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Proposed Hazard Identification Methodology for Assessment of Dermal Sensitization Risk

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Introduction

Among the many types of risk assessments conducted in the EPA's Office of Pesticide Programs (OPP) is an assessment of the dermal sensitization potential of pesticide chemicals. As noted in 40 CFR 798.4100, "Information derived from tests for skin sensitization serves to identify the possible hazard to a population repeatedly exposed to a test substance." Information from this test is qualitatively assessed and, if appropriate, precautionary language is included on the pesticide label as well as the Occupational Safety and Health Administration's Material Data Safety Sheets (MSDS). Occupational dermal exposures to known or suspected dermal sensitizing pesticide chemicals can be then dealt with appropriately, either through engineering controls or use of personal protective equipment. Non-occupational exposures can normally be dealt with through precautionary label statements.

Data available through the National Institute for Occupational Safety and Health (NIOSH) indicate that occupational exposure to dermal irritants and contact allergens accounts for a significant number of occupational illness and that chemical agents are the most frequent cause of such illness. Specific national occupational disease and illness data are available from the U.S. Bureau of Labor Statistics (BLS). The BLS conducts annual surveys of approximately 174,000 employers, selected to represent all private industries in the U.S. The goal is to ascertain the total numbers and incidence rates of occupational injuries and illnesses. The survey results are then projected to estimate the numbers and incidence rates of injuries and illnesses in the American working population. All occupational skin diseases or disorders, including occupational contact dermatitis (OCD), are tabulated in this survey. In 1999, of over 372,000 occupational illnesses

reported, 12% were reported as skin diseases/disorders, making this the most common non-trauma related occupational illness (NIOSH, 2001). The economic impact of occupational skin diseases/disorders is also significant. As measured by direct medical cost and worker compensation, the total annual cost of occupational skin disease may range from $222 million to $1 billion (NIOSH, 2001).

While pesticide chemicals can usually be labeled to warn of potential dermal sensitization effects, there also exists the manufacture of "treated articles or substances" (40 CFR 152.25), in which a registered pesticide is incorporated into the article to protect the integrity of the article or substance itself (such as paint treated with a pesticide to protect the paint coating or wood products treated to protect the wood against fungal or insect decay). Under such circumstances of use, the general public may unknowingly be exposed to pesticide chemical residue in the treated article. Therefore, prior to such use, the pesticide chemical must first be registered under FIFRA, which requires that the manufacturer of the pesticide demonstrate that it can be used without unreasonable risks to humans or the environment. Treated articles such as preserved wood, however, do not bear a pesticide label or effectively use other communication methods to inform and protect people against potential hazards, including the potential for dermal sensitization

Purpose

The focus of this paper is on the Agency's interest in developing the foundation of a

scientifically sound approach to quantitative assessment of dermal sensitization risk to pesticide chemicals, including pesticide chemicals that are incorporated into other materials (i.e. treated articles). The Agency is interested in obtaining expert advice on methods published in the scientific literature that have been proposed for use in determining induction thresholds and elicitation thresholds for chemicals known or suspected of causing allergic contact dermatitis. The Agency is also interested in seeking advice on whether there are any susceptibility issues in the general population with respect to development of allergic contact dermatitis, including any potential special sensitivity of children. The Agency will present hexavalent chromium as a case study of a known dermal sensitizer, and possible approaches to quantitating risk of allergic contact dermatitis from exposure to hexavalent chromium.

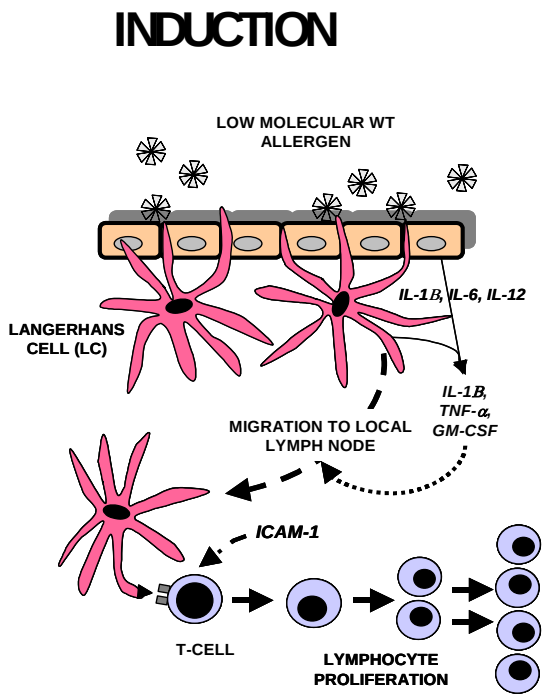
Dermal Sensitization

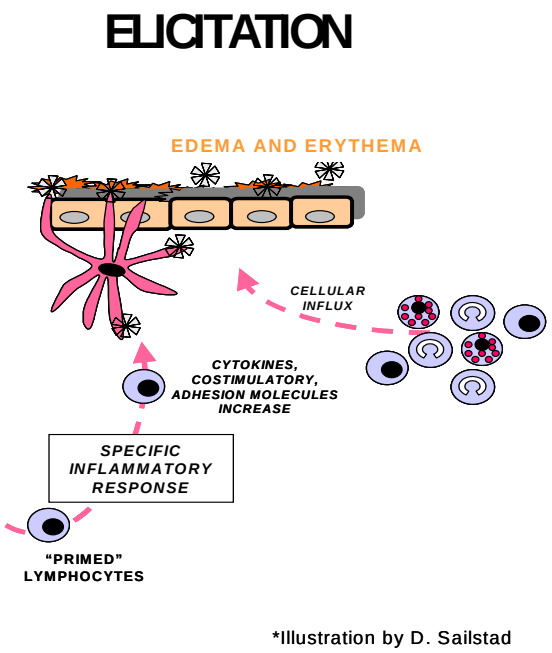
Dermal sensitization, also known as allergic contact dermatitis (ACD), delayed contact hypersensitivity, or Type IV allergic contact dermatitis, is defined by Marzulli and Maibach (1996) as a delayed, immunologically mediated, inflammatory skin disease consisting of various degrees of erythema, edema, and vesiculation. Kimber (2004) has also defined sensitization as "stimulation by chemical allergen (in an inherently susceptible individual) of an immune response of the quality and vigor required to permit the provocation of an elicitation reaction upon subsequent encounter with the same chemical." ACD is typically characterized by two phases, termed induction and elicitation. Induction occurs when there is an exposure of sufficient magnitude and/or duration to activate specific immune mechanisms resulting in the

acquisition of sensitization, while elicitation occurs from a subsequent exposure to the same chemical allergen. As it is generally recognized that a certain level of allergen exposure must be attained to induce immune activation in susceptible individuals, dermal sensitization is characterized as a threshold type of response. However, dose-response relationships are observed for both the induction and elicitation phases of ACD (Gerberick and Robinson, 2000; Kimber et al., 2003; Scott et al., 2002), and thresholds for induction can be reached following either a single sufficiently high amount of exposure to the allergenic chemical, or after contact with a large area of skin, or as a consequence of repeated skin applications (Marzulli and Maibach, 1996). Experiments with 2,4-dinitrochlorobenzene (DNCB) and other sensitizers have shown that a single contact can be sufficient for sensitization, but less data exist of the relationship between lower area doses and repeated contacts over a longer time period (Griem et al., 2003). A study summarized by Griem et al., (2003) and conducted by Vandenburg and Epstein (1963) in which previously non-sensitized persons were exposed to nickel chloride suggested that subclinical sensitization occurred in some of the subjects who responded negatively from the first test, as an increased percentage of non-sensitized subjects responded positively upon a repetition of the test four months later. More studies are needed in this area.

To be capable of inducing an allergenic response, the chemical itself must possess certain characteristics. Those chemicals able to cause sensitization are usually low molecular weight protein-reactive substances that can gain access to the viable epidermis via the stratum corneum, and are also able to cause sufficient local trauma to induce cutaneous cytokines and be inherently antigenic and recognized by responsive T lymphocytes.

Once through the stratum corneum, the allergen makes contact with the Langerhans cell, a member of the bone-marrow derived dendritic cell family whose function is to act as a 'sentinel' cell and serve as a trap for antig Langerhans cells then direct the allergen to a regional lymph node, where interaction with T lymphocytes occurs, followed by proliferation of lymphocytes that have been 'primed' to react against the presented antigen. ens entering the skin (Kimber, in Marzulli and Maibach, 1996). A subsequent contact with the allergen will result in elicitation of the sensitization response due to the reaction of sensitized lymphocytes with the allergen. The process is illustrated in the following diagram:





From: Sailstad, D.M. (2003): Allergic Contact Hypersensitivity: Mechanisms and Methods. In: Alternative Toxicological Methods. Harry Salem and Sidney Katz, eds. , CRC Press, Boca Raton, Florida. Pages 193-205.

It should also be noted that in addition to Langerhans cells, epidermal cytokines and chemokines may also play a role in the development of the sensitization response. This is based on the observation that the functional activity of Langerhans cells and presumably other cutaneous antigen-presenting cells, is regulated largely by the availability of cytokines (Kimber, in Marzulli and Maibach, 1996).

While it is generally accepted that the necessary exposure for induction of dermal sensitization is greater than the exposure needed to elicit sensitization, it is important to recognize that thresholds are largely determined by the potency of the chemical allergen and that induction and elicitation thresholds vary among individuals (Kimber et al., 2003). It is thus necessary to consider dose-response relationships in establishing “safe” levels for prevention of induction and elicitation. A recent investigation by Scott et al. (2002) examined the quantitative relationship between sensitization and elicitation concentrations and the ability to elicit an ACD reaction in murine models. Using two established sensitizers (DNCB and squaric acid dibutyl ester (SADBE), dose-response relationships were determined using the LLNA to derive EC3 values for both chemicals. Then, for DNCB, various elicitation concentrations were tested in mice that

had been induced to various concentrations of DNCB. As the sensitizing concentration of DNCB increased, it was observed that the concentration required to elicit measurable sensitization in sensitized mice decreased. That is, mice who had been sensitized to higher concentrations of DNCB required less DNCB to elicit a measurable sensitization response. For SADBE, two different elicitation concentrations were compared over a range of induction concentrations. The group given the higher elicitation concentration showed measurable sensitization at lower induction concentrations. The results of this study suggested that, as the induction dose was increased (using DNCB), the concentration required for elicitation was decreased. Correspondingly, as the elicitation concentration was increased (using SADBE), the concentration required for induction was decreased.

Hazard Identification

It is desirable to be able to conduct quantitative assessments for dermal sensitization in order to prevent consumers especially from developing ACD when dermal contact, including repeated dermal contact, could not be completely avoided (Griem et al., 2003). In the case of hexavalent chromium as a component of treated wood, this is important, as there would be repeated dermal contact with the treated wood surface when this treated wood is used in residential decking and playground structures.

There are several accepted methods for hazard identification of dermal sensitization, including

the Buehler occluded patch test, the guinea pig maximization test, and the murine local lymph node assay (LLNA). The guinea pig maximization test and the Buehler test, while providing reliable information on whether a substance is a skin sensitizer or not, are best suited only for hazard identification.

By contrast with the Buehler test and maximization test, the Mouse Local Lymph Node Assay (LLNA) is a more recent test method for assessing the allergic contact dermatitis (skin sensitization) potential of chemicals, specifically the induction phase of sensitization. Using the incorporation of radiolabeled thymidine or iododeoxyuridine into DNA, the LLNA measures lymphocyte proliferation in the draining lymph nodes of mice topically exposed to the test article. The stimulation index (ratio of lymphocyte proliferation in treated mice compared to controls) is used as the indicator of potential sensitization. In 1998, following review by the FIFRA Scientific Advisory Panel (SAP), the LLNA was incorporated as a screening test in OPPTS Test Guideline 870.2600 Skin Sensitization. In 1999, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Immunotoxicity Working Group (IWG) recommended the LLNA as a stand-alone alternative for contact sensitization hazard assessment, provided that certain protocol modifications were made. Following additional studies to validate the method, the FIFRA SAP agreed with the Agency proposal that the LLNA was applicable for testing chemicals to elicit contact sensitization and should be considered a preferred, stand-alone assay. The OPPTS guideline 870.2600 (Skin Sensitization) has been revised to include the LLNA as a stand-alone assay for appropriate applications. The

OPPTS guideline has also been harmonized with OECD's Guideline 429 for LLNA, which was adopted in April 2002.

Although the LLNA has not been validated for determination of sensitization potency of chemical allergens and sensitization to metals has not been extensively studied , approaches for determination of quantitative assessment of sensitization induction thresholds have been proposed in the scientific literature using LLNA data (Gerberick 2000, 2001; Griem et al., 2003). It may therefore be useful to consider data from the LLNA as a starting point for quantitation of induction thresholds, as dose response data can be generated from this assay, and a NOAEL can potentially be identified (Felter et al., 2003). However, while the LLNA has been validated and accepted as a stand-alone test method for assessment of dermal sensitization potential by the Interagency Coordinating Committe on the Validation of Alternative Test Methods (ICCVAM , 1999), the test itself has not been validated for its utility in dermal risk assessment (Felter et al., 2003). It has been proposed to group sensitizing chemicals according to relative potency as determined in the LLNA, and then compare these categories with the relative sensitization potency in humans on the basis of clinical experience and/or prevalence of ACD in the population (Griem et al, 2003). While a good correlation between LLNA results and sensitization potency in humans has been reported (Griem et al., 2003), there is not yet general agreement on categories and ranges that should be used in classification of relative potency.

Induction Threshold Methods

Gerberick (2000, 2001) proposed a methodology for determination of a 'sensitization reference dose' for sensitizers in consumer products. The lower boundary of the potency category for a sensitizing chemical is used as the starting point, with application of uncertainty factors for interindividual variability, product matrix effects, and use pattern. This approach was applied to the fragrance component cinnamic aldehyde and the preservative methylchloroisothiazolinone/methylisothiazolinone for which both LLNA and human sensitization potency were available (Griem et al., 2003).

A use for the LLNA in quantitative risk assessment was investigated by Griem et al (2003). Identification of known human sensitizing chemicals for which both an EC3 value from an LLNA test and a NOAEL or LOAEL from human repeat insult patch tests (HRIPT) or the human maximization test (HMT) were available were identified. The reported concentrations were converted into specific and molar area doses. Comparison of the area doses of the LLNA and human test results indicated that sensitization thresholds were similar in mice and humans despite the fact that the area doses for different chemicals ranged over several orders of magnitude (Griem et al., 2003). It was concluded from this analysis that the LLNA EC3 value is a useful measure of sensitizing potency in humans, and that the EC3 value can be used as a surrogate value for the human NOAEL which, in turn, can be used as a starting point in quantitative risk assessment.

Elicitation threshold Methods

The above approaches describe methods that may be used to estimate thresholds for safe area doses that are considered protective against induction of sensitization. There are also proposed approaches for estimation of safe area doses that are considered protective against elicitation of sensitization in already sensitized persons. By inference, protection against elicitation would also be protective of induction, as thresholds for induction are generally higher than those for elicitation (Kimber et al., 2003).

An approach to estimate an acceptable area dose for protection against elicitation is the concept of the Minimum Elicitation Threshold, or MET. This approach has been discussed in previous publications (Nethercott et al., 1994; Zewdie, 1998; NJDEP, 1998; Basketter et al., 2003) specifically with respect to hexavalent chromium. The concept behind the MET is that there is an 'elicitation threshold' below which no sensitization reaction is expected; thus, the MET is analogous to an RfD (Horowitz and Finley, 1994). The estimation of an MET is usually based on the results of tests in previously sensitized individuals; thus, the MET is considered protective of elicitation reactions. However, there has not been an extensive discussion of the criteria for employing this concept for purposes of risk assessment. Nethercott (1994) calculated a value of 0.089 ug/cm^2 as a 10% MET (i.e. the concentration at which 10% of the study group responded) based on results of a human repeat insult patch test in 54 chromium-sensitized volunteers and claimed that this value should be protective against ACD for hexavalent chromium in at least 99.99% of the population exposed to contaminated soil. Paustenbach (1992) estimated a 10% threshold response of 54 parts per million for hexavalent chromium in soil, but

no discussion of the relevance of the 10% response level was presented. Two states (Massachusetts and New Jersey) have proposed soil cleanup standards based on an ACD endpoint using either the human patch test data of Nethercott (1994) or the human forearm water exposure data of Fowler (2000).

Griem et al. (2003) also proposed an approach for derivation of a safe area dose at which ACD would not be manifest in sensitized individuals. As several of the factors that influence induction of sensitization (skin penetration, uptake by antigen-presenting cells, metabolism) are also relevant for elicitation, it was postulated that a correlation between the induction potency and elicitation potency of a chemical could be established. However, comparison of induction and elicitiation area doses from limited data in humans did not show an obvious correlation. While induction threshold doses spanned five orders of magnitude, values for elicitation were mainly within one order of magnitude. Using the log transformation of the ratio of induction/ elicitation to elicitation, it was proposed that the ratio of the induction/sensitization threshold could be predicted on the basis of an established sensitization (induction) threshold. Examples of the derivation of safe area doses for three chemicals (MCI/MI, a preservative in many cosmetics and household products; cinnamic aldehyde, a fragrance and flavor ingredient; and nickel) were presented. For strong sensitizers such as MCI/MI, it was demonstrated that the safe area doses for induction and elicitation were close together, while for weaker sensitizers such as nickel, the safe area doses for induction and elicitation were farther apart, consistent with the mathematical relationship of the ratio of induction/elicitation threshold vs. sensitization threshold. That is, for lower potency sensitizers, a relatively high area dose may be needed to cause induction of

sensitization, but elicitation may be possible with much lower area doses, while for a potent sensitizer, the area dose needed for induction is close to the area dose that will elicit the reaction in a sensitized individual.

Uncertainty

After the appropriate level of concern has been identified (e.g. NOAEL determination, for example), areas of uncertainty need to be considered in extrapolating the result to conditions relevant to the human exposure of interest. Areas of uncertainty that have been identified for dermal risk assessment include (1) interspecies variability/susceptibility (i.e. extrapolation from animals to humans); (2) inter-individual variations in response within humans; (3) vehicle or product matrix effects; and (4) exposure considerations (i.e., area of the body exposed, repeated exposures). Briefly, and as discussed in more detail by Felter et al. (2002) and Griem et al. (2003), the inter-individual variation in response to induction and elicitation of dermal sensitization must be taken into account, as there may be differences in response based on age, sex, and genetic factors, or health status of the skin. In addition, formulation of chemical allergens into product matrices that may result in an enhancement or inhibition of ACD must be considered in the risk assessment paradigm, as must also extrapolating from experimental conditions to real-world exposure conditions, i.e. site of the body exposed , effects of occlusion, and environmental conditions (temperature, humidity, and repeated dermal exposures). For each of the 4 areas, a range from 1-10 has been suggested for uncertainty in each area.

Populations of Concern

Approaches to estimating safe area doses for ACD have been proposed using EC3 values derived from the murine LLNA (Gerberick and Robinson, 2000; Felter et al., 2003, and MET values from human repeat insult patch tests (Nethercott et al., 1994; Basketter et al., 2001; Hansen et al., 2003). Approaches using the results of murine LLNA data are intended to estimate area doses that are protective against induction of ACD, while use of the MET approach is intended to be protective against elicitation of ACD in sensitized persons. Griem et al. (2003) have also proposed an approach for calculation of safe area doses designed to be protective against both induction and elicitation of ACD through use of appropriate uncertainty factors applied to the results of murine LLNA or human patch test study results. This proposal is worth examining, as it has been acknowledged in the past for sensitizing chemicals such as nickel and hexavalent chromium that it is difficult to protect individuals who are already sensitized (Felter et al., 2003; USEPA, 1998).

In addition, consideration should be given to whether there are potentially susceptible subpopulations who may be more susceptible to the induction and/or elicitation of ACD. Paustenbach et al. (1992) and Felter et al. (2002) have discussed the issue of whether children are more or less at risk for development of ACD. Paustenbach et al. addressed this issue specifically for hexavalent chromium, and it was concluded that risk to children ages 3 to 8 is not likely to be greater than risk to adults as there is no evidence that repeated exposures to hexavalent chromium places a person at greater risk of sensitization. Felter et al. suggested that infants and children may actually be at lower risk for development of ACD based on data

gathered from dinitrochlorobenzene and pentadecylcatechol (poison ivy allergen). These views are somewhat counter to the opinion of Griem et al. (2003) who suggested a possible higher sensitizing potency of a chemical upon repeated exposures. This would make sense in the case of hexavalent chromium, as the significant irritancy of the chemical could lend itself to an increased sensitizing potency by allowing more chemical to penetrate the stratum corneum.

Case Study- Hexavalent Chromium

As noted in the 1998 IRIS Toxicological Review for hexavalent chromium (USEPA, 1998) as well as in numerous publications, hexavalent chromium is one of the most common and potent contact sensitizers. Exposures to hexavalent chromium occur in a number of occupational settings including including chrome plating baths, chrome colors and dyes, cement, tanning agents, wood preservatives, anticorrosive agents, welding fumes, lubricating oils and greases, cleaning materials, and textiles and furs (USEPA, 2003). Non-occupational exposures to hexavalent chromium have also been noted in household detergents (Basketter et al., 2003; Stern et al., 1993) as well as in cement.

Elicitation thresholds in persons sensitized to hexavalent chromium have been described in the literature (Nethercott, 1994; Fowler, 2000). However, there are no recent data on induction thresholds for hexavalent chromium. Some investigation has been performed on the question of induction thresholds in general, as it has been stated (Marzulli and Maibach, 1996; Griem et al., 2003) that repeated dermal contact over a longer time period may also result in a threshold for

induction. Although more work is needed in this area, Griem (2003) proposed an uncertainty factor be applied for repeated dermal contact with chemical allergens, as there may be a higher sensitizing potency of a chemical upon repeated exposure.

The Antimicrobials Division of OPP is concerned with the risk from dermal exposure that may occur from dermal contact with hexavalent chromium on the surface of wood treated with a wood preservative product containing hexavalent chromium, as hexavalent chromium is known to be a potent dermal irritant and sensitizing agent. The Antimicrobials Division, using existing science policies in OPP, currently performs hazard and risk assessments for non-cancer endpoints through selection of a level of concern (e.g., a NOAEL or LOAEL value) and compares this level of concern to estimated or actual exposures to derive a Margin of Exposure. The Margin of Exposure is then weighed against the "acceptable" Margin of Exposure, which takes into account uncertainties in the risk assessment (e.g., inerspecies differences in response, intraspecies differences in sensitivity).

Hazard Identification for hexavalent chromium

Murine LLNA hazard data reported by Kimber et al. (1995) from five different laboratories reported EC3 values for hexavalent chromium using potassium dichromate as the test substance. These data are shown below:

laboratory	A	B	C	D	E	Avg.	US Avg
country	UK	US	UK	US	US		
area dose µg/cm^2	5.12	11.56	13.24	10.77	11.2	10.36	11.15

Several published studies (Nethercott et al., 1994; Basketter et al., 2001; Hansen et al., 2003) have reported elicitation thresholds in persons previously sensitized to chromium. In the study by Nethercott et al., a 10% MET of 0.089 µg/cm^2 was reported from results of patch testing using 54 human volunteers known to be sensitized to hexavalent chromium. The lowest dose tested in this study, 0.018 µg/cm^2, also showed evidence of elicitation in one subject.

Basketter et al. (2001) reported elicitation reactions to potassium dichromate in 17 volunteers giving fully informed consent using closed-patch and open appliation techniques. Skin pre-treated with 0.2% sodium lauryl sulfate showed reaction to potassium dichromate at 1 ppm, with a dose-response evident at the higher concentrations. Using open application techniques, 3 of 15 volunteers reacted to a level of 5 ppm potassium dichromate. To protect those already sensitized to chromium as well as to prevent development of additional chromium-sensitive subjects, a chromium contamination level of 1 ppm was suggested on the basis of this study.

Hansen et al. (2003) compared the 10% MET for both hexavalent and trivalent chromium in 18 volunteers known to have chromium allergy. The results of this study indicated a 10% MET of 0.03 µg/cm^2 for hexavalent chromium and 0.18 µg/cm^2 for trivalet chromium, and suggest that both trivalent and hexavalent chromium should be taken into consideration when characterizing chromium skin allergy.

The data reported above using human volunteers are from subjects previously sensitized to hexavalent chromium and give some indication of an elicitation threshold, while the LLNA data reported in Kimber et al. (1995) show induction thresholds in the murine LLNA test.

Estimation of 'safe' area doses for protection from hexavalent chromium ACD can be performed in both cases using published methdologies. For the LLNA study results, uncertainty factors for interspecies extrapolation, intraspecies variation, product matrix, and exposure considerations should be taken into account. For the interspecies uncertainty factor, Griem et al. (2003) proposed a factor of 3 based on comparison of human and murine data showing that sensitizing doses are within a factor of 3 of each other, and that skin penetration tends to be higher in rodents than in humans. An uncertainty factor of 10 is proposed for intraspecies variation in humans, as there are few data on induction thresholds in humans. A product matrix uncertainty factor of 10 is proposed for hexavalent chromium. The LLNA assay is performed using an acetone/olive oil vehicle, while the wood preservative formulation containing hexavalent chromium is likely more complex and could affect the availability and potency of the allergen. An exposure uncertainty factor of 10 is proposed based on uncertainty regarding the repeated dermal exposure that could occur to the treated wood and how this would affect the potency of hexavalent chromium as a dermal sensitizer. The total uncertainty factor from this analysis is 3000 applied to the calculated area dose from the average of 5 LLNA assays to yield a 'sensitization reference dose.' This is illustrated below:

laboratory	A	B	C	D	E	Avg.	US Avg
country	UK	US	UK	US	US		
area dose µg/cm^2	5.12	11.56	13.24	10.77	11.2	10.36	11.15
interspecies extrapolation UF	3	3	3	3	3	3	3
intraspecies variation UF	10	10	10	10	10	10	10
matrix UF	10	10	10	10	10	10	10
exposure UF	10	10	10	10	10	10	10
S-RfD µg/cm^2	0.0017	0.0038	0.0044	0.0035	0.0037	0.0034	0.0038

The S-RfD can then be compared to estimated or measured human exposure to determine if the Margin of Safety is adequate. If, as suggested by Griem et al. (2003) that the maximum uncertainty factor should be no greater than 1000, then the S-RfD values shown above, using the maximum uncertainty factor of 1000, would be 0.005, 0.01, 0.013, 0.01, and 0.01 µg/cm^2 respectively for the five studies, with an average U.S. value of 0.01 µg/cm^2.

A similar approach can be applied to the MET values from the Nethercott et al., Hansen et al., and Basketter et al. studies. As the data are from human studies, the interspecies extrapolation factor could be reduced to 1. An intraspecies uncertainty factor of 3 is proposed based on the use of sensitized persons, as elicitation thresholds have been found to be less variable than induction thresholds. An uncertainty factor of 3 is also applied for the use of LOAEL values, as the studies were not designed for specific determination of a NOAEL. An uncertainty factor of 1 is proposed for exposure considerations, based on the use of a sensitized study group. The total

uncertainty factor of 10 applied to the reported human LOAEL valuesof 0.018 µg/cm^2 , 0.01 µg/cm^2, and 0.03 µg/cm^2, results in 'safe' area doses of 0.0018, 0.001, and 0.003 µg/cm^2 for persons previously sensitized to hexavalent chromium.

Comparison of the values derived from the induction studies using the LLNA and the patch test data shows under the current scheme that induction and elicitation does for hexavalent chromium do not differ appreciably, consistent with the fact that hexavalent chromium is a potent sensitizer and that induction and elicitation doses will not differ widely, as discussed by Griem et al (2003). This factor could change from application of uncertainty factors of differing magnitude; a reasonable case has been presented using the available data.

Environmental Exposures

Application of the experimental data to environmental exposures is also a significant aspect of the risk assessment, as for hexavalent chromium, there will be dermal contact not only with the treated wood product, but with soil in contact with or in proximity to the treated wood structure. As the experimental hazard dose metric (i.e., the area dose) for induction and/or elicitation of dermal sensitization may differ according to the matrix of exposure, it is desirable to characterize as accurately as possible the influence of the exposure matrix variables on determination of an acceptable area dose level. For contact with a wood matrix into which a chemical allergen is incorporated, the Office of Pesticide Programs estimates a safe area dose from available scientific data and compares that level of concern to the estimated or measured level of exposure

to calculate an acceptable Margin of Exposure. Variables that influence the calculation of the exposure to the chemical on the surface of wood include transfer efficiency of the chemical from the wood to the skin, number of dermal contact events, surface area of skin exposure, and level of the chemical on the surface of the wood. Approaches to assessing treated wood exposures have been considered recently by the FIFRA SAP in a December, 2003 meeting in which the SHEDS model was presented and considered as a probabilistic approach to assessing exposures to arsenic and chromium in treated wood, including children's exposures.

For determination of an acceptable area dose from contact with a chemical in a soil matrix, many of the variables are similar to the wood matrix. However, other soil matrix properties may have a greater impact on the transfer of the chemical from the soil to the skin. Additional variables are taken into account in calculating skin contact dose, such as skin surface area of contact, soil adherence to skin, contact frequency (important for determination of children's potential hazard and risk), bioavailability of the chemical in soil, physio-chemical properties of the soil (i.e. moisture content, soil type), valence or complex state of the chemical, and chemical solubility in sweat. Guidance for determination of acceptable soil levels for Superfund cleanup sites is found at the following web address: http://www.epa.gov/superfund/resources/soil/ssgmarch01.pdf. It is noted here that soil cleanup values estimated for dermal contact in the Superfund program are based upon systemic effects resulting from dermal exposures, although dermal sensitization effects should also be considered in the assessment.

Water also represents a matrix of exposure that is different than wood or soil, in that it represents a three-dimensional matrix of contact (i.e. $\mu g/cm^3$) vs. a two-dimensional matrix of contact (i.e. $\mu g/cm^2$). Activities such as showering represent exposure scenarios where potential dermal sensitization hazard may need to be characterized, but as with soil, other variables may influence the estimation of a safe area dose in this matrix. Thus, while the experimental hazard data for hexavalent chromium indicate that low levels are adequate to induce and/or elicit sensitization, the actual concentration necessary for such reactions may differ according to the matrix in which the chromium is found.

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