906 LATEX ALLERGY IN THE WORKPLACE.

M. Toraason and D. Germolec. *NIOSH, Cincinnati, OH.*

The United States Occupational Safety and Health Administration (OSHA) estimates that 8-12% of healthcare workers are sensitized to natural-rubber latex. In addition, approximately 0.5-1% of the general population is reported to be sensitized. Clinical signs and symptoms of latex induced disease range from simple irritation to immunologic manifestations such as urticaria, asthma, and anaphylaxis. The mechanisms of latex allergy are complex, and are induced by exposure to numerous allergenic proteins found in natural-rubber latex as well as other chemicals used in latex products manufacturing. For example, there are 250+ proteins containing multiple epitopes in latex of which at least 30 have allergenic potential. Several latex proteins have been epitope mapped. Sequencing demonstrates both unique epitopes and sequences commonly found in other plant proteins. These common epitopes result in cross-reactivity to other plant allergens found in pollens and foods. A further complication arises from the ability of latex proteins to associate with glove powder. This enhances the potential for respiratory sensitization from aerosolized powder associated proteins, and both humans and experimental animals have demonstrated hypersensitivity following exposure to latex via the respiratory route. The diagnosis of latex allergy is complicated by these variables, which in turn hinders the development of intervention strategies. Further epidemiological assessment can more explicitly define the scope, trends, and demographics of latex allergy. Diagnostic accuracy can be improved through greater knowledge of proteins involved in the development of latex allergy, and factors analysis of presently available diagnostic tests. *In vivo* and *in vitro* models can elucidate mechanisms of sensitization and provide an understanding of the role of exposure route in latex associated diseases. Combined, these efforts can lead to intervention strategies for reducing latex allergy in the workplace.

907 LATEX ALLERGY: CLINICAL AND EPIDEMIOLOGICAL DATA.

G. Sussman. *University of Toronto, Toronto, Ontario, Canada.* Sponsor: M. Toraason.

Natural rubber latex (NRL) allergy has become an important occupational health concern particularly among healthcare workers (HCWs). Clinical manifestations include irritant contact dermatitis, allergic contact dermatitis (type 4), and type 1 immediate hypersensitivity responses. Type 1 (IgE mediated) NRL allergy includes contact urticaria, systemic urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm and anaphylaxis. Diagnosis of type 1 latex allergy is made by accurate history including questions on atopic status, food allergy, reactions to latex devices (gloves, balloons, condoms), and reactions during medical and dental procedures. To confirm a diagnosis either *in vivo* skin prick testing (SPT) or *in vitro* assays for latex specific IgE are performed. The major source of workplace exposure has been the powdered NRL gloves used by HCWs. Surveys of HCWs have demonstrated that the prevalence of sensitization to latex ranges from 2.9% in Finland to 4.7% in Belgium among hospital workers as a group, and from 6.2% in operating room staff in Finland to 9-10% in Canada and France. We recently observed that the prevalence of latex sensitization based on SPT was 12.1% with a minimum prevalence of 9.5% among 1351 HCWs in two hospitals. There were significant associations with atopic status, positive SPT to certain foods, work related symptoms, and departmental use of gloves per HCW. In this study about 60% of the latex SPT positive participants had work related symptoms. It has been reported that 2.5% of HCWs have latex induced occupational asthma confirmed by specific inhalational challenge. Sensitization to latex has extensive cross-reactivity with certain foods and leads to clinical allergic reactions. Positive food SPTs occurred in our patients with the following frequency: avocado (53%), potato (40%), banana (38%), tomato (28%), chestnut (28%), and kiwi (17%). As well we reported that dental school students were at high risk for latex sensitization with prevalence rates of 0% for year one and two students, 6% of year 2 students, and 10% of year four students having a positive latex SPT. The prevalence of latex sensitization in occupationally unexposed groups is quite low, generally less than 1%.

908 MOLECULAR CHARACTERIZATION OF LATEX ALLERGENS.

D. Beezhold. *Guthrie Research Institute, Sayre, PA.* Sponsor: M. Toraason.

Type 1 latex allergy is an IgE mediated response to antigenic proteins found on products made from natural rubber latex. Natural rubber latex is harvested from trees and ammoniated to prevent coagulation resulting in the hydrolysis of the latex proteins. Prior to use in manufacturing, the latex is formulated by the addition of multiple chemicals. Thus, human exposure is to a mixture of residual chemicals and hydrolyzed latex peptides. The hydrolyzed nature of the allergens has complicated identification of major allergens and the development of reagents for *in vivo* and *in vitro* diagnostic tests. Multiple investigators, using a variety of methodologies, have succeeded in identifying the major IgE binding allergens (Hev b 1-8). More recently, these proteins have been cloned, sequenced and expressed as recombinant proteins. Skin testing with recombinant Hev b 2, 3, 5, 6, 7, and 8 revealed Hev b 5, 6 and 7 to be the most common allergens for healthcare workers. Using overlapping synthetic peptides, IgE binding epitopes have been determined for these allergens. Hev b 5 contained at least 6 epitopes, while Hev b 7 contained 12 epitopes all with limited sequence homology to other known plant proteins. Hev b 6 however, contained six epitopes with sequence homology to defense proteins common to many different plants. Sequence homology helps to explain the cross reactivity to a variety of foods experienced by latex allergic individuals. The development of recombinant allergens provides reagents which should greatly improve the diagnostic accuracy of tests for latex allergy.

909 COMPLICATIONS IN INTERPRETATION OF DIAGNOSTIC TESTS FOR LATEX ALLERGY.

R. Biagini. *NIOSH, Cincinnati, OH.*

The diagnosis of natural rubber latex allergy begins with a clinical history and often involves a confirmatory test. While the puncture skin test (PST) has been regarded as a primary confirmatory test for the assessment of patients for IgE-mediated disease, the absence of an FDA-licensed Hevea brasiliensis latex extract in the USA has restricted its use in the diagnosis of latex allergy. Serological tests have therefore become critically important as alternative diagnostic tools. Three manufacturers have currently obtained 510K clearance from the FDA for their latex *in vitro* reagents: the CAP System (PharmaciaUpJohn); the AlaSTAT, (Diagnostic Products Corporation) and the HY-TEC assay (HYCOR Biomedical). Although all of these commercial assays are based on non-ammoniated latex (NAL) as their primary allergen, there are differences in their solid or soluble supports and detector systems. Paired-comparisons of the three assays indicates that they disagree on the antibody status of an individual serum. This leads to patient's sera being "positive" by one or two tests and negative in (an)other(s). It is speculated that the disagreement among tests is due to IgE antibody assays detecting different subsets of IgE antibody of a given specificity, possibly as a result of differential specificities of their allergen-containing reagents. Reasons for this include variability in allergen content in different batches of source latex; sensitized individuals producing specific IgE antibody to at least 8 *Hevea* allergens, Hev b 1-Hev b 8, each of which differs in its structure, size, net charge (pI), relative allergenicity and abundance in natural rubber latex. The relative content and ratios of Hevs in the final allergen preparation most probably could enhance the diagnostic accuracy of a specific test. Other potential causes of allergen-containing reagent heterogeneity include variable stability during storage and variable binding of allergen to labels (e.g., biotinylated co-polymer in AlaSTAT) or solid supports (sponge in CAP; cellulose disc in HYTEC). Using receiver operating characteristic (ROC) curve analysis, and positive PST to NAL as the discriminator, the HY-TEC system has significantly greater ($P<0.01$) area under the curve (AUC, 0.924 + 0.017, standard error) than CAP (0.869 + 0.024) or AlaSTAT (0.858 + 0.024), suggesting it may be more accurate under the comparison conditions evaluated.

910 ANIMAL MODELS AND MECHANISMS OF LATEX ALLERGY.

B. J. Meade. *NIOSH, Morgantown, WV.*

Animal models are frequently used to conduct mechanistic studies that due to test article toxicity or sensitization potential would be unethical to perform in humans. Several laboratories have developed models to study latex allergy and although these include rabbit and guinea pig models, most animal research has been conducted in murine models. Although clinical and exposure data have been gathered on the factors affecting the elicitation of responses in latex allergic individuals, less is known regarding the development of sensitization. Coupled with *in vitro* dermal penetration studies, murine models were established to investigate the role of the route of exposure in the development of latex sensitization. Time course and dose response

studies have shown multiple subcutaneous (s.c.) administrations of as little as 0.19µg non-ammoniated latex proteins (NAL) elicited IgE production in 5 weeks. Animals exposed s.c., intratracheally (i.t.) or topically to 12.5µg NAL demonstrated IgE production within 2, 3 and 5 weeks, respectively. Although elevations in total and latex specific IgE have been observed following topical, intranasal (i.n.), i.t. and s.c. exposures, pulmonary responses (as measured by plethysmography) following respiratory challenge was only seen in mice sensitized by the topical or respiratory routes. Both *in vitro* penetration and *in vivo* studies highlight the importance of skin condition in the development of latex allergy with enhanced penetration and earlier onset of IgE production seen with experimentaly abraded skin. These models are also being used to investigate the role of concurrent exposure to other chemicals and agents in the workplace on the development of latex allergy. I.n. co-exposure to endotoxin with recombinant Hev b 5 was reported to increase the Hev b 5 specific IgE response without altering total IgE. In our model, i.n. co-exposure of endotoxin with a mixture of NAL proteins was found to suppress the elevation in total IgE seen in response to NAL alone. These observations underscore the complexity of the mechanisms involved in the development of an allergic response to a complex mixture.

911 HARMONIZATION OF CANCER AND NON-CANCER RISK ASSESSMENT: MOVING BEYOND THE NRC BOOK.

H. Zenick[1] and M. S. Bogdanffy[2]. [1]*NHEERL, Research Triangle Park, NC and* [2]*E.I. Du pont de Nemours & Co., Newark, DE.*

The publication of the 1983 NRC report, Risk Assessment in the Federal Government: Managing the Process established the framework and principles for risk assessment that are still applied today, essentially unmodified. At that time, the primary focus was on cancer risk assessment with the consequence being the emergence of a somewhat dichotomous approach to assessing cancer and non-cancer risks. The rapid increase in our understanding of toxicokinetic and toxicodynamic mechanisms is now challenging the validity of these assumptions and the value of retaining such a disparate approach. Evidence suggests that carcinogens may work initially through a variety of less direct targets/processes, some of which may have thresholds. Similarly, because of factors such as differences in individual susceptibility and existing background rates, certain non-cancer effects may not exhibit a threshold. In this workshop, a more consistent and integrated approach to human health risk assessment will be discussed. In exploring the future directions that risk assessments will take, mechanistic commonalties between cancer and non-cancer effects will be examined as well as issues related to differences in disease expression (e.g. exposure parameters, disease latency). Discussions in this workshop will include an historical perspective, the central roles of mode of action and tissue dosimetry, and stochastic vs. tolerance distribution models in integrated approaches to cancer and non-cancer risk assessment.

912 HARMONIZATION IN RISK ASSESSMENT—OVERVIEW HISTORICAL ASSUMPTIONS AND PRACTICES.

G. Kimmel and V. Vu. *USEPA, Washington, DC.* Sponsor: H. Zenick.

In 1983, the National Research Council published Risk Assessment in the Federal Government: Managing the Process. Since then, much has been done in the way of producing guidance for carrying out risk assessments, as well as developing new approaches. Recently, the risk assessment field has begun to challenge the traditional approaches to risk assessment. This is especially true in the separation of cancer and non-cancer risk assessments. Historically, cancer has been considered a non-threshold response, while other health endpoints were considered threshold effects. However, in 1994 NRC, in Science and Judgement in Risk Assessment, noted the importance of an approach that is less fragmented, more consistent in applications of similar concepts, and more holistic than endpoint-specified guidelines. The report questions the application of a non-threshold quantitative approach as a default in all cancer risk assessments. Conversely, the use of a threshold concept as a default for agents that cause nerve, reproductive and developmental toxicity or that act on various systems through receptor-medicated events is also questioned. The EPA has begun to address this changing philosophy, and its revised cancer risk assessment guidance has proposed departing from the assumption that all cancer effects show linear dose-response relationships. The Agency is also developing an over-arching framework for human health risk assessment. The Agency is seeking the input of the risk assessment community as evidenced by a recent SOT Contemporary Concepts in Toxicology workshop, cosponsored by several governmental and non-governmental groups, on the harmonization of risk assessment approaches including incorporation of mechanistic information. The present talk will briefly review the historic assumptions underlying current approaches to health risk assessment and will summarize EPA's current interest in a more integrated approach to risk assessment in the future.

913 MODE OF ACTION AND TISSUE DOSIMETRY—LINCHPINS OF HARMONIZATION OF CHEMICAL RISK ASSESSMENT.

M. E. Anderson[1] and H. A. Barton[2]. [1]*Colorado State University, Fort Collins, CO and* [2]*NHREEL, Research Triangle Park, NC.*

Chemical risk assessments have evolved as knowledge of toxicological and biological processes has matured. However, there is divergence of risk assessment practices among agencies and offices within the same agencies. As chemical risk assessments become more objective, there is increasing emphasis on more consistent guidelines for these assessments. Increasingly, the emphasis has been on how the chemical interacts with the biological system to produce the adverse outcome, the so-called mode of action. Mode of action is especially helpful in defining approaches for low dose extrapolation. Comprehensive mode of action statements, however, should convey both the biological consequence of the exposure and the form of chemical that initiates changes in the biological system. The form of chemical relates to proper tissue dosimetry. Quantitative integration of dosimetry and mode of action occurs through pharmacokinetic (PK) and pharmacodynamic (PD) models. Biologically based dose response (BBDR) models link dosimetry from PK models quantitatively to adverse response through mode of action. Presently and perhaps well into the future, our confidence in PK and precursor effect models will be much higher than that in complete BBDR models. Harmonization will be accelerated by consistent use of mode of action data to infer the nature of low dose curves and dosimetry/precursor effect models that allow more confident prediction of the shape of dose response curves over a wide range of exposure conditions. This talk illustrates mode of action and dosimetry concepts qualitatively and quantitatively by reference to harmonization of cancer and non-cancer risk assessment and efforts to create BBDR models for carcinogens.

914 MODE OF ACTION AS A GUIDE TO QUANTITATIVE ANALYTICAL APPROACHES.

L. Rhomberg. *Gradient Corporation, Cambridge, MA.* Sponsor: H. Zenick.

Harmonization of quantitative risk assessment methodologies should aim at achieving logical consistency among methods. Mere imposition of similarity in the operational steps of calculation can actually work against this more fundamental harmony by hiding important differences in interpretation. The same growing insight into underlying mechanisms of toxicity that suggests some commonalities between cancer and noncancer toxicities also reveals an impressive diversity of fundamental mechanisms within these two classes. Some aspects of underlying modes of action relevant to choosing quantitative analytical approaches are discussed, including action at different levels of biological organization, functional redundancy of targets, and the distinction between stochastic processes and tolerance distributions as a basis for the existence of a dose-response relationship. The pursuit of biologically based mechanistic models for characterizing dose-response relationships will engender more diversity as each endpoint comes to be analyzed in a way appropriate to its underlying biology. Too rigid a notion of what "harmonization" means, therefore, may stultify development of models yielding deeper and more reliable insight into toxicity and may cloud proper interpretation of risk analysis results.

915 INTEGRATIVE APPROACHES TO RISK ASSESSMENT BASED ON MODE OF ACTION: CANCER AND NON-CANCER ENDPOINTS.

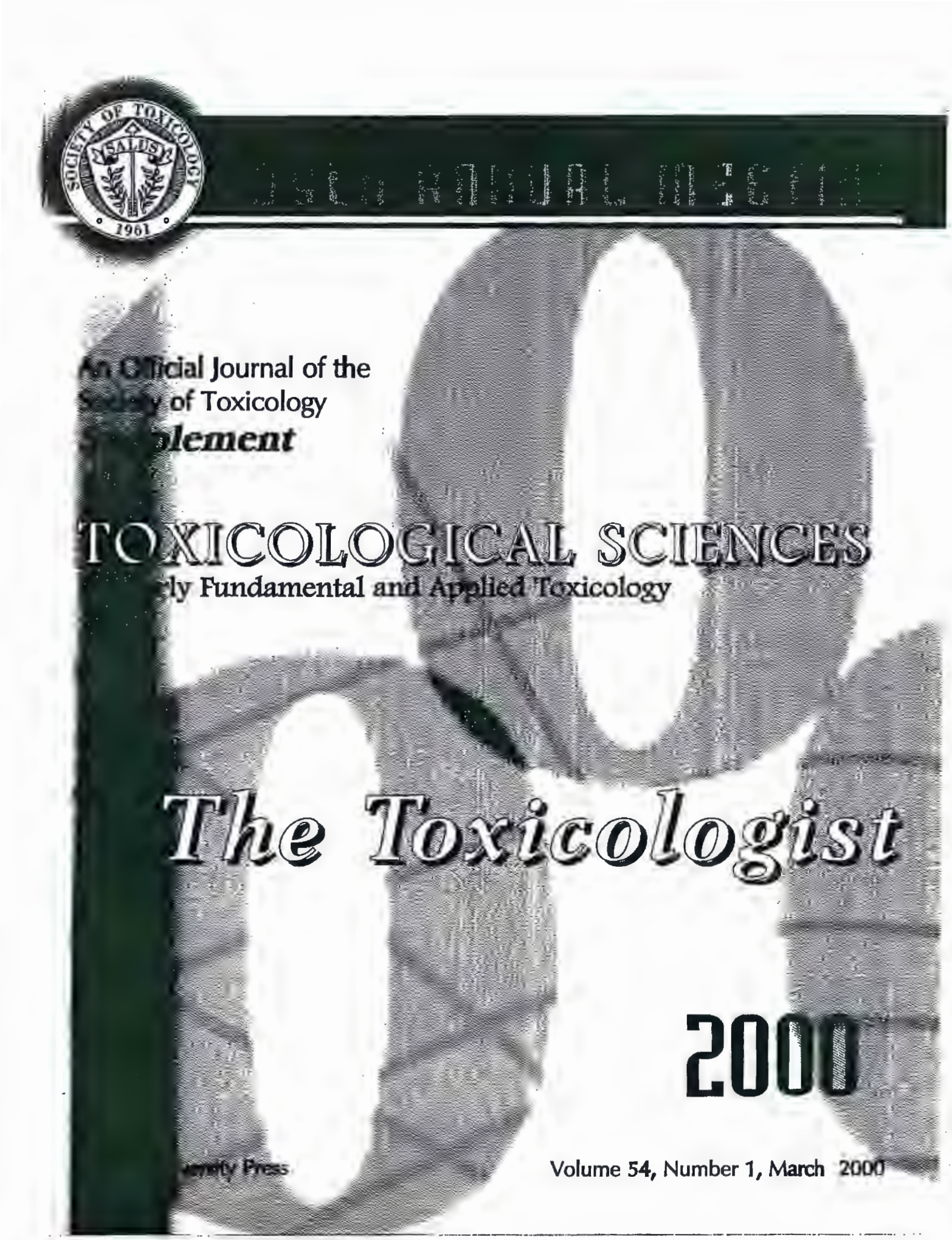
W. Farland, A. Jarabek and V. Vu. *USEPA, Washington, DC.*

There is general agreement in the scientific community that increased use of more and different information will be required to improve our understanding of risks from environmental toxicants. Recent advances in approaches to risk assessment are designed to accommodate such information. Among other things, these advances focus on breaking down the traditional dichotomy between approaches to evaluating cancer and non-cancer endpoints. The focus on better metrics for dose, understanding the basis for outcomes within

An Official Journal of the
Society of Toxicology
Supplement

TOXICOLOGICAL SCIENCES

Formerly Fundamental and Applied Toxicology



The Toxicologist

2000

Academic Press

Volume 54, Number 1, March 2000

The Toxicologist

An Official Publication of the Society of Toxicology

and

Abstract Issue of

TOXICOLOGICAL SCIENCES

An Official Journal of the Society of Toxicology

Published by Oxford University Press, Inc.

Abstracts of the
39th Annual Meeting
Volume 54, Number 1
March 2000