Immunotoxoicology Specialty Section Newsletter

The *Immunotoxicology Specialty Section Newsletter* is published quarterly. Please address all questions, comments, news items or other submissions to:

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President's Message

by Kathleen Rodgers

Welcome back from another intense, but exciting year at the Society of Toxicology meeting in Seattle. The Immunotoxicology Specialty Section was well represented with a Continuing Education course on cytokines, a symposium on cytokine receptors, several workshops on QSAR in contact allergy, the toxicology of protein allergenicity, the development of strategies to assess autoimmune potential and the toxicologic impact of wood smoke, along with a variety of platform sessions, poster discussion sections and poster sessions. Every one of these events was well attended. This shows our strength as researchers and the support and continuing interest we have for this field. Most exciting to me personally

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President-Elect's Message

by Judith Zelikoff

As the past chairperson of the Immunotoxicology Specialty Section Program Committee, I'd like to thank everyone who submitted proposals for the 1999 meeting in New Orleans. This year, as in those gone by, we had a large number of excellent submissions including a Continuing Education Course, a Roundtable, and 5 Workshops/Symposia. The CE course was suggested by Drs. Karol and Descotes and concerned Chemical Hypersensitivity, while the Roundtable, submitted by Drs. Cohen and Rodgers, tossed out the question of physiological relevance of cytokine endpoints measured by bioassays, ELISA, and molecular tools. Five Workshops/Symposia were "sent forth" to SOT and included proposals by: (1) Drs. Sikorski and Haggerty concerning drug hypersensitivity: mechanisms of immune-mediated reactions; (2) Drs. Zelikoff and Gordon (co-sponsored by Inhalation) on animal models of cardiopulmonary disease for assessing the impact of air pollution on at risk populations; (3) Drs. Gerberick and Munson on validation of toxicology test methods: immunotoxicology case studies; (4) Drs. House and Hastings on the immunotoxicology of novel therapeutics; and Dr. Toraason, from the newly-organized Occupational Health Specialty Section, concerning latex allergy: emerging issue in occupational health. The SOT Program Committee will meet the last week in May and we should be informed of their decisions sometime in early June. Thanks again for all your help and support, you made my job easy. Here's wishing Dori success for the first program in the new millennium. ■

President's Message

. . . *continued from page 1*

was the overwhelming attendance at the Immunotoxicology Specialty Section Business meeting. We had not only standing room only, but standing room in the hall only. Congratulations to all the presenters and organizers, and thank you for representing Immunotoxicology so well!

The other thing that was impressive was the willingness of our group to work in the day to day and year to year running of our Specialty section. Every year at the business meeting, we give an opportunity for people to sign up for our committees. As in previous years, we had most of our available spaces filled. The following are the committees, the committee chairs and those that signed up to help:

Awards Committee
Chair-Stephen Pruett
Ian Kimber
Jean Regal
Don Frazier
Larry Updyke
Liz Sikorski
Judy Zelikoff

Program Committee
Chair-Dori Germolec
Kathy Rodgers
Ian Kimber
Michael Lynes
David Lawrence
Lorraine Twerdok
Don Frazier
Michael McCabe

Methods Committee
Chair-Frank Gerberick
Robert Luebke
Robert House
Kenneth Hastings
Dennis Flaherty
Kamran Ghoreishi

Regulatory Committee
Chair-Eizabeth Sikorski
Jim Blank
Joe Griffin
Larry Updyke
Dennis Flaherty

Membership Committee
Chair-Michael McCabe
Scott Thurmond
Mitchell Cohen

Education Committee
Chair-Mitchell Cohen
Larry Schook
Mike Murphy

Communications Committee
Chair-Robert House

As you can tell, the last few committees could use a few more members. If you would like to help, please contact the Chairpersons and offer. We had a few changes in the running of these committees this year. At the request of a lifetime committee chairperson, it was suggested and approved that the chairpersons of committees that are not assigned by our bylaws (e.g., Program Committee is chaired by the Vice President Elect) only serve for three years. Therefore, if you have an interest in serving in this capacity, please contact me to let me know of your interest and to find out if this is an assigned or volunteer chair position. Our other changes was the addition of a new committee, the Communications committee, to help with the establishment and maintenance of our Web Page, and the change in chair of the Methods committee from Robert Luebke to Frank Gerberick. I want to extend our thanks to Robert Luebke as a lifer as chair of this committee for his service.

Thanks also to our outgoing officers, Scott Burchiel as President and Dori Germolec as Councilor and congratulate our incoming officers, Dori Germolec as Vice President Elect and John Barnett as Councilor! Have a great year and I look forward to hearing from any of you with questions. ■

Student Representative's Report

by Beth Vorderstrasse

Thank you to everyone who introduced themselves to me in Seattle. It was great meeting all of you.

Because a number of students have asked me questions regarding becoming a member of the Immunotoxicology Specialty Section, I thought I'd briefly address that issue. Realizing that non-members are unlikely to receive a copy of this newsletter, I'd like to request that people who know students who are not members please pass this information along to them.

To join the Immunotoxicology Specialty Section you must first apply for SOT membership. This involves filling out a short application form and sending it in along with a resume or CV and two sponsorship forms. Forms are available on the SOT website (www.toxicology.org) or contact me and I'll make sure you receive a set. Once your membership is accepted by SOT, you will receive a form which allows you to select one Specialty Section to join as part of your $20/year SOT dues. Additional Specialty Section memberships will cost extra. With your SOT membership you will receive the SOT *Communique* and be eligible to apply for SOT graduate student travel funds. Specialty Section members also receive the Specialty Section newsletter. Joining SOT as a student can help in your transition to full membership once you graduate, and of course it is helpful in terms of networking.

If you have any other questions/concerns/suggestions for me, please contact me by email at vordersb@ucs.orst.edu. ■

Regulatory Committee

by Elizabeth Sikorski, Chair

FDA Center for Food Safety and Applied Nutrition

In a recent update from Dr. Dennis Hinton, the FDA Center for Food Safety and Applied Nutrition hopes to finish the entire Redbook II and publish it on the Internet by the end of 1998. Regarding immunotoxicity testing guidelines in the Redbook II, the authors have responded to many comments received in 1994 and are very close to finalizing the guidance document. Currently, there is no intention to obtain further public comment on the document. Dr. Hinton stated that there will be an expanded section on cytokines and allergy and hypersensitivity. There have also been steps to ensure that the new guidelines are in harmony with OECD guidelines, primarily, OECD Guideline 407 (repeated dose 28-day oral toxicity study in rodents). The guidance on immunotoxicity testing is similar to that recommended by OECD. Therefore, recommendations for immunotoxicity evaluation of a food additive will include standard nonclinical tests assessing histopathology, immune organ weights and hematology. Expanded histopathology will include evaluation of the thymus, bone marrow and draining and distal lymph nodes. If a chemical alters any of the recommended parameters, additional testing, most likely immune function assays, will be recommended. The CFSAN hopes the Redbook II will be available on the FDA homepage in late 1998.

FDA Center for Devices and Radiological Health (CDRH)

The CDRH announced the availability of a draft guidance document entitled *the Immunotoxicity Testing Framework* in the Federal Register on March 18, 1997. Please see the May 1997 newsletter for more information. This document was made available for public comment and during that time the CDRH received comments from over 25 companies, individuals and organizations in the U.S. and abroad. Since the last Immunotoxicology Specialty Section newsletter, a revised version of the guidance document has been completed, incorporating comments received. Currently the document is going through a final review and clearance by the CDRH. When the document has been cleared by the FDA, the finalized document will be announced in the Federal Register and made available on the Internet.

FDA Center for Drug Evaluation and Research (CDER)

An update on the CDER guidance document for immunotoxicity testing of drugs has been provided by Dr. Ken Hastings. Additional information on this document can be found in the May 1997 and November 1997 newsletter. The original document written by Dr. Hastings was reviewed by the FDA Council and a decision was made to rewrite it as a concept document. This represents a change in the manner in which the FDA is producing guidance documents. The concept document is a first step in development of a guidance document. The concept document needs to be signed off by the FDA and then will be made available for public comment via the Federal Register and Internet. Please watch for the announcement in the Federal Register if you wish to comment.

The concept document is an important step in the revised process to form guidance documents as it provides a way for the FDA to (1) collect comments from the public and (2) ensure harmonization of the guidance with other agencies and groups (i.e. OECD and the ICH). As with the current OECD Guideline 407 and ECETOC recommendations, this concept document will recommend immunotoxicity evaluation using standard nonclinical tests and evaluating histopathology, organ weights, and hematology. If a chemical produces a significant alteration in any of these parameters, CDER is proposing to request flow cytometric analysis of blood and/or spleen as the next step. If further alterations are shown upon flow cytometric analysis, additional immune function assays may be requested on a case-by-case basis. The primary criticism of this approach is the recommendation for flow cytometric analysis in the second tier of immunotoxicity testing. Some critics of this approach feel that an immune function assay, specifically, the sheep red blood cell assay would be a better choice in the second tier as flow cytometric analysis (1) has not been evaluated to an appreciable extent, (2) has not been proven to be predictive of immunotoxic potential and (3) has not been shown to be more sensitive than the SRBC assay (therefore, may not be useful in determining a NOEL).

The comments on the concept document will be collected and reformulated into a guidance document. The guidance document will then be reviewed in-house and, if approved, will be

finalized and published in the Federal Register.

FIFRA Immunotoxicity Testing Guidelines

Dr. Sheryl Reilly provided an update on the FIFRA Immunotoxicity Testing Guideline 870.7800. There is currently no scheduled release for the immunotoxicity testing guidelines. The content of these guidelines was discussed in the May 1997 newsletter. Dr. Reilly has stated that the most common question she has received regarding the revised document centers on the optional immune function assays recommended in the guideline, the NK cell assay and flow cytometric analysis. Many individuals have asked when the EPA will require these assays. Dr. Reilly understands that this is a major concern for those involved in immunotoxicity testing, and says that currently this decision will be made on a case-by-case basis. It is an issue that the EPA feels is important to resolve and will consider further.

OECD

As mentioned in the November 1997 newsletter, the OECD is involved in two major activities of importance to immunotoxicity testing: (1) updating immunotoxicity test guidelines and (2) the development and finalization of classification criteria proposals for immunotoxicity endpoints.

I. **Classification Criteria Proposal for Immunotoxicity Endpoints**

As mentioned in the November 1997 newsletter, the OECD classification proposal on immunotoxicology was in the process of development and finalization was expected in 1998. One of the debates taking place in 1997 was whether immunotoxicity should be considered as a separate endpoint with a separate classification system or if it should be included in the classification system for target-oriented repeated-dose toxicity. One of the advantages of including immunotoxicity in the classification system for target-oriented repeated dose toxicity is that separate studies assessing immunotoxicity would not have to be done for a given chemical. Therefore, evaluation of the immune system could be attached to standard toxicity studies. In addition, the overall toxicity of a compound could be used in immunotoxicity evaluation to determine if an immunotoxic effect was a primary effect of the chemical or a secondary effect due to other toxicities. At the VIth Advisory Group on Harmonization and Classification of Chemical that recently took place, it appears that the OECD is currently considering immunotoxicity in the scope of target-oriented repeated dose toxicity and not as a separate endpoint. Even though this decision seems to have been made, the OECD cannot address immunotoxicity testing in detail as revision of test guidelines have not been completed.

II. **Updating Immunotoxicity Test Guidelines (Information provided by Angela Auletta.**

As stated in earlier newsletters, the OECD convened an ad hoc Workshop on Immunotoxicity to work on three goals: (1) review the currently available test methods for immunotoxicity safety evaluation of chemicals, (2) recommend minimum test requirements to predict immunotoxicity and (3) make recommendations for test method development. Twenty three individuals from 10 Member Countries attended the meeting.

An initial draft of the Workshop report was made available in late 1997 to the participants for their review. In summary, the conclusions from the workshop were (1) Guideline 407 (Repeated Dose 28-day Oral Toxicity Studies in Rodents) should be revised to include an expanded version of histopathology for both lymphoid cells and the components of the immune organs; (2) criteria for grading systems for both lymphoid cells and the lymphoid organs need to be developed and both will be considered separately; (3) if histopathology indicates an alteration in the immune system, a sheep red blood cell (SRBC) assay will be performed as a separate test; and (4) the SRBC assay may also be triggered by an increase in the total number of white cells. During this meeting, it was also decided that the SRBC assay be written as a separate Guideline. Comments were requested by January 5, 1998.

The comments received from the Workshop participants have been incorporated into the report and the report has been finalized and distributed to the OECD National Coordinators for informational purposes. Now the goal is to begin the task of revising OECD Guideline 407 and developing a new Guideline for the SRBC assay. No start

date has been given for revising Guideline 407. The public will be able to comment on Guideline 407 once it has been revised. The draft will be made available through the OECD Test Guidelines pages on the World Wide Web. Interested parties will be able to download the guidelines and return their comments to their respective National Coordinator who will in turn submit all comments received to the OECD Secretariat.

Validation of the Local Lymph Node Assay (LLNA) - Information provided by Dee Sailstad

In the November 1997 newsletter, the ICCVAM effort to review the LLNA was discussed. The objective of this effort is to determine whether the LLNA can be accepted as a validated alternative to guinea pig assays to predict contact sensitization potential of chemicals. As mentioned in the last newsletter, ICCVAM established an Immunotoxicity Working Group (IWG) composed of knowledgeable scientists nominated by participating ICCVAM agencies. Since the beginning of 1998, Dave Hattan (FDA) and Dee Sailstad (EPA) have stepped in as co-chairs of the IWG for the LLNA evaluation. To date, the IWG has (1) modified the ICCVAM submission guidelines to suit the LLNA, (2) received the initial LLNA submission from the Sponsors, (3) reviewed the Submission and requested alterations in specific areas, (4) received the revised submission, (5) identified a list of candidates for the Peer Review Panel and (6) compiled information pertinent to the review process for the peer panel.

Currently, the IWG is in the process of contacting Peer Panel candidates and establishing the final Peer Panel. Once this Panel is established, a date for the Peer Panel Meeting will be set and is expected to occur in early Fall 1998. The outcome of this meeting will be a comprehensive evaluation report of the LLNA submission. This report along with IWG and ICCVAM input will then be relayed to the appropriate federal agencies for consideration. The IWG will assist ICCVAM in this process. The LLNA is the first test method to go through the ICCVAM process and the IWG is working hard to make this process go as smoothly and completely as possible.

Evaluation of Topical Drug Ingredients in the Local Lymph Node Assay

In an earlier newsletter (May 1997), it was stated that the FDA felt additional information was needed on the ability in the MLLNA to detect the contact sensitization potential of ingredients in topical pharmaceuticals. As a result of this concern, an interlaboratory evaluation (five laboratories) of the LLNA was undertaken assessing several agents in topical drugs. The results of this study were recently presented at the 1998 SOT meeting. The inter-laboratory evaluation demonstrated that (1) "the LLNA is sufficiently robust to yield equivalent results when performed independently in separate laboratories" and (2) the "LLNA is of value in assessing the skin sensitization potential of chemicals used in topical drug products". The abstract can be found in *The Toxicologist* Volume 42, Number 1-S, pp. 268.

The Chemical Industry

The Chemical Industry is working on a "Long Range Health and Environmental Research Initiative" to shape future research agenda. The CMA and CIIT commissioned nine White Papers to help in this process. These topics were reviewed by technical experts in a November 1997 workshop and modified in response to input received. For each White Paper, a number of research areas (data gaps) were identified. In December of 1997 small teams of company experts were asked to prepare additional information on these White Papers and they have been compiled into a Handbook.

One of the White Papers was of direct interest to this Specialty Section and was entitled "Immunotoxicity and Allergy". The issues that are listed in this white paper are (1) optimization of immunotoxicity hazard identification and determination of the relationship between immune parameters and host resistance, (2) influence of age on susceptibility of the immune system, (3) assessment of immunotoxicity in humans using exposure and epidemiological studies, (4) development of methods for identification of chemicals inducing autoimmune disease, (5) development of methods for identification of respiratory allergens and (6) development of quantitative methods for determining relative potency of skin sensitizing chemicals.

The Chemical Industry has already solicited input on these White Papers. The Handbook was distributed to executive contacts of all CMA member companies in February along with a survey asking them to identify which of the nine White Papers were most important to their business as well as the research areas listed under those White Papers.

In addition, CMA, CIIT, ECETOC and CEFIC will sponsor a State of the Art workshop in 1998. The participants will be asked to identify the areas outlined in these white papers that are of most significance to their business and document why they are important. At the workshop, the participants will also outline how to incorporate all the input received and reduce it to an action plan.

ASTM

The ASTM compiled a draft standard for F04.16.08 Immunotoxicity Tests entitled "Recommended Practice for Selecting Tests for Determining the Propensity of Material to Cause Immunotoxicity". Generally these guidelines pertain to medical devices and other foreign materials. The guidance document was distributed for balloting (approval or disapproval of the draft guideline) to various committees within ASTM in May 1997. The deadline was March 27, 1998. An ASTM subcommittee meeting has been scheduled for May 1998 in Atlanta to discuss the balloting and address concerns listed by those voting. If the concerns are persuasive, revisions will be made to the guidelines.

The guideline will be approved if balloting is successful and there is resolution of negative votes or comments. Once the guideline is approved, it will then proceed to publication. F04 standards are published in the ASTM Book of Standards, Volume 130. ASTM guidelines are voluntary unless cited in a regulation or contract. For additional information contact Teresa Androwska (610) 832-9718 at ASTM. ■

Communications Committee

by Robert House, Chairperson

At present, our main outlets for information are the quarterly newsletter and the Immunotoxicology Specialty Section homepage. We are constantly striving to make these more valuable to our Section in particular, and to the Society of Toxicology in general. New development on the newsletter include:

1. Changing the look of the printed newsletter to give it a more professional look;
2. Making the digital version of the newsletter available from the homepage in a PDF (Portable Document Format) format, which will allow you to print it more conveniently.

Developments on the homepage are more extensive, and include the following:

1. Adding a "hit counter" to record how often the site is being visited;
2. Final implementation of our "Technical Resources" section;
3. Addition of pertinent Specialty Section information such as the Section By-laws and a list of the Council officers and Committee members;
4. A welcome notice for visitors to the homepage.

As you are probably aware, we are in the process of collecting Immunotoxicology course descriptions and literature citations from the membership. These will eventually be formatted and indexed, with the ultimate aim of creating a keyword-searchable database. As you might imagine, this is an ambitious undertaking and will probably take the remainder of 1998 to accomplish. We hope to have a working version available by the next Annual Meeting. My sincerest thanks go to Mitchell Cohen for his tireless work in soliciting this information from the membership. ■

Membership Committee

by Michael McCabe, Chairperson

The goal of the membership committee is to spearhead the recruitment of new members to the Immunotoxicology Specialty Section. This mission is accomplished by networking with the immunotoxicology community and the Society of Toxicology at large. The membership committee needs the active participation of Immunotoxicology Specialty Section members to establish a more broadly based and balanced network. Invite your colleagues and students to join the Society of Toxicology and to become members of the Immunotoxicology Specialty Section. In our student liason section, Beth Vorderstrasse, has outlined the process for becoming a member of the SOT and the ITSS as well as the benefits of membership. The application process and the benefits apply to all membership candidates - ranging from students to senior scientists. We are a growing Specialty Section (33 new members last year = 15% growth), and we will continue to grow and diversify with your input. If anyone has questions regarding the Immunotoxicology Specialty Section, contact me by email at m.j.mccabe.jr@wayne.edu, or contact any of the Membership Committee members (Mitch, Cohen, Scott Thurmond, Mike Lynes). ■ .

Awards Committee

by Stephen Pruett, Chair

The awards committee of the Immunotoxicology Specialty Section wants to remind everyone to plan early to submit the work of graduate students and postdoctoral fellows for a research award at the 1999 annual meeting in New Orleans. In spite of a rather significant cash award ($250), the number of submissions in recent years has not been as large as we would hope. This probably relates to the challenges of putting a presentation together months before the meeting. Perhaps this problem can be attenuated by making a note on your calendar now that graduate student and postdoctoral presentations will probably be due about the same time as they were this year (mid-January). Remember, the work to be evaluated must be presented at the annual meeting, but the whole presentation must be submitted, not just the abstract. As before there will be up to 4 awards. The guidelines will be the same as previously, and they are described below.

The awards are given in recognition of the scientific excellence of the research conducted by graduate students and postdoctoral fellows in the specialty of Immunotoxicology. Presentations will be judged on the scientific merit and significance of their work, the soundness of their experimental approach and methodology, and the quality of their writing and data presentation.

Candidates for these awards are requested to submit copies of their entire presentation, including abstracts, introduction, all figures and data tables, summary and conclusions. It is important that all of the above be included, as the decision on the awards will be based upon the written submission only, and not on the actual presentation at the meeting. The submission will be evaluated by the Awards Committee prior to the annual meeting and the winners will be announced at the Specialty Section meeting in New Orleans. To be eligible the student or postdoctoral fellow must be first author on the paper.

The deadline for submission of this information will be announced in the fall newsletter, but it will likely be in mid-January. If there are questions please feel free to contact:

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Some Recent Immunotoxicology Publications

Abate, A. and Schroder, H. (1998). Protease inhibitors protect macrophages from lipopolysaccharide-induced cytotoxicity: possible role for NK-kappaB. *Life Sci.* 62: 1081-1088.

Bagenstose, L.M., Salgame, P. and Monestier, M. (1998). IL-12 down-regulates autoantibody production in mercury-induced autoimmunity. *J. Immunol.* 160: 1612-1617.

Descotes, J. (1998). Regulating immunotoxicity evaluation: issues and needs. *Arch. Toxicol. Suppl.* 20: 293-299.

Hilton, J., Dearman, R.J., Harvey, P., Evans, P., Basketter, D.A. and Kimber, I. (1998). Estimation of relative skin sensitizing potency using the local lymph node assay: a comparison of formaldehyde with glutaraldehyde. *Am. J. Contact Dermat.* 9: 29-33.

Kim, B.S. and Smialowicz, R.J. (1997). The role of metabolism in 2-methoxyethanol-induced suppression of in vitro polyclonal antibody responses by rat and mouse lymphocytes. *Toxicology* 123: 227-239.

Kimber, I. (1998). Regulatory immunotoxicology--the scientist's point of view: an introduction. *Arch. Toxicol. Suppl.* 20: 271-274.

Kishikawa, H. and Lawrence, D.A. (1998). Differential production of interleukin-6 in the brain and spleen of mice treated with lipopolysaccharide in the presence and absence of lead. *J. Toxicol. Environ. Health* 53: 357-373.

Lappin, M.B., Dearman, R.J., Noval, M. and Kimber, I. (1998). Lack of association between interleukin-6 production by contact allergen-activated draining lymph node cells and lymphoproliferative activity. *Am. J. Contact Dermat.* 9: 34-39.

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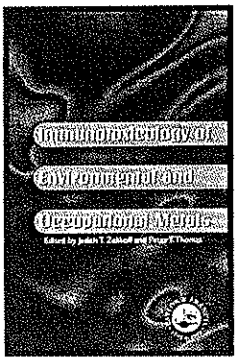
Book Review

Immunotoxicology of Metals

Edited by Judith T. Zelikoff and Peter T. Thomas

ISBN 0-7484-0390-6, 374 pp. including index, Copyright 1998

Taylor & Francis, $49.95



Metals (which, in the context of this book, generally refers to the heavy metals) are a ubiquitous component of our environment. Their versatility and useful properties make them an essential component of human technology. The steadily increasing industrialization has increased the burden of metals in the biosphere to the point where they are now serious environmental pollutants. The overt toxicity of certain metals such as lead and mercury are well known. However, the potential for metal exposure to alter the immune response has only recently been investigated at a detailed level.

Immunotoxicity of Metals is the first book to comprehensively describe the range of immunotoxic sequelae of exposure to metal. Although usually associated with autoimmunity, exposure to metals can also result in hypersensitivity (nickel, chromium), altered host resistance to infection (cadmium, lead), and other alterations in both cellular and humoral immune function.

Each chapter covers the history (including basic chemistry, physical properties, and historical use of the metal), occurrence (potential routes and levels of exposure, environmental and occupational sources of exposure, etc.), biological essentiality (when known), general toxicology, and immunotoxicology. Metals covered include arsenic, beryllium, cadmium, chromium, indium, lead, mercury, nickel, and platinum.

Of course, certain metals such as iron, zinc and copper are more clearly essential for normal physiological processes, serving as cofactors for metalloenzymes. However, even these molecules exhibit toxicity at high levels. Therefore, a separate chapter covers potential immunotoxicity of these essential elements.

Perhaps one of the most useful features of the book is the final chapter, which consists solely of tables listing the immunotoxicities of compounds within the general classes of metals covered in the previous chapters.

This book will be a valuable addition to any immunotoxicology library. It is available from Taylor & Francis for $49.95. Contact them at 44 (0)1245 813000, or visit their website at www.tandf.co.uk. ■