



Billing Code 6355-01-P

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

CPSC Docket No. CPSC-2012-0005

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”).¹

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

¹ The Commission voted 4-0 to publish this notice in the **Federal Register**. Commissioner Robert S. Adler issued a statement, which can be found at <http://www.cpsc.gov/pr/statements.html>.

ADDRESSES: You may submit comments, identified by Docket No. CPSC–2012–0005, 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>.

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

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

Tab A of the CPSC staff's briefing package, available at <http://www.cpsc.gov/library/foia/foia12/brief/imidazolines.pdf> 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

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

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

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

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 ²	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

² 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.

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,

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.

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

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-

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, Bucaretschi 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

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?

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.

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?

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

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

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.

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).

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 <http://www.epsc.gov/library/foia/foia12/brief/imidazolines.pdf>.

List of Subjects in 16 CFR Part 1700

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

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: January 20, 2012

Todd A. Stevenson,
Secretary, Consumer Product Safety Commission