SECTION C

Literature Citations:
Occupant, Fire, and Environmental Characteristics

Occupant Characteristics

- **PANIC:** It is well documented in the fire literature that in a fire situation people do not panic or exhibit irrational behavior. Rather, they "appear to apply rational decision-making in relation to their understanding of the situation at the time of the fire" (17).

- **INTERACTION WITH FIRE GROWTH:** "Change in ventilation conditions from occupant action during a fire contributes to fatalities among occupants located away from the source of fire, as it may affect fire growth and/or induce sudden change in smoke conditions along egress paths" (1, p.123). The occupant(s) role in fire growth has to be considered, otherwise, the effectiveness of fire safety measures may be exaggerated.

- **PREVIOUS EXPERIENCE WITH FIRE:** "Previous experience of a fire or of a near fire often does not induce permanent behaviour change...The immediate rewards are stronger than any recognized negative consequences...for each episode where the damage is small and the fire self-extinguishes or is controlled, the person may learn that these incidents are not *dangerous*...they have the evidence from personal experience that the dire consequences that others warn them of simply do not happen" (1, p. 128).

- **SOCIAL AFFILIATION:** "The presence of other people will influence behavior and decision making. Response to alarms or fire cues is affected by whether people are alone or with others. The presence of other people can have an inhibiting effect on the definition and initiation of action from initial ambiguous cues. However, the presence of other people may increase the chances of a person being notified of an emergency and allow for group decisions of what actions to take. People who are alone tend to respond more rapidly to ambiguous cues" (9, p. 8).

- **GENDER and ROLE ASSIGNMENTS**: "In general, females are more likely to alert or warn others and evacuate in response to fire cues than males...in the residential environment...men were more likely to fight the fire while women were more likely to gather family members and call the fire department." Gender-specific behavior may be due, in some part, to role assignments, e.g. head of household, caretaker. For example, "In residential fires, the protective actions that have long been assigned to women may actually be shared more equally in households where parental responsibilities are shared" (9, p.10).

- **MOBILITY IMPAIRMENT:** "People with mobility impairments represent a segment of the population with one of the highest risks of dying in a fire...Typical home construction may present people with disabilities with unnecessary impediments to escape... Mobility impairments hinder attempts by the disabled not only to escape fires, but also to confine or extinguish small fires" (25, p.3).

  "People with mobility impairments living in private residences may receive little or no help in the event of a fire. Whether the disabled person is living alone or with friends and family members, a house fire can trap him or her inside a room. Often the door is the only exit, and escape through a window may not be possible" (25, p. 12).

- **HEARING IMPAIRMENT:** "The most pressing fire safety issue for people who are deaf or hard-of-hearing is whether they will be alerted to the danger in time to escape ...Other people may not be a reliable alerting mechanism in the event of a fire...A hearing family member or caregiver overcome by fumes may not be able to alert a sleeping deaf person in time for both to escape" (26, p.11).

- **DOMESTIC FIRE FIGHTING:** "Very few people are killed trying to fight fires...For fire victims who are injured, however, the activity profile is sharply different. The leading activity when injured is "fire control," that is, trying to put out or contain the fire. The best estimate is that over one-third of fire injuries are occurring from this problem alone. Injuries while trying to escape are second" (29, p.238).

  "Indications from a range of findings suggest that there is a certain threshold, definable in terms of size of fire, extent of smoke and overall containability, above which people would not be willing to tackle a domestic fire, but below which the majority would attempt to deal with the threat themselves. The types of fire most people would be willing to tackle include 'a small fire in a waste paper bin'...and 'a burn smoldering on an armchair'... while many respondents had clear strategies for dealing with such fires, some of these are particularly misguided and potentially dangerous" (32, p. viii).

  In a study of domestic firefighting in Britain, it was found that the "mean time spent putting out the fire was 2 ½ minutes. However there was a range of responses." Twenty-nine percent of the respondents stated "they spent less than 10 seconds putting the fire out." Forty-nine percent stated "they spent less than 1 minute" firefighting" (32, p.117).

  "Occupant fire fighting behavior appears most prevalent in occupancies in which the individuals are emotionally and economically involved –that is, in their homes or where such behavior is an assigned role as a result of training" (32, p. 7-13).

- **ALCOHOL:** "Intoxication ...acutely diminishes one's ability to detect a fire. Under the sedative effects of alcohol, an alcohol-impaired person may fail to notice the smell of smoke or fail to hear a smoke alarm. Escape from a fire can be hampered by the loss of motor coordination and mental clarity caused by alcohol, even when warning signs are heeded. Furthermore, burns are more physiologically damaging in the presence of alcohol" (31, p. 1). "When used together, alcohol and smoking increase one's chance of starting a fire while at the same time decrease the chances of detection, mitigating, and escaping the fire" (31, p.20).

  "Several researchers have found that about half of all adult fire fatalities were under the influence of alcohol at the time of the fire" (31, p.1). "Alcoholics have a disproportionately high rate of fire fatalities relative to their percentage of the total population" (31, p.1).

  One study found evidence to suggest "that alcohol not only impedes the detection of smoke, but also helps to facilitate its passage into the body" (31, p.13).

Fires involving occupants impaired by alcohol often affect children. One study found "that of the juvenile fatalities examined, approximately 15 percent died in fires where the surviving adult was impaired by alcohol or other drugs" (31, p. 16). Another study involving a review of case files of fire fatalities under 16 years and over 60 years found that "fire deaths of children were attributed to the parents failure to perceive and respond to a fire emergency because of impairment of their sensory, judgment, or physical functions by alcohol consumption" (31, p.17).

- **AGE:** "The very young and the very old have a much higher fire death rate than the average population. The risk of fire death drops considerably after the age of 5 and experiences minimal change until the age of 55, at which point the risk begins to rise substantially. Young children and older adults are typically high-risk groups because they are physically unable to escape a fire. People between the ages of 5 and 55 years generally do not suffer from physical inability and are capable of removing themselves from danger..."(31, p.15).

- **CHILDREN:** Children are a high-risk group for fire fatalities because they "may be too young to escape from a fire or may not have the reasoning ability to safely exit a burning structure" (30, p. 170). "Children age 4 and under are 40 percent more likely to die in a fire than the general population" (30, p.168).

  "More than half of children fatalities occur when the victim is asleep...For the youngest age group (age 4 and under), 22 percent were unable to react because of their young age...About 25 percent of children are injured while trying to escape...even the very youngest try to escape when they can (34 percent)...A large portion of children are still sleeping when they are injured (30 percent)...The oldest children are as likely to be injured trying to control the fire (33 percent) as they are to be escaping (34 percent)" (30, p.171).

- "A small child often will hide behind a bed or in a corner during a fire while awaiting help from parents or caretakers. In the case of an alcohol-impaired caretaker, the help is unlikely to arrive and the child is left behind. Furthermore, a rapidly evolving fire leaves little chance for a firefighter to find and rescue the child in time" (31, p.17).

- Each year children perish in fires in situations in which no rescuer is present (34, 35). One report analyzed cases where children "were left alone for periods ranging from 15 minutes to several days." There is no data available that specifies how many children die each year under these circumstances or what ages are represented.

  "Experts agree that there is no single age at which children can be considered "old enough" to be left alone, whether for a few minutes or overnight" (34, p.55). It depends on the maturity of the child and how well the child can accept responsibility. However, some jurisdictions have provided guidelines, others have legal requirements, on when and for how long children of certain ages can be left alone and at what age they can babysit younger children. "Experts strongly recommend that you not leave children under 10 at home alone for any extended period of time (i)." Recommended minimum ages for babysitting range from 13 to 14 years (ii, iii).

- **OLDER ADULTS:** "Elderly fire victims usually come in close contact with the heat source that starts the fire...Adults in the age group between 65 and 75 have a fire death rate twice that of the national average; between 75 and 85, three times the national average; and over 85, four times the national average...Many older adults take multiple medications, the interaction of which can cause a variety of side effects, including confusion, that may alter the decision-making process and increase the potential for accidents...The impairments caused by the combination of alcohol and prescription drugs in older adults can be significant. Such impairments may lead to an increased likelihood of accidentally starting a fire, not detecting a fire, and not being able to escape a fire" (28, pp.3-4.).

  "Older adults face an unusually high risk of dying in a fire...Fires caused by smoking are the leading cause of fire deaths among older adults...medications that cause drowsiness or the use of alcohol increase the risk of starting a fire with smoking material. Fires of this nature are particularly injurious as the most commonly ignited material is the victim's clothing or bedding, a situation that substantially reduces the victim's ability to extinguish or escape a fire before being overcome" (28, p. 10).

  "Nearly one-fifth of all people over 65 who die in fires are bedridden or challenged by some other physical disability...While smoke inhalation is the leading cause of fire deaths, there is a direct correlation between the age of the victim and deaths from burns: as the age of the fire victim increases, the percentage of burn-induced deaths also increases" (28, p.12). "Aging bodies have decreased healing mechanisms. As a result, older adults tend to die from smaller burns, have longer hospital stays, and require more time to recuperate from burn injuries" (28, p. 23).

  "Forty percent of older adults who die in fires are asleep. This statistic is largely a result of the fact that most fatal residential fires occur in the late evening and early morning hours when most people are sleeping. Twenty-four percent of the oldest old* fatalities were unable to act, due in large part to advanced age. The oldest adults who are awake during a fire appear to have neither the cognitive nor the physical ability to safely escape from a fire. One-third of older adults are injured while trying to escape...Trying to control the fire is the leading cause of fire-related injuries in older adults. Forty-two percent of older adults are injured when they try to control the fire; even the oldest old try to extinguish the fire (22 percent). Escaping the fire is the second leading cause of fire injuries (22 percent). A large portion of adults are sleeping when they are injured (18 percent), with the oldest old most likely to be asleep (22 percent)" (30, pp.177-178).

  **85 and over (30, p.174)*

  "Age can also be expected to influence the ability of the individual to withstand exposure to by-products of fires (9, p. 10)

Fire Characteristics

- **OCCUPANT RESPONSE:** Fire characteristics "can play an important role in the occupant response. During a fire, people perceive different cues from the fire and their interpretation of the situation will change rapidly, influencing their behaviour. Perceiving a smell of smoke will initiate a different response than directly seeing the fire" (17, p. 4).

  "The extent of available actions depends very much on the circumstances of the fire" (8, p.5). Fire environment can produce reduced visibility, breathing difficulties, fatigue and incapacitation (9).

- **FIRE GROWTH**: Occupant(s) may play a role in fire growth. "In practice, fire growth and spread is almost always due to doors or windows being left open or opened at a crucial stage in the fire's development. Such occurrences are usually the result of escapes, fire-fighting, or rescues" (20, p.413). People tend to underestimate the speed of fire growth" (9, p.17).

- **SMOKE:** "The overwhelming majority of fire fatalities perish as a result of smoke and toxic fume inhalation as opposed to burn injuries"(31, p.13).

  "Often related to fire fighting behavior, and a definite component of evacuation behavior in many fires, is the movement of occupants through smoke. The principal variables influencing an occupant's decision to move through smoke appear to be recognition of the location of the exit and thus of the travel distance, the appearance of the smoke, the smoke density, and the presence or absence of heat. To achieve evacuation, occupants have moved through smoke, even for extended distances under conditions of extremely limited visibility at personal risk, and sometimes have been forced to turn back without completing the evacuation" (32, p.7-14).

  "...occupants are prepared to move through smoke even if they know that smoke kills. The movement speed of occupants in a smoke environment can drop dramatically due to the difficulty of seeing and breathing" (17, p. 12).

Environmental Characteristics

- **FAMILIARITY:** "The more familiar the occupants are with the building and the ways out, the more likely they are to use the most efficient routes during an evacuation" (9, p.25).

- **SMOKE ALARMS:** "In a single family house, occupants tend to respond right away when the smoke alarm activates because they know they are responsible to investigate and initiate adaptive action (9, p. 20)." "...an alarm signal alone does not generate immediate action – but starts the search for confirmation of a second clue" (9, p. 14).

  "...where children are present, reliance on audible alarms to wake children will likely not be sufficient. It will be necessary to use adults, who can be depended upon (if they are not impaired) to notify children such that they can take appropriate actions" (9, p.18).

From a study conducted over two nights on arousal from sleep by a smoke alarm: "In the junior age group* over two thirds (69.3%) slept through the three minute alarm (this is an average across both nights). By contrast, all adults** awoke on both alarm nights" (4, p.4)

** 6 to 17 years of age ** 30-59 years of age*

The above study demonstrates "that children will not reliably awaken to a smoke alarm located in the standard hallway location within the home...85% of this sample of children did not awake on both nights" (4, p. 6). This study also indicated "that adults will reliably awaken within half a minute...those who awoke reported feeling moderately clearheaded within the first three minutes and improved thereafter" (4, p. 6).

- **ARCHITECTURE:** Building characteristics that can impact human behavior in fire include: number of floors, floor area, location of exits, location of stairwells, complexity of space, building shape and visual access (17, p.4).

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Tab E

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Memorandum

Date: October 25, 2004

TO : Margaret Neily, Director, Division of Combustion and Fire Sciences, Directorate for Engineering Sciences

THROUGH: Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Health Sciences
Lori E. Saltzman, M.S., Director, Division of Health Sciences

FROM : Treye A. Thomas, Ph.D., Toxicologist, Division of Health Sciences
Patricia Brundage, Ph.D., Pharmacologist, Division of Health Sciences

SUBJECT : Qualitative Assessment of Potential Risk From the Use of Flame Retardant Chemicals in Mattresses

EXECUTIVE SUMMARY

In addressing the hazard associated with the ignition of mattresses, the U.S. Consumer Product Safety Commission (CPSC) staff is working to develop a draft performance standard to reduce mattress ignitions without creating other hazards to consumers. The CPSC's Directorate for Health Sciences (HS) conducted a qualitative assessment of the potential risk that might result from consumer exposure to fire retardant (FR) chemicals applied to mattresses designed to meet the draft proposed mattress flammability standard.

The staff completed toxicity reviews on five chemicals/chemical classes that may be used to meet the draft proposed standard. These chemicals are: antimony trioxide, boric acid/zinc borate, decabromodiphenyl oxide, melamine, and vinylidene chloride. Data on potential exposures to FR chemicals from mattresses does not exist. Because of the lack of exposure data, a quantitative risk assessment could not be made. Instead, staff conducted a qualitative assessment of the potential risk of health effects from exposure to FR chemicals that may be incorporated to meet the draft proposed standard based on their assessment of available toxicity data, knowledge of how FR chemicals might be used in mattresses, and staff's professional judgment.

HS staff believes there are fire retarding materials (e.g., FR-treated barriers) available to mattress manufacturers that are expected to present only a negligible risk of adverse health effects in consumers. This staff opinion is based on the use of polymerized melamine compounds (resins) and vinylidene chloride in the manner described by the manufacturers of the barriers containing these compounds. This preliminary qualitative assessment may change if additional data on the toxicity and/or exposure potential of mattresses become available. Exposure data for antimony, boric acid/zinc borate, and decabromodiphenyl oxide are needed before more definitive conclusions about the potential risk of adverse health effects can be made.

INTRODUCTION

The U.S. Consumer Product Safety Commission (CPSC) initiated a regulatory proceeding in 2001 to address the hazard of flame ignitions of mattresses (Neily, 2001). From 1995-1999, mattresses and bedding were associated with an estimated 19,400 fires, 440 deaths, 2,230 injuries, and $273.9 million in property damage in the U.S. annually (Smith and Miller, 2004). The CPSC staff is developing a draft performance standard to address mattress flammability. In order to meet the proposed mattress performance standard, manufacturers of mattresses would be able to select from a number of available technologies (e.g., barriers and foam). The Commission's Directorate for Health Sciences and Directorate for Engineering Sciences staff requested information from manufacturers of products including barriers, foams, or other materials that were known to use, or where manufacturers were considering using, flame retardant (FR) chemicals to meet a possible flammability standard for mattresses.

The definition of an FR chemical varies within the barrier and mattress industries. The definition of an FR chemical for the purposes of this review may be broader in scope than definitions used by some groups. The CPSC staff considers an FR chemical to be any compound that is added to a material for the purpose of inhibiting, suppressing, or stopping the combustion process of the material. The FR may be added to the surface of a material; or incorporated into a material, the fibers of a fabric, or a component of an article such as foam. There are generally two types of FR chemicals; reactive and additive. Reactive FR's may be polymerized along with the base polymer, or chemically bonded to a material. Additive compounds are typically attached to a material through some form of adhesive substance. The staff requested information on: the method of application of FR chemicals to fabrics and fibers during any stage of production; the toxicity of the FR chemical; and the potential exposure and bioavailability of these chemicals to consumers using mattresses containing these chemicals.

Manufacturers suggest that the FR chemicals incorporated into their products are not likely to pose a hazard to consumers sleeping on mattresses that contain these products. They suggest that the amount of chemical migrating from many of these materials is minimal and consumers would not be exposed to it. They believe that the method by which the FR chemicals are applied to the fabric and/or placed in the mattress sequester the chemicals within the fabric fibers or fabric matrix. However, the question arises as to whether some of the technologies that may involve the use of FR chemicals may not be as durable as suggested by the manufacturers, resulting in the release of FR chemicals from treated materials. In order to evaluate this question, CPSC staff conducted a qualitative assessment of the potential health effects that might result from consumer exposure to FR chemicals applied to mattresses designed to meet the draft proposed mattress flammability standard.

CPSC Staff Approach to Addressing Health Hazards under the Federal Hazardous Substances Act (FHSA)

CPSC staff assesses a product's potential chronic health effects to consumers under the Federal Hazardous Substances Act (FHSA). The FHSA is risk-based. To be considered

a "hazardous substance" under the FHSA, a consumer product must satisfy a two-part definition. 15 USC 1261 (f)(1)(A). First, it must be toxic under the FHSA, or present one of the other hazards enumerated in the statute. Second, it must have the potential to cause "substantial illness or injury during or as a result of reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards under the FHSA (CPSC, 1992).

The FHSA addresses both acute and chronic hazards. While the FHSA does not require manufacturers to perform any specific battery of toxicological tests to assess the potential risk of chronic health hazards, the manufacturer is required to label a product appropriately according to the requirements of the FHSA. The first step in the risk assessment process is hazard identification, that is, a review of the available toxicity data for each chemical under consideration and a determination of whether the chemical is considered to be "toxic" under the FHSA. The chronic toxicity data are assessed by CPSC staff using CPSC's chronic hazard guidelines (CPSC, 1992; summarized at 16 CFR 1500.135). If it is concluded that a substance is toxic under the FHSA due to chronic toxicity, then a quantitative assessment of exposure and risk is performed to evaluate whether the chemical may be considered a "hazardous substance" under the FHSA.

For the chemicals reviewed in this memo, acceptable daily intake values (ADI's) were calculated when a given chemical was considered "toxic" due to chronic effects and sufficient toxicity information was available. The ADI is the amount of a compound that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers. For other compounds, there were insufficient data available to calculate an ADI. The potential toxicities of the reviewed chemicals were subjectively categorized in this document as low, moderate, or high based on the ADI, the severity of the potential health effects of the compound, and professional judgment of CPSC staff.

Data on potential exposure to FR chemicals from mattresses does not exist. Because of the lack of exposure data for FR chemicals in mattresses, a quantitative assessment of the risks could not be completed, even for those chemicals for which an ADI could be calculated. Instead, staff conducted a qualitative assessment of the potential risk of health effects of exposure to FR chemicals that may be incorporated to meet the draft proposed standard. Thus, exposure potential was categorized as low, moderate, or high by assuming exposures were similar to those that might occur with FR-treated upholstered furniture (for which we have some data), knowledge of how FR's would be applied to mattresses, and the professional judgment of the CPSC staff.

Use of FR Chemicals in Mattresses

FR chemicals may be incorporated into a variety of components that are used in the construction of a mattress. Thus, based on the broad definition of FR chemicals, staff's assessment includes a number of compounds, products, and technologies that may be used in mattresses to meet the draft proposed standard.

Mattress manufacturers will be able to choose from a variety of methods to meet the draft proposed flammability standard. CPSC Engineering Sciences (ES) and Economics (EC) staff conversations with manufacturers suggest that some intend to use barriers, most of which will contain FR materials that are incorporated into the barriers in a variety of ways.

Barriers vary in construction and the method by which they reduce potential flammability. Some barriers are composed of materials (e.g., Kevlar®) that are inherently flame resistant; others are made of cotton or other materials that have been treated with an FR chemical; and there are others that use both of these approaches.

Treating foam with FR chemicals is another option that some mattress manufacturers may use to meet the draft proposed standard. Although the amount of foam present in mattresses varies, the foam is often the major constituent and primary fuel source for fires. Given the amount of foam that is potentially used and its relatively high flammability potential, one could speculate that the total amount of FR chemicals that is needed in the foam may be higher than that needed for barriers to achieve the same result. However, one could also speculate that the layers of other materials between the foam and the external fabric covering the mattress (ticking) that are often present may reduce exposure to chemicals that could be released from foam.

CPSC staff has not received any information from manufacturers that they intend to apply FR chemicals directly to the mattress ticking. However, based on informal staff conversations with mattress manufacturers, staff believes that this may occur in mattresses that are produced for markets where comfort is not the most important consideration in purchasing decisions (e.g., school dormitories).

CPSC staff believes that once the mattress flammability standard has been finalized, the approaches to meeting a mattress flammability standard may include a greater variety of FR chemicals than currently available. These new FR chemicals may be used in barriers, foams, and direct application to the ticking. In addressing the hazard associated with the ignition of mattresses, the CPSC staff is working to develop a draft performance standard to reduce mattress ignitions without creating other hazards to consumers. At this time, the CPSC's Directorate for Health Sciences (HS) staff has completed toxicity reviews on five chemicals/chemical classes that may be used to meet the draft proposed standard.

Currently, exposure data are not available for all of these chemicals and data on inhalation exposure are lacking. Due to the lack of chemical-specific exposure data for these FR chemicals in mattress materials, the staff assessed the method of application of FR chemicals to barriers, and extrapolated the exposure data from the upholstered furniture risk assessment (Babich and Thomas, 2001) in order to make qualitative estimates of the exposures that may occur when sleeping on mattresses. Based on a review of the available toxicity and exposure data, HS staff believes there are fire retarding methods (e.g., FR-treated barriers and foam) available to mattress manufacturers that are not likely to result in a risk of adverse health effects in consumers.

HAZARD IDENTIFICATION

This section of the memo consists of summaries of the health effects for FR chemicals/chemical classes that mattress manufacturers may use. These chemicals are: antimony trioxide, boric acid/zinc borate, decabromodiphenyl oxide, melamine, and vinylidene chloride.

Not all chemicals have been tested for carcinogenicity, reproductive and developmental toxicity, or neurotoxicity. Should new data become available to fill these data gaps some of the conclusions of this report may be altered.

In evaluating the toxicity data for the selected FR chemicals, staff applied the definitions for toxicity in the regulations (16 CFR 1500.3 (c)(2)(ii)) and chronic hazard guidelines (CPSC 1992; summarized at 16 CFR 1500.135) promulgated under the FHSA (15 U.S.C. 1261-1278). A substance or mixture is classified as "known to be toxic" in humans only if there is sufficient evidence in humans, and is regarded as "probably toxic" if there is either limited evidence in humans, or sufficient evidence in animals (Table 1). If a chemical or substance is known to be toxic or probably toxic in humans, it is considered "toxic" under the FHSA. If a chemical or substance is possibly toxic, it would not be considered "toxic" under the FHSA.

Table 1. Classification of Chronic Hazards under the FHSA.

Evidence	**Human studies**	**Animal studies**
Sufficient evidence	**Known** [a]	**Probable** [a]
Limited evidence	**Probable** [a]	Possible
Inadequate evidence	Possible	---

[a] Considered "toxic" under the FHSA.

Antimony trioxide

The following is a summary of the toxicity data on antimony trioxide based on the CPSC staff's antimony trioxide (AT) toxicity review (Hatlelid, 1999a) and the staff update for FR chemicals (Bittner, 2001). Additional information recently reviewed by staff (Babich et al., 2004) is also included here. All doses and exposures are expressed in terms of antimony.

General Background

Antimony trioxide is found in nature as valentinite and senarmonite. It is also formed through a reaction of antimony trichloride with water. In combination with chlorinated or brominated flame retardants, it is used on commercial furniture, draperies, wall coverings and carpets; typically at 2-10% by weight of fabric. It is also used in enamels, glasses, rubber, plastics, adhesives, textiles, paper, and as a paint pigment.

Toxicity

Acute and Systemic Effects

There are no data regarding the health effects of antimony trioxide in humans following oral exposure.

Several studies of antimony smelter workers reported that chronic inhalation exposure to antimony trioxide is associated with pneumoconiosis, chronic cough, and upper airway inflammation (Cooper et al., 1968; McCallum, 1963; McCallum, 1967; Potkonjak and Pavlovich, 1983). In another study, systemic effects, including weight loss, metallic taste, nausea, vomiting, nerve tenderness, and tingling, were reported in a population of smelter workers (Renes, 1953). However, the health effects observed in these studies could not be directly linked to antimony trioxide inhalation exposure because of the lack of quantitative exposure data and the potentially confounding presence of other compounds such as arsenic, lead, alkali, and other dusts in the work place.

No studies on the systemic effects of dermal exposure to antimony trioxide were found in humans.

In rats, the acute oral median lethal dose (LD_{50})[1] is greater than 20 g/kg (ATSDR, 1992a; Ebbens et al., 1972). The acute dermal LD_{50} in rabbits is greater than 6.7 g/kg (Myers et al., 1978).

Oral exposure caused systemic toxicity in experimental animals. In dogs administered antimony trioxide by gavage (Fleming, 1938), the lowest-observed-adverse-effect-level (LOAEL) for severe diarrhea is 6.6 mg/kg-day in 5% citric acid (for 11 days) and 84 mg/kg-day in water (for 21 days). The greater toxicity of antimony trioxide dissolved in 5% citric acid could be related to increased solubility in citric acid compared to the solubility in water. Subchronic oral administration of 420-890 mg/kg-day in rats caused swelling of hepatic cords, a decrease in red blood cell counts, reduced weight gain, and slight changes in absolute or relative organ weights (Hiraoka, 1986; Smyth and Thompson, 1945; Sunagawa, 1981). In Wistar rats fed antimony trioxide in the diet for 24 weeks, a LOAEL of 420 mg/kg-day was identified, based on mild liver toxicity and a decreased red blood cell count (Sunagawa, 1981).

Male (71, 354, and 1416 mg/kg-day) and female (81, 415, and 1573 mg/kg-day) Wistar rats fed antimony trioxide for 90 days in the diet exhibited minor hematological changes (increased erythrocyte count, decreased mean cell volume) and minor hepatic changes (increased liver weight; lipid perturbations; decreased plasma alkaline phosphatase activity; increased aspartate aminotransferase activity) in the absence of histopathological changes at the highest doses (Hext et al., 1999). A small, but statistically significant decrease in alkaline phosphatase activity was noted in females receiving 415 mg/kg-day, which was attributed to effects on nutritional status. Based on the increase in serum

[1] The median lethal dose (LD_{50}) is the amount of a chemical which kills 50% of a sample population; typically expressed as milligrams per kilogram of body weight.

enzymes and liver weight, the LOAEL was 1573 mg/kg-day. The no-observed-adverse-effect-level (NOAEL) in males was 354 mg/kg-day.

Inhalation studies in experimental animals conducted using whole-body exposure identified the lungs as the primary target tissue. Inhalation of antimony trioxide dust caused interstitial fibrosis, pneumonia, and pneumonitis in guinea pigs, rabbits, rats, and swine in subchronic and chronic inhalation studies (Dernehl et al., 1945; Gross et al., 1955b; Groth et al., 1986; Newton et al., 1994; Watt, 1983). Other effects associated with inhalation exposure included decreased body weight, lung hypertrophy and hyperplasia, and liver and spleen effects.

In F344 rats exposed by inhalation (0.01-3.8 mg/m^3; 6 hours/day, 5 days/week, for 1 year; with 1 year observation), the only exposure related changes appeared in the lungs and included chronic interstitial inflammation, granulomatous inflammation, and an increase in alveolar macrophages (Newton et al., 1994). The LOAEL (adjusted for intermittent exposure) for increased alveolar/intraalveloar macrophage proliferation due to chronic inhalation was 0.009 mg/m^3. A NOAEL was not identified.

Dermal administration in rabbits caused systemic toxicity and even death (Fleming, 1938; Myers et al., 1978). Death was observed in rabbits after a single dermal application of 6.7 g/kg in corn oil (Myers et al., 1978). Fleming et al. (1938) reported systemic toxicity and death after 5-8 days of daily dermal applications of an unspecified dose in a paste of artificial acidic or alkaline sweat. The dosing vehicles used in these studies appeared to increase the bioavailability, and consequently the toxicity of the compound (Hatlelid, 1999a).

Dermal and Ocular Effects

Dermatitis, characteristic of antimony exposure, was reported in workers occupationally exposed to 0.4-71 mg/m^3 antimony trioxide dust (McCallum, 1963; Potkonjak and Pavlovich, 1983; Renes, 1953; White et al., 1993). Though the workers were exposed to other substances in the workplace, the dermatitis has not been associated with those substances. The illness resolved when the work environment improved or the worker was moved out of the exposure.

In experimental animals, dermal exposure does not cause a corresponding dermatitis. No skin effects were noted in rabbits treated with 21 grams antimony trioxide in an aqueous methylcellulose paste for 1 week (Gross et al., 1955a). Mild irritation was noted 72 hours after 420 mg was applied to the premoistened skin of rabbits for 24 hours (Ebbens et al., 1972).

In one study, installation of the dry compound into the eyes of rabbits was extremely irritating, although washing the eyes after a four-second contact period resulted in a much lower irritation score (Ebbens et al., 1972). Instillation of the dry compound into the eyes of rabbits caused mild irritation in another study (Burlingham et al., 1979). Rats also developed corneal irregularities after two weeks of whole body exposure (0.21-19.6 mg/m^3) for 6 hours/day, 5 days/week (Newton et al., 1994). It is unclear

whether this effect, which did not resolve after termination of exposure at week 13, was due to direct contact with the dust or related to the effects of the absorbed material.

Carcinogenicity and Genotoxicity

Three epidemiological studies (Jones, 1994; Potkonjak and Pavlovich, 1983; Schnorr et al., 1995) evaluated the potential carcinogenicity of antimony following occupational exposure. Although no malignancies were observed in 51 smelter workers exposed to 5.5-64 mg/m^3 for an average of 18 years (range, 9-31 years) (Potkonjak and Pavlovich, 1983), a cohort study reported a correlation between antimony exposure and lung cancer risk (Jones, 1994). It however, lacked appropriate controls, did not measure workplace exposure levels, and did not account for exposure to other chemical compounds in the workplace. Additionally, a retrospective study of smelter workers by Schnorr et al. (1995) reported a marginally statistically significant increased risk of lung cancer, although no data on cigarette smoking were reported and work place exposure levels were not measured.

No difference in sister chromatid exchange and micronuclei tests were found in workers involved with the application of antimony trioxide to fabric compared to controls (Cavallo et al., 2002). However, an enzyme (formamido pyrimidine glycosylase)-modified comet assay showed that a significantly higher proportion of workers directly exposed to antimony trioxide had oxidative DNA damage. The oxidative DNA damage may be, for instance, indirectly due to chronic inflammation or any other process that releases active oxygen species. Confounding or effect modifications due to other chemical exposures cannot be ruled out as a cause for this DNA damage.

Two animal studies have shown a treatment-related increase in lung tumors in two strains of rats by inhalation (Groth et al., 1986; Watt, 1983). Groth et al. (1986) detected lung tumors in 27% of female Wistar rats after intermittent exposure to 38 mg/m^3 for 1 year, followed by an additional 20-week observation period. In another study, 82% of female Charles River CDF rats developed lung tumors after intermittent exposure to 4.2 mg/m^3 for 1 year (Watt, 1983). Male rats were not studied. A third study found no neoplastic effects related to intermittent exposure to 3.8 mg/m^3 antimony trioxide for 1 year with an additional 1-year observation period in male or female F344 rats (Newton et al., 1994). No tumors were found in female swine at the end of a 1-year exposure (Watt, 1983). Differences in exposure doses or protocols, animal strains, species, or sexes studied, or other factors of the experimental design may account for the inconsistent results (Hatlelid, 1999a).

Antimony trioxide was negative for mutagenicity in *Salmonella* and *E. coli* strains (Kanematsu et al., 1980; Kuroda et al., 1991). However, DNA damage was noted following antimony trioxide treatment of *Bacillus subtilis* in Rec assays (Kanematsu et al., 1980; Kuroda et al., 1991). It also caused sister chromatid exchange in V79 Chinese hamster cells (Kuroda et al., 1991). A single oral dose of 330-840 mg/kg did not induce chromosomal aberrations in mouse bone marrow cells of either sex, though the same

study showed a dose-dependent increase in chromosomal aberrations following repeated administration of these doses for 21 days (Gurnani et al., 1992).

Another study examined the genotoxicity of antimony trioxide using a range of *in vitro* and *in vivo* genotoxicity assays (Elliott et al., 1998). *In vitro*, antimony trioxide was not mutagenic in *Salmonella* or mouse lymphoma cells, although a positive clastogenic response to antimony trioxide was reported in isolated human peripheral lymphocytes. Oral gavage administration of doses up to 4,200 mg/kg did not cause unscheduled DNA synthesis in the liver cells of rats. Additionally, *in vivo*, antimony trioxide was non-clastogenic in the mouse bone marrow micronucleus assay following oral gavage administration for 1, 7, 14, or 21 days at dose levels up to 4,200 mg/kg (single dose) or 840 mg/kg (repeat dose). This failed to confirm the observed clastogenicity in mouse bone marrow micronucleus assay previously noted following repeated oral administration (Gurnani et al., 1992). Elliott et al. (1998) also noted no toxicity at dose levels Gurnani et al. (1992) reported to be fatal.

Reproductive and Developmental Effects

One human occupational study reported reproductive effects. Menstrual cycle disturbances, early interruption of pregnancy, and increased incidence of spontaneous late abortions were noted in metallurgic workers, although the control group and workers' exposure were not well characterized and no statistical analyses were presented (Belyaeva, 1967).

Additionally, two animal studies have reported reproductive and developmental effects. Exposure to 209 mg/m^3 by inhalation for two months reduced the number of offspring and disrupted the ovulation of exposed rats, but did not cause changes in fetal body weight or teratogenic effects (Belyaeva, 1967). Another study reported fetal growth retardation and embryo death after exposing pregnant rats to 0.068-0.23 mg/m^3 during gestation (21 days) (Grin et al., 1987). The inhalation LOAEL in rats for preimplantation loss, fetal growth retardation, and pre- and post-implantation embryo death was 0.082 mg/m^3. The NOAEL was 0.023 mg/m^3.

A study (Omura et al., 2002) evaluated testicular toxicity in Wistar rats and CD-1 mice dosed 5 days/week for 4 weeks in mice and 3 days/week for 4 weeks in rats with 1,000 mg/kg suspended in water. No significant treatment-related effects were observed in either species in the weights of testis, epididymis, ventral prostate, and seminal vesicles; sperm count, sperm motility, and sperm morphology; or histopathologic changes of the testis.

A recent study looked at the developmental effects of antimony trioxide in rats (Schroeder et al., 2004). Dams were exposed by inhalation on gestation days 0-19 by nose only inhalation for 6 hours per day, at levels up to 5.3 mg/m^3. Average particle sizes (mass median aerodynamic diameters) were within the respirable range. Macrophages were found in the lungs of exposed dams and antimony levels were elevated in their erythrocytes at all dose levels, as compared to the controls. The authors reported that there were no statistically significant effects on implantation, resorption,

fetal body weight, sex ratios, or crown to rump distances. At the high dose, there was a small, non-significant increase in resorptions per implant. The authors also reported no significant increases in external, visceral, or skeletal variations or malformations. The percentage of fetuses with unossified metacarpals was significantly decreased at the mid-dose. Anophthalmia (congenital absence of one or both eyes) was reported in 0.6% (1/173) of fetuses and 4% (1/25) of litters at the high dose, as compared to zero in the controls and other dose groups. Though the finding was not statistically significant and has not been reported by other studies, the observation of a rare lesion is a potential concern.

Neurological Effects

One smelter worker exposed to high levels of antimony trioxide in the air (10 mg/m^3) reported nerve tenderness and tingling (Renes, 1953) although the worker was also exposed to several other chemicals.

Abnormal gait was noted in one rabbit after dermal exposure to 6.7 g/kg in corn oil for 24 hours (Myers et al., 1978). In another study, muscle weakness and difficulty moving the hind limbs were observed in one of two dogs orally administered antimony trioxide (Fleming, 1938). These effects may have been secondary to the severe systemic toxicity caused by the compound.

Sensitization

There were no human studies on sensitization.

A single animal sensitization study in guinea pigs with dermal exposure to 42 mg for 6 hours, every other day for 18 days followed by a 6 hour challenge 2 weeks later was negative (Ebbens et al., 1972).

Pharmacokinetics

Antimony trioxide is absorbed following oral exposure (Fleming, 1938; Gross et al., 1955a; Smyth and Thompson, 1945; Sunagawa, 1981). Absorption of antimony trioxide can also occur dermally (Fleming, 1938; Myers et al., 1978). The elevated blood and urine antimony trioxide levels reported in occupationally exposed workers suggest antimony trioxide is also absorbed via inhalation exposure (Cooper et al., 1968; Kim et al., 1997; Ludersdorf et al., 1987). However, no quantitative correlation between air concentration levels and the urine levels of workers was found (Kim et al., 1997).

Little quantitative data is available regarding the oral absorption of antimony trioxide. A 1% absorption rate is assumed when estimating gastrointestinal absorption, based on studies of various inorganic and organic antimony compounds (ICRP, 1981).

With regard to the antimony trioxide that is absorbed, high concentrations were measured in the thyroid and gastrointestinal tract in rats following chronic ingestion of 2% antimony trioxide in the feed (Gross et al., 1955a). Detectable levels were also found in the spleen, blood, kidneys, lungs, liver, hair, and heart.

Excretion is primarily in the feces, although a portion of ingested or inhaled antimony trioxide is excreted in the urine (Gross et al., 1955a). Intratracheal instillation of antimony trioxide in hamsters suggests a two-phase clearance of antimony trioxide from the lungs (Leffler et al., 1984) with biological half-lives of approximately 40 hours for the initial phase and 20-40 days for the second phase.

Summary

The original staff review (Hatlelid, 1999a) concluded that antimony trioxide would not be considered acutely toxic by oral or dermal routes under the FHSA regulatory definition. Antimony trioxide does, however, in staff's opinion meet the FHSA regulatory definition for toxic based on its chronic toxicity. Inhalation of antimony dust caused non-cancerous effects in both animals and humans, and systemic toxicity in several animal species following oral exposure. It may be regarded as a probable human carcinogen based on sufficient evidence of carcinogenicity in animals exposed by inhalation. Sufficient evidence in animals and limited evidence in humans also indicates antimony trioxide is a probable skin and eye irritant. The evidence for developmental toxicity, reproductive toxicity, and neurotoxicity was not sufficient to satisfy the definition of toxic under the FHSA.

CPSC staff calculated an oral ADI of 2.3 mg/kg-day (Hatlelid, 1999a). This was based on the NOAEL of 230 mg/kg-day from a subchronic feeding study in Wistar rats (Sunagawa, 1981) using an uncertainty factor of 100 (10 for interspecies variability and 10 for sensitive populations). In the recent update on the toxicity of selected flame retardants (Babich et al., 2004), a NOAEL of 354 mg/kg-day was identified from a 90-day subchronic oral study in Wistar rats (Hext et al., 1999). This study is consistent with other subchronic studies previously reviewed by the staff (Hatlelid 1999a). However, some of the previous studies were quite old and all of the studies had limitations such as small number of animals, incomplete histopathology, or durations less than 90 days. If the Hext et al. study were available at the time of the previous staff review, it would have been preferred for setting an ADI. This would result in an ADI of 3.5 mg/kg-d, or slightly greater than the current ADI of 2.3 mg/kg-d. Therefore, even if a new ADI is derived, it would not change the staff's conclusion that AT would not present a risk of potential adverse health effects to consumers by oral or dermal exposure (Babich and Thomas, 2001).

For the inhalation route of exposure, the ADI originally calculated for a 70-kg adult male breathing 23 m^3/day was 0.003 μg/kg-day (Hatlelid, 1999a). This was based on the LOAEL of 0.009 mg/m^3 for alveolar/intraaveolar macrophage proliferation as a result of chronic inhalation exposure in rats using an uncertainty factor of 1000 (10 for interspecies variability, 10 for sensitive populations, and 10 for use of the LOAEL rather than the NOAEL). The assumptions of standard respiratory rate (i.e., 23 m^3/day) were then applied to convert the acceptable exposure level for airborne antimony trioxide particles of 9 ng/m^3 to an ADI. In a later review (Bittner, 2001), the ADI for the inhalation route was revised to reflect the use of a more standard value for the respiratory rate of an adult man (U.S. EPA, 1997). Using this revised value (i.e., 15 m^3/day) for

respiratory rate, the ADI was amended to 0.002 μg/kg-day. This recalculation does not alter staff's conclusion regarding the toxicity of antimony trioxide.

Boric Acid and Zinc Borate

Following is a summary of the toxicity data on zinc borate and boric acid based on the CPSC staff's zinc borate toxicity review (Hatlelid, 1999b) and the staff update for FR chemicals (Bittner, 2001). It also includes information presented in the toxicity assessment of FR chemicals by the National Research Council (National Research Council, 2000).

Due to the lack of toxicological information on zinc borate, it was appropriate to consider the larger body of knowledge concerning zinc oxide and boric anhydride. The typical composition of zinc borate is 45% zinc oxide and 34% boric anhydride with 20% water hydration. Boric acid is formed by the reaction of boric anhydride and water. All doses and exposures are expressed in terms of zinc or boron to allow for comparison between the different zinc and boron compounds.

General Background

Zinc borate is used in flame retardant mixtures for textiles, and rubber and plastic products. It is typically used in conjunction with other chemicals such as antimony trioxide, magnesium hydroxide, alumina trihydrate, and some brominated flame retardants. Zinc borate is also used in medicines, and as a fungicide and a mildew inhibitor in polymer, paper, and textile products. Zinc oxide is used as a pigment and mold inhibitor in paint; as an ointment; as a semiconductor in electronics; in dietary supplements, cosmetics, dental and quick setting cements, enamels, and rubber products. Boric acid is used as a flame retardant in wood and textiles. Boric acid is also used in enamels, porcelain, glass, crockery, soaps, and cosmetics, and as an astringent and an antiseptic. Boric anhydride is used in glass, electronics, and herbicides (HSDB, 1998).

Boron and zinc are widely distributed in the environment. Zinc is considered essential for all living things (Hubbard and Sullivan, 1996). Boron is an essential nutrient for plants and may be required for humans and animals as well.

The recommended daily intake of zinc is approximately 0.21 mg/kg-day. There is no recommended intake level for boron, but the mean dietary intake in the United States is estimated to be approximately 1 mg/day (Coughlin, 1998).

Toxicity

Acute and Systemic Effects of Boric Acid and Boric Anhydride

Acute ingestion of boric acid in humans causes vomiting, diarrhea, shedding of the skin, and changes in the liver, kidney, and brain (Linden et al., 1986; Wong et al., 1964). The ingestion of 505 mg/kg-day boric acid for 3 to 5 days by children has also been reported to cause death (Wong et al., 1964). Human accidental ingestion of 241 mg/kg caused vomiting and diarrhea (Linden et al., 1986).

Workers exposed to a mean concentration of 4.1 mg/m^3 of boric acid and boric anhydride for an average of 11.4 years experienced no systemic effects (Garabrant et al., 1984).

There are no reports of systemic toxicity resulting from contact with intact skin. Application of boric acid to inflamed skin caused severe erythema, gastrointestinal symptoms, and even death in infants with diaper rash treated with boric acid powder (Goldbloom and Goldbloom, 1953).

The toxicity of boric anhydride following oral exposure is not well studied. One study determined the oral LD_{50} of boric anhydride in mice to be approximately 3.2 g/kg (HSDB, 1998). The oral LD_{50} of boric acid in rats is 0.55-0.9 g/kg (Smyth et al., 1969; Weir and Fisher, 1972). In dogs, a dose of 0.7 g/kg boric acid orally administered had no effect (Weir and Fisher, 1972).

Subchronic administration of boric acid at doses greater than about 14 mg/kg-day in rats and dogs caused changes in feeding behavior, kidney and liver changes, and reproductive and developmental effects (Heindel et al., 1992; Weir and Fisher, 1972). Similar toxic systemic effects were observed in mice at slightly higher doses (Heindel et al., 1992; NTP, 1987). The NOAELs for chronic oral administration of boric acid, which varied among animal species, were approximately 48 mg/kg-day in mice, 18 mg/kg-day in rats, and 8.8 mg/kg-day in dogs (NTP, 1987; Weir and Fisher, 1972).

In dogs, intermittent inhalation exposure to 57 mg/m^3 boric anhydride for 23 weeks caused an increase in urine volume and urine pH (Wilding et al., 1959). Inhalation exposure to 470 mg/m^3 for 10 weeks caused nasal irritation in rats. No lung damage was noted in either species.

Acute and Systemic Effects of Zinc Borate and Zinc Oxide

Smelter workers presumably swallowing large amounts of zinc oxide-containing dust experienced nausea (ATSDR, 1994; HSDB, 1998). Exposure to zinc oxide fumes or ultra fine zinc oxide particles (0.2-1 μm) is associated with metal fume fever, which is a self-limiting occupational illness characterized by fever, chills, myalgias, vomiting, and malaise. Welders exposed to approximately 0.034 mg/m^3 zinc oxide welding fume for 6-8 hours/day exhibited no effects (Marquart et al., 1989). Long term effects or effects due to chronic exposure in humans have not been reported.

The acute oral LD_{50} of zinc borate in rats is 10 g/kg and 9.74 g/kg in males and females, respectively (Silaev, 1981). The LC_{50} in rats is 104 mg/m^3. No oral LD_{50} has been reported for zinc oxide.

Subchronic exposure to 195 mg/kg-day zinc oxide caused anemia and nephrosis in ferrets (Straube et al., 1980). In the same study, 390 mg/kg-day zinc oxide caused pancreatitis and intestinal hemorrhage, and all animals died within 14 days. The NOAEL for oral subchronic exposure in ferrets was approximately 65 mg/kg-day.

Acute exposure to zinc oxide ultra-fine particles at levels as low as 0.8 mg/m^3 for as little as one hour caused decreased lung function and inflammation in guinea pigs (Amdur et al., 1982).

Dermal and Ocular Effects of Boric Acid and Boric Anhydride

Workers exposed to airborne boric acid and boric anhydride experienced more eye irritation and respiratory tract irritation than non-exposed workers (Garabrant et al., 1984).

Boric anhydride dust also caused irritation when applied to the eyes (50 mg) and skin (1 g) of rabbits (Wilding et al., 1959).

Dermal and Ocular Effects of Zinc Borate and Zinc Oxide

Dermal application of zinc oxide to human skin or experimental animals did not cause irritation. Zinc oxide is available in over-the-counter preparations to treat minor skin irritations, burns, chafed skin, and diaper rash (Riley, 1999).

Occupational exposure to zinc oxide has been associated with dermatitis as a result of poor hygiene and dust in the workplace (Turner, 1921). This dermatitis may be partly attributed to the mechanical irritation caused by the dust. Mechanical irritation from airborne dust may be expected to cause conjunctivitis (HSDB, 1998).

Zinc borate (50 mg) instilled in the eyes of rabbits caused conjunctivitis and keratolucoma (Silaev, 1981). Twenty applications of 50% zinc borate in a lanolin ointment was not a dermal irritant to rats or guinea pigs in the same study.

Carcinogenicity and Genotoxicity of Boric Acid and Boric Anhydride

A two-year cancer bioassay in mice fed boric acid for 103 weeks found no evidence of carcinogenicity at doses (48-96 mg/kg-day) causing systemic effects and increased mortality (NTP, 1987). Furthermore, several *in vitro* assays found no evidence to support that boric acid causes mutagenicity or chromosomal aberrations (Benson et al., 1984; Demerec et al., 1951; Haworth et al., 1983; NTP, 1987).

Carcinogenicity and Genotoxicity of Zinc Borate and Zinc Oxide

Although no chronic cancer bioassays were conducted with either zinc oxide or zinc borate, two retrospective epidemiological studies found no link between cancer mortality and living or working near zinc/lead or zinc/copper smelters.

Zinc borate was not mutagenic in the *Salmonella* mutagenicity bioassay with or without metabolic activation (U.S. Borax, 1996). *In vitro* assays for mutagenesis of other zinc compounds were negative. However, inhalation exposure of mice to zinc oxide caused chromosomal aberrations in bone marrow cells (ATSDR, 1994).

In a three-generational study (Weir and Fisher, 1972), Sprague-Dawley rats were fed boric acid (5.9-58.5 mg/kg-day). Doses of 58.5 mg/kg-day caused testicular atrophy and decreased ovulation. The LOAEL for reproductive effects from this study was 58.8 mg/kg-day and the NOAEL was 17.5 mg/kg-day.

In a multi-generational continuous breeding study, Swiss CD-1 mice were fed boric acid (19, 105, and 222 mg/kg-day for males and 32, 148, and 291 mg/kg-day for females) for 27 weeks (Fail et al., 1991; NTP, 1990). Animals (F_0) receiving mid-dose levels had decreased numbers of litters/pair, decreased live pups per litter, and decreased pup weight. High dose animals were infertile, which was linked to the adverse reproductive effects of boric acid on the male. At all dose levels, animals (F_0) had decreased sperm motility. In the female offspring (F_1) of the low-dose animals, significant increases in uterine weight, and kidney plus adrenal weight were observed. A LOAEL of 19 mg/kg-day (the lowest dose tested) was identified based on the decreased sperm motility in the low-dose males.

The developmental effects of boric acid were investigated in Sprague-Dawley rats fed 13.6, 28.5, or 57.7 mg/kg-day during gestational days 0-20 (Heindel et al., 1992). Maternal effects (increased liver and kidney weights relative to body weights) were noted at and above 28.5 mg/kg-day. At doses at or above those causing maternal effects, significant fetal malformations (effects on the eyes, central nervous system, cardiovascular system, and axial skeleton) were noted. Significant decreases in fetal weight occurred at all doses in a dose-dependent manner. The LOAEL was 13.6 mg/kg-day for reduced fetal weight (the lowest dose in the study).

The same study investigated the developmental effects of boric acid in mice (Heindel et al., 1992). Female Swiss mice were fed 43-175 mg/kg-day boric acid in their food during gestational days 0-17. A dose-dependent decrease in fetal body weight that was statistically significant at higher doses (79 and 175 mg/kg-day) was noted. Increased skeletal variations were also noted at these two doses. Maternal toxicity was also seen at those doses. A LOAEL of 79 mg/kg-day and a NOAEL of 43 mg/kg-day were identified for developmental effects in mice.

In a follow-up study, pregnant Sprague-Dawley rats were fed boric acid in their diet (3.3, 6.3, 9.6, 13.3, or 25 mg/kg-day) on gestational days 0-20 (Price et al., 1996). There were no maternal deaths or other overt signs of maternal toxicity at any treatment dose. Boric acid did not affect maternal weight gain, liver weight, the percentage of dams delivering pups, implantation sites/litter, live litter size, the percentage of resorptions, or late fetal death. However, on gestation day 20, there was a significant decrease in fetal body weight and an increase in short rib XIII and wavy ribs at the two highest doses (13.3 and 25 mg/ kg-day). The LOAEL for developmental effects was 13.3 mg/kg-day and the NOAEL was 9.6 mg/kg-day.

Reproductive and Developmental Effects of Zinc Borate and Zinc Oxide

One study found that 100 mg/kg-day zinc oxide fed to rats (strain unclear) for 36 days (21 days prior to mating and gestational days 1-15) had no effect. In the same study, a dose of 200 mg/kg-day administered during gestation days 1-15 caused a decrease in fetal weight and 29% fetal resorption (Schlicker and Cox, 1968). One hundred percent resorption occurred when a dose of 200 mg/kg-day was administered for 36 days, including gestation days 1-21. No reproductive effects of zinc oxide have been reported in animals, and there have been no reports of reproductive or developmental effects associated with zinc exposure in humans.

Neurological Effects

No reports of neurological effects were found for boric acid.

In rats, 487 mg/kg zinc oxide administered for 10 days caused minor neuronal degeneration in the brain, decreased acetylcholinesterase and acid phosphotase, and increased thiamine pyrophosphatase in brain tissue (Kozik et al., 1980). No neurological effects have been reported in other human or animal studies.

Sensitization

No sensitization effects were reported for boric acid, boric anhydride, or zinc oxide.

Pharmacokinetics

Zinc oxide and other zinc compounds were absorbed following application to both intact and abraded skin (Agren, 1990; Agren, 1991; Hallmans, 1977). Absorption may also occur through the lungs, or from swallowing particles cleared from the respiratory tract following inhalation exposure. The rate of gastrointestinal absorption of all zinc compounds is highly variable, ranging from 8-80% in humans depending on an individual's diet (ATSDR, 1992b); absorption can be influenced by the amount of protein, fiber, and trace metals in the diet. Once various zinc compounds are absorbed, zinc is widely distributed in the body. The highest concentrations are found in the muscle, bone, gastrointestinal tract, kidney, brain, skin, lung, heart, and pancreas. Zinc binds to the sulfhydryl, amino, and imidazole groups of proteins and other biomolecules. Excretion is primarily in the feces, although some zinc is excreted in the urine.

Zinc borate is metabolized to zinc oxide and boric acid before being absorbed (National Research Council, 2000). Boric acid is readily absorbed from the gastrointestinal tract, serous cavities, and abraded or inflamed skin (ATSDR, 1992b; HSDB, 1998). Absorption through intact skin is minimal, and the extent of absorption occurring following inhalation is unknown. After absorption, it is distributed throughout the body tissues in both humans and other mammalian species (Murray, 1998). Boron does not accumulate in soft tissue over time, but does concentrate in bone. Boric acid itself is not metabolized and is excreted primarily unchanged. Excretion is mainly through the urine and estimates of the half-life of ingested boric acid range from 4-24 hours.

Summary

Boric Acid and Boric Anhydride

CPSC staff has previously provided its opinion that boric anhydride and boric acid are acutely toxic, as defined in the FHSA regulations, by the oral route of exposure (Bittner, 2001; Hatlelid, 1999b). Moreover, it is staff's opinion that boric acid falls within the CPSC's chronic toxicity guidelines issued under the FHSA. It is a probable reproductive and developmental toxicant in humans, based upon sufficient animal data. There was sufficient evidence of systemic toxicity in animals. Both boric acid and boric anhydride were considered to be probable human skin and eye irritants. There was no evidence of carcinogenicity or neurotoxicity for boric acid.

The dog was the most sensitive species. A NOAEL of 8.8 mg/kg-day was based upon testicular effects observed in a 90-day study in dogs (Hatlelid, 1999b). Therefore, the ADI for oral exposure was 0.088 mg/kg-day. The estimation of the ADI relies on the use of an uncertainty factor of 100 (10 for interspecies variability and 10 for sensitive populations). However, in other species, developmental toxicity, not reproductive toxicity, was the more sensitive endpoint. If there had been a developmental toxicity study in dogs, the ADI might be lower.

Zinc Borate and Zinc Oxide

Staff concluded that zinc oxide fell within the FHSA regulatory definition of acute toxicity by the oral route of exposure (Bittner, 2001; Hatlelid, 1999b). Acute and subchronic oral administration in one species of experimental animal caused anemia, pancreatitis, nephrosis, neurological effects, intestinal hemorage, and death. There was insufficient data on the acute toxicity by inhalation or dermal exposure to make a determination. Zinc oxide did not meet the definition for toxic under the FHSA. Based on the limited evidence of systemic toxicity in subchronic feeding studies in ferrets, zinc oxide may be considered possibly toxic to humans. It also is considered a possible developmental and neurological toxicant in humans, as well as a possible skin irritant. Regarding the carcinogenicity of zinc oxide, there is insufficient evidence to make a conclusion.

CPSC staff concluded that while studies in experimental animals indicate zinc oxide may cause certain treatment-related adverse effects, the available data was insufficient to estimate an ADI (Hatlelid, 1999b).

Decabromodiphenyl Oxide

A series of memos by CPSC staff have reviewed several issues associated with the use and toxicity of brominated FR chemicals including decabromodiphenyl oxide (DBDPO) (Babich et al., 2004; Babich and Thomas, 2001; Bittner, 1999; Bittner, 2001). The following is a brief summary of the important points relating to the toxicity of decabromodiphenyl oxide discussed in those four memos.

Summary

Decabromodiphenyl oxide is a flame retardant that is typically used in combination with antimony trioxide.

Decabromodiphenyl oxide has low acute toxicity by the inhalation, oral, and dermal routes of exposure, and thus in staff's opinion, is not toxic under the FHSA regulatory definition.

Decabromodiphenyl oxide is a possible developmental toxicant in humans, based on limited evidence in animals. Staff is closely monitoring new developments in this area of research as a result of the recent observation of cardiac malformations in two Sprague Dawley rat pups in a developmental toxicity study (Hardy, 2002). Though the finding was not statistically significant, the observation of a rare lesion is a potential concern.

Staff is also monitoring developments relating to the neurobehavioral effects of decabromodiphenyl oxide as the result of the adverse effects reported in a recent developmental toxicity study (Viberg et al., 2003). In this study, decabromodiphenyl oxide induced neurotoxic effects in adult mice exposed on postnatal days (PND) 3, 10, or 19. Changes in spontaneous behavior tests (locomotion, rearing, and total activity) were observed, and about 5% of the ^{14}C-labeled compound was found in the brain 24 hours after dosing. However, there are a number of limitations of the study (i.e., relatively small number of animals per treatment group; dosing done with a fat emulsion; behavioral tests conducted only once; evaluation of only one neurobehavioral endpoint; and the use of only one species) and the relevance of the results to human health is uncertain. At present, decabromodiphenyl oxide is considered a possible neurotoxicant in humans, based on limited evidence in animal studies.

Based on the minimal evidence of carcinogenicity in animals along with the lack of genotoxicity, it was concluded by CPSC staff that DBDPO is possibly carcinogenic in humans according to the CPSC's chronic hazard guidelines. The evidence for carcinogenicity, developmental toxicity, and reproductive toxicity was not sufficient to satisfy the definition of toxic under the FHSA. There is no evidence to indicate that decabromodiphenyl oxide causes dermal irritation or sensitization. Additionally, no clinical or histopathological signs of neurotoxicity have been reported in any of the acute, subacute, or chronic studies examined.

Decabromodiphenyl oxide is considered toxic under the FHSA regulatory definition. This conclusion is based on the liver and thyroid effects in subchronic and lifetime feeding studies in rodents (NTP, 1986).

Staff calculated an oral ADI of 3.2 mg/kg-d (Bittner, 2001), based on the liver effects observed in male mice in a 2-year chronic feeding study (NTP, 1986). The LOAEL of 3,200 mg/kg-day was divided by an uncertainty factor of 1000 (10 for interspecies variability, 10 for sensitive populations, and 10 for use of the LOAEL rather than the NOAEL).

Melamine

No prior toxicity assessment of melamine was done by CPSC staff.

General Background

Melamine is produced by heating dicyandiamide or urea under pressure. Melamine may be used as both an additive (e.g., foam) or reactive FR. When reacted with formaldehyde, it forms synthetic resins that can be molded into objects such as dishes, containers, utensils, or handles, or used as laminating agents or coating materials for wood, paper, and textiles. Melamine and melamine derivatives (e.g., melamine cyanurate and melamine polyphosphate) are also used as flame retardants in a variety of plastics, sealants, and paints.

Toxicity

Acute and Systemic Effects

The acute oral LD_{50} of melamine is 3.2 and 3.8 g/kg in male and female Fisher 344/N rats, respectively, and 3.3 and 7 g/kg in male and female $B6C3F_1$ mice (NTP, 1983). Lethal doses were associated with lacrimation, dyspnea, intermittent tremors, and coma prior to death. Paralysis of forequarters was also noted.

In rats, single doses of 2.4 g/kg caused no effects other than crystalluria and diuresis (Lefaux, 1968). The crystalluria was attributed to the excretion of dimelamine monophosphate crystals. Rats administered five successive intraperitoneal doses of 500 mg/kg exhibited moderate transient weight loss and crystalline deposits in the renal tubules.

In a 13-week subchronic study (Melnick et al., 1984), melamine was fed to F344 rats (560-1,700 mg/kg-day for males and 560-1,600 mg/kg-day for females) and $B6C3F_1$ mice (1,400-4,700 mg/kg-day for males and 1,800-5,900 mg/kg-day for females). A dose-dependent increase in urinary bladder calculi was found in all treated male rats. In female rats, calculi were observed in some animals fed 1,400 mg/kg-day melamine or more. Calculi were found in male mice receiving 2,800 mg/kg-day, and female mice consuming 3,500 mg/kg-day or more. Ulceration of the bladder epithelium was observed in male mice fed diets containing 2,000 mg/kg-day and female mice fed 4,800 mg/kg-day or more. Sixty percent of the mice with bladder ulcers also had bladder stones. In the second part of this study, F344 rats were fed a reduced amount of melamine (72-1,300 mg/kg-day for males and 84-1,300 mg/kg-day for females) for the same duration to determine a no-effect level for urinary bladder stone formation. There was a dose-dependent increase in the incidence of calculi in male rats with urinary bladder calculi present in the animals receiving even the lowest dose (2/10). Hyperplasia of the bladder epithelium was noted in male rats receiving 300 mg/kg-day melamine or more. No urinary bladder stones or hyperplasia were found in any of the female rats. The

LOAEL for the presence of calculi in male rats was 72 mg/kg-day. The NOAEL was 800 mg/kg-day in female rats and 2,000 mg/kg-day in mice of either sex.

Dermal and Ocular Effects

A 1% aqueous solution caused little or no irritation on occluded guinea pig skin (Trochimowicz et al., 1994). In rabbits, melamine caused no primary skin irritation or signs of systemic toxicity when applied under an impervious cover at doses up to 1 g/kg for 18 hours. Mild, transient irritation resulted when a dry compound was instilled into the eyes of rabbits, though a 10% aqueous melamine suspension was without effect.

Carcinogenicity and Genotoxicity

There are no case reports or epidemiological studies available to evaluate the carcinogenicity of melamine to humans.

The carcinogenicity of melamine was investigated by administering F344 rats (126-263 mg/kg-day for males and 262-542 mg/kg-day for females) and $B6C3F_1$ mice (327-688 mg/kg-day for males and 523-1065 mg/kg-day for females) in their diet for 103 weeks (Melnick et al., 1984; NTP, 1983). Melamine was not carcinogenic in female rats or mice of either sex. A statistically significant increase in transitional cell carcinomas of the urinary bladder in male rats was observed in the group receiving 263 mg/kg-day. There was also a statistically significant association between urinary bladder tumors and calculi formation in male rats exposed to the high dose. No tumor formation was observed at the lowest dose (126 mg/kg-day) administered to male rats.

In a subsequent study, male F344/DuCrj rats fed melamine in their diet (430 or 1,200 mg/kg-day) for 36 weeks had urinary calculi and bladder tumors, including papillomatosis, papillomas, and carcinomas (Ogasawara et al., 1995). Co-treatment with 5% and 10% sodium chloride (NaCl) decreased the formation of both the calculi and bladder tumors. The increase in water intake caused by the NaCl, which increased urinary volume diluting the urinary melamine, was thought to be responsible for reduction in the precipitation of urinary melamine. The decrease in calculi was considered to be directly related to the reduction in bladder tumors (Melnick et al., 1984; NTP, 1983; Ogasawara et al., 1995).

In an initiation-promotion study, a single topical application of 1 μmol melamine (60 mg/kg, assuming a 20 g mouse) in acetone was applied to the back of shaved female CD-1 mice (Perrella and Boutwell, 1983). This was followed by twice weekly applications of the chemical promoter, 12-O-tetradecanoyl phorbol 13-acetate (TPA), for 31 weeks. In this two-stage mouse-skin assay, there was no increase in the incidence of papillomas in melamine-treated mice.

Sex-linked recessive lethal mutations were not induced by melamine administered in the diet (Rohrborn, 1962). Melamine was not mutagenic to *Salmonella* in the presence or absence of an exogenous metabolic system (Haworth et al., 1983; Lusby et al., 1979; NTP, 1983; Seiler, 1973). Negative results were also reported in sister chromatid

exchange in Chinese hamster ovary cells *in vitro*, and micronuclei in mouse bone marrow *in vivo* (Mast et al., 1982a; Mast et al., 1982b).

Reproductive and Developmental Effects

Intraperitoneal injections of 70 mg/kg administered to pregnant rats (strain unclear) on gestation days 5 and 6, 8 and 9, or 12 and 13 caused no toxic effect or gross malformation in the fetuses (Thiersch, 1957). However, this study has been determined to be inadequate for evaluating prenatal toxicity because of incomplete reporting of experimental methods and fetal examination results (IARC, 1986).

Neurological Effects

No neurological studies were found for melamine.

Sensitization

Human subjects given melamine patch tests showed no evidence of either primary irritation or sensitization (Schaffer, 1955).

A 1% aqueous solution applied to occluded guinea pig skin caused no sensitization (Trochimowicz et al., 1994).

Pharmacokinetics

In adult rats administered a single oral dose of 0.38 mg of ^{14}C-radioactively labeled melamine, the highest amounts of melamine were found in the kidneys and bladder (Mast et al., 1983). Ninety percent of the melamine was excreted in the urine within the first 24 hours. Negligible amounts could be measured in the exhaled air or feces. Chromatographic analysis of the plasma and urine indicated that melamine is not metabolized in the rat.

Summary

Melamine has a low order of acute toxicity based on the oral LD_{50} of 3.2-3.8 g/kg in rats, but, in staff's opinion, does meet the regulatory definition of acute toxicity under the FHSA.

Melamine is a possible eye irritant, based on limited evidence in animals. Melamine as a dry compound was mildly irritating to the eyes of rabbits (Trochimowicz et al., 1994).

There is no evidence of neurotoxic, reproductive, or developmental effects for melamine. There is also no evidence that melamine causes sensitization.

Melamine is not mutagenic and the evidence for carcinogenicity was not sufficient, in staff's opinion, to satisfy the definition of toxic under the FHSA regulations. A significant association was found between urinary bladder carcinogenesis and bladder calculi in male rats, but not in female rats or mice of either sex. The data indicate that

urinary bladder tumors in the male rat are the result of a non-DNA-reactive mechanism involving epithelial hyperplasia secondary to the presence of melamine bladder calculi when rats are administered a dose of melamine sufficient for precipitation in the urine. Although the formation of bladder calculi is possible in humans, calculi are typically not present in the human urinary tract for a length of time to cause epithelial hyperplasia. Calculi in humans are typically quickly voided as a result of the anatomy of the urinary tract and the upright, bipedal nature of humans (Burin et al., 1995; Rodent Bladder Carcinogenesis Working Group, 1995).

Since evidence for melamine, in staff's opinion, does not meet the definition of toxic under the FHSA, the calculation of an ADI is unwarranted at this time.

Vinylidene chloride

No prior toxicity assessment of vinylidene chloride was done by CPSC staff.

General Background

Vinylidene chloride is produced by dehydrochlorination of 1,1,2-trichloroethane in the presence of excess base, or by thermal decomposition of methyl chloroform (1,1,1-trichloroethane). Vinylidene chloride is mainly used for the production of polyvinylidene chloride polymers, which contain as much as 85% vinylidene chloride. Vinylidene chloride is co-polymerized with other vinyl monomers, such as acrylonitrile, alkylates and methacrylates, vinyl acetate and vinyl chloride (Gibbs and Wessling, 1983). These co-polymers are used as flexible films for the food packaging industry; as coating for steel pipes and structures; and in adhesive applications. Halogenated polymers such as polyvinylidene chloride are used as flame retardant coatings for fiber, carpet backing, and piping. Thus, consumers mostly come in contact with the polymer.

Toxicity

The toxicity of vinylidene chloride is attributed not to the parent compound but to the reactive intermediate metabolites of vinylidene chloride that bind covalently to cellular macromolecules. The amount of binding to macromolecules in tissues is inversely related to the decline of glutathione, so that the severity of tissue damage parallels the loss of glutathione. Therefore, nutritional state, species, strain, and sex, which affect glutathione levels, can have a significant impact on the toxic effects of vinylidene chloride.

Acute and Systemic Effects

The oral LD_{50} in rats is 1,500 mg/kg (Jenkins et al., 1972). The LC_{50} in rats following exposure for 4 hours with a two-week observation was 25,000 mg/m^3 (Siegel et al., 1971).

Experimental studies using mice and rats indicate that the liver, kidney, and lung are the primary targets of acute oral or inhalation exposure. The acute effects of vinylidene

chloride on the liver include increased liver enzymes in the serum (Jaeger et al., 1977a; Jaeger et al., 1977b; Jenkins and Andersen, 1978; Jenkins et al., 1972; Reynolds et al., 1980; Short et al., 1977c) and histopathological changes, including disruption of bile canaliculi, cytoplasmic vacuolization, and hemorrhagic necrosis (Short et al., 1977c) (Kanz and Reynolds, 1986; Reynolds et al., 1984). The acute toxic effects of vinylidene chloride on the kidney consist of increased kidney weight, increased plasma urea nitrogen and creatinine concentrations, and histopathological changes such as vacuolization, tubular dilatation, and necrosis (Jackson and Conolly, 1985; Jenkins and Andersen, 1978; Short et al., 1977c). Vinylidene chloride also caused extensive histopathological changes in the Clara cells of the lungs, pulmonary edema, hemorrhage, and focal lung collapse in mice (Forkert et al., 1985; Forkert et al., 1990; Forkert and Reynolds, 1982).

Male and female F344 rats were administered 10, 50, 100, 500, or 1,000 mg/kg-day by oral gavage in a 14-day study (NTP, 1982). Mean body weight was significantly depressed at doses $\geq$ 500 mg/kg-day. Hemorrhagic necrosis of the liver was associated with the fatality of rats receiving 500 mg/kg-day (3/10) and 1,000 mg/kg-day (7/10).

NTP (1982) also conducted a 14-day study in male and female B6C3F$_1$ mice administered 10, 50, 100, 500, or 1,000 mg/kg-day by oral gavage. All mice receiving 1,000 mg/kg-day died. Hemorrhagic necrosis of the liver was observed in all of mice that died.

In a 13-week subchronic study, F344 rats of either sex were orally administered 5, 15, 40, 100, or 250 mg/kg-day five times a week (NTP, 1982). Representative tissues from controls and animals receiving 250 mg/kg-day were examined microscopically and the livers of all groups were examined. Mean body weight was depressed 13% in males receiving 250 mg/kg-day compared with control. Three female rats receiving 250 mg/kg-day died; all showed severe centrilobular necrosis of the liver. Minimal to moderate hepatocytomegaly was noted in the remainder of the rats receiving 250 mg/kg-day. Minimal to moderate hepatocytomegaly was seen in male (6/10) and female (3/10) rats receiving 100 mg/kg-day. Centrilobular necrosis of the liver was observed in both male and female mice receiving doses of 100 and 250 mg/kg-day. No biologically significant changes occurred in animals receiving 40 mg/kg-day or less. The NOAEL was 40 mg/kg-day (adjusted to a continuous daily exposure of 28.6 mg/kg-day) and the LOAEL was 100 mg/kg-day (adjusted to a continuous daily exposure of 71.4 mg/kg-day).

NTP (1982) also evaluated B6C3F$_1$ mice of either sex orally administered 5, 15, 40, 100, or 250 mg/kg-day five times a week. Representative tissues from controls, and animals receiving 100 and 250 mg/kg-day were examined microscopically. The livers of all groups were examined. Mean body weight was depressed by 14% in males receiving 250 mg/kg-day. Centrilobular necrosis of the liver was seen in 50% of the male and females receiving 250 mg/kg-day, and in 20% of the males and females receiving 100 mg/kg-day. No biologically significant changes occurred in animals receiving 40 mg/kg-day or less. The NOAEL was 40 mg/kg-day (adjusted to a continuous daily

exposure of 28.6 mg/kg-day) and the LOAEL was 100 mg/kg-day (adjusted to a continuous daily exposure of 71.4 mg/kg-day).

In a 2-year chronic toxicity study, male and female Sprague-Dawley rats were administered 50, 100, or 200 ppm in the drinking water (Quast et al., 1983). The time weighted average exposure over the 2-year period was 7, 10, or 20 mg/kg-day for the males and 9, 14, or 30 mg/kg-day for the females. In the male rats receiving 20 mg/kg-day, there was a statistically significant increased incidence of minimal hepatocellular fatty change and minimal hepatocellular swelling. In female rats receiving 14 and 30 mg/kg-day, there was a statistically significant increased incidence of minimal hepatocellular fatty change at the termination of the study. There was also a statistically significant increase in minimal hepatocellular swelling observed in females at all doses. No hepatocellular necrosis, change in liver weight, change in clinical chemistry measurements diagnostic for liver damage, or other indication of abnormal liver function occurred at any exposure in either sex. Based on this, the hepatocellular swelling was not considered to be an adverse affect in this study (U.S. EPA, 2002). The NOAEL was 10 mg/kg-day in males and 9 mg/kg-day in females. The LOAEL for increased incidence of hepatocellular mid-zonal fatty change was 20 mg/kg-day in males and 14 mg/kg-day in females.

A chronic toxicity study examined the effect of inhaled vinylidene chloride in Sprague-Dawley rats exposed to 100 or 300 mg/m^3 for 6 hours/day, 5 days/week for 18 months (Quast et al., 1986). Interim sacrifices were made at 1, 6, and 12 months. Treatment-related histopathological findings included minimal hepatocellular fatty change in the mid-zonal region of the hepatic lobule at the 6- and 12-month sacrifices in both males and females. However, there was no progression of severity. At the 18-month sacrifice, a statistically significant fatty change was only seen in female rats receiving 300 mg/m^3. Six months after exposure was discontinued, the effect was no longer evident suggesting a reversibility of the effect. No changes in mortality, appearance and demeanor, body weight, clinical chemistry determinations, hematological evaluations, urinalysis, or cytogenetic evaluation of the bone marrow were attributable to vinylidene chloride exposure; though, exposure to vinylidene chloride was less than 2 years, the standard length of time for a chronic study. In female rats, the NOAEL was 100 mg/m^3 and the LOAEL is 300 mg/m^3. The NOAEL in male rats was 300 mg/m^3 (the highest exposure tested).

Dermal and Ocular Effects

Liquid vinylidene chloride causes irritation when applied directly to the skin of rabbits after only a few minutes of contact (Torkelson, 1994). Although, this may partially be due to the presence of the skin irritant, hydroquinone monomethyl ether (Chivers, 1972). Vinylidene chloride was also moderately irritating to the eyes of rabbits causing pain, conjunctival irritation, and some transient corneal injury (Torkelson, 1994).

Carcinogenicity and Genotoxicity

The health records of 138 individuals occupationally exposed to vinylidene chloride, but not vinyl chloride, were studied (Ott et al., 1976). Career exposures were estimated for

employees who worked in polymerization operations, a monomer production process, or the manufacturing of monofilament fiber. No significant differences in hematology, clinical chemistry, or mortality between the exposed group and the controls were found. However, the study was limited by an inadequate number of subjects, short exposure time, and the examination of a limited number of endpoints.

In a study of the mortality experience of a cohort of 629 males working at two plants in the Federal Republic of Germany producing vinylidene chloride and polyvinylidene chloride, 39 deaths were observed over the length of the study (approximately 20 years) (Thiess et al., 1979). Five cases of bronchial carcinomas were observed. Although greater than expected, the result was not statically significant. Workers in the factory were also potentially exposed to vinyl chloride and acrylonitrile. Furthermore, no data on smoking, a confounding factor, was provided.

Another epidemiological study (Waxweiler et al., 1981) was inadequate to assess the cancer effects of vinylidene chloride because the increased risk of lung cancer in a population of workers in a synthetic plastics plant could not be specifically connected to vinylidene chloride because of multiple chemical exposures.

Multiple studies evaluated the carcinogenicity of vinylidene chloride in laboratory animals following oral exposure. No dose-related, significant increases in tumor incidences were found in BD IV rats (Ponomarkov and Tomatis, 1980), Sprague-Dawley rats (Maltoni et al., 1985; Quast et al., 1983), F433 rats (NTP, 1982), and $B6C3F_1$ mice (NTP, 1982).

A carcinogenicity study exposed male and female Sprague-Dawley rats by inhalation to 10, 25, 50, 100, or 150 ppm for 4 hours/day, 4 to 5 days/week for 52 weeks (Maltoni et al., 1985). Animals were observed until spontaneous death (total duration 137 weeks) at which time full necropsy and histopatological examination were performed. There was a statistically significant increase in each treatment group as compared to controls in the number of females with mammary fibromas and fibroadenomas (i.e., non-malignant tumors). The incidence was 44/56 (78.6%), 24/24 (100%), 20/20 (100%), 21/22 (95.4%), 21/23 (91.3%), and 38/43 (88.4%) in the control, 10, 25, 50, 100, and 150 ppm groups, respectively. The incidence of mammary carcinomas in the exposed animals was consistently less than that of control. No significant increase in tumors was found in males at any site. There were no biologically significant changes in mortality, body weight, or non-cancer effects in any organ of either sex.

In the same study, Maltoni et al. (1985) exposed male and female Swiss mice by inhalation to 40 or 100 mg/m^3 for 4 hours/day, 4 to 5 days/week for 52 weeks. Following the 52-week exposure, animals were observed until natural death (total duration 126 weeks). All incidence data was reported as the number of tumor bearing animals compared with the number of animals alive when the first tumor was observed in that organ. There was a statistically significant increase in kidney adenocarcinomas in male mice exposed to 100 mg/m^3 vinylidene chloride, but not in males exposed to 40 mg/m^3 or in female mice at either exposure. The incidence was 0/126 (0%), 0/25 (0%), and

28/119 (23.5%) in male mice in the control, 40 mg/m^3, and 100 mg/m^3 groups, respectively (U.S. EPA, 1985). There was also a statistically significant increase in mammary carcinomas in female mice at both exposures, although there was no clear exposure-response relationship. The incidence was 3/185 (1.6%), 6/30 (20%), and 16/148 (11%) in females in the control, 40 mg/m^3, and 100 mg/m^3 groups, respectively (U.S. EPA, 1985). The statistically significant increased incidence of pulmonary adenomas in both sexes was not dose-dependent. The incidence was 3/185 (3.9%), 11/28 (39.3%), and 23/141 (16.3%) in males and 6/178 (3.4%), 3/30 (10%), and 18/147 (12.2%) in females in the control, 40 mg/m^3, and 100 mg/m^3 groups, respectively (U.S. EPA, 1985). No pulmonary carcinomas were observed in any of the mice. The researchers discounted the significance of the mammary and pulmonary tumors due to a lack of a dose-response effect. The design of the study makes it difficult to assess tumor development in relation to histopathological changes associated with the usual age-related changes of the kidney as there was no evaluation at the termination of exposure. Additionally, the animals were exposed for only one year.

CD-1 mice were exposed by inhalation to 55 ppm vinylidene chloride for 6 hours/day, 5 days/week for up to 12 months (Lee et al., 1978). No significant increase in tumors was noted as compared to controls. Additionally, in albino Wistar, CD, and Sprague-Dawley rats exposed to vinylidene chloride by inhalation for up to 12, 10, and 18 months, respectively, there was no significant increase in tumors attributed to exposure (Hong et al., 1981; Quast et al., 1986; Viola and Caputo, 1977). However, exposure was less than 2 years in all of these bioassays.

Carcinogenicity in male and female non-inbred Ha:ICR Swiss mice was also evaluated using a dermal initiation-promotion assay, a repeated dermal application assay, and a subcutaneous injection assay (Van Duuren et al., 1979). In the initiation-promotion assay, a significant increase was noted in skin papillomas in female mice treated with 121 mg once. No sarcomas were observed in mice exposed to 40 or 121 mg three times weekly for 595 days in a repeated dermal application assay. In the subcutaneous injection assay, no tumors were found at the injection site after 548 days in mice that received weekly injections of 2 mg for 78 weeks.

The ability of vinylidene chloride to induce DNA alkylation, DNA repair, and DNA replication in the liver and kidneys of male Sprague-Dawley rats and CD-1 mice exposed to 40 or 200 mg/m^3 by inhalation for 6 hours was studied (Reitz et al., 1980). The lungs were not examined in either species. In both rats and mice, a minimal increase in DNA alkylation in the liver and kidney was seen at 200 mg/m^3. In mice, DNA repair in the kidneys was minimally increased at 200 mg/m^3. An increase in tissue damage (kidney nephrosis), DNA replication, and mitotic figures in the kidneys of mice was also noted at this dose. No histopathological damage or increased DNA replication in the liver was observed at either dose in mice. In rats, at 40 mg/m^3, there was a small increase in DNA replication in the kidney. The effects of 200 mg/m^3 in the rat were not studied.

In *Salmonella* and *E. coli* in the presence of an exogenous metabolic system, vinylidene chloride induced mutations (Bartsch et al., 1979; Jones and Hathway, 1978c; Malaveille

et al., 1997; Oesch et al., 1983; Roldan-Arjona et al., 1991; Simmon and Tardiff, 1978; Strobel and Grummt, 1987; Waskell, 1978). Vinylidene chloride also induced reverse mutation and mitotic gene conversion *in vitro* and in a host-mediated assay in mice in *Saccharomyces cerevisiae* (Bronzetti et al., 1983; Koch et al., 1988). In one study vinylidene chloride induced aneuploidy in *Saccharomyces cerevisiae* in the presence and absence of metabolic activation (Koch et al., 1988). Vinylidene chloride increased gene mutations in mouse lymphoma cells (McGregor et al., 1991), but not in Chinese hamster lung cells with and without exogenous metabolic activation (Drevon and Kuroki, 1979). Another study found that vinylidene chloride induced sister chromatid exchanges and chromosomal aberrations in Chinese hamster lung cells only in the presence of an exogenous metabolic system (Sawada et al., 1987). In *in vivo* studies, vinylidene chloride did not induce micronuclei or chromosomal aberrations in bone marrow cells or fetal erythrocytes of mice (Rampy et al., 1977; Sawada et al., 1987). Studies of genotoxicity *in vivo* reported negative results for dominant lethal mutations in mice and rats following oral administration (Andersen and Jenkins, 1977; Short et al., 1977b).

Reproductive and Developmental Effects

The reproductive and developmental toxicity of vinylidene chloride was evaluated in Sprague-Dawley rats (Nitschke et al., 1983). Three generations of male and female rats were continuously exposed to 50, 100, or 200 ppm (approximately 9, 14, or 30 mg/kg-day) vinylidene chloride in the drinking water. Six sets of litters were produced. The physical appearance, body weight, and water consumption of the F_0 animals was not altered. There were also no biologically significant changes in the fertility index, average number of pups per litter, average body weight of pups, or survival of pups at any exposure. In the F_2 and F_{3a} litters of dams, neonatal survival decreased from control values. However, the survival indices were within the range of control values for this strain of rats in this laboratory. Histopathological examination of tissue from adult animals exposed *in utero*, during lactation, and post-weaning revealed slight hepatocellular fatty changes and an accentuated hepatic lobular pattern of a reversible nature. Although the authors did not report the incidence data or statistical analysis of these findings, this effect, seen in the F_1 generation exposed to 100 and 200 ppm (approximately 14 and 30 mg/kg-day) and all the exposure groups of the F_2 generation, is consistent with the effects reported by Quast *et al.* (1983). The NOAEL for reproductive and developmental toxicity was 200 ppm (the highest exposure tested; approximately 30 mg/kg-day).

A developmental study administered female Sprague-Dawley rats 0.02 or 18 mg/kg-day vinylidene chloride in the drinking water for 48 or 56 days before mating and for 20 days during gestation (Dawson et al., 1993). Two additional groups of female rats were administered vinylidene chloride in the drinking water only before mating: 0.02 mg/kg-day for 82 days or 18 mg/kg-day for 61 days. Dams were sacrificed on gestational day 22, and the gravid uterus was removed and examined. In the dams exposed before mating and during gestation, there was a statistically significant increase in the percentage of fetuses with cardiac changes (atrial septal, mitral valve, and aortic valve changes). This was based on the total occurrence of affected fetuses. The number of affected litters was: control, 5/21 (24%); 0.02 mg/kg-day, 8/11 (73%); and

18 mg/kg-day, 13/17 (76%). The mean number of affected fetuses per litter for affected litters only was: control, 1.4 (13% of the fetuses in the litter); 0.02 mg/kg-day, 1.75 (16% of the fetuses in the litter); and 18 mg/kg-day, 1.85 (17% of the fetuses in the litter). The mean number of affected fetuses per litter of all litters was control, 0.33 (3% of the fetuses in the litter); 0.02 mg/kg-day, 1.27 (12% of fetuses in the litter); and 18 mg/kg-day, 1.41 (13% of the fetuses in the litter). No exposure-response relationship was demonstrated. These fetal cardiac changes were not seen when dams were only treated prior to mating. This study consisted of a much more thorough evaluation of cardiac development than is done in standard developmental toxicity testing protocols (U.S. EPA, 2002). Whether this effect was unique to this study or previously overlooked in other studies cannot be ascertained. The functional consequence of these fetal cardiac changes remains unclear. To date, no effect on growth or survival relating to these changes has been reported. However, as this is a potential concern, staff will continue to closely monitor new developments in this area of research.

In an inhalation study, pregnant Sprague-Dawley rats were administered 80, 320, or 630 mg/m^3 vinylidene chloride for 7 hours/days on gestation days 6-15 (Murray et al., 1979). Although no maternal toxicity was noted in animals administered 80 mg/m^3, there was a statistically significant depression in weight gain at gestational days 6-9 in dams administered 320 mg/m^3 (45%) and 630 mg/m^3 (86%). There was also a statistically significant, dose-dependent increase in the incidence of skeletal variations (wavy ribs and delayed ossification of the skull) in the embryos of dams receiving 320 and 630 mg/m^3. The NOAEL for developmental and maternal toxicity was 80 mg/m^3 and the LOAEL was 320 mg/m^3; values were not adjusted to continuous exposure.

Developmental neurotoxicity was evaluated in CD-1 rats administered 220 or 1100 mg/m^3 by inhalation for 22-23 hours/day on gestational days 8-20 (Short et al., 1977a). Vinylidene chloride exposure caused a weight loss of 7 grams per dam at 220 mg/m^3 and 15 grams per dam at 1100 mg/m^3. There was also complete resorption of three litters at 1100 mg/m^3. No evidence of developmental neurotoxicity was observed at either exposure when pups exposed to vinylidene chloride were tested at various times from postnatal day 1 to day 21 in a battery of behavioral tasks.

Neurological Effects

Central nervous system depression and signs of drunkenness have been associated with exposure to high concentrations of vinylidene chloride, although the concentration was not specified (Torkelson, 1994). No other neurological effects were reported in animal studies.

Sensitization

A study examined the skin sensitizing potential of vinylidene chloride using the local lymph node assay[2] (Warbrick et al., 2001). Concentrations of 10%, 25%, or 50%

[2] The local lymph node assay is an *in vivo* method measuring increased proliferation of lymphocytes in the auricular lymph nodes, which drain the site of exposure (i.e., ears); sensitizers induce a primary proliferation of lymphocytes in the lymph node draining the site of chemical application.

(acetone:olive oil; 4:1 v/v) vinylidene chloride were topically applied to the dorsum of both ears of mice daily for three consecutive days. None of the concentrations tested elicited a sensitization reaction.

No long-term studies evaluating the immunotoxicity of this compound in laboratory animals were found.

Pharmacokinetics

Vinylidene chloride is rapidly absorbed following ingestion (Jones and Hathway, 1978a; Jones and Hathway, 1978b; Putcha et al., 1986) and inhalation (Dallas et al., 1983). Although the extent of absorption by the skin is unknown, it is thought that dermal absorption is probable due to the low molecular weight and hydrophobic nature of the substance (U.S. EPA, 2002).

Pharmacokinetic studies in animals have shown that vinylidene chloride metabolism is dose-dependent and saturable (Andersen et al., 1979; Dallas et al., 1983; Filser and Bolt, 1979; Filser and Bolt, 1981). Low to moderate levels of inhaled (794 mg/m^3) or ingested (up to 50 mg/kg) vinylidene chloride are excreted mainly as breakdown products in the urine. However, the oxidative metabolism of vinylidene chloride in rats is saturated at concentrations above 794 mg/m^3, and 50 mg/kg administered orally. Any unmetabolized vinylidene chloride following oral or inhalation exposure is expelled unchanged through the lungs.

Murine hepatic and lung microsomal preparations indicate that vinylidene chloride is oxidized by cytochrome P450 CYP2E1 to the reactive metabolites 1,1,-dichloroethylene oxide (DCE-epoxide), 2-chloroacetyl chloride, and 2,2-dichloroacetaldehyde (Dowsley et al., 1995; Dowsley et al., 1996; Lee and Forkert, 1994; Liebler et al., 1988; Liebler et al., 1985). High concentrations of CYP2E1 have been identified in certain cell populations of the kidney, lung, and liver (Forkert, 2001).

These intermediate metabolites can react with water, glutathione, or cellular macromolecules. The metabolite DCE-epoxide efficiently conjugates with glutathione in murine lung and liver microsomes (Dowsley et al., 1995; Dowsley et al., 1996), as well as in i*n vitro* microsomal preparations of human liver and lung (Dowsley et al., 1999). However, when glutathione is depleted, DCE-epoxide and possibly 2-chloroacetyl chloride are associated with increased covalent binding to macromolecules and vinylidene chloride-induced injury (Dowsley et al., 1995; Forkert et al., .1996a, 1996b).

The kidney subsequently catabolizes the glutathione cognates to a variety of urinary excretion products (Jones and Hathway, 1978a). Fifty four percent of a single oral dose of 5 mg of ^{14}C-radioactively labeled vinylidene chloride in rats was eliminated through renal excretion (Reichert et al., 1979). Twenty one percent of the dose was recovered in the expired air, 14.5% in the feces, 2.8% in the carcass, and 7.5% in the cage rinse.

Summary

In CPSC staff's opinion, vinylidene chloride is acutely toxic as defined by the FHSA regulations. Acute oral or inhalation exposure adversely affected the lung, kidney, and liver of experimental animals. Toxic effects included extensive histopathological changes of the Clara cells of the lungs, necrosis of the proximal tubules, and hemorrhagic necrosis of the liver.

In staff's opinion, vinylidene chloride also meets the definition of toxic under the FHSA since there is sufficient evidence of systemic toxicity caused by oral or inhalation exposure in experimental animal. In addition to the minimal fatty change in the mid-zonal hepatocytes of the liver (Quast et al., 1983; Quast et al., 1986), which is considered the critical effect of both oral and inhalation chronic exposure, subchronic oral exposure caused hemorrhagic necrosis of the liver and death in rats and mice (NTP, 1982).

Based on limited evidence in animals (Torkelson et al., 1994), vinylidene chloride is a possible dermal and ocular irritant in humans.

Vinylidene chloride may also be regarded as a possible developmental toxicant in humans, based on limited evidence of developmental toxicity in animals (Dawson et al., 1993). The functional consequences of the fetal cardiac changes associated with the ingestion of vinylidene chloride by pregnant rats in one study remain unclear. Other studies demonstrated developmental toxicity (wavy ribs, delayed ossification of the skull, and fetal resorptions) only in the presence of maternal toxicity (Murray et al., 1979; Short et al., 1977a). New developments in this area of research will be closely monitored by staff. There is no evidence vinylidene chloride causes reproductive toxicity as shown in a three-generational study (Nitschke et al., 1983).

There are no data to indicate that sensitization (Warbrick et al., 2001) or neurotoxicity is a critical effect of vinylidene chloride exposure.

Most mammalian cells show no evidence of genetic toxicity although vinylidene chloride did cause gene mutations in microorganisms in the presence of an exogenous activation system. Numerous studies also assessed the carcinogenicity of vinylidene chloride in rats and mice by inhalation and oral routes of exposure, and in mice by subcutaneous administration and topical application. Although vinylidene chloride showed initiating activity in the two-stage carcinogenesis experiments, it was inactive as a whole-mouse dermal carcinogen and after subcutaneous injection (Van Duuren et al., 1979). None of the bioassays provides any evidence that vinylidene chloride is carcinogenic by oral exposure. One inhalation study demonstrated a sex- and species-specific increase in kidney adenocarcinomas (Maltoni et al., 1985). However, the design of this study (i.e., exposure for only one year and no evaluation at the termination of exposure) makes it difficult to draw any conclusions. Accordingly, vinylidene chloride may be regarded as a possible carcinogen in humans in view of this limited evidence of carcinogenicity in

animals. However, vinylidene chloride would not be considered toxic by virtue of its carcinogenicity under the FHSA.

For oral exposure, the subchronic NOAEL of 28.6 mg/kg-day in rats administered vinylidene chloride five times a week for 13 weeks (NTP, 1982) can be used to estimate the ADI by using an uncertainty factor of 100 (10 for interspecies variability and 10 for sensitive populations). Thus, the subchronic oral ADI is 0.29 mg/kg-day.

QUALITATIVE ASSESSMENT OF POTENTIAL RISK FOR CHRONIC HEALTH EFFECTS

The risk assessment process involves addressing the toxicity potential of a compound, and the potential exposure to the compound. The previous section quantified the toxicity potential of selected FR chemicals. The following section will address the potential exposures to consumers sleeping on mattresses that contain FR-treated barriers.

Exposure Assessment

The approach to determining the potential risk of adverse health effects from consumer products follows guidelines established under the FHSA (CPSC, 1992). After toxicity reviews are conducted and ADI's are derived by CPSC staff, the most likely exposure scenarios are identified and available exposure data are used to estimate the potential health risks that may result from likely exposures. In this assessment, toxicity reviews have been completed for five chemicals/chemical classes including antimony trioxide, boric acid/zinc borate, decabromodiphenyl oxide, melamine, and vinylidene chloride. However, no exposure data have been quantified for these FR chemicals in mattresses. Without specific exposure data on barriers and other treated mattress components, a quantitative assessment of the potential exposure to FR chemicals from mattresses and the potential for risk is not appropriate. However, a qualitative assessment can be conducted by using available FR chemical exposure data from the upholstered furniture risk assessment (Babich and Thomas, 2001) as a surrogate and by making assumptions about the potential exposure from mattress materials.

Included in the CPSC staff risk assessment of 16 FR chemicals used for upholstered furniture was exposure data generated in the CPSC laboratories (Babich and Thomas 2001). Only one of the mattress compounds, antimony trioxide, was assessed in the upholstered furniture risk assessment. A number of experiments were completed to estimate the amount of FR chemical that would migrate from treated upholstery fabrics in scenarios such as dermal contact, mouthing by young children, and cleaning. Although these data were based on FR chemical application to upholstered furniture fabrics, these data will be reviewed and used as a surrogate for exposure to FR's in mattress application scenarios.

Exposure Scenarios

Because of the dearth of available data (i.e., migration studies) on the potential exposure of consumers to FR chemicals used in mattresses, a qualitative assessment of the potential exposure and chronic health effects is presented.

The location of the barrier containing FR chemicals in mattresses may significantly impact consumer exposure to these compounds. Mattresses typically contain a cover fabric referred to as the ticking, foam that comprises the core of the mattress, and an intermediate layer(s) of material such as cotton batting that lies between the ticking and the foam. A barrier may be placed directly beneath the ticking, or under the intermediate layer of material. The intermediate layer of material is referred to as the "sacrificial layer" when the barrier is placed beneath it. When this occurs, the sacrificial layer is expected to burn relatively quickly compared to the material that lies beneath the barrier.

FR-treated barriers can be placed directly beneath the cover fabric (ticking). The potential exposure to consumers from this configuration may be greater compared to scenarios where a sacrificial layer of material lies between the FR-treated barrier and the ticking. Based on this assumption, two exposure scenarios have been created. In scenario 1 which is also referred to as the "typical" scenario, an FR-treated barrier is assumed to be under a sacrificial foam or batting layer. The ticking is quilted to the sacrificial layer to increase the comfort and feel of the mattress. Scenario 1 is considered the most likely method of incorporating barriers into mattresses, particularly in middle to higher cost mattresses. In scenario 2, the FR-treated barrier is assumed to lie directly under the ticking. Scenario 2 is considered the "worst case" scenario in terms of potential FR exposures from the use of barriers, and may include mattresses purchased for hotels, prisons, dormitories, many children's mattresses (twin and bunk beds), and lower-cost mattresses.

Another important factor that may have an impact on exposure is the form of the compound in the barrier. Some of the FR chemicals have been spun into the fiber matrix along with the base polymer. Incorporating the FR chemicals directly into the barrier fibers is expected to significantly reduce the exposure potential. However, FR chemicals may still be released from the fiber in quantifiable amounts. This was illustrated in an investigation by the Danish Environmental Protection Agency (DEPA), evaluating the release of antimony (Sb) from polyester fibers. Antimony is often used as a catalyst in fiber production and is found in measurable quantities in synthetic fibers with the highest concentrations found in polyester, between 160 and 240 ppm. The researchers attempted to extract antimony from the polyester material with artificial saliva and artificial perspiration. Measurable quantities of antimony (3.5 ppm) were found in only one perspiration extractant. However, the detection limits for this procedure was relatively high at 0.5 ppm for saliva extracts and 1.0 ppm for perspiration extracts (DEPA, 2002) and may have influenced the results for antimony. Additional exposure data that quantifies antimony release from barrier fibers are needed before a more conclusive assessment of the potential risk of adverse health effects of this compound can be made.

FR chemicals are incorporated into barriers through a variety of processes. FR chemicals can be attached to materials or fabrics such as polyester, cotton, or fiberglass by using an adhesive polymer or resin. This procedure is commonly referred to as backcoating. Some FR chemicals are bonded to cotton barrier materials through heat-treating. Polyester is also applied in this process to increase the durability of the bonding. The potential release of FR chemicals from these applications is expected to be reduced, but still may be higher than the release of FR chemicals that are directly incorporated into the fiber matrix.

The CPSC staff reviewed a number of factors that may affect FR chemical exposure in order to categorize as low, moderate, or high the potential for consumers who sleep on a mattress to be exposed to FR chemicals. The staff considered the method of application of the FR to the barrier (e.g., polymerization), the expected durability of the FR in the fabric, and the potential for migration of the chemical from the interior of the mattress to the surface. Generally, staff assumed that compounds that are polymerized or incorporated into a fiber matrix will not be released in significant quantities. For the purposes of this assessment, compounds that are polymerized or incorporated into barrier fibers are considered to have low exposure potential (see Tables 2 and 3). FR chemicals that are applied to barriers are assumed to have moderate exposure potential. These application methods include heat treatment and adhesive bonding.

This exposure classification does not specifically consider the potential routes of exposure – dermal, oral, and inhalation. For the purposes of this qualitative assessment, a conservative assumption was made that all of the FR chemical that is expected to be released from a mattress will be absorbed through a combination of all three routes of exposure. In many use scenarios, articles such as mattress pads and mattress covers, are applied to the mattress or sleepwear to the body of the consumer. Staff believes that these articles may reduce exposure to FR chemicals released from the interior of the mattress. Thus the presence of these articles contributes to the conservative nature of this qualitative assessment of risk.

Risk Assessment

This risk assessment qualitatively categorizes the potential for chronic health effects for selected FR chemicals (Tables 2 and 3). This categorization is based on the combination of two factors: 1) the degree of concern, which is presented in the toxicity review for each FR chemical and 2) the exposure potential. As with exposure potential the degree of concern is a qualitative assessment of the potential toxicity of the FR chemical. The degree of concern was subjectively categorized as low, moderate, or high, based on a number of factors including whether any ADI's were calculated for the compound and the severity of the potential health effects. There were no available data that quantify consumer exposure to FR chemicals in mattresses.

The potential for chronic health effects (i.e., risk) has also been categorized as low, moderate, or high, consistent with the assessment scheme for the exposure potential and degree of concern for each FR chemical (see above). In the final designation of the

health effects potential of each compound, FR chemicals categorized in the low category are expected to present only a negligible risk to consumers from exposures that may be experienced by sleeping on mattresses containing these compounds. FR chemicals that are classified in the moderate category may present a greater than negligible risk to consumers, and therefore require additional exposure and/or toxicity data in order to clearly define their potential risk of health effects to consumers. Those chemicals that are placed in the high categories are anticipated to present a greater than negligible risk of health effects in humans. This qualitative assessment of the potential risk of adverse health effects is preliminary, and additional exposure and toxicity data are required before more definitive conclusions can be made.

Table 2. Sacrificial Material Between FR-Treated Barrier and Ticking Preliminary Analysis (Scenario 1)

Degree of Concern[2]	**Exposure Potential**		
	Low	Moderate	High
Low	**Melamine Resin**[1]		
Moderate	**Polyvinylidene Chloride**[1] **with Antimony Trioxide**		
High			

1- This assessment is for the polymerized form of the compound only
2- Degree of Concern refers to the toxicity of the compound

Chart Legend

Potential Risk of Adverse Chronic Health Effects	Low

Table 3. FR-Treated Barrier Directly Beneath Ticking Preliminary Analysis (Scenario 2)

Degree of Concern[2]	**Exposure Potential**		
	Low	Moderate	High
Low	**Melamine Resin**[1]		
Moderate	**Polyvinylidene Chloride**[1] **with Antimony Trioxide**		
High			

1- This assessment is for the polymerized form of the compound only
2- Degree of Concern refers to the toxicity of the compound

Chart Legend

Potential Risk of Adverse Chronic Health Effects	Low

Antimony Trioxide

Antimony is regarded as a possible inhalation carcinogen. The results of the upholstered furniture risk assessment suggested that additional exposure data are needed before a definitive assessment of the potential health effects in consumers can be made. In upholstered furniture, antimony was expected to be backcoated directly onto the cover fabric of the furniture. Mattress barrier manufacturers have reported that antimony will be incorporated directly into the polymer matrix before it is spun into a yarn. Because of the incorporation into fiber matrix, CPSC staff believes that this will significantly reduce the potential for consumer exposure. However, there is limited data to suggest that antimony may be released from a polymer matrix. When antimony is used with decabromodiphenyl oxide, it is incorporated into a resin that is attached to the barrier fabric. Although significant amounts of antimony are not expected to be released from the resin, the potential exposures may be higher compared to antimony incorporated into a fiber matrix.

The results of the limited testing suggest that antimony may be released in measurable quantities from a polymer matrix. Although the concentrations released from fibers were low, the amount of antimony found in a barrier is expected to be higher than in the polyester fabrics described in the Danish Environmental Protection Agency (DEPA) study. The amount of antimony migrating from treated barriers is expected to be higher as well. Antimony incorporated into a resin may be released in greater quantities. In the typical scenario (scenario 1), the barrier will be placed beneath a sacrificial layer of material, which is expected to lower the potential exposure to antimony that may be released from the barrier.

The overall degree of concern for antimony is moderate for both exposure scenarios. When antimony is incorporated into a barrier through a resin in combination with decabromodiphenyl oxide, the exposure potential for the typical and worst case scenarios is moderate resulting in an overall potential of chronic health effects of moderate. In barriers where antimony is incorporated directly into the polymer with polyvinylidene chloride, the exposure potentials are low for the typical and worst case scenarios, resulting in an overall low potential risk for chronic health effects.

Boric Acid/ Zinc Borate

Boric acid is typically applied to cotton batting through an immersion process. Boric acid is applied to the cotton fibers along with a small amount of oil and chemical surfactant to facilitate the bonding of the boric acid to the cotton fibers. To further achieve even distribution and adherence to the fibers, the boric acid is ground to a very fine consistency prior to application. Thermal bonded batting involves adding low melt polyester to cotton fibers and heat treating the mixture.

In a worst case scenario (scenario 2), the amounts of boric acid released are expected to be considerably lower than the amounts that are needed to cause any chronic health

effects, but are expected to be higher compared to FR chemicals that are polymerized into a fiber matrix. Because of the potential developmental effects of this compound, additional data are needed to ensure minimal risk to consumers. The degree of concern for boric acid is moderate, and the exposure potential for the typical and worst case scenarios is moderate. This results in an overall moderate potential risk for chronic health effects in both exposure scenarios.

There is a dearth of information on the potential health effects of zinc borate, therefore the effects of this compound have been evaluated along with the similar compound, boric acid. Exposure data from barrier/mattress applications are needed to fully evaluate any potential health risk to consumers exposed to this compound through mattresses.

Decabromodiphenyl Oxide

Decabromodiphenyl oxide (DBDPO) is used extensively in plastic electronic cabinets. It is also used in upholstered furniture fabrics in the UK. Decabromodiphenyl oxide is considered to be "toxic" by CPSC staff based on the liver and thyroid effects in feeding studies in rodents. However, this compound is poorly absorbed by humans and is less toxic than other less brominated congeners.

Degradation studies have reported that DBDPO may degrade into less brominated congeners in the presence of ultraviolet (UV) light (reviewed in Babich 2004). It is unknown whether, or to what extent, degradation will occur inside a mattress where little, if any, UV light is present. DBDPO has been reported to degrade *in vivo* in laboratory animals and aquatic biota, although the degree to which this may occur in humans is unknown (Mörck et al. 2003).

DBDPO is likely to be incorporated into barriers through the use of adhesive resins, which are applied to synthetic materials. Because it is mixed with a resin, the exposure potential of DBDPO is considered moderate. Additional laboratory data are needed to quantify the potential releases of DBDPO from mattresses that contain barriers treated with DBDPO. Given the moderate degree of concern and the moderate exposure potential, the estimated overall potential risk for chronic health effects resulting from exposure to DBDPO from treated mattresses is moderate when the barrier is placed directly beneath the ticking or when a sacrificial layer is placed between the ticking and the barrier (i.e., in both exposure scenarios).

Melamine

Information on the use of melamine provided by barrier manufacturers indicates that this compound would be incorporated into barriers as a polymer. The polymerization of the melamine into a resin is expected to significantly decrease any potential exposure to consumers. The toxicity potential of melamine is considered low, and exposures that are expected from the use in mattresses are not expected to result in adverse health effects in consumers. However, additional data are needed on the neurological and reproductive effects of this compound before a more definitive conclusion can be made.

This risk assessment is focused on the potential chronic health effects of the FR chemical monomer although the compound is used in the polymeric form in barriers. In this latter case, melamine is reacted with formaldehyde and other non-FR compounds to form fibers that are used to construct a barrier. Formaldehyde is a known sensitizer, and is also regarded as a carcinogen. If melamine-containing products release formaldehyde, sensitization (induction and elicitation of symptoms) may result in some susceptible individuals. Data are needed to determine the conditions for, and potential releases of, formaldehyde from barriers made with melamine/formaldehyde resin fibers. Although the ethylene urea formaldehyde melamine polymer (EUMF) has been shown to be a contact sensitizer, this is primarily through direct contact with EUMF treated fabrics. Staff believes that the mattress ticking should provide a barrier that reduces the potential for contact sensitization.

The overall degree of concern for potential health effects in consumers is low. The exposure potential for the typical and worst-case scenarios is low. The potential risk for chronic health effects is expected to be low for both exposure scenarios.

Vinylidene Chloride

Vinylidene chloride is polymerized along with other compounds such as antimony and spun into fibers. Vinylidene is rapidly absorbed through inhalation, and toxicity resulting from these inhalation exposures has been observed in laboratory animals. Although it is unlikely that significant quantities of this compound will be released from polymers, exposure data are needed to make a more definitive evaluation of the potential health effects that may result from exposure to this compound through mattresses.

Based on available data and staff judgment, the degree of concern for health effects for vinylidene chloride is moderate. Vinylidene chloride is used in a polymerized form in barriers, and is expected to have a low exposure potential. The overall potential risk for chronic health effects in the typical and worst-case scenarios is low.

SMOKE TOXICITY

As part of the upholstered furniture project, comments were raised by the public on the application of FR chemicals and the potential impact of irritant gases produced during combustion of these compounds. CPSC staff has previously reviewed the potential of irritant gases to impact egress in a home fire scenario (Thomas et al., 2003). Because of the dearth of data, very conservative estimates were used for application of FR chemicals to upholstered furniture and the resulting concentrations in air. It was estimated that FR chemicals would not significantly increase egress time for a normal healthy adult. These results can be qualitatively extrapolated to mattress fires to estimate the impact FR chemicals incorporated into mattresses may have on egress. If we assume an estimated 30 minute smoldering time from a mattress that meets the staff's draft proposed mattress flammability standard, staff does not expect that the combustion of FR chemicals that could be used in mattresses will significantly increase egress time during a typical fire

scenario. The potential long-term health effects of the combustion by-products of FR chemicals, are not expected to be severe since the exposures to these compounds are assumed to be short in duration. Melamine (and related compounds) has been shown to produce hydrogen cyanide (HCN) during combustion. If elevated exposures to this compound occur in a fire scenario, it may produce health effects in exposed individuals.

CONCLUSIONS AND RECOMMENDATIONS

Based on available information on toxicity and qualitative estimates of potential exposures, HS staff believes that the use of polymerized melamine compounds (resins) and vinylidene chloride in the manner described by the manufacturers of the barriers containing these compounds is expected to present only a negligible risk of health effects to consumers who sleep on mattresses that contain these compounds. Vinylidene chloride has a higher degree of concern than melamine, but it is used in a polymerized form in barriers which is expected to decrease the potential exposure to consumers. The toxicity potential (degree of concern) and potential exposures to consumers have been subjectively categorized by the staff, based on the best available data on the toxicity potential of each FR chemical, the method of incorporation of the FR chemicals into barriers, and the staff's professional judgment. However, this preliminary assessment may change if additional data on the toxicity and/or exposure potential in mattresses become available. Exposure data for antimony, boric acid/zinc borate, and decabromodiphenyl oxide are needed before more definitive conclusions about the potential risk of health effects to consumers can be made.

Many mattress manufacturers may choose the lowest-cost options to meet the draft proposed flammability standard. These options are likely to include the application of FR chemicals to various mattress components including the ticking, foam, and barriers.

CPSC staff will continue to obtain information on the possible techniques the manufacturers will likely use to meet the draft proposed standard, including the specific FR chemicals that will be used, and the amounts applied to specific mattress components. CPSC staff is planning migration/exposure assessment studies on treated mattress components to obtain data needed to quantify the amount of FR chemical that may be released from these mattress components. These data can then be used to more reliably estimate the potential health risks associated with the use of FR chemicals in mattresses.

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