TAB B

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Memorandum

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SUBJECT: Review of the Health Effects of Natural Rubber Latex*

* This document includes recommendations made by Federal experts.

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Executive Summary

Prior to declaring a substance to be a strong sensitizer, the Federal Hazardous Substances Act (FHSA) requires the Commission to find that the substance has significant potential for causing hypersensitivity upon consideration of the frequency of occurrence and the severity of the reaction. Products containing natural rubber latex (NRL) are capable of causing both immunoglobin E (IgE)-mediated (type I) and cell-mediated (type IV) allergic reactions (hypersensitivity). The staff report focuses on IgE-mediated hypersensitivity, which is an immunological reaction to certain NRL proteins that can act as allergens. Exposure to NRL allergens can initiate the production of allergen-specific IgE antibodies (sensitization). Re-exposure to the allergens may cause an immune response that is associated with clinical symptoms (allergic response). Sensitization, marked by the presence of IgE antibodies, does not necessarily predict the development of clinical symptoms.

An IgE-mediated allergic reaction to NRL can range from mild to severe. Most individuals experience a mild dermatitis or nasal symptoms, but asthma, anaphylactic shock, and death are reported in association with NRL products. The prevalence of NRL allergy in the general population is estimated to be less than 1%. The prevalence of severe reactions (e.g., anaphylaxis) to NRL in the general population is much less. An anaphylactic reaction is more likely in specific groups determined to be at high risk (i.e., occupationally exposed, surgically exposed, and atopic individuals). The prevalence of NRL sensitization and allergy is also significantly greater in these high risk populations.

Several factors including route of exposure, the frequency and duration of exposure, the bioavailability of allergens in different products, and the genetic background of individuals influence the risk of sensitization and allergic reactions to NRL. In addition, the levels of possible allergens in consumer products are rarely known and 1000-fold variations have been reported in groups of products that have been analyzed. Given the lack of information concerning consumer exposure, a quantitative or qualitative estimate of risk for NRL is not possible at this time.

Technical advances in manufacturing and new occupational guidelines for NRL exposure may well impact the prevalence of IgE-mediated hypersensitivity to NRL products in the future, especially in the defined high risk groups where NRL clinical reactions are the most prevalent and severe. Although the only current remedy is avoidance, advances in medical treatment (e.g., immunotherapy) may provide relief to vulnerable individuals.

I. Introduction

In 2000, the U.S. Consumer Product Safety Commission (CPSC) docketed a petition requesting that natural rubber latex (NRL) be declared a strong sensitizer and consumer products containing NRL be labeled accordingly. The Federal Hazardous Substances Act (FHSA) defines the term "strong sensitizer" as a substance that will cause on normal living tissue, through an allergic or photosensitive process, a hypersensitivity which becomes evident on reapplication of the same substance [15 U.S.C. 1261(k)]. The FHSA requires that before making such a declaration, [the Commission], upon consideration of the frequency of occurrence and severity of the reaction, shall find that the substance has significant potential for causing hypersensitivity.

The Code of Federal Regulations at 16 CFR § 1500.3(c)(5)(i) supplements the FHSA by defining a sensitizer as a substance that will induce an immunologically-mediated (allergic) response following sensitization by contact, ingestion, or inhalation. The Commission is directed to consider the available data on the frequency of occurrence and range of severity in healthy and susceptible populations. The minimal severity for designating a substance as a strong sensitizer is a clinically important allergic reaction that may produce physical discomfort, distress, hardship, and functional or structural impairment [16 CFR § 1500.3(c)(5)(iii)]. The minimal frequency is not defined.

The CFR further indicates that the determination that a substance has significant potential for causing hypersensitivity must be made for each individual substance [16 CFR § 1500.3(c)(5)(iv)]. Depending on availability of information, the Commission may consider cross-reactivity with other substances, potency (the threshold of human sensitivity and dose response data), bioavailability (exposure), and results of quantitative or qualitative risk assessment.

This memorandum reviews the available scientific evidence on the potential of NRL-containing products for causing IgE-mediated hypersensitivity[1] based on the severity of the reaction, the frequency of occurrence of the reaction, or the combination of both. Where possible, the staff addresses the additional considerations specified in the regulations (e.g., cross-reactivity).

II. Reactions to NRL

NRL products can cause two general types of reactions: non-immunologically mediated and/or immunologically mediated.

A. Non-Immunologically Mediated Reactions to NRL

Irritant contact dermatitis is a non-immunologically mediated reaction. It is characterized by dryness, fissuring, burning or itching, and erythema (redness) of the skin. It is most commonly associated with the use of NRL gloves and is generally confined to the area of immediate contact. This localized response is caused by exposure to irritants that produce cellular damage to the skin (Hjorth and Fregert, 1979). Some irritants, such

[1] Hypersensitivity is a condition where an individual reacts with allergic signs or symptoms after exposure to a substance after previous exposure to the same substance.

as powder or cornstarch that are often associated with NRL gloves, can mechanically damage skin. Others, such as many of the chemicals added to NRL, can complex with skin proteins causing chemical damage. Irritants can also increase the likelihood of developing an immune-mediated reaction to NRL-containing products when the protective barrier of the skin is breached (Auton et al., 1995; McLelland et al., 1991).

B. Immunologically Mediated Reactions to NRL

An allergic or immune-mediated response[2] to NRL develops in two stages. The first of these involves skin, mucosal, inhalation, or parenteral[3] exposure to a foreign substance, termed an antigen[4], in a quantity sufficient to evoke an immune response (sensitization). Upon re-exposure, the same antigen or one structurally comparable may cause an immune response associated with clinical symptoms (allergic response). Sensitization (immunological priming) can occur in the absence of any clinical manifestations (Hepner and Castells, 2003). It is also important to note that sensitization does not always lead to the development of an allergic reaction, even if re-exposure occurs.

Hypersensitivity to NRL products is either cell- or IgE-mediated depending upon the immunological mechanism involved (discussed further below). Cell- and IgE-mediated hypersensitivity are independent reactions (Nettis et al., 2001). Although both can occur in an individual, one does not inevitably precede the other.

1. Cell-Mediated Hypersensitivity

Cell-mediated hypersensitivity (type IV hypersensitivity, delayed hypersensitivity, allergic contact dermatitis) is characterized by swelling, blistering or vesicle formation, erythema, severe itching, cracking, crusting, desquamation and possible major tissue destruction. These reactions are typically confined to the immediate area of contact, although they may extend beyond the area directly exposed (Belsito, 2000; Lachapelle et al., 1988). While not fatal or life threatening, delayed hypersensitivity reactions can occasionally be serious and debilitating. The similarity of the visible symptoms of both irritant and allergic skin reactions may confuse an accurate diagnosis of true NRL allergy (Wilkinson, 2000).

In cell-mediated hypersensitivity, certain groups of white blood cells known as T cells become sensitized by antigens, resulting in their activation and proliferation. Upon

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[2] Allergy, derived from the Greek term meaning altered reactivity, is an exaggerated immune response to a foreign substance causing tissue inflammation and organ dysfunction. Diverse allergic responses can arise from the activation of different immune pathways resulting in the manifestation of clinical symptoms (Terr, 1997).

[3] Parenteral refers to the introduction of substances into an organism by intravenous, subcutaneous, intramuscular, or intramedullary injection.

[4] An antigen is any substance (protein or other chemicals) specifically recognized by cells of the immune system (i.e., lymphocytes) that induces sensitization and/or an immunological reaction. Antigens that can elicit an IgE response are called allergens.

subsequent exposure to the antigen, a cascade of cellular events may lead to a skin reaction within 48 to 72 hours.

The majority of the cell-mediated reactions to NRL are attributed to one or more of approximately 200 chemicals added during the harvesting, processing, and manufacturing of NRL (Conde-Salazar et al., 2002; Nettis et al., 2003; von Hintzenstern et al., 1991; Wilkinson and Burd, 1998). The chemicals responsible for the bulk of these reactions are added as preservatives, vulcanizing agents, retarders, and accelerators (Zak et al., 2000). These residual low-molecular weight chemicals include thiurams, carbamates, amines, and benzathiazoles (Kurup and Fink, 2001). Although the common NRL chemical additives are well characterized, many of the chemicals are also used in the production of non-NRL products such as resins, graphics, dyes, and adhesives, and may be equally allergenic in these products (Kanerva et al., 1994; Wakelin et al., 1999).

In 1986, a report from the CPSC's Directorate for Health Sciences (HS) considered whether 20 different NRL additives should be labeled as strong sensitizers under the FHSA (Feinman, 1986). The report concluded that although several of these chemicals caused allergic contact dermatitis, additional consumer exposure data were needed for the individual chemicals and chemical groups under discussion.

Staff agrees with the position taken in the earlier CPSC report that the causal agent(s) in a given cell-mediated hypersensitivity reaction could be any one of the chemical additives in NRL. Although a few reports of cell-mediated hypersensitivity reactions to latex with no chemical additives suggest the NRL proteins themselves may be responsible for the reaction (Nettis et al., 2003; Wilkinson and Beck, 1996; Wilkinson and Burd, 1998), staff does not believe that NRL proteins can be identified as the causal agent(s) in cell-mediated reactions to NRL-containing products at this time. Therefore, this report will not discuss cell-mediated hypersensitivity to NRL further.

2. IgE-Mediated Hypersensitivity

IgE-mediated hypersensitivity (type I hypersensitivity, immediate hypersensitivity), develops when an allergen[5], through a relatively complex series of cellular events, causes a second group of white blood cells termed B cells to produce allergen-specific IgE antibodies. These antibodies then bind to receptors on the surface of inflammatory cells, such as tissue mast cells and circulating basophils. This is referred to as sensitization. Upon re-exposure, the allergen cross-links with the IgE antibodies bound to the inflammatory cells and triggers the secretion of mediators from the mast cells and basophils that results in the clinical symptoms of an IgE-mediated reaction.

The targets of these inflammatory mediators include the gastrointestinal tract, the skin, the respiratory system, and the vasculature. The symptoms range from flushing,

[5] An allergen is a type of antigen that can initiate an immunoglobulin E (IgE) response or interact with IgE antibodies, causing an allergenic response (Plaut and Zimmerman, 1993); IgE antibodies are a class of proteins that bind specific allergens and subsequently cause the release of inflammatory mediators from specialized cells.

urticaria (localized or diffuse)[6], and nasal symptoms to bronchospasm, hypotension, arrhythmia, and cardiac or respiratory arrest. Other clinical reactions include conjunctivitis, nausea, vomiting, shortness of breath, generalized edema (swelling), edema of the tongue and larynx, and tachycardia (rapid heart beat).

NRL contains a varied assortment of proteins, some of which are potential allergens capable of generating and reacting with IgE antibodies. The presence of NRL-specific IgE antibodies does not necessarily predict the development or the severity of clinical symptoms (Akasawa et al., 1995); it is merely an indication of sensitization. Individuals with relatively high concentrations of IgE circulating in their blood may experience no clinical symptoms when exposed to NRL allergens; conversely comparatively low levels of allergen-specific IgE antibodies may be associated with clinical symptoms.

Despite the large number of scientific studies on allergic reactions and sensitization, such as those to NRL, case histories do not or cannot identify the initiating event resulting in sensitization. The allergen exposure levels (threshold levels) expected to sensitize an individual and the point at which a sensitized individual may develop a clinical reaction or a severe clinical reaction may occur are also not defined and are likely to differ between individuals.

III. Severity of IgE-Mediated Reaction

According to 16 CFR §1500.3(c)(5)(iii), the minimal severity for designating a substance as a strong sensitizer is a clinically important allergic reaction. The strong sensitizer may produce substantial illness, including physical discomfort, distress, hardship, and/or functional impairment that may, but not necessarily, require medical treatment or produce loss of functional activities. The spectrum of IgE-mediated hypersensitivity reactions extends beyond these minimal regulatory requirements to the possibility of life-threatening reactions, such as anaphylaxis[7].

About 10 to 20% of individuals exhibiting clinical IgE-mediated reactions to NRL experience symptoms that extend beyond localized urticaria, conjunctivitis, sneezing, and rhinitis (de Groot et al., 1998; Hunt et al., 1995; Jaeger et al., 1992; Rankin et al., 1993; Rueff et al., 1998). However, the number of individuals experiencing more severe, potentially life threatening anaphylactic reactions, has remained relatively low. A comprehensive literature review of anaphylaxis in the general population of the United States determined that annually between 8.7 and 63 million individuals were at risk of an anaphylactic reaction from all the causative agents studied (i.e., drugs, foods, insect stings, and NRL) with approximately 1,500 deaths per year resulting (Neugut et al., 2001). As for NRL-induced anaphylaxis, the Food and Drug Administration (FDA) received a total of 1,100 reports between 1988 and 1993, 15 of which proved fatal (Matasar and Neugut, 2003). This yields an average of 220 cases of NRL-induced anaphylaxis per year. Thus,

[6] Urticaria an eruption of raised edematous patches of skin, referred to as wheals or hives, typically accompanied by intense itching.

[7] Anaphylaxis is a rapidly developing clinical syndrome involving bronchoconstriction, gastrointestinal distress, and cardiovascular collapse.

based on a population of 285 million (2001 U.S. census), it is estimated that annually approximately 0.00008% of the United States population would experience an anaphylactic reaction to a NRL product. Because most of the incidents of NRL induced anaphylaxis are associated with invasive mucosal membrane exposure during surgical or other medical procedures (Weido and Sim, 1995), the estimated annual number of individuals likely to experience an anaphylactic reaction is presumed to consist largely of these specific populations, not the general population.

IV. Prevalence of Sensitization and Allergic Reactions to NRL

A. General Background

In order to estimate the prevalence[8] of NRL allergy, an accurate diagnosis of NRL allergy is needed. Currently, there is no universally accepted standard approach for diagnosing NRL allergy. In the United States, a diagnosis of NRL allergy is based on patient history and *in vitro* testing[9] (Warshaw, 1998). Outside the United States, *in vivo* skin testing[10] is also used to make a diagnosis. Provocation testing[11] may be used if a patient's history and *in vitro* test results are discordant. These tests are described in Appendix A.

A number of factors complicate the comparison and use of available peer-reviewed epidemiological studies on the prevalence of NRL sensitization and allergy: (1) the lack of standardized *in vivo* test reagents and provocation test methodologies; (2) the low prognostic value of clinical reactions and *in vitro* tests measuring serum IgE antibodies in the general population; (3) the varied specificity and sensitivity of the test methods used to measure NRL-specific IgE; (4) erroneous use of the term NRL allergy in lieu of NRL sensitization when discussing prevalence; and (5) the discordance between a patient's history and laboratory testing. For example, only two-thirds of individuals with self-reported upper or lower respiratory symptoms attributed to NRL glove exposure demonstrated a positive skin prick testing response illustrating the discrepancies that exist between test results and clinical histories (Tarlo et al., 1997). Studies estimating the prevalence of NRL allergy in a population by measuring NRL-specific IgE antibodies in blood samples (Merrett et al., 1999; Ownby et al., 1996) are actually measuring the prevalence of NRL sensitization, not NRL allergy. Because the FDA has not yet approved a standard NRL reagent for use in the United States, current non-standardized NRL test extracts used for *in vivo* skin prick testing can vary greatly in allergenicity; this makes comparisons between the results of different studies problematic (Hamilton et al., 2002;

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[8] Prevalence refers to the percentage of existing cases of a given condition affecting a given population at a given point in time, whereas incidence is the number of new cases that occur during a specified time period in a given population (Gordis, 1996). Although both measure the frequency of occurrence, when discussing NRL sensitization and/or allergy, prevalence is the appropriate terminology to use.

[9] *In vitro* tests quantify serum IgE antibodies.

[10] *In vitro* skin prick tests involve monitoring the reaction to a small amount of a preparation containing soluble NRL allergens introduced into the skin.

[11] Provocation testing puts the individual in an NRL-containing environment or directly exposes them to an NRL-containing product.

Kelly et al., 1993). Also, the specificity of IgE immunoassays used to diagnose NRL sensitization is less than 95% (Hamilton et al., 1999; Ownby et al., 2000) and consequently can lead to an overestimation of the prevalence rates when used for screening low risk populations (Yeang, 2000).

B. Prevalence of NRL Allergy

Many studies have been conducted to examine and define the prevalence of NRL sensitization and NRL allergy within the general population and certain high risk groups. The prevalence of NRL allergy, especially in the occupational setting, has increased during the past years. Possible explanations for the rising numbers are the increase in the use of NRL gloves since the 1980's in the healthcare fields, increased awareness of NRL allergy, and employee screening.

Several investigators speculate that the increased prevalence of allergic reactions to NRL reflects the increased use of NRL gloves by healthcare workers due to concerns about exposure to the human acquired immunodeficiency disease (AIDS) and hepatitis B viruses (Heese et al., 1997; Roy et al., 1997). In 1987, the Centers for Disease Control (CDC) published a guidance document that came to be known as "universal precautions" (Centers for Disease Control, 1987). It emphasized the need for all healthcare workers to routinely use barrier protection, such as NRL gloves, when contacting body fluids. Annual glove imports into the U.S. rose from less than 2 billion to 22 billion between 1988 and 1997 (Food and Drug Administration, 1999). In 1997, the number of NRL gloves in use worldwide was estimated as 200 billion (Valliere, 1999). Increased demand for NRL gloves, coupled with the removal of a major supplier (Liberia) from the marketplace due to internal political conflicts, was believed to lead to poorer quality manufacturing practices (Charous, 1994). For example, manufacturers shortened the storage time for crude NRL and discontinued steam sterilization of gloves (Dalrymple and Audley, 1992). These events may have increased the levels of allergenic proteins in gloves and in turn, may have increased the number of NRL sensitized individuals in healthcare professions.

Increased awareness, mandatory reporting of illness or injury due to a medical device, improved diagnostic testing, employee screening and referrals to allergists, educational campaigns, and government announcements and public health alerts (e.g., Occupational Safety and Health Administration [OSHA] and FDA) are also speculated to have contributed to the increased documentation of NRL allergy. However, because the epidemiological evidence is limited, there is no conclusive explanation at the present time for the apparent increase in reports of IgE-mediated hypersensitivity to NRL products.

1. High Risk Populations

Specific sub-populations of individuals may be at increased risk for developing NRL sensitization and allergy. These include occupationally exposed individuals, children who have undergone multiple surgical procedures, and individuals with atopy[12]. The prevalence of NRL allergy within each sub-population, and the dominant factor(s)

[12] Atopy is a predisposition, possibly genetically controlled, for developing an IgE-mediated response to common environmental allergens (Izuhara and Shirakawa, 1999).

responsible for the development of NRL allergy within each group are addressed directly below.

a) Occupationally Exposed Individuals

Workplace NRL exposure is a risk factor. A major source of occupational exposure is NRL gloves. Healthcare workers, dental workers, laboratory workers, hairdressers, food service workers, and housekeeping personnel are some of the individuals who are likely to have repeated exposure to NRL gloves.

Healthcare workers constitute the majority of occupationally exposed individuals at risk for IgE-mediated hypersensitivity to NRL, primarily due to repeated glove changes. The prevalence of NRL allergy in healthcare workers ranges from 2.2 to 17% as determined by *in vitro* serologic tests and/or *in vivo* skin prick tests (Arellano et al., 1992; Brown et al., 1998; Grzybowski et al., 1996; Holm et al., 1995; Kibby and Akl, 1997; Larese Filon et al., 2001; Turjanmaa, 1987; Yassin et al., 1994). Some of the specific subgroups of healthcare workers studied include anesthesiologists, registered nurses, physicians, and operating room staff. The variation in prevalence can be attributed to different patterns of NRL exposure (from airborne allergens and wearing NRL gloves), the varied allergen levels of NRL gloves, and the use of different diagnostic tests for determining NRL hypersensitivity.

The prevalence of NRL cell- and IgE-mediated hypersensitivity has also been studied in dental students and dental professionals (Burke et al., 1995; Jacobsen and Hensten-Pettersen, 1995; Katelaris et al., 1996). Heese et al. (1995) detected a positive skin prick test against different NRL solutions in 18 of 206 (8.7%) dental students (Heese et al., 1995). This study, in addition to two others (Levy et al., 1999; Tarlo et al., 1997), also noted an increase in the prevalence of NRL allergy in students as they progressed through dental school. This increase was primarily attributed to the use of high protein powdered NRL gloves.

Laboratory workers were another group studied due to the frequent use of NRL gloves (de Groot et al., 1998). In a study of laboratory workers in the Netherlands, 5 of 66 (8.3%) were positive by skin prick test, although 16 of the 66 (24%) reported NRL-related symptoms (urticaria, rhinoconjunctivitis, and/or asthma).

A recent study examined the prevalence of NRL allergy in construction workers (Conde-Salazar et al., 2002). Sixteen of 230 (7%) construction workers who attended a clinic between 1996 and 2000 had a positive skin prick test to NRL. Fifteen of the 16 workers also had measurable NRL-specific IgE levels.

As for NRL glove manufacturers, a small study in Canada found 7 of 64 (11%) factory workers had a positive skin prick test to NRL (Tarlo et al., 1990). Another study of workers in a NRL glove manufacturing plant in Malaysia demonstrated a positive skin prick test in 2% of the workers (Azizah et al., 1996). A larger study looked at the prevalence of NRL sensitization in NRL tree tappers (n = 475) and NRL glove factory workers (n = 583) in Thailand (Chaiear et al., 2000). Of the tree tappers and factory workers exposed to moderate aeroallergen levels (2.3-2.4 micrograms per cubic meter ($\mu g/m^3$)), 1.3 to 1.7%

were NRL sensitive as determined by a symptom questionnaire and skin prick test. The prevalence of NRL sensitivity in factory workers exposed to higher aeroallergen levels (15.4 $\mu g/m^3$) was 2.4%. The relatively low prevalence of NRL sensitization in the factory workers [as compared to that of United Kingdom healthcare workers (14.6%) who were exposed to lower aeroallergen levels (0.4-0.5 $\mu g/m^3$) in a prior study by this research group] was attributed to the duration of exposure to NRL. More than 50% of the factory workers had worked in the factory for one year or less with NRL. The prevalence of sensitization in a subgroup of factory workers exposed to NRL for 5-10 years was 11.9%.

b) Surgically Exposed Individuals

Children with spina bifida were one of the first groups established to be at risk for NRL sensitization and allergy. The prevalence of NRL sensitization in individuals with spina bifida ranges from 29 to 64.5% as determined by skin prick testing or *in vitro* methods to measure IgE antibodies in the blood serum (Cremer et al., 1998; De Swert et al., 1997; Mazon et al., 1997; Michael et al., 1996; Pittman et al., 1995; Tosi et al., 1993; Yassin et al., 1992). Hypersensitivity to NRL has also been established in children with congenital gastrointestinal malformations (31%) and those with hydrocephalus internus not associated with spina bifida (42%) (Bode et al., 1996) both of which have undergone multiple surgical procedures.

Children requiring numerous surgical procedures at an early age are subjected to repeated mucosal and visceral exposure to various medical devices containing NRL, including NRL gloves (Edlich et al., 1997). NRL allergens present on the outer surface of surgeon's gloves are transferred to the mucosal membranes where they are readily absorbed (Grote et al., 2000; Levy and Leynadier, 2001).

A positive correlation has been established between the prevalence of NRL hypersensitivity and the number of surgical procedures a child has undergone (Bode et al., 1996; Buck et al., 2000; De Swert et al., 1997; Degenhardt et al., 2001; Mazon et al., 1997; Michael et al., 1996; Niggemann et al., 1998; Pittman et al., 1995). A recent study of 1263 children enrolled prior to their first elective surgery under general anesthesia found that prior surgeries increased the risk of NRL allergy (Hourihane et al., 2002).

Another risk factor may be the child's age at the time of the surgical procedures. Children undergoing one or more surgical procedures within the first 3 to 12 months of life appear to be at greater risk for developing NRL hypersensitivity (Bode et al., 1996; Kwittken et al., 1995; Pires et al., 2002). Certain surgical procedures, such as those involving the gastrointestinal tract and ventricular shunt implantation, are also associated with a risk of developing NRL hypersensitivity (Bode et al., 1996). In the case of ventricular shunt implantation, the increased risk appears to have more to do with the increased number of surgical procedures required than the nature of the surgical procedure itself (Buck et al., 2000).

Szepfalusi et al. (1999) suggest that individuals with spina bifida may have a disease-associated propensity for NRL sensitization independent of increased exposure (Szepfalusi et al., 1999). This group found elevated NRL-specific IgE antibodies in 43% of children with spina bifida in comparison to 6% of children with hydrocephalus and a

ventriculoperitoneal shunt who had undergone a comparable number of operations (n=2) at a young age.

c) Atopic Individuals

One of the risk factors for developing NRL allergy is being atopic. Studies of atopic adults using skin prick testing demonstrated a prevalence of NRL allergy that ranged from 0.85 to 9.4% (Moneret-Vautrin et al., 1993; Turjanmaa et al., 1995). Another study examining children with no history of surgical operations found that the prevalence of NRL hypersensitivity was 8.9% in atopic children compared to 0% in non-atopic children (Bode et al., 1996).

Moreover, atopy as a risk factor appears to act synergistically with other risk factors, such as multiple surgical procedures or occupational exposures. This is illustrated by a study of 596 subjects of all ages using skin prick testing (Moneret-Vautrin et al., 1993). A positive response to skin prick testing was detected in 0.4% of non-atopic, non-exposed subjects. In non-atopic subjects with repeated NRL exposure, the prevalence rose to 7%. The prevalence of positive skin prick testing in atopic subjects with no exposure was 9%, whereas 36% of atopic individuals with a history of frequent NRL exposure demonstrated positive skin prick tests.

2. General Population

In the general population, the prevalence of NRL allergy based on *in vivo* skin tests is estimated to be less than 1% (Gautrin et al., 1997; Liss and Sussman, 1999; Moneret-Vautrin et al., 1993; Tarlo et al., 1997). Of 569 patients seen in a hospital, 272 were classified as non-atopic and having nominal exposure to NRL after answering a questionnaire (Moneret-Vautrin et al., 1993). Skin reactivity to a NRL solution was detected in one individual (0.37%) exhibiting no symptoms to NRL. A study of apprentices starting careers in animal health, pastry making, and dental hygiene determined 5 of 758 (0.7%) had positive skin prick test responses to NRL (Gautrin et al., 1997). Lastly, a cross-sectional study at a dental school using a questionnaire and skin prick testing found that none of the 20 second-year students had a positive skin prick test response (Tarlo et al., 1997).

Higher estimates of the prevalence of NRL allergy in the general population are cited in studies that solely measured NRL-specific IgE antibodies using serological assays. These assays have low specificity and can generate false positive test results that can lead to an overestimation (Ebo et al., 1997; Liss and Sussman, 1999). Measurement of NRL-specific IgE antibodies in the residual serum samples of 1,000 volunteer Red Cross blood donors using an *in vitro* serologic test found 6.4% of the samples positive for NRL-specific IgE, with 2.3% exhibiting strongly positive results (Ownby et al., 1996). Saxon et al. (2000) reported a similar prevalence of NRL-specific IgE levels in blood samples of the general population using the same serological assay (Saxon et al., 2000).

Two additional studies (Garabrant et al., 2001; Sosovec et al., 1998), analyzing stored sera for NRL-specific IgE antibodies levels, estimated the prevalence of NRL sensitization in the general population to be equivalent to that of healthcare workers. The sera samples were part of the National Health and Nutrition Examination Survey

(NHANES III) conducted between 1988 and 1991, and represented a weighted, random sample of a non-institutionalized population in the United States aged 2 months and older. The data collected by the NHANES III also included information on the occupation, health conditions, and demographics of the 5,524 individuals. However, the elevated prevalence of NRL sensitization in the general population reported by these two studies has been attributed to several limitations of the database, in addition to the low specificity of the serological assay used (Wartenberg and Buckler, 2001; Yeang, 2000). There was no quantitative data on the frequency or duration of glove use, no information was provided on the type of glove used (e.g., powdered NRL, powder-free NRL, or non-NRL), and only current and longest-held occupations rather than a complete job history were reported making it difficult to delineate the different populations (Wartenberg and Buckler, 2001). Further, the FDA has concluded that the data in the Sosovec study are not scientifically credible due to poor laboratory practices (www.fda.gov/cdrh/ocd/latexcrada.html).

3. Non-occupational Incidents Reported to CPSC

While the circumstances of sensitization are seldom known, incidents confirming non-occupational allergic reactions to NRL-containing products are reported. Appendix B contains a discussion of the CPSC injury reports citing allergic reactions associated with NRL products. The information provided in these reports did not allow identification of the majority of the reactions as non-immunologically related, cell-mediated, or IgE-mediated, thus precluding an estimate of the prevalence of NRL IgE-mediated allergy. This was primarily the result of a lack of information regarding the individual's history relating to NRL and *in vitro* and/or *in vivo* test results confirming a diagnosis of NRL allergy.

C. Summary of Prevalence

The overall number of reported cases of IgE-mediated allergic reactions to NRL increased after 1987. Possible reasons include increased exposure to NRL products (notably NRL gloves) following the implementation of "universal precautions", altered manufacturing practices, and increased awareness in the general public and in healthcare professionals. The majority of documented IgE-mediated sensitization and/or clinical reactions to NRL occur in healthcare workers, primarily due to repeated glove use.

Excluding the high risk populations (i.e., occupationally exposed, surgically exposed, and atopic individuals), NRL allergy in the general population is estimated to be less than 1%. An even smaller percentage of the United States population (0.00008%) is expected to experience a severe reaction (e.g., anaphylactic reaction) to an NRL product.

V. Cross-Reactivity

A. Fruit-Latex Syndrome

Several IgE-mediated reactions to allergens have been linked with particular food hypersensitivity; this is attributed to the cross-reactions of allergens with molecular homologies[13]. Blanco et al. (1994b) proposed the concept of a fruit-latex syndrome after

[13] Homologous allergens are proteins with similar amino acid sequences and often with similar functions.

noting a significantly high rate of fruit-related hypersensitivity in a group of individuals diagnosed with NRL allergy (Blanco et al., 1994b). On the basis of a suggestive clinical history and a positive skin prick test, 52% of individuals diagnosed as having NRL allergy also demonstrated sensitivity to various fruits and vegetables. Moreover, in a larger study, 42.6% of 136 patients with NRL allergy reported adverse symptoms after consuming several different fruits (Brehler et al., 1997b). RAST inhibition[14] data confirmed the presence of cross-reacting antibodies that recognized NRL and various fruit allergens in these patients.

More than 20 different foods, fruits, or plants have been identified as immunologically cross-reactive with NRL (Abeck et al., 1994; Alenius et al., 1996c; Anliker et al., 2001; Antico, 1996; Blanco et al., 1994a; Blanco et al., 1994b; De Greef et al., 2001; Duque et al., 1999; Fuchs et al., 1997; Garcia Ortiz et al., 1998; Kim and Hussain, 1999; Levy et al., 2000; Reindl et al., 2000; Seppala et al., 2000; Weiss and Halsey, 1996). Some of the most common cross-reactive foods reported are bananas, avocados, kiwi fruits, and chestnuts.

B. Cross-reactive Allergens

The protein patatin found in potatoes is structurally homologous with the patatin in NRL (Hev b 7) (Sowka et al., 1998). Cross-reactivity has been attributed to the homology of patatins found in foods and NRL (Schmidt et al., 2002). A group of cytoskeletal proteins, the profilins, are another important cross-reactive IgE-binding component in several plants including *Hevea brasiliensis*, the source of NRL (Ganglberger et al., 2001; Valenta et al., 1992; Vallier et al., 1995). Patients sensitized to profilin react to profilins of many plant species (Docena et al., 1999). Class I chitinases may also act as multi-species, cross-reacting NRL allergens (Blanco et al., 1999; O'Riordain et al., 2002). The recently described proteins enolase (Hev b 9) and manganese superoxide dismutase (Hev b 10) show strong homology with identified mold allergens, although the degree of cross-reactivity needs to be clarified (Wagner et al., 2000; Wagner et al., 2001). Cross-reactions with plant-derived aeroallergens (e.g., pollens) are also possible (Palosuo et al., 2002b). Specific cross-reactions are discussed further in Appendix C.

C. Primary Sensitizing Allergen

There is conflicting evidence as to whether NRL allergy precedes or follows allergic reactions to various fruits and vegetables. In one study, the onset of NRL allergy preceded that of the food allergy in 12 of 29 patients (41%), whereas 11 of the 29 (38%) indicated that the onset of food allergy preceded NRL allergy (Kim and Hussain, 1999). Only one individual reported a simultaneous onset. Another study examined the prevalence of NRL hypersensitivity among patients diagnosed with food allergy (Garcia Ortiz et al., 1998). In all the patients identified in this study as having both NRL and food hypersensitivities (11%), the onset of clinical symptoms to fruit preceded those to NRL. It

[14] Radioallergosorbent test (RAST) inhibition determines the portion of NRL-specific IgE antibodies that can be inhibited from binding to NRL allergens by extracts of different fruits. Soluble allergens in the fruit extracts binding to NRL-specific IgE antibodies prevent the antibodies from binding to the solid phase NRL allergen. The amount of inhibition is proportional to the quantity of cross-reactive allergen in the extract.

is possible that NRL hypersensitivity may precede food allergy in some, while the opposite happens in other individuals (Blanco, 2003).

VI. Exposure to NRL Allergens

Retrospective studies suggest a relationship between exposure to certain allergens and the risk of sensitization to those allergens (Nieuwenhuijsen et al., 1999; Sporik et al., 1999). Frequent contact with products containing NRL allergens increases the likelihood of an individual developing NRL sensitization.

A. NRL Allergens in Products

Natural latex can be used to manufacture both NRL and dry natural rubber (DNR) products. The manufacturing of DNR products uses coagulated natural latex, which is formed into dried or milled sheets after extensive washing and exposure to temperatures exceeding 100°C. Examples of DNR products include tires, hoses, belts, balls, syringe plungers, vial stoppers, and injection ports. The high heat and the extensive washings used in the processing of DNR are thought to reduce the protein content of DNR products. In comparison, NRL products are manufactured using a concentrated colloidal suspension of natural latex from which NRL products are dipped, extruded, or coated.

The level of NRL allergen in consumer products can vary considerably from product to product. Differences in manufacturing procedures can generate different finished products that vary greatly in allergenicity. For example, the allergen content varied by 3000-fold in 10 different brands of NRL gloves, which were manufactured using different methods, standards, and processing times (Yunginger et al., 1994). Another study quantified the releasable protein and allergen contents in 37 brands of latex gloves and 26 other latex products (i.e., balloon catheters, balloons, condoms, a rubber teat, textile rubber, NRL mattresses, mattress covers, NRL pads, and a rubber tube) (Baur et al., 1997). The water-extractable protein content varied from 5 to 5,000 μg/g, and the allergen content, based on serologic measurements, varied from less than 2 to 1,000 μg/g. These studies demonstrate the presence of widely varied protein and allergen contents in various latex articles.

Although many different products are made of NRL, relatively few consumer products are known to elicit IgE-mediated reactions. Other than NRL gloves and NRL medical devices, reports of IgE-mediated reactions to NRL consumer products in the medical literature are infrequent (Burke et al., 1995; Cogen and Beezhold, 2002; Fiocchi et al., 2001; Freishtat and Goepp, 2002; Hawkins and Katelaris, 1997). At this time, deficiencies in the scientific information noted in this report precluded a qualitative or quantitative risk assessment of NRL in consumer products.

Available evidence implicates occupational exposure to NRL gloves (especially high protein, powdered gloves) as the cause of the majority of IgE-mediated sensitization to NRL (Alenius et al., 1994b; Yunginger et al., 1994; Zucker-Pinchoff and Stadtmauer, 2002). No data are available to confirm what specific NRL consumer product or products are responsible for the sensitization of individuals not classified as high risk. It is likely that

products that are known major elicitors, such as high protein powdered gloves, are responsible for the sensitization of these individuals.

Establishing an accurate qualitative and quantitative assessment of the relevant extractable allergenic NRL proteins in products that is practical, sensitive, and consistently reproducible is essential for determining the allergenic potential of finished NRL products. Presently, there are two main types of tests used: assays that measure total extractable proteins and assays that detect the NRL allergens. These assays, and their advantages and disadvantages are discussed in Appendix D.

B. Routes of Exposure

Individuals can be exposed to NRL allergens through mucosal, parenteral, cutaneous, percutaneous, and/or aerosol exposure. Different routes of exposure may have an effect on the level of allergen exposure required to elicit NRL sensitization as well as an allergic response.

1. Aerosol/Inhalation Exposure

Exposure to NRL through inhalation is well documented (Baur and Jager, 1990; Jaeger et al., 1992; Lagier et al., 1990). The inhalation of aerosolized NRL allergens is associated with an increase in NRL sensitization, especially in healthcare professionals (Brehler et al., 1997a). This inhalation exposure is primarily due to the airborne powder/cornstarch associated with NRL gloves. The cornstarch functions as a carrier of NRL allergens by binding the allergenic NRL proteins present in the gloves (Tomazic et al., 1994) and becomes airborne upon the donning and removal of NRL gloves. The highest airborne NRL allergen levels are associated with operating rooms or medical centers where NRL gloves are used and changed frequently (Heilman et al., 1996; Swanson et al., 1994). Furthermore, NRL-related allergic symptoms and the presence of IgE-specific antibodies have been associated with measurable levels of NRL aeroallergens in hospitals (Baur et al., 1998). In rooms with a NRL aeroallergen concentration greater than or equal to 0.6 ng/m^3, there was a significant increase in the prevalence of IgE-mediated NRL sensitization in hospital employees. Similar environments with lower NRL aeroallergen levels were neither associated with IgE-mediated sensitization nor NRL-related symptoms.

2. Cutaneous and Percutaneous Exposure

The stratum corneum functions as a primary barrier against the free movement of substances across human skin. Compounds with a high molecular weight (greater than 500 daltons[15]) cannot penetrate stratum corneum (Bos and Meinardi, 2000). Consequently, the penetration of intact proteins through normal healthy skin is negligible. However, if this barrier is compromised, penetration of proteins through the outer layer of the skin can occur. Several different factors including physical or chemical damage, hydration of the corneum, dehydration, and atopy, reduce the barrier resistance of the outer layer of skin.

[15] Protein size is expressed as daltons or kilodaltons.

Damage to the outer layer of skin may occur as a result of using NRL products. Adverse reactions to the chemicals and localized abrasion from the powder present in NRL gloves can cause contact dermatitis and urticaria, both of which compromise the barrier efficiency of the stratum corneum (outer-most layer of skin) and increase the probability of allergen penetration (Nettis et al., 2002). Extended use of NRL gloves is also associated with increased hydration of the stratum cornea. NRL gloves obstruct the evaporation of perspiration from the hands reducing the skin's barrier efficiency (Baker, 1979). The probability of percutaneous exposure may also be greater in atopic individuals. Atopic dermatitis patients have been shown to have a reduced level of ceramides[16] (Imokawa et al., 1991; Yamamoto et al., 1991), which protect the stratum corneum (Wertz et al., 1987). A reduction in ceramides diminishes the barrier function of the skin, increasing the probability of large molecule penetration.

Use of *in vitro* cell cultures of animal and human skin to model diffusion showed that within 24 hours of exposure, less than 1% of NRL proteins penetrated into and through intact skin (Hayes et al., 2000). However, up to 23% of NRL proteins ranging in size from 3 to 26 kilodaltons, penetrated abraded skin. The amount of penetration of NRL proteins correlated with the degree of dermal abrasion, demonstrating that the skin can be a major route of exposure when the outer layer has been compromised.

3. Mucosal and Parenteral Exposure

Mucosal and/or parenteral exposure pose the greatest risk of a severe allergic reaction, such as anaphylaxis (Laxenaire and Mertes, 2001). Mucosal and parenteral exposure occur primarily during surgery and other medical procedures (e.g., urethral catheterizations, barium enemas, and dental work) (Slater, 1994).

In children with spina bifida and children who have undergone multiple surgical procedures, sensitization to NRL results primarily from wound or mucosal contact with medical devices containing NRL. This population is subjected to frequent mucosal and visceral NRL exposure early in life as the result of urethral catheterizations, multiple surgeries, and ventriculoperitoneal shunt placement.

Allergic reactions associated with parenteral exposure are connected with the use of injection ports, vial stoppers, and syringe plungers composed of DNR (Jones et al., 1996; Lear and English, 1995; MacCracken et al., 1996; Towse et al., 1995). No NRL or DNR consumer products are associated with allergic reactions resulting from parenteral exposure.

C. Effects of Different Routes of Exposure

The systemic absorption of various NRL allergens may differ depending on the route of exposure. This may be the reason for the different sero-recognition patterns for specific allergens in healthcare workers and children with spina bifida. Selective reactivity to the Hev b 1 and Hev b 3 allergenic proteins in NRL were more common in patients with spina bifida or other urogenital malformations, while Hev b 5, Hev b 6, and Hev b 7 have

[16] Ceramides are lipids present in the stratum corneum that minimize dehydration and the penetration of substances.

been shown to be the most common allergens responsible for NRL hypersensitivity in healthcare workers. A possible explanation is a reduced bioavailability of the particle-bound, less soluble allergens Hev b 1 and Hev b 3 across skin as opposed to mucosal membranes (Yeang et al., 1996).

BALB/c mice administered NRL proteins via subcutaneous, topical, intranasal, or intratracheal routes demonstrated dose-dependent increases in IgE for specific NRL allergens depending upon the route of exposure (Woolhiser et al., 2000). Immunoblot analysis[17] of IgE from subcutaneously sensitized mice showed that the IgE antibodies recognized proteins similar to the NRL allergens Hev b 1 and Hev b 3. The IgE of mice sensitized via topical or intratracheal routes of exposure recognized proteins with molecular weights similar to the NRL allergens Hev b 2, Hev b 4, and Hev b 6. This study also demonstrated differences in the NRL-induced clinical symptoms depending upon the sensitization route. Respiratory challenge with NRL allergens resulted in broncho-constriction in mice sensitized via topical, intranasal, and intratracheal routes, whereas mice subcutaneously sensitized were unresponsive to the challenge. Thus, the route of exposure may determine which NRL allergens sensitize an individual, as well as the clinical symptoms upon re-exposure.

VII. Threshold for Sensitization and Eliciting Clinical Symptoms

Allergens elicit physiological responses in two distinct stages, sensitization to the allergen and the allergic response. Therefore, when discussing threshold allergen exposure levels it is necessary to consider the dose for sensitization, as well as the dose that elicits an allergic response in a sensitized individual. It is probable that the threshold levels for the two different stages are not the same. Determining the level of NRL allergens necessary to sensitize an individual and the level of NRL allergen that is needed to elicit a reaction upon re-exposure is complicated by several factors including the genetic susceptibility of the individual, the route of exposure, and the quantity of allergen that is bioavailable in various NRL products. Induction studies[18], which control an individual's exposure to NRL allergen(s) could be used to establish the doses (both single and repeated doses) needed for sensitization. However, such studies, would necessitate sensitizing a previously non-sensitized individual.

While no threshold for the development of NRL-specific IgE sensitization or allergic reaction has been established, several studies indicate the quantity of NRL allergens in products and the frequency of exposure influence the degree of the allergic reaction. Elicitation studies in previously sensitized individuals tend to show a dose-response relationship. NRL gloves with a high protein content can elicit a bronchial allergic response on inhalation challenge, whereas gloves with a lower protein content produce little or no response (Vandenplas et al., 1995). Protein levels of NRL glove extracts also correlated with skin prick test reactivity (Beezhold et al., 1996; Palosuo et al., 1998). A recent study quantifying NRL allergen content in extracts of gloves found a significant correlation between the quantitative sum of four allergens (Hev b 1, Hev b 3, Hev b 5, and

[17] Immunoblotting is a process by which proteins are identified by staining with labeled antibodies.

[18] Induction studies involve exposure to different incremental doses of allergen to determine the dose necessary to induce allergen-specific IgE antibodies.

Hev b 6.02) and the skin prick test reaction of NRL allergic adults (Palosuo et al., 2002a). In general, when the sum of the four allergens exceeded 1 μg/g, the majority of patients showed a positive skin prick test reaction. However, due to the presence of multiple allergens in varying amounts in the NRL glove extracts, the authors remark on the difficulty of determining safe levels of the individual allergens. Sensitive, accurate, and reproducible methods for determining the biologically available NRL allergens in products are necessary to determine a threshold level that will elicit allergic reactions in sensitized individuals.

The frequency of exposure also appears to influence the development of NRL sensitization and allergy. Repeated exposure to NRL products appears to increase an individual's risk. This is most apparent in individuals working in an area where there is frequent exposure to protein-rich NRL gloves and in spina bifida patients. A study at the Faculty of Dentistry of the University of Toronto demonstrated a positive skin prick test response to NRL in 6% of third year dental students and 10% of fourth year students (Tarlo et al., 1997). No positive response was detected in any of the first and second year students. Additionally, at a dental school in Paris, following two years of clinical work where there was daily exposure to NRL powdered gloves, 15% of the students had a positive skin prick test response (Levy et al., 1999). Again, no positive skin prick test response was noted in any of the pre-clinical students. The number of surgical procedures children undergo appears to influence the development of allergy to NRL. Children with spina bifida undergoing more than 5 surgical procedures at an early age are at a greater risk for developing NRL-related symptoms (Mazon et al., 1997). The frequent mucosal and visceral exposure to NRL products during surgical procedures is believed to account for the increased prevalence of NRL allergy in these patients.

VIII. Remediation

A. Primary Prevention

Primary prevention programs that substitute low-protein powder-free NRL gloves, synthetic gloves, or both, for powdered NRL gloves appear to reduce the prevalence of NRL allergy. A change from using powdered gloves to low-protein powder-free gloves at a dental school decreased positive skin prick test responses from 10% (13/131) to 3% (3/97) in staff and students over a five-year time span (Saary et al., 2002). Replacing powdered NRL gloves with powder-free NRL or synthetic gloves at a hospital also significantly decreased the NRL-specific IgE antibody concentration in 6 of the 7 healthcare workers who had both positive skin prick test responses and NRL-specific IgE antibodies prior to the intervention (Allmers et al., 1998). Replacement programs also decreased the NRL allergen concentration in the air below the level of detection in areas where replacement gloves were used.

The FDA proposed recommendation to limit the amount of protein in NRL-containing gloves to lower NRL sensitization and allergy (64 FR 41710) (Food and Drug Administration, 1999). The FDA recommends that gloves contain no more than 1,200 micrograms (μg) of extractable protein per glove and 120 milligrams (mg) of powder per glove with the presumption that lower levels would result in lower rates of sensitization.

The levels, which are based on technological considerations, are not considered to be "safe levels" of protein or powder since this has yet to be established.

B. Minimizing Protein Levels in NRL Products

The amount of extractable protein in different NRL products prepared from the same NRL source can vary depending on the processing procedure employed during the manufacturing process. A number of different manufacturing strategies and methods are used to reduce the protein content in NRL products. These include creaming, leaching, chlorination, and enzyme treatment.

The concentrated latex used in the processing of NRL products after centrifugation contains approximately 25% of the total protein present in the natural latex (Moir, 1959). Creaming of NRL, in lieu of centrifugation, is another way of concentrating the rubber particles and reducing total protein levels. This process, which concentrates the rubber particles by letting them slowly rise to the top, requires the addition of creaming agents (alginate and methylcellulose type polymers). The colloidal creaming agents added may release some of the proteins bound to the rubber particles, explaining the larger reduction in small latex proteins present in the concentrate (Perrella and Gaspari, 2002).

Water leaching of NRL products, in particular NRL gloves, decreases the extractable protein content by decreasing the water-soluble components. Leaching the wet coagulated rubber gel, in addition to leaching the dry surface of the rubber film is necessary to effectively reduce the protein content (Lai and Ng, 1995; Perrella and Gaspari, 2002). The leaching time, water temperature, and the rate of water turnover (1 to 2 gallons per minute and large volumes of water) significantly effect the efficiency of leaching (Kamath and Abraham, 1992).

Post-washing and chlorination of NRL products are two additional ways of reducing the amount of protein. Recently, it has been demonstrated that enzyme treatment of NRL reduces the antigenic protein in NRL without compromising the physical properties and performance of NRL products. The enzyme treatment cuts the NRL proteins into smaller non-antigenic proteins (Perrella and Gaspari, 2002). Enzyme treatment is suitable for large-scale production of NRL gloves and can produce low allergen gloves with acceptable physical, aging, and barrier properties (Perrella and Gaspari, 2002)

C. Therapies

Currently, the principal means of preventing a serious allergic reaction in individuals diagnosed with NRL allergy is avoidance of NRL-containing products. However, immunotherapy may become a viable option. Traditional immunotherapy is based on the premise that administration of increasing amounts of allergen (e.g., crude NRL preparations) to individuals with IgE-mediated hypersensitivity will alleviate the clinical symptoms on exposure to the allergen.

The medical literature contains several examples of immunotherapy with NRL extracts. While under close surveillance in the hospital, a radiology technician with occupational NRL allergy was administered incremental injections of NRL extracts

subcutaneously until 0.5 μg caused a systemic reaction. A weekly maintenance dose of 0.4 μg caused a steady decline in the mean diameter of NRL-specific skin prick tests and reactivity on NRL provocation testing. Although there was no significant change in the patient's IgE serum levels to NRL, there was a sufficient improvement in clinical symptoms to allow the individual to return to work (Pereira et al., 1999). Another case study involved the sublingual desensitization of a medical student (Nucera et al., 2001). A reduction in symptoms and reactivity to NRL provocation testing was reported.

In a multi-center randomized, double-blind, placebo-controlled trial, 17 healthcare workers with NRL allergy received a maximally tolerated dose of NRL extract by injection using a 12-month maintenance protocol (Leynadier et al., 2000). A significant improvement of rhinitis, conjunctivitis, and cutaneous symptoms was noted after 12 months. Most injections were well tolerated, however several adverse effects were noted including hypotension, urticaria, wheezing, and pharyngeal edema during the treatment phase.

An original exposure protocol successfully demonstrated five cases of NRL desensitization (Patriarca et al., 2002). This preliminary study required five healthcare workers with an IgE-mediated NRL allergy to wear NRL gloves for 10 seconds a day on one hand. The end goal, ultimately obtained by all five subjects, was to wear NRL gloves on both hands twice daily for a period of one hour. At the end of the one-year period, all the subjects were able to wear NRL gloves without any clinical symptoms. Furthermore, there was a marked decrease in the measurable NRL-specific IgE levels. Although larger studies are needed to confirm these preliminary results, the study demonstrates a contact desensitization protocol that appears to be safe and effective.

Future approaches for NRL immunotherapy are being explored and include DNA vaccinations (Slater et al., 1998), and the use of T-cell epitope peptides (Bohle et al., 2000; de Silva et al., 2000; Raulf-Heimsoth et al., 1998) and hypoallergenic mutants[19] (Beezhold et al., 2001) to decrease IgE cross-linking. At this time, the potential for severe side effects associated with immunotherapy using NRL extracts limits their usefulness.

IX. Conclusions

The FHSA requires that the Commission consider the frequency of occurrence and the range of the severity of the reaction in healthy or susceptible populations in order to make the finding that a substance has a significant potential for causing hypersensitivity. Although the reaction need not be both frequent and severe to make the necessary finding, both factors are to be taken into account.

A. Frequency of Reactions to NRL

The reported prevalence of IgE-mediated hypersensitivity reactions to NRL increased after 1987, mostly in distinct high risk groups. Possible reasons include increased exposure to NRL products (notably NRL gloves) following the implementation of "universal precautions", altered manufacturing practices, and increased awareness in the general public and in healthcare professionals. The majority of documented IgE-mediated

[19] A hypoallergenic mutant is a synthetic allergen with reduced IgE-binding ability.

sensitization and/or clinical reactions to NRL occur in healthcare workers, primarily due to repeated glove use.

Excluding the high risk populations, the prevalence of IgE-mediated hypersensitivity in the general population is thought to be considerably lower than that evidenced in occupationally exposed individuals. NRL allergy in the general population is estimated to be less than 1%.

B. Severity of Reactions to NRL

The definition of a clinically important allergic reaction includes possible physical discomfort, distress, hardship, or functional impairment [16 CFR 1500.3(c)(5)(iii)]. The spectrum of IgE-mediated hypersensitivity reactions to NRL extends beyond these minimal requirements to the possibility of life-threatening reactions, such as anaphylaxis. The number of individuals experiencing more severe, potentially life threatening anaphylactic reactions, has remained relatively low. It is estimated that annually approximately 0.00008% of the U.S. population would experience an anaphylactic reaction to a NRL product. The greatest risk of a severe systemic reaction is associated with mucosal and parenteral NRL exposure and/or high risk groups (i.e., occupationally exposed, surgically exposed, and atopic individuals).

Appendix A: Diagnosis of NRL Allergy

An accurate diagnosis of NRL allergy is essential for the effective management and a precise estimation of the prevalence of NRL allergy. Currently there is no single gold standard test to diagnose NRL allergy that is universally accepted. In the United States, a diagnosis of NRL allergy is based on a history of the patient and an *in vitro* test (Warshaw, 1998). Outside of the United States, *in vivo* diagnostic skin testing is also used in making the diagnosis. An *in vivo* cutaneous or inhalation provocation test can be performed to resolve diagnostic test results that contradict the clinical history of the patient.

Each *in vivo* or *in vitro* method provides useful information, but all have their limitations. There are currently no diagnostic test methods for NRL allergy that are 100% sensitive and specific. Therefore, the screening of individuals in the absence of a positive history is currently not recommended (Hepner and Castells, 2003; Porri et al., 1997).

Patient History

A comprehensive history of the patient is an important first step in the diagnostic process. This should include ascertaining the allergic symptoms associated with exposure to NRL product(s), the time course and magnitude of any allergic symptoms, the frequency of the reactions, an individual's general atopic history, and occupational information (Hamilton et al., 2002). This information will assist in identifying individuals at risk for NRL allergy and help the clinician to distinguish between cell-mediated and IgE-mediated hypersensitivity.

In vitro IgE Antibody Measurement

In vitro quantification of serum IgE antibodies is used to confirm a diagnosis of IgE-mediated hypersensitivity. Three different FDA-approved serum tests can verify the sensitization status of the individual. In these radioallergosorbent tests (RAST), the NRL allergens immobilized on a solid surface are exposed to patient sera. Any allergen-specific IgE present in the sera will bind to the immobilized allergen, which is then detected with a radiolabeled antibody against human IgE. Varying results regarding the sensitivity and selectivity of this method have been demonstrated. Two of these tests, the AlaSTAT and ImmunoCAP, were shown to have a false-negative rate of approximately 25% (Hamilton et al., 1999). The third RAST assay, the HY-TEC assay, was found to have a 27% false-positive rate. None of the three are completely reliable diagnostic methods.

In vivo Skin Prick Testing

In vivo skin prick testing with soluble allergens is another way to demonstrate IgE-sensitization and confirm a diagnosis of NRL allergy. This simple and relatively sensitive test for NRL allergy is performed using skin testing reagents made from NRL. A small drop of the reagent is placed on the forearm and a slight needle prick is made through the drop and into the skin. A positive reaction results in the formation of a wheal and flare

reaction[20] typically within 15 minutes. Due to the possible risk of an adverse reaction, such as anaphylaxis, the test needs to be conducted at a medical center equipped to handle a severe reaction. This test is currently available only outside of the United States (Nettis et al., 2001).

In vivo Provocation Testing

An *in vivo* provocation test may be performed when serological testing and/or skin tests are discordant with a patient clinical history that convincingly indicates a NRL hypersensitivity (Kurtz et al., 1999). Provocation testing establishes a direct connection between latex allergen exposure and the generation of an allergic response. There are several different types of provocation tests. The most basic is environmental exposure where an individual is placed in a NRL allergen-containing environment and monitored (Hamilton et al., 2002). Inhalation provocation tests, which mimic exposure to powdered NRL gloves, involve progressive NRL aeroallergen exposure to the individual's conjunctiva, nose, and lungs simultaneously using a hooded chamber (Kurtz et al., 2001a; Kurtz et al., 2001b). Glove use tests involve the application of NRL gloves to the hands of an individual followed by the observation of their skin and presence of any bronchial or nasal symptoms after a period of time has elapsed (Hamilton and Adkinson, 1997; Hamilton and Adkinson, 1998). The results of provocation tests are difficult to compare due the lack of standardized protocols and all tests must be performed by individuals capable of treating an anaphylactic reaction (Vandenplas et al., 1995).

Other Tests

Several other *in vitro* assays can also be used to diagnose NRL IgE-mediated hypersensitivity such as basophil histamine release (Marais et al., 1997; Sainte-Laudy et al., 1996; Turjanmaa et al., 1989) and lymphocyte proliferation (Ebo et al., 1997; Johnson et al., 1999; Murali et al., 1994; Raulf-Heimsoth et al., 1996; Turjanmaa et al., 1989). Technical difficulties, cost, and controversial clinical benefits limit their use. Flow-cytometric basophil activation tests are also currently being evaluated for diagnosing NRL allergy (Boumiza et al., 2003; Ebo et al., 2002; Sainte-Laudy et al., 1996; Sanz et al., 2003). This method is not sensitive, but further clinical evaluation and modifications may improve diagnostic reliability.

[20] A wheal is an elevated patch of skin often associated with intense itching, whereas a flare refers to a diffuse reddening of the skin.

Appendix B: CPSC Injury Reports on Allergic Reactions to NRL Products

CPSC Databases

CPSC maintains several databases including the National Electronic Injury Surveillance System (NEISS), the Injury and Potential Injury Incident (IPII) file database, and the In-Depth Investigation (INDP) and Death Certificate (DTHS) file databases. The NEISS database collects data on visits to emergency rooms from a sample of hospitals that are statistically representative of hospital emergency rooms throughout the United States. The IPII database file contains summaries of newspaper articles, hotline reports, internet entries, letters to CPSC, and reports from medical examiners. Summaries of death certificates provided by state health departments, which involve consumer products, comprise the DTHS file. Lastly, the INDP file consists of summaries of investigations conducted by CPSC into events involving product-related injuries or incidents.

Staff reviewed all four database files between January 1997 and December 2002[21]. From this search, all records involving incidents of an allergic reaction associated with natural rubber latex (NRL)-containing products were identified by the information in the narrative comments and/or diagnosis.

In either the DTHS file or the INDP file, staff found no cases involving a reaction to NRL-containing products. Staff was therefore limited to the information provided by the records identified in the NEISS and IPII database files discussed below to determine the frequency of occurrence and the severity of reactions to NRL.

NEISS

A review of the NEISS database identified 62 cases involving allergic reactions reportedly linked to exposure to NRL-containing products under the jurisdiction of CPSC; cases involving occupation-related products and/or medical devices were excluded.

A reliable national annual estimate of the frequency and severity of allergic reactions to NRL products could not be established due to the limited information provided. Consequently, staff assessed each individual case of an allergic reaction reportedly linked to a NRL-containing product.

The clinical symptoms associated with NRL exposure were provided, but were generally non-specific. This made it difficult to determine whether the allergic reaction to the specified NRL-containing product was a cell-mediated or IgE-mediated reaction. Furthermore, there was no evidence that diagnostic tests (e.g., skin prick testing or allergen-specific IgE assays) were performed to confirm a clinical diagnosis of NRL allergy.

[21] Directorate for Epidemiology staff conducted a search of all ages and codes using the keywords latex, NRL (natural rubber latex), and rubber.

The possible misclassification of reactions as NRL allergy is also a concern. The diagnosis of NRL allergy following exposure to latex paint in six cases exemplifies the misdiagnosis of NRL allergy in the emergency room, as NRL is not found in latex paint.

The limited information provided in the reports also precludes identifying whether the individual was part of a known high risk population (i.e., occupationally exposed, surgically exposed, and atopic individuals).

The overall severity of the reactions to these products is presumed to be minimal as the majority of the cases were treated and released.

IPII

All reports in the IPII database file involving allergic reactions to NRL-containing products were identified and assessed. The reports were either CPSC hotline reports or internet entries, and did not represent a statistical sampling. The cases identified in the IPII database were accounts of reactions to NRL products reported by the general public; no medical confirmation was provided.

Forty-four cases describing an allergic reaction to a NRL-containing product regulated by the CPSC were identified. Reports involving reactions to NRL-containing medical devices, food handled by latex gloves, and occupation-related NRL-containing products were excluded as those items are beyond the scope of CPSC's jurisdiction.

In the majority of the reports, cell-mediated reactions to the chemicals present in NRL could not be distinguished from the IgE-mediated reactions to the NRL proteins. Thus, an accurate estimation of the prevalence of IgE-mediated allergic reactions to NRL-containing products could not be made.

Furthermore, staff were not able to accurately identify the individuals in populations outside of the known high-risk groups to determine the prevalence of NRL allergy in the general population.

The severity of the reaction was estimated from the symptoms described. No deaths were directly attributed to an allergic reaction to a NRL-containing CPSC regulated product and all reported reactions involved symptoms that were resolved with treatment.

Conclusions

A clinical diagnosis of NRL allergy should be made on the basis of a background history, the confirmation of clinical symptoms resulting from NRL exposure, and confirmatory diagnostic tests (e.g., skin testing or allergen-specific IgE assays) (Hamilton et al., 2002). The majority of the reports from the NEISS and IPII database files describing an allergic reaction associated with exposure to NRL-containing product(s) only provided information about the clinical symptoms, which were generally non-specific. The notable lack of information regarding the individual's background history of latex exposure, and confirmatory testing preclude staff from estimating the prevalence of IgE-mediated allergy to NRL-containing products regulated by the CPSC in the general non-atopic population. A recent study looking at the clinical records of patients admitted to the emergency

department with a suspected allergic reaction found that of the 42 patients who sought further evaluation after discharge (skin prick tests and/or specific IgE assays), 28 (66.6%) were positive for an allergy (Bellou et al., 2003) exemplifying the difficulty of making a diagnosis of allergy in the emergency department.

Appendix C: NRL Allergens

Allergen Name/IUIS Reference	Conventional Name	MW (kDa)	Structural Homology	References
Hev b 1	Rubber elongation factor	58	Hev b 3	(Czuppon et al., 1993) (Attanyaka et al., 1991)
Hev b 2	Beta-1,3-glucanase	34-36	Plant beta-1,3-glucanase	(Sunderasan et al., 1995) (Chye and Cheung, 1995) (Breiteneder and Scheiner, 1998)
Hev b 3	Small rubber particle protein	24	Hev b 1	(Wagner et al., 1999) (Yeang et al., 1998) (Alenius et al., 1995)
Hev b 4	Microhelix protein complex	100-115		(Sunderasan et al., 1995)
Hev b 5	Acidic C-serum protein	16	Kiwi fruit protein	(Slater et al., 1996) (Akasawa et al., 1996)
Hev b 6.01	Prohevein (hevein precursor)	20		(Lee et al., 1991) (Beezhold et al., 1997) (Chen et al., 1997c)
Hev b 6.02	Hevein (prohevein N-terminal domain)	5	Avocado, banana, and chestnut chitinases	
Hev b 6.03	Prohevein C-terminal domain	14	Wound-inducible proteins	
Hev b 7	Patatin-like protein	42-44	Patatin storage proteins in potatoes	(Beezhold et al., 1994) (Kostyal et al., 1998) (Sowka et al., 1998)
Hev b 8	Profilin	14	Profilin of other plant species	(Vallier et al., 1995) (Fuchs et al., 1997)
Hev b 9	Enolase	51	*Cladosporium herbarum* and *Alternaria alternata* enolase	(Posch et al., 1997b) (Posch et al., 1997a) (Wagner et al., 2000)
Hev b 10	Manganese superoxide dismutase (MnSOD)	26	*Aspergillus fumigatus* and human MnSOD	(Miao and Gaynor, 1993) (Posch et al., 1997b) (Wagner et al., 2001)
Hev b 11	Class I chitinase	N/A	Avocado Chitinase and The N-terminal hevein domain	(O'Riordain et al., 2002) (Rihs et al., 2003)
Hev b 12	Lipid transfer protein	9.3	Non-specific lipid transfer proteins	(Beezhold et al., 2003)
Hev b 13	Esterase	42		www.allergen.org (AY057860)

Hev b 1 has as many as five different epitopes[22] that are believed to be responsible for its allergenicity (Czuppon et al., 1993). The Hev b 3 protein shares structural homology with Hev b 1 (Yeang et al., 1996). Both Hev b 1 and Hev b 3 are major IgE-binding allergens[23] in spina bifida patients and children having undergone multiple surgical procedures at an early age (Alenius et al., 1996b; Alenius et al., 1994a; Chen et al., 1997b; Lu et al., 1995; Wagner et al., 1999; Yeang et al., 1996). Other major allergens are the defense-related protein Hev b 2, and the acidic proteins Hev b 4 and Hev b 5; both spina bifida patients and healthcare workers with NRL allergy possess IgE antibodies against these allergens (Akasawa et al., 1996; Kurup et al., 2000; Slater et al., 1996).

Prohevein (Hev b 6.01) is a two-domain protein that is processed into an N-terminal domain called hevein (Hev b 6.02) and a C-terminal domain (Hev b 6.03). Prohevein and hevein are considered major allergens in NRL allergic individuals, whereas the prohevein C-terminal domain is regarded as a minor allergen (Alenius et al., 1996a; Banerjee et al., 1997; Breiteneder and Scheiner, 1998; Chen et al., 1997c; Posch et al., 1998). The major allergenic epitopes are located in the N-terminal domain of prohevein (Alenius et al., 1996a; Banerjee et al., 1997).

The patatin-like protein Hev b 7 binds IgE antibodies from both healthcare workers and spina bifida patients, but is considered to be a minor allergen (Beezhold et al., 1994; Kurup et al., 2000; Seppala et al., 2000). Several other minor allergens include Hev b 8 (profilin) (Vallier et al., 1995), Hev b 9 (enolase) (Posch et al., 1997b), Hev b 10 (MnSOD) (Posch et al., 1997b), Hev b 11 (class I chitinase) (O'Riordain et al., 2002), and Hev b 12 (lipid transfer protein) (Beezhold et al., 2003). All five are ubiquitous proteins that function in the defense of *Hevea brasiliensis* against pathogens and environmental stressors and have strong homologies with proteins in many other plants.

[22] Epitopes are the portion of an allergen that binds with the antibody or T cell receptor.

[23] A major allergen has been defined as a peptide to which greater than 50% of an NRL sensitive population respond by generating NRL-specific IgE antibodies (Nel and Gujuluva, 1998).

Appendix D: Determining NRL Allergen Content

Determination of Total Extractable Proteins from NRL

There are three general methodologies for determining the amount of extractable protein: the modified Lowry method, amino acid analysis, and the LEAP assay. All of the methods detect the total protein present, not just the NRL allergens. Nevertheless, they are useful in distinguishing between low, moderate, and high protein amounts in NRL products.

The modified Lowry assay is the method currently used in production control. As described in American Society of Testing and Materials (ASTM) D 5712-95, it is used to determine the protein levels of products made of NRL. This relatively simple assay measures protein levels using a colorimetric dye that binds to amino acids and uses a reference protein standard for comparison. The modified Lowry assay is relatively insensitive (lower limit of protein detection = 50 μg/g) and is subject to interference from chemicals added during manufacturing that can generate false high values (Chen et al., 1997a).

Amino acid analysis by HPLC is another method used to measure the total protein of NRL products. This is a relatively sensitive method that is able to measure a lower level of protein than the Lowry and is not affected by the presence of other chemicals. However, HPLC analysis requires expensive technical instruments and experienced staff and is unsuitable for production control. It is recommended as a reference method to validate the results of the modified Lowry.

Lastly, the LEAP assay quantitates the proteins in NRL product extracts using an indirect ELISA (enzyme linked immunosorbent assay). This assay uses pooled rabbit antiserum containing IgG antibodies that react with all proteins isolated from the rubber tree. Therefore, the assay does not provide an accurate assessment of the NRL allergenic proteins (Sosovec et al., 1998).

Determination of NRL Allergen Content

Total protein content does not necessarily correlate with NRL allergen content, as not all proteins present in NRL are allergenic and other proteins may be added to the NRL during manufacturing that increase the total protein content. Therefore, it would be advantageous to be able to measure just the allergen content. Clinical and serological tests are available that offer higher specificity and precision than the assays measuring total protein.

One method to evaluate and measure the allergenicity of different products is to use extracts of NRL products in skin prick testing in NRL allergic adults. However, this requires NRL sensitized individuals to be subjected to repeated testing, which may not be prudent. For ethical reasons, this method can not be routinely used to monitor the allergen content of products (Palosuo et al., 2002a).

The RAST and ELISA assays can be used to quantitate the amount of total allergen in a NRL extract (Baur et al., 1997; Palosuo et al., 1998; Yunginger et al., 1994). In these IgE inhibition assays, soluble allergens in NRL product extracts bind to NRL-specific IgE in pooled human serum. This in turn, prevents the antibody from binding to the solid phase NRL allergen preparation. The amount inhibited from binding is proportional to the quantity of soluble allergen in the extract. However, the cost and the lack of standardized NRL allergens and NRL IgE antibodies limit its worldwide use.

A recently developed quantitative assay that measures individual NRL allergens is the capture-ELISA-based assay, which uses specific monoclonal antibodies developed against four clinically relevant NRL allergens (Hev b 1, Hev b 3, Hev b 5 and Hev b 6.02). This method is specific, standardizable, and sufficiently sensitive and reproducible. Additionally, the quantitative sum of the four allergens isolated from NRL gloves correlated with positive skin prick test reactions in NRL allergic patients indicating that it provides reliable information regarding the allergenic properties of NRL gloves (Palosuo et al., 2002a). The only known notable limitation is that the assay quantifies only four of the thirteen identified allergens.

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TAB C

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Memorandum

Date: 4 September 2003

TO : Suzanne Barone, Ph.D.
Project Manager for the Latex Petition

THROUGH: Dale Ray
Acting Associate Executive Director
Directorate for Economic Analysis

FROM : Robert Franklin
Economist
Directorate for Economic Analysis

SUBJECT : Market for NRL Consumer Products and Societal Cost of Latex Allergies

On 15 March 2000, Debra M. Adkins petitioned the Consumer Product Safety Commission requesting that the Commission declare natural rubber latex (NRL) and products manufactured from it to be strong sensitizers. Allergenic proteins contained in the latex are the causes of the sensitization process. This memorandum contains a description of the product, a preliminary discussion of the market for NRL and a preliminary discussion of the societal costs associated with allergic reactions to NRL-containing consumer products.

Product and Market Information

Although latex is contained in many different plants and trees, 99 percent of natural rubber latex is obtained from the Hevea brasiliensis tree. The tree is native to South America, but today most latex is produced in Indonesia, Malaysia, Thailand, and Sri Lanka.

Once collected, if the latex is prevented from coagulating and drying it can be used to manufacture "latex" or NRL products. If the latex is allowed to dry, it can be used to manufacture "dry natural rubber" (DNR) products. To prevent the latex from drying, the latex collected from the tree is concentrated and prevented from coagulating by adding ammonia or another preservative to the solution. The ammonia also inhibits the growth of bacteria. Other chemicals may be added to the latex solution to stabilize it or to impart other desired characteristics.

NRL is used in the manufacture of gloves, balloons, pacifiers, some tubing, elastic thread, various adhesives (e.g., rubber cement), and backings for carpets and rugs. Many NRL products are manufactured by dipping formers or molds into the latex solution. After being dipped in the latex, the product undergoes further processing that may involve soaking, leaching, or rinsing in substances such as water, cleaning solutions, and coagulants. In the case of gloves, the product may also be dipped in slurries that contain powder or silicone to make them easier to put on. The product is then heated in ovens to "cure" the latex. After curing, the product may undergo further

processing, including rinsing, leaching, and chlorination, before being removed from the formers and packaged for sale. Since many of the potentially allergenic proteins are water soluble and rise to the surface of the product during the curing process, the rinsing, leaching, and chlorination may remove many proteins.

If the latex is intended for the manufacture of DNR products, the latex is allowed to coagulate soon after it is collected. The coagulum is then creped or crumbled and washed extensively before being pressed and dried at temperatures exceeding 100° C. DNR is used in a very wide range of products, including tires, rubber thread, various adhesives, toys, bottle stoppers, washers, pencil erasers, various appliance parts, and so on.

There is some evidence that the protein content of products made out of DNR tends to be lower than that of NRL products. This is probably due to extensive washing (which may remove water soluble proteins) and the high heat (which may breakdown or neutralize proteins) used in processing DNR. Although the extractable protein content of NRL products tends to be higher than for DNR products, it varies widely among products and even within different samples of the same product. Much of the variability is probably explained by variations in the manufacturing process. For example, longer periods of leaching or more extensive rinsing during the manufacture of the product probably removes more of the water soluble proteins from the product.

Number and Types of NRL and DNR Consumer Products

More than 6.5 million tons of natural rubber (NRL and DNR) are consumed worldwide each year. The United States' consumption accounts for about 20 percent of the total consumption. A wide variety of products is manufactured from NRL and DNR. The most frequently cited estimate of the number of types NRL or DNR products is 40,000, including industrial, medical, and consumer products. This estimate can be traced to the article on "Rubber" in the World Book Encyclopedia. However, the article does not describe the methodology used to derive this estimate. Therefore, the estimate should be taken more as a statement that NRL and DNR are widely used and may be pervasive in the consumer environment.

By far most reported problems with latex allergies have involved medical products and devices, including latex examination gloves. However, allergic reactions also occur from exposure to consumer products. A list of consumer products that may be manufactured from NRL or DNR is in the Appendix. This list is not comprehensive, nor does each individual product in these categories necessarily contain NRL or DNR. However, this list does illustrate the potential pervasiveness of latex in the consumer environment. Virtually all consumers are regularly exposed to some NRL or DNR products unless they make special efforts to avoid it.

Current Labels on NRL and DNR Consumer Products

The intent of the petitioner is to require manufacturers of NRL or DNR consumer products to add labels to their products that advise consumers of the latex content of the products. Although most NRL and DNR consumer products do not currently have such labels, there are some exceptions. For example, most manufacturers of NRL rubber gloves include some mention of latex on the packaging. In some cases, this is accomplished only by clearly referring to the product as "latex" gloves. Other manufacturers have more complete cautionary labels on their products. For example, one major manufacturer of household gloves includes the following label on their products:

> "Caution: This product contains natural rubber latex, which may cause allergic reactions in some individuals. If signs of an allergic reaction appear, discontinue use immediately and consult your physician."

The labels of many pacifiers and bottle nipples identify the component of the product, usually "latex" or "silicone" (a latex substitute). Many latex balloons contain the word "latex" on the label. Sometimes it is simply a description of the product as in "latex balloons." In some cases, the label states that the product was manufactured from "natural rubber latex." However, even when the labels do not mention latex, it is relatively easy to distinguish a latex balloon from Mylar balloons based on the appearance or feel of the product.

Staff has also found references to latex on a Halloween mask and a toy rubber duck. In both cases, the label advertised the fact the product was made from NRL, but did not contain any references to the possibility of allergic reactions to latex.

Cost to Society of the Hazard

The total cost to society of latex allergies includes the medical costs involved in diagnosing the latex allergy and in treating its effects. The costs also include costs such as lost productivity, forgone opportunities, the pain and suffering of the victims, and the time and effort expended by allergy sufferers in trying to avoid exposure to latex products. The benefits of a rule that declared NRL to be a strong sensitizer or that required the labeling of products containing NRL would be the reduction in the societal costs that could be attributed to the rule. Although the total cost to society of latex allergies may be substantial, the available data are not sufficient to provide a quantitative estimate of either the societal costs of latex allergies or the portion of these costs that are associated with consumer products. The data also are not available to estimate the degree to which these costs could be reduced by either a rule declaring NRL to be a strong sensitizer or requiring products containing NRL to be labeled.

Appendix

Household Products That May Be Manufactured From Natural Rubber Latex or Dry Natural Rubber

The following is a list of household products that may be manufactured from natural rubber latex or dry natural rubber. This list is largely based on information provided by the people who submitted comments regarding the latex petition. This list is not comprehensive, nor are all products in the categories below necessarily manufactured from NRL or DNR.

Adhesives: rubber cement; adhesives used for bonding hair extensions and wigs; adhesives used on envelopes, labels, and stamps, tape; adhesives used in shoe construction; adhesives used in furniture construction for bonding foam to foam or foam to fiber or wood; adhesives used in packaging,

Air Mattresses

Art Materials: some paints and adhesives

Balloons

Bathmats

Bottle Stoppers

Carpets and Rugs: latex rubber backings; pads

Children's Products: disposable diapers; bottle nipples; pacifiers; teethers

Clothing: elastic or rubber thread (including most undergarments and hosiery)

Computer Equipment: keyboards; mice; mice pads

Furniture: foam rubber; adhesives

Gloves: household rubber gloves, commonly used in chores such as washing dishes and cleaning; disposable examination type gloves used in chores such as painting

Grips and Handles: such as may be on gardening tools, hand tools, bicycle handlebars sporting equipment such as rackets and golf clubs; exercise equipment; kitchen utensils

Hoses: garden; washing machine; dishwasher

Non-Skid Surfaces

Office Supplies: pencil erasers; rubber bands; pens with rubber grips; some adhesives (rubber cement); rubber stamps

Rain Gear: coats, boots

Roofing Materials

Rubber Gym Floors

Rubber Seals: such as may be found in showerheads or on reusable vacuum cleaner filters.

Shoes: rubber soles; adhesives

Shower Curtains

Swimming and Diving Gear: goggles; masks; flippers

Tires: automobile; bicycle

Toys: various balls; Koosh balls; squeeze toys (e.g., rubber ducks, pet toys); whoopee cushions; various pool toys

Tubing

Window Insulation

In addition to the products listed above, there are other products that are commonly found around the house that may contain NRL or DNR that may also fall under the jurisdiction of other Federal agencies. These include some automotive components, medical devices (such as bandages and hot water bottles), and some cosmetic products.

TAB D

United States
CONSUMER PRODUCT SAFETY COMMISSION
Washington, D.C. 20207

MEMORANDUM

DATE: June 21, 2000

TO : HS

Through: Sadye E. Dunn, Secretary, OS

FROM : Martha A. Kosh, OS

SUBJECT: Petition Requesting Rule Declaring Natural Rubber Latex a Strong Sensitizer

ATTACHED ARE COMMENTS ON THE CH 00-4

COMMENT	DATE	SIGNED BY	AFFILIATION
CH 00-4-1	6/20/00	Regina Kellner RN, BSN	402 Grand Avenue Mukwonago, WI 53149
CH 00-4-1a	6/20/00	Regina Kellner	address same as above
CH 00-4-2	3/25/00	Nancy Mauser	M235mauser@aol.com
CH 00-4-3	3/27/00	K. Bernard	kbernard@earthlink.net
CH 00-4-4	3/28/00	Richard Edlick Distinguished Professor of Plastic Surgery & Professor of Biomedical Engineering	University of Virginia Health Sciences Center Box 376 Charlottesville, VA 22908
CH 00-4-5	3/30/00	Lauri J. Harris RDH	733 Yorkshire Rd. Neenah, WI 54956
CH 00-4-6	4/28/00	Robert Hamilton Associate Prof. of Medicine and Pathology, Dir. DACI Reference Laboratory	The Johns Hopkins University School of Medicine Room 1A20/5501 Hopkins Bayview Circle Baltimore, MD 21224
CH 00-4-7	5/02/00	Barbara Leather RT	220 W Sylvania Ave, #24 Neptune City, NJ 07753
CH 00-4-8	5/03/00	Colleen Baker BS, RN	39 Greenridge Crescent Hamlin, NY 14464

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CH 00-4-9	5/03/00	Kelly Clinton Ali Clinton Majica Alba Tammy Tahara Veronica Ramirez Sandra Carr	BrsBoots@aol.com
CH 00-4-10	5/11/00	Wayne Gainey	406 Drake Drive Dothan, AL 36305
CH 00-4-11	5/15/00	Anne Clark	118 Ashland Ave. River Forest, ILL 60305
CH 00-4-12	5/18/00	Patricia Szabo MHA, PT	159 Spook Rock Rd. Montebelio, NY 10801
CH 00-4-13	5/12/00	Debbie Butler	111 Princeton Road Exton, PA 19341
CH 00-4-14	5/18/00	Kathleen Caleb	Jordache Lane Spencerport, NY 14559
CH 00-4-15	5/18/00	Bryan Lakin Vice President	Alcan Rubber & Chemical, Incorporated 29 Broadway New York, NY 10006
CH 00-4-16	5/19/00	Sam Heyman VP & General Manager	R Tape Corporation 6 Ingersoll Road CN 2002 South Plainfield, NJ 07080
CH 00-4-17	5/19/00	Brenda Ray M.S.N.	390 South Tyndall Pkwy PMB 228 Panama City, FL 32404
CH 00-4-18	5/16/00	Daniel Flynn Chairman	The Balloon Council 5000 E 29th St, N Wichita,KS 67220
CH 00-4-19	5/19/00	Jack Trautman Ph.D	Allergen Reduction, Inc 1202 Ann Street Madison, WI 53705
CH 00-4-20	5/18/00	Gail Rechowicz	GailRech@webtv.net
CH 00-4-21	5/19/00	Tan Choon CEO	Malaysian Rubber Export Promotion Council 11th Floor, Bangunan Getah Asli 148 Jalan Ampang 50450 Kuala Lumpur Malaysia

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CH 00-4-22	5/19/00	Lisa Kamenides	kamfam@mediaone.net
CH 00-4-23	5/19/00	John Friar II Owner	North American Rubber Thread Co., Inc. 106 Ferry Street P.O. Box 1709 Fall river, MA 02722
CH 00-4-24	5/19/00	Richard Oldack President	Dyna-Tech Adhesives Incorporated P.O. Box 628 Country Club Road Grafton, WVA 26354
CH 00-4-25	5/20/00	Nancy Mitchell Michael Mitchell	3 Folsom's Pond Rd Wayland, MA 01778
CH 00-4-26	5/21/00	Marianne McAndrew	405 William Salesbury Dr Downingtown, PA 19335
CH 00-4-27	5/21/00	Linda Shaw	107 Catherwood Pl. Cary, NC 27511
CH 00-4-28	5/16/00	Marisa Mitchell RN	324 Goodlette Rd S. Naples, FL 34102
CH 00-4-29	5/16/00	Diana Cutright RN	4940 Deerfield Way, #101 Naples, FL 34110
CH 00-4-30	5/22/00	Rochelle Spiker Exec. Director	Potomac latex Allergy Association P.O. Box 52 Greenbelt, MD 20768
CH 00-4-31	5/19/00	Paula Wilkins	28 Wickliffe Drive Naples, FL 34110
CH 00-4-32	5/22/00	Roslyn Hamilton President	Oregon Ecobuilding Network P.O. Box 86444 Portland, OR 97286
CH 00-4-33	5/22/00	Anna Salanti	asalanti@worldnet.att.net
CH 00-4-34	5/22/00	Barbara Truitt	trukaras@expecpc.com
CH 00-4-35	5/22/00	Lise Borel DMD/Elastic Inc	P.O. Box 2228 West Chester, PA 19380
CH 00-4-36	5/22/00	Tim Mulvihill	t.mulvihill@worldnet.att.net

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CH 00-4-37	5/22/00	Lillie Thomas Vice President Of Quality Assurance	Custom Services International, Inc. 3111 West Post Rd Las Vegas, NV 89118
CH 00-4-38	5/22/00	Susan Lesica	337 East Capitol Drive Hartland, WI 53029
CH 00-4-39	5/22/00	Ursula Gregg	PMB # 117 303 91st Ave, NE, G701 Everett, WA 98205
CH 00-4-40	5/15/00	Tom Harrington Latex Chemist	2850 W. Bath Rd. Akron, OH 44333
CH 00-4-41	5/15/00	Lisa Butler	111 Princeton Road Exton, PA 19341
CH 00-4-42	5/22/00	Jean Mahoney RN	omahoney@dellnet.com
CH 00-4-43	5/22/00	Diane Flanagan President	A.L.E.R.T., Inc. American Latex Allergy Association P.O. Box 13930 Milwaukee, WI 53213
CH 00-4-44	5/22/00	Robert Worthen President	Worthen Industries, Inc. 3 East Spit Brook Rd. Nashua, NH 03060
CH 00-4-45	5/25/00	Nancey Agard Assoc. Director Practice and Governmental Affairs	nancey.agard@nysna.org
CH 00-4-46	5/27/00	Dorcas Stein	cdstein@barrow.com
CH 00-4-47	5/27/00	Herbert Hoos RN	jem4141@msn.com
CH 00-4-48	6/06/00	Rev. Craig Lantz	3312 Boose Rd. Glen Rock, PA 17327
CH 00-4-49	6/08/00	LaVar Riniker DDS	3912 No. Mason Ave. Tacoma, WA 98407
CH 00-4-50	6/13/00	A. Clarke	118 Ashland Ave River Forest, IL 60305
CH 00-4-51	6/12/00		mjb-pmb@webtv.net
CH 00-4-52	6/05/00	Donna Donlon	p.donlon@worldnet.net

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CH 00-4-53	6/08/00	Carol Kuczora	P.O. Box 536 Grass Valley, CA 95945
CH 00-4-54	6/15/00	Anne Fehr	morefehr6@sprint.ca
CH 00-4-55	6/09/00	Gerald Mainman CEO	Northwest Coatings Corp 7221 South 10th St. Oak Creek, WI 53154
CH 00-4-56	6/16/00	Katy Wolf Exe. Director	Institute for Research and Technical Assistance 2800 Olympic Blvd., Suite 101 Santa Monica, CA 90404
CH 00-4-57	5/22/00	Dave Kinnaman	P.O. Box 621 Vashon, WA 98070
CH 00-4-58	6/18/00	Cathy Cunningham	walc@lycosmail.com
CH 00-4-59	6/19/00	Bernie Liebler Director Technology and Regulatory Affairs	Health Industry Manufacturers Assoc. 1200 G St, NW Ste 400 Washington, DC 20005
CH 00-4-60	6/20/00	Thomas Tillotson Chairman/CEO	Tillotson Health Care Corporation TILLOTSON@thcnet.com
CH 00-4-61	6/16/00	Daniel McLain Director Becton Dickson Medical Toxicology	BDMT International Operations 21 Davis Drive P.O. Box 12016 Research Triangle Park NC 27709
CH 00-4-62	6/20/00	Michael Burnhill Vice President Medical Affairs	Planned Parenthood Federation of America, Inc. 810 Seventh Ave New York, NY 10019
CH 00-4-63	6/21/00	James Chatterton Vice President Regulatory	Ansell Perry 1875 Harsh Ave, SE Massillon, OH 44646
CH 00-4-64	6/20/00	Dr. Ong Englong Deputy Director General Malaysian Rubber Board	drong@pop.jaring.my

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CH 00-4-65	6/21/00	Kathryn Beaubien	Lindsay, Hart, Neil & Weigler, LLP 1275 Pennsylvania Ave, NW, Ninth Floor Washington, DC 20004
CH 00-4-66	6/21/00	Peter Friedmann Esq. On Behalf of Microflex Corporation	Address same above
CH 00-4-67	6/21/00	Tracey Norberg Director Environmental Affairs	Rubber Manufacturers 1400 K St., NW Washington, DC 20005
CH 00-4-68	6/21/00	Jan Amundson Vice President & General Counsel	National Association of Manufacturers 1331 Pennsylvania Ave, NW, Washington, DC 20004
CH 00-4-69	6/21/00	Ronald Johnson Associate Exe. Director	Gay Men's Health Crisis, Inc. 119 West 24 St. New York, NY 10011
CH 00-4-70	6/21/00	Sheila Millar Eric Singer Counsel for Bridgestone/ Firestone	Keller and Heckman, LLP 1001 G St, NW, Ste 500 W Washington, DC 20001
CH 00-4-71	6/21/00	Ethan Trull	Allegiance Healthcare Corporation 1430 Waukegan Rd. McGaw Park, IL 60085
CH 00-4-72	6/21/00	Ray Taylor Executive Vice President	Textile Rubber and Chemical Co. 1300 Tianco Dr., SW Dalton, GA 30720
CH 00-4-73	6/21/00	Rachel Subler	American Apparel Manufacturers Assoc. 2500 Wilson Blvd. Suite 301 Arlington, VA 22201
CH 00-4-74	6/21/00	Joan Martellotto PhD, RN	1011 Delles Rd Wheaton, IL 60187

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CH 00-4-75	6/21/00	Judith Herkimer RN	32 Warren Hill Rd Cornwall Bridge, CT 06754
CH 00-4-76	6/21/00	Leslie Gahagan	110 Amherst Ave, #D101 Sheboygan Falls, WI 533085
CH 00-4-77	6/20/00	Sid Smith President and CEO	The Hosiery Association 3623 Latrobe Dr. Suite 130 Charlotte, NC 28211
CH 00-4-78	6/21/00	Frederick Locker Atty	Locker Greenberg & Brainin, P.C. 420 Fifth Ave. New York, NY 10018
CH 00-4-79	6/21/00	Aaron Locker Atty	Locker Greenberg & Brainin, P.C. 420 Fifth Ave. New York, NY 10018
CH 00-4-80	6/22/00	Ellen Meeropol Ms, RN, CS, PNP	Shriners Hospital for Children Springfield, MA
CH 00-4-81	6/22/00	Sandra Whitehouse	SandraWte@aol.com
CH 00-4-82	6/22/00	E.K. McIntosh Technical Dir.	The Carpet and Rug Institute 310 Holiday Ave. P.O. Box 2048 Dalton, GA 30722
CH 00-4-83	6/26/00	Maureen Glynn Assistant Atty General	150 South Main St. Providence, RI 02903
CH 00-4-84	6/29/00	Judith Weinstein Associate General Counsel	Geber Products Company 560 Morris Ave. Summit, NJ 07901
CH 00-4-85	9/13/00	Marvin Bozarth Exec. Director	International Tire & Rubber Association, Inc P.O. Box 37203 Louisville, KY 40233

TAB E

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

MEMORANDUM

September 4, 2003

To: Suzanne Barone, Ph.D., Project Manager for Poison Prevention
Directorate for Health Sciences

Through: Hugh McLaurin, Associate Executive Director
Directorate for Engineering Sciences

Robert B. Ochsman, Ph.D., Director
Division of Human Factors

From: Catherine A. Sedney, Engineering Psychologist
Division of Human Factors

Subject: Response to Comments on Natural Rubber Latex Petition (HP 00-2)

Background

On September 30, 1997, in response to reports of severe allergic reactions and deaths related to medical devices containing natural rubber latex (NRL), the Food and Drug Administration (FDA) issued a final rule requiring labeling of medical devices, and their packaging, that contain NRL that contacts humans (Federal Register; Volume 62, Number 189). The rule requires such products and packaging to carry the following statement: "Caution: This product [packaging of this product] contains natural rubber latex which may cause allergic reactions." Content labeling of products containing dry natural rubber latex is also required. The FDA declined to require labeling of non-medical products as beyond its authority.

On March 21, 2000, the Commission published notice of a petition from Debra M. Adkins requesting it to issue a rule declaring NRL to be a strong sensitizer under the Federal Hazardous Substances Act (FHSA), and require that products containing NRL be labeled accordingly. If NRL and products containing NRL were declared to be strong sensitizers, then a product containing NRL would require cautionary labeling under the FHSA if the nature and level of exposure to the product were such that during reasonably foreseeable use or misuse of the product substantial illness or injury would occur.

The following is the response of the Division of Human Factors to comments related to labeling issues received regarding the petition.

Discussion

Comments in Support of Labeling

Comments in support of labeling all products containing NRL were received primarily from individuals who reported that either they themselves, or a family member, suffer from latex sensitivity. Complaints centered on the difficulty of avoiding NRL in unlabeled products, and of avoiding unexpected exposure to products known to contain NRL. Comments ranged from a general statement of support for labeling, to support for content labeling, to a request for a

specific warning stating that a product contains NRL, and that it is a hazardous substance "...proven to cause life-threatening allergies that may cause an injury and/or death..." (Comment 27)

Response: Provided no other approach is feasible, it is accepted safety practice to use a warning label on a product when it clearly poses a hazard, and a level of risk is established. The information that is available at present on NRL in consumer products does not meet these conditions. NRL is known to contain specific proteins (antigens) that may produce type I hypersensitivity in some individuals. Sensitized individuals, when exposed to NRL, may then experience clinical allergic reactions ranging from a skin rash to potentially fatal anaphylaxis. However, the majority of people exposed to NRL antigens do not become sensitized, and not all those who show evidence of NRL sensitization have, or will have, clinical symptoms (Warshaw, 1998). Further, the levels of NRL exposure required for sensitization or a clinical reaction have not been established (Poley & Slater, 2000).

The last poses particular difficulties in determining what products might be hazardous, and thus should be labeled. It is unknown what quantity of NRL, what product formulations, and what level of exposure may result in sensitization, or may trigger clinical reactions in previously sensitized persons. Should adequate information be developed, it could support use of a warning label for some products. At present, however, a warning requirement seems unwarranted as no hazard exists for the large majority of the public, and may not exist even for sensitized individuals from many products that contain NRL.

Beyond the lack of basic information necessary to support a requirement for labeling, the available incident data suggest that labeling NRL-containing consumer products is of uncertain value. Consumers with a known sensitivity to latex are already aware of common sources of NRL, such as balloons, latex pacifiers, and latex gloves. Labeling these products thus serves no purpose. Similarly, in many of the circumstances described by supporters of the petition, labeling of the products involved would have no effect. For example, a number of commenters requesting labeling described events, such as exposure to balloons used as decorations in stores or schools, and food handled by workers wearing latex gloves, that resulted in allergic reactions. Product labels would have no impact in such situations. In the case of balloons, the product was both obvious and separated from its packaging, and in the case of food handlers, exposure was indirect.

One incident submitted by several commenters (e.g., Comment 1a) differs from those described above, but illustrates issues regarding the potential effect of the warning requirement the comments support. The case concerns the death of a young fashion designer following exposure to hair glue that contained NRL. According to reports the staff initially received, the victim was unaware that she had been sensitized, and had used the product previously without incident. Had this been the case, a warning label on the product could not have prevented her death – if she did not know she was sensitized she would have had no reason to seek out information regarding latex in the product, and no reason to avoid it if it had been labeled. The facts of the case, however, are more complicated. According to a more complete account of the incident (Pumphrey, Duddridge & Norton; 2001; R. Pumphrey; electronic mail to S. Barone, 4 February, 2003), the product carried a warning,[1] and the victim was aware that she was allergic to latex.

The victim, a 28-year-old woman, was asthmatic and allergic to several varieties of nuts and inhalant allergens. She had previously required emergency treatment for an acute reaction to food, presumably nuts, and was said to have been fastidious in checking food labels. She had tested strongly positive for latex allergy, and experienced skin irritation and eczema from using

[1]The bonding glue was reported to carry a warning that it should not be used if latex allergy were suspected. As described by one of the authors, who in turn received the information from the coroner, "...the pack information included 'for professional use only' and 'not suitable for those with latex allergy' or words to that effect."

latex gloves. Her treatment included "...detailed advice and written instructions on latex avoidance." Although it was thought that the victim had never before used the specific adhesive implicated in her death, the reports suggest that she had used a similar product. Pumphrey et al. note that the adhesive that triggered the reaction was used in an area of scalp that had previously been affected by eczema. No information is available regarding the cause of this earlier occurrence; however, it seems possible that it was a reaction to a type of hair glue.

On the day of the incident, the victim was preparing for a formal occasion, and her cousin used a hair bonding glue to attach an extension. It is reported that within five minutes after use of the glue the victim experienced itching at the site of application. The hairpiece was removed, and an attempt made to wash off the adhesive. As the reaction progressed, the victim first took chlorpheniramine (an oral antihistamine), then used a salbutamol inhaler (a bronchodilator used to treat the symptoms of asthma and other lung disorders). Although she had an epinephrine injector available (used in the emergency treatment of allergic reactions to insect stings, medicines, foods, or other substances, including latex), she did not use it.

The details in these reports raise as many questions as they answer. The victim had received verbal and written guidance on latex avoidance. However, the authors refer to hair glue as a "less obvious source of latex allergen," and she may not have known to check for latex in the product. Although the product information included a warning, where it was located and how conspicuous it was are unknown. Another person, not the victim herself, applied the adhesive, and it is unclear if either of them had read the warning.

It is possible, however, that the victim was aware that the product contained latex, and used it despite the warning (cf. reviews, DeJoy, 1999; Silver & Braun, 1999). Her previous reactions to latex, and possibly to hair glue containing latex, were limited to eczema, and she may have expected no worse on this occasion. A warning is unlikely to be effective if one perceives that the consequences of ignoring it are not very serious. This is particularly true when there is a perceived benefit expected from noncompliance. In this instance, the potential gain was aesthetic, and may have been a personally important one to someone in the field of fashion design.

Alternatively, the victim might not have understood that her latex allergy created the potential for an acute reaction similar to that which she experienced in response to food. Her failure to use the epinephrine injector she had with her suggests that, despite her previous acute reaction, she may not have associated her symptoms on that day with the potentially fatal anaphylactic response for which an injector is prescribed. Panic and inexperience may also have played a role. While the use of oral antihistamines and inhalers are routine for someone who suffers from asthma and allergies, epinephrine injectors are used only in emergencies. Based on the information available, it seems likely that the victim had never used one before, and the authors use the case to urge better training for patients at risk of acute reactions.

Superficially, the incident presents a best-case scenario: The product information is available, the consumer is aware of the condition, is educated regarding the risks, and is equipped to respond to an emergency event. The death of the young woman, despite these potentially preventive factors, highlights some of the limitations of the labeling strategy proposed by the petitioner and many commenters. First, a warning label does not guarantee that latex sensitive consumers will be informed. Unlike food allergens, which are largely limited to a single product category, NRL is present in a wide array of consumer products. Yet even concerned consumers

are likely to check for warnings only on products they suspect may contain latex. Second, and more importantly, there is at least some potential that widespread use of warning labels on such products could do harm (cf. Frantz, Rhoades, Young & Schiller, 1999). As noted above, it is not yet possible to distinguish which among the variety of consumer products may contain hazardous levels of NRL. If warnings were required for all products that contain NRL, there is a high likelihood that some non-hazardous products would carry warning labels. This would lower the credibility, and therefore the effectiveness, of warnings regarding NRL. Some latex-sensitive consumers would avoid using the products because of the label. Others, however, who previously used these products without negative effects, may develop a false impression of their own level of risk, and subsequently fail to avoid labeled products that are hazardous.

Comments Opposing Labeling

Comments in opposition to labeling were received from individuals representing firms whose products contain NRL, and from organizations promoting health and safety uses of NRL products such as condoms. The general content of the comments is that labeling would alarm and confuse consumers who are otherwise unaffected by NRL, and discourage them from using beneficial products.

Response: To the extent that consumers notice, read, and understand a warning label, and are persuaded of the seriousness of the potential consequences of noncompliance, there is some merit to the commenters' concerns. New warning labels could initially cause unnecessary concern and avoidance among some consumers, particularly, as noted above, those who know they are latex sensitive. Also, consumers who are not particularly motivated to use a product, for example, because of its perceived inconvenience, may find in a warning label a reason to justify avoiding its use. For consumers in general, however, the commenters probably overestimate the impact of labels on NRL-containing products. Most consumers are not latex sensitive, and therefore have had no negative reactions to NRL. They are unlikely to perceive products containing NRL as hazardous, and are unlikely to be concerned about the effects of using them. These factors (i.e., benign experience, the perception of low hazardousness, and the perception that the consequences of disregarding a label are not serious) are associated with low levels of compliance with warning labels. In this instance, they lower the likelihood that a warning label would cause undue alarm and unnecessary avoidance among consumers who are not allergic to NRL.

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