales are estimated at $1,037.5 million (Chain Drug Review, 2010b). This sales estimate, however, excludes sales at Wal-Mart Stores, Inc., which are estimated to account for between 20 to 30 percent of total sales (Chain Drug Review, 2003). Augmenting annual sales to account for sales at Wal-Mart increases the annual sales estimate to about $1,383.3 million ($1,037.5 ÷ 0.75). Because approximately 13 percent of "Eye/Lens Care" product sales are attributed to decongestants (OTC Update, 1997), annual sales for ophthalmic decongestants may be estimated at about $180 million ($1.383 billion • 0.13). Therefore, based on an average price of $4, annual sales are estimated at about 45 million units ($180 million ÷ $4).[41]

SymphonyIRI Group estimates annual sales for "Nasal Spray/Drops/Inhalers" at $500.6 million for the 52-week period ending December 27, 2009 (Chain Drug Review, 2010a). This sales estimate, however, excludes sales at Wal-Mart, which are estimated to account for between 20 to 30 percent of total sales (Chain Drug Review, 2003). Augmenting annual sales to account for sales at Wal-Mart increases the sales estimate to about $667 million. Based on a review of top selling products, out of all nasal products sold, approximately 35 percent contain imidazoline (Chain Drug Review, 2010a). Therefore, approximately $233 million ($667 million • 0.35) are attributed to sale of nasal decongestants that contain imidazoline. Assuming an average unit price of $6, annual sales would be about 38.8 million units ($233 million ÷ $6).

Table 1: Ophthalmic and Nasal Products Containing Imidazoline

	Number of Manufacturers	**Annual Retail Sales (millions)**	**Annual Unit Sales (million)**
Ophthalmic *Products*	17	$180	45.0
Nasal Products	37	$ 233	38.8
Total		$ 413	83.8

II. Societal Cost of Pediatric Exposures of Imidazolines

Exposure to imidazolines may cause serious, potentially life-threatening health effects, including central nervous system depression, respiratory depression, and cardiovascular instability (Osterhout, 2011). Although CPSC staff is not aware of any deaths resulting from accidental pediatric exposures, some patients have required medical treatment in intensive care settings (Osterhout, 2011). In children, these effects have been reported after the child has ingested as little as 1.5 milliliters (three-tenths of a teaspoon) of an imidazoline product (Katar,

[41] As noted above, these figures apply only to products sold OTC as prescription sales have been excluded due to lack of information.

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2010), or about one-tenth of the contents of the most common size package (15 milliliters or one-half ounce).

This analysis uses CPSC's Injury Cost Model (ICM) to estimate the societal costs of medically attended injuries associated with imidazolines. The ICM is integrated with the National Electronic Injury Surveillance System (NEISS), a national probability sample of U.S. hospital emergency departments (EDs) that provides estimates of product-related injuries treated in hospital EDs. The ICM estimates the cost of injuries initially treated in EDs. Based on the empirical relationship between the number of medically-attended injuries treated in EDs and the number treated in other settings, the ICM also produces estimates of the number and societal costs of medically attended injuries treated outside of EDs, such as at doctors' offices or clinics. The cost estimates include all costs to society associated with the injuries, including the costs of medical treatment and work loss, as well as the intangible costs of injuries, sometimes referred to as pain and suffering (Miller et al., 2000; Zamula 2007). These cost estimates are based on the injury diagnoses (*e.g.*, poisoning), affected body part(s), age, and gender of the victims.

Table 2 provides *annual* estimates of injuries and the associated societal costs for imidazoline exposures by children under age five years based on estimates from the 13-year period from 1997 through 2009. According to NEISS estimates, there were an estimated 5,675 emergency department treated imidazoline ingestions involving children under age five years from 1997 through 2009; about 80 percent involved eye drops and about 20 percent involved nasal sprays (O'Brien, 2011). As shown in Table 2, NEISS estimates from this 13-year period suggest an estimated annual average of about 351 injuries involving eye drops (with 325 treated and released and 26 admitted to the hospital) and an estimated annual average of about 85 injuries involving nasal sprays (with 78 treated and released and 7 admitted to the hospital). Additionally, based on estimates from the ICM, there were another 496 eye drop and 119 nasal spray incidents medically treated annually outside of hospital EDs.

Table 2: Estimated Average Annual Medically-Attended Injuries and Societal Costs of Imidazoline Exposure to Children under Age Five , 1997 to 2009

		Eye drops		Nasal Sprays	
		Number	Societal Cost (millions)	Number	Societal Cost (millions)
1	Treated and Released from Hospital Emergency Department (NEISS)	325	$ 5.5	78	$ 1.3
2	Admitted to Hospital Through the Emergency Department(NEISS)	26	$ 1.9	7	$ 0.5
3	Medically Treated Outside of Hospital Emergency Department (ICM)	496	$ 5.9	119	$ 1.5
4	Total Medically-Attended Injuries	848	$ 13.3	204	$ 3.3

Note: The average annual estimates presented in this table are based on NEISS and ICM estimates from the 1997–2009 time period. Sums may not add to totals due to rounding.

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In total, there were an estimated 848 eye drop and 204 nasal spray injuries that were medically treated annually during the 1997–2009 time period. These incidents resulted in annual societal costs of about $16.6 million, including $13.3 million for eye drops and $3.3 million for nasal sprays. Medical costs and work losses accounted for about 23 percent of these injury cost estimates; the intangible costs of injury associated with pain and suffering accounted for about 77 percent of the injury costs (Miller et al., 2000). On a per-unit basis, the societal cost of eye drop injuries was about 29.6 cents per container ($13.3 million ÷ 45.0 million), and the societal cost of nasal spray injuries was about 8.5 cents per container ($3.3 million ÷ 38.8 million).

III. Effectiveness of Child-Resistant Packaging

The purpose of child-resistant (CR) packaging is to prevent children from opening packages and ingesting toxic products. CR packaging is expected to reduce pediatric ingestions of imidazoline eye drops and nasal sprays, but it will not prevent all of them: some children under age 5 years are able to open CR packages,[42] some consumers may not properly close CR packaging after use (Jacobson et al, 1989), and the PPPA allows manufacturers to supply some products covered by CR packaging requirements in non-CR packages (provided that the noncomplying package is offered in only one size and complying packages are also supplied in popular sizes).

Studies evaluating the effectiveness of CR packaging in preventing child poisonings suggest that CR packaging may reduce poisoning incidents by about 40 percent (Walton, 1982; Rodgers, 1996, 2002). Assuming CR packaging reduces imidazoline poisonings by 40 percent, CR packaging would prevent an estimated 421 medically attended injuries annually (including an estimated 339 eye drop and 82 nasal spray injuries) and reduce the societal costs associated with the incidents by an estimated $5.3 million ($13.3 million • 0.4) for nasal spray and $1.3 million ($3.3 million • 0.4) for eye drops. On a per-product basis, the expected reduction in societal costs is about 11.8 cents per container for eye drops ($5.3 million ÷ 45.0 million) and 3.4 cents per container for nasal sprays ($1.3 million ÷ 38.8 million).

IV. Cost of CR Packaging

The costs of CR packaging may be separated into two categories: the additional cost to manufacture the products with CR closures and the additional time and effort needed by consumers to use the packaging.

A. Manufacturing Costs

The manufacturing cost includes the cost of designing the CR closures (including any changes required to the package), making the molds and other equipment required for manufacturing the closures, any additional material costs, the cost of redesigning the production lines to accommodate the redesigned packages, and the cost of any additional time or steps

[42] To be considered CR, a package needs to prevent 80 percent of the children from opening it during the qualifying tests.

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required in the manufacturing process. Some of these costs can exceed several hundred thousand dollars, but when spread over millions of units, the costs may be low on a per-unit basis. Based on cost data that CPSC staff has collected over the years, the manufacturing costs typically range from about 0.5 cent to 4.6 cents per unit. However, the incremental costs for any particular closure will depend on factors such as the specific changes required in the packaging and production volume. For example, if an existing CR closure can be easily adapted to the product, the costs would probably be low. However, if a manufacturer must make more extensive changes to its package to accommodate a CR closure, and if the production volume for the product is low, the incremental costs for that manufacturer could be higher. Overall, on a per-unit basis, the expected cost to manufactures of requiring CR packaging for eye drops and nasal sprays is toward the lower end of the range presented, or about 1.5 cents per unit sold (Franklin, 2006).

B. Consumer Costs

The primary cost of CR packaging for consumers is the added time and increased difficulty associated with the use of CR closures, as compared to conventional closures. This added time and difficulty will likely vary among consumers and packages. For example, elderly or arthritic consumers may have greater difficulty opening CR packaging than younger and healthier consumers. Additionally, some types of CR closures may be easier to use than others. The time and possible difficulty associated with CR packaging is explicitly recognized in the PPPA, which allows consumers to request pharmacists to provide their prescription drugs in non-CR packaging. Additionally, in order to accommodate consumers who may have difficulty opening CR packaging, manufacturers are also allowed to supply regulated products in one size package that is not CR, provided that the size offered is not the most popular size.

While data on the additional time required for opening and resecuring CR packaging is limited, the additional time would apply each time the package is used.[43] The number of times a nasal spray or eyedrop product is used can vary, depending upon the size of the bottle and consumer usage patterns. As noted previously, ½-ounce bottles represent the most common sizes for eye drops and nasal sprays. A ½-ounce bottle of eye drops contains about 300 drops, which is enough for 75 to 150 doses, at one to two drops per eye. A ½-ounce bottle of nasal spray contains about 150 sprays, which is enough for 25 to 38 doses, at 2 to 3 sprays per nostril.

For purposes of this discussion, we assume that containers of eye drop products are opened and closed an average of 75 times over its product life.[44] This estimate is roughly

[43] Among other studies, a February 2004 article in ASTM Standardization news reported that older adults, ages 60 to 75 years, who were tested across a variety of CR packaging types, took an average of about 11.7 seconds to open a CR package on the first exposure. A CPSC staff pilot study (O'Brien 2007, Osterhout 2008) found that the difference between the mean time to use a CR package and the mean time to use a non-CR package was small, but statistically significant. The pilot study (which was based on a sample of non-elderly CPSC employees) estimated that the extra time required by subjects to open and close a continuous thread, non-CR closure, versus a comparable push-and-turn CR closure, was 0.59 seconds (95 percent confidence interval, 0.27 to 0.90 seconds). Additionally, studies by Keram and Williams (1988) and Kou (2006) evaluated a number of commonly used CR and non-CR packages with older consumers and found greater mean opening times for the CR packaging.

[44] We are implicitly assuming that each container will be used within one year, and hence, that all benefits occur within the one year timeframe. This assumption would result in a slight overstatement of benefits if the products remained in use for more than one year, because benefits accruing beyond the first year would need to be discounted.

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equivalent to assuming that a consumer who purchases a ½-ounce bottle of eye drops uses an average of two drops in each eye, and that a consumer who uses less than two drops per eye or purchases the larger size container "wastes" a substantial portion of the contents (*e.g.*, by losing or disposing of a partially used bottle). Similarly, containers of nasal spray products might be opened and closed an average of about 25 times each. This is roughly equivalent to consumers using an average of three sprays per nostril and assumes that consumers who use fewer sprays or use larger than 1/2-ounce containers waste a portion of the contents.

Table 3 presents information on the added time and costs that might be associated with the use of CR packaging for eye drops and nasal sprays. Because the added time is not known with certainty, the table provides various alternative estimates, under the assumption that, relative to conventional non-CR packaging, CR packaging adds, on average, anywhere from zero to two seconds per use. For example, if eye drop containers are used 75 times, and the CR packaging adds a second to the opening and closing process, then the added time would be about 75 seconds per package. Similarly, if nasal spray containers are used 25 times, and the CR packaging adds a second, the added time would be about 25 seconds per container.

Table 3 also attempts to monetize the costs associated with the added time. Based on several published studies, Zamula (2011) found that $12 per hour (in 2008 dollars) may be a reasonable estimate of the value of a consumer's time when a safety-related change in a product requires additional time to perform a given task. If, for example, the additional time amounts to one second per use, and 90 percent of eye drops and nasal spray containers are CR, the value of the additional time per container would be about 22.5 cents for eye drops [(75 seconds ÷ 3600 seconds per hour) • $12 per hour • 0.90] and about 7.5 cents for nasal sprays [(25 seconds ÷ 3600 seconds per hour) • $12 per hour • 0.90]. Of course, if the added time is less than one second, or the value of a consumer's time is less than $12 per hour, then the CR packaging time costs would be less. Alternatively, if the added time is more than one second, or the value of a consumer's time is more than $12 per hour, then the CR packaging time costs would be more.

Table 3: Potential Time Costs of Using CR Packaging, per Container*

	Eye drops*		Nasal Sprays*	
	Added Time per Container (seconds)	Time Costs‡ (cents)	Added Time per Container (seconds)	Time Costs‡ (cents)
Added Time per Use:				
0 seconds	0.0	0.0 ¢	0.0	0.0 ¢
0.5 seconds	37.5	11.3 ¢	12.5	3.8 ¢
1.0 seconds	75.0	22.5 ¢	25.0	7.5 ¢
1.5 seconds	112.5	33.8 ¢	37.5	11.3 ¢
2.0 seconds	150.0	45.0 ¢	50.0	15.0 ¢

*Assumes that a container of eye drops is opened and closed 75 times and that a container of nasal sprays is opened and closed 25 times.
‡ Time has been valued at $12 per hour.

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V. Discussion

The ingestion of imidazoline-containing eye drops and nasal sprays can cause serious health effects in children. While CPSC staff is not aware of any deaths that have resulted from accidental pediatric exposures of imidazoline eye drops and nasal sprays, several hundred children are taken to hospital emergency departments each year because it is suspected that they have ingested imidazoline products. In most cases, the symptoms fully resolve within 36 hours, with no significant lasting effects (Osterhout, 2011).

Using the CPSC's Injury Cost Model and annual sales estimates, the societal cost of pediatric exposures to imidazoline is about 29.6 cents per container for eye drops and 8.5 cents per container for nasal sprays. Based on studies of the effectiveness of CR packaging at reducing poisonings, CR packaging for imidazoline products may reduce these societal costs by about 11.8 cents per container for eye drops and 3.4 cents per container for nasal sprays. These reduced societal costs represent the expected benefits of a rule requiring the use of CR closures with imidazoline-containing eye drops and nasal sprays.

In comparison to these benefits, the costs of CR packaging include both the added costs associated with manufacturing CR packages and the added time and inconvenience associated with the use of CR packaging. The added manufacturing costs may amount to under 2 cents per container. Additionally, the added time costs, per container, could range from 0 cents, if it were assumed that CR packaging resulted in no added time or inconvenience, to about 45 cents per eye drop container and about 15 cents per nasal spray container, if it were assumed that the use of CR containers added an average of two seconds per use.

VI. Small Business Effects

Nasal and ophthalmic products are classified within the NAICS 325412 *Pharmaceutical Preparation Manufacturing* industry. According to the U.S. Small Business Administration's Office of Advocacy, a firm classified within NAICS 325412 is considered a small business if the firm has fewer than 750 employees. Based on such classification, out of the approximately 45 firms that manufacture imidazoline-based eye drops and nasal sprays, approximately 20 firms are defined as "small businesses." There may be more manufacturers, in particular firms that manufacture under generic labels, that were not identified but that may be small businesses.

There are several reasons to believe that a rule would not have a significant impact on a substantial number of small businesses. First, as noted above, the incremental costs of CR packaging for manufacturers are low, estimated at 1.5 cents per unit for imidazolines products. Manufacturers are likely to be able to pass on at least some of these costs to consumers. Second, most manufacturers of over-the-counter drug products have diverse product lines that include other products that would not be covered by this possible regulation. Therefore, the products that would be affected by aproposed regulation may represent a small proportion of any one manufacturer's production. Finally, the requirements would apply only to products packaged after the effective date of the requirements. Therefore, businesses would have time to use up existing inventories of product and packaging.

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VII. Environmental Impact

Requirements for CR packaging are not expected to have an adverse impact on the environment. CR packaging has virtually the same impact on the environment as non-CR packaging and is considered to be a "categorical exclusion" for the purposes of the National Environmental Policy Act (16 CFR § 1021.5(c) (3)).

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