As the Holiday season is upon us, we hope this installment of our Specialty Section newsletter finds you enjoying this special time of the year. In early November, we held our annual officers face-to-face meeting at SOT headquarters in Reston VA. I will take a few moments to summarize the key outcomes of this productive meeting.

Our section is large and financially strong. We currently have 359 dues-paying members with an account of over $50,000. As our mission is to give back to our membership and not to accrue money, we discussed various ways the section would be able to put this money to good use. Among the suggestions was sponsoring a workshop which addressed critical issues in Regulatory/Safety Toxicology through the SOT, or initiating a lecture program in Regulatory/Safety Toxicology at a selected University, or to offer scholarship funding for gifted students. We would, of course, be interested in hearing any additional suggestions that our membership might have regarding alternate uses of our Section’s monies. If you have any novel ideas please feel free to contact anyone of the Section’s officers.

We chose the nominees to run on the upcoming annual ballot for VP-elect and Councilor from our membership roster at our face-to-face meeting. I think you will find this group of nominees particularly well suited to lead our organization into the future. Keep posted for the ballot in your email shortly after the first of the year and be sure to cast your vote.

The topic for this year’s “Great Debate” to be held at our annual business meeting was selected and it promises to be quite a lively and enlightening discussion. The debate will be entitled “The rodent carcinogenicity assay: relevant or relic?” and will feature speakers Drs. Sam Cohen, Abby Jacobs and Chris Portier. The subject for the debate was derived from a recent article by Sam Cohen published in Tox Sci proposing that rodent carcinogenicity testing is no longer necessary. Our business meeting will be held on Tuesday night March 8th beginning at 6PM. Keep posted for the location and try to get there early as this event has been quite well attended in past years – seating is at a premium!

According to the SOT Council approved Nominating Committee rotation schedule, 2005 is the year for the RSESS to provide a Nominating Committee candidate for the general ballot. Our Secretary/Treasurer, Frank Sistare has volunteered to be the nominee from RSESS on the general ballot – please be on the lookout for the SOT ballot and give Frank your support (Frank is an equal opportunity nominee as he will accept votes from SOT members from both Blue and Red states!).

Council is also forming a working group made up of five specialty section representatives which will develop a Specialty Section strategic plan in recognition of the crucial role Specialty Sections play in moving the sub-disciplines of toxicology forward, particularly through developing, reviewing and presenting cutting-edge science at the SOT Annual Meeting. In addition, the Specialty Sections provide a small-group setting for networking between scientists with a shared scientific interest at the very large SOT Annual Meeting. Our newest councilor, Vijay Reddy has volunteered to represent us on this new working group.

In closing we look forward to seeing each of you at the upcoming meeting in March. Keep posted for more details on the location of our business meeting reception and the “Great Debate”. In addition keep posted for revised Specialty Section by-laws which we also dis-
cussed at our recent face-to-face officers meeting. The by-laws have been updated to better reflect the practices of our Section and will be the subject of a membership vote in order to enact them. Lastly, may each of you have a wonderful holiday season and may the New Year be one of health, happiness and success.

Ron Gerson
President, RSESS
NAS to Review EPA’s Proposed Risk Assessment of Dioxins

The National Academy of Sciences’ expert committee charged with reviewing EPA’s Draft Dioxin Reassessment met November 22nd and 23rd in Washington, D.C. to begin its review of EPA’s proposed reassessment of dioxin risks. The review, sponsored by an interagency working group comprised of EPA, OSTP, FDA, and USDA will focus on a spectrum of technical questions that straddle the boundary between science and science policy in the risk assessment and risk characterization for 2,3,7,8-tetrachlorodibenzo-p-dioxin and related “dioxin-like” compounds.

The review of the Draft Reassessment was requested by the interagency working group to help resolve or clarify the scientific issues and science policy choices made by EPA. The Draft Reassessment concludes that current dioxin exposures in the general population are associated with an upper bound cancer risk of 1x10^{-3} (or higher, for persons exposed above the mean level) and that current dioxin exposures exceed any Reference Dose that EPA would derive, perhaps by a factor of 10 or more. These conclusions contrast sharply with conclusions from several recent international scientific review committees including those sponsored by the World Health Organization and the UN Food and Agriculture Organization (WHO/FAO), the European Commission and the United Kingdom. Each of these organizations has recently reviewed dioxin risks and derived tolerable daily intakes above current U.S. exposures, and concluded that dioxin likely has a threshold for carcinogenic action.

The expert committee will address issues of cancer and non-cancer dose-response assessment, risk characterization of epidemiological and animal data, interspecies and low-dose extrapolation, mixture additivity, and uncertainty characterization. Among other questions, the expert committee has been asked to … assess whether EPA’s risk estimates are scientifically robust and whether there is a clear delineation of all substantial uncertainties and variability. To the extent possible, the review will focus on EPA’s modeling assumptions, including those associated with the dose-response curve and points of departure; dose ranges and associated likelihood estimates for identified human health outcomes; EPA’s selection of studies as a basis for its assessments; and gaps in scientific knowledge.

In the area of carcinogenesis, the expert committee will examine both the qualitative judgment of EPA that TCDD is a human carcinogen and the quantitative methods used to assess risk based on both animal and human data. Central to that assessment will be issues including the possibility of non-linear dose response with a practical threshold for tumorigenesis from TCDD due to its action as a tumor promoter. The role of the human epidemiology and the quantitative methods used to estimate dose and model response from such data will be critical to the evaluation.

Similarly, the non-cancer component of the Draft Reassessment presents further technical issues for consideration. Among these will be EPA’s methods for assessing point of departure and margin of exposure. The Draft Reassessment includes several novel features, including a focus on body burden as the exposure metric of interest from both acute and chronic dose studies, the use of benchmark dose methodology to evaluate a wide array of biochemical effects as well as endpoints more traditionally considered to be adverse, the choice of benchmark dose modeling methods, the identification of ED_{50} benchmarks for use as points of departure, and the characterization of likely human sensitivity relative to laboratory animal species.

An important aspect of the risk assessment is the use of Toxicity Equivalency Factors, or TEFs, in the assessment of exposures to and risks from mixtures of dioxin-like compounds. In particular, the EPA decision to apply the TEF approach to assessments of exposure and risk on a body burden basis, rather than an administered dose basis, as specified in the WHO development of TEF methodology, is complicated by different pharmacokinetics and distribution patterns among dioxin-like compounds.

Other important charges to the expert committee include exposure assessment and quantitative and qualitative characterization of uncertainty. While EPA has acknowledged uncertainty in the document, the magnitude and direction of the uncertainty in the Draft Reassessment conclusions will be a subject of scrutiny by the expert committee.

The NAS expert committee is chaired by former SOT president Dr. David Eaton of the University of Washington. Its membership includes scientists in the areas of exposure assessment, reproductive and immunotoxicology, carcinogenesis, molecular biology, pharmacology, epidemiology, and biostatistics. The expert committee is scheduled to complete its assessment within one year, but the breadth and depth of the technical issues included in the charge will make that schedule challenging. The full text of the NAS expert committee’s scope of work and further information on the review is available at the National Academy of Science’s Current Projects web site: http://www4.nas.edu/cp.nsf/Projects+_by+_PIN/ BEST-K-03-08-A?OpenDocument.

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Dietary Supplement FDA Meeting Summary

The Food and Drug Administration (FDA)'s Center for Food Safety and Applied Nutrition held a public meeting November 15, 2004 asking industry and consumers to respond to a number of questions related to FDA's dietary supplement premarket notification program for new dietary ingredients (NDIs) (Fed. Reg. Wed. Oct. 20, 2004, p. 61680-61684). A NDI is defined as one that was not marketed prior to the passage of the Dietary Supplement Health and Education Act (DSHEA) of 1994. The purpose of the meeting was to receive input into when a dietary supplement ingredient should be considered "new", and what FDA should require as adequate information that would establish a reasonable expectation of safety. There was also a request to provide an idea of the type of guidance needed to assist manufacturers in knowing what was required.

Prior to hearing comments from nine speakers representing a diverse group of industry organizations and legal consultants, Susan Walker, M.D., Director of the Division of Dietary Supplement Programs of the Office of Nutritional Products, Labeling and Dietary Supplements of the Center, presented the language from DSHEA related to NDIs and gave an overview of some of the problems the Agency had encountered in reviewing the notifications received.

Written comments in response to the questions posed in the Federal Register notice were due to the Agency on Dec. 3, 2004, although many of the speakers indicated that more time was needed to adequately respond in writing given the breadth and volume of questions posed in the Federal Register notice. A complete transcript of the meeting is available at http://www.fda.gov.

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Potential Toxicity of Extractables and Leachables in Drug Products

As early as 1846, Americans have been concerned about the purity of their drug products. In fact, the Mexican-American War (1846-1848) was largely responsible for the Import Drugs Act of 1848. More soldiers died from the impure, imported and domestic drugs given to them when injured than died from actual combat. In passing the Import Drugs Act of 1848, Congress specified that all drugs must meet the purity and potency standards set by the U.S. Pharmacopeia (USP). In 1906, in response to many social pressures and the book, The Jungle by Upton Sinclair, Congress passed the 1906 Food and Drugs Act that forbade commerce in adulterated and misbranded drugs. However, drug manufacturers were given a choice. They could either abide by the drug standards in the USP/National Formulary (NF) or meet individual drug standards chosen by the manufacturer and stated on a drug’s label. Following the Elixir of Sulfanilamide tragedy of 1938 in which more than 100 children died and many more were injured from ingestion of diethylene glycol used as the product excipient, Congress passed the Food, Drug and Cosmetic Act of 1938. This Act placed the burden of safety testing upon the drug product manufacturer and not the government.

Extractables and leachables are chemicals that can be released or can migrate from containers, closure systems and/or other packaging components that have the potential to contaminate the drug or drug product. Sources of these chemicals are plastic components, coatings, adhesives, elastomers, antioxidants, vulcanizing agents and accelerants. Examples of extractables and leachables, plasticizers such as bis(2-diethylhexyl)phthalate, and nitrosamines (found in rubber products) and acrylonitrile are ubiquitous and are found in various drug products. At present, safety concerns for extractables and leachables reside in the Office of New Drugs, the Office of New Drug Chemistry and its Office of Generic Drugs.

Primary container or closure systems have the potential to interact with the drug product. Factors to consider in evaluating containers are: construction materials of the container, surface treatments or processing aids, dosage form active ingredients and excipients, sterilization and/or other processing and storage conditions. An extractable is a chemical species that can be released from a container that has the potential for contaminating the drug product. Under stressed conditions such as exposure to exaggerated solvent concentration, high temperature for a specified length of time, an extractable may be generated through an interaction with the container. A leachable is a chemical species that has migrated from the container into the dosage form under normal conditions of use. Extractables and leachables in drug products offer no therapeutic benefit to a patient. They should be characterized for potential toxicities and safe exposure levels should be determined. Exposures to extractables or leachables can occur during transportation of the drug substance or a component of the drug product.
Potential Toxicity of Extractables and Leachables in Drug Products—Cont.

to a manufacturing unit while in its primary container or while the drug product is being transported and/or stored in its primary container. FDA’s Center for Food Safety and Applied Nutrition (CFSAN) has similar concerns for leachables and extractables from food packaging and their migration into food. Similar concerns exist within FDA’s Center for Veterinary Medicine (CVM) with respect to animal drugs and feeds.

Leachables have the potential to interfere with drug product assays. If leachables react with one or more drug product components, a precipitate may form or a pH change could occur. Extractable screening during safety studies is an important part of choosing the appropriate container for a dosage form. Chemical extraction studies should be done to identify potential leachates. If leachates are found in the drug product during storage, toxicological evaluations should be performed as well as routine chemical testing of the drug stability lot.

If the leachable cannot be identified by chemical analysis, a structure-activity assessment can be made as the first step in a toxicological evaluation. Using the International Conference on Harmonisation (ICH) guidances, Q3A and Q3B, one could follow the Decision Tree for Identification and Qualification and ask:
1-Is the impurity level above threshold?
2-Is the molecular structure known?
3-Are the toxicity data documented and sufficient?
4-Is the impurity related to others of known toxicity?
In addition, consider the patient population and use. If toxicity data are lacking, consider what may be needed, i.e., genotoxicity studies, repeat dose studies by the route and duration of drug product exposure and other specific studies, (i.e., teratology, carcinogenicity).

If genetic toxicology information is lacking, consult the ICH guidances S2A and S2B for information on the suggested battery of tests. If a structural alert or positive genetic toxicology data is obtained and carcinogenicity studies are being considered, refer to ICH guidances of S1A, S1B, S1C and S1C(R). If any of the three assays in the ICH genotoxicity standard battery is positive, the sponsor should consider completing the fourth test in that battery. Positive responses in one or more assays suggest that the sponsor consider either a weight-of-evidence approach, alternative assays or defining the mechanism of action of the genotoxic event. Sponsors should discuss these options with the relevant CDER division. Recommendations regarding reproduction toxicity and teratogenicity testing may be found in ICH guidances S5A and S5B.

Drug products that are liquids or semi-solids have the greatest potential to contain leachates. Products such as topical ointments and creams, ophthalmic, parenteral and pulmonary drugs are examples. An example of a toxic leachable in a parenteral product is p-tert-butyl phenol that leached from an uncoated rubber stopper. This chemical is a cross-linker and a skin sensitizer and over time at elevated temperatures, its amount in the product increased. Coating the rubber stopper solved the problem. Another example concerns an ophthalmic drug product where, over time, water migrated out of the container, concentrating the amount of drug and any impurities in the solution. By adding an aluminum coating to the container, water migration was prevented.

Impurities over 0.1% in ophthalmic products will trigger quality and safety concerns. Concern for reactive airways engenders additional concerns for leachables in pulmonary drug products. Various safety factors come into play when setting acceptable levels of leachables and other impurities in these inhalation products. At present, depending upon the species, animal or human, and the route of impurity exposure, either oral or inhalation, safety factors of 1 to 1,000 could be used to set acceptable levels as suggested by the relevant CDER division. These safety factors and other concerns are being discussed at the Product Quality Research Institute (PQRI) with the hope of reaching a consensus.

In conclusion, CDER believes that the concentrations of leachables in drug products should be as low as possible to ensure high quality. However, CDER is flexible in determining or establishing safe levels of impurities—usually on a case-by-case basis. Many pharmacology/toxicology and ICH guidances are available on the CDER website for consultation (www.fda.cder.gov/cder/guidance/index.htm).

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CDER, FDA

Safety Testing of Drug Metabolites

A draft guidance on general testing considerations for unique metabolite(s) and recommendations on the tim-
Regulatory and Safety Evaluation Specialty Section

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ing of these studies relative to clinical development has been written by FDA/CDER. This guidance includes information on identification, characterization, and safety evaluation of unique human metabolite(s). In addition, it includes a recommended level of unique metabolite(s) that could be used as a default trigger for stand-alone safety testing.

The guidance describes a unique metabolite as one produced only in humans or formed to a much greater extent in humans compared to animal species used in toxicology studies. Quantitative and qualitative differences in metabolite profiles are important when comparing exposure and safety of a drug in a nonclinical species relative to humans during risk assessment. In vitro and in vivo metabolism studies usually confirm that all human metabolites are adequately characterized in the standard nonclinical safety evaluation exposure. In some cases, clinically relevant and/or biologically active metabolites have not been evaluated in these studies. The metabolite might be formed in humans and absent in the animal test species (unique human metabolite) or is more prevalent in humans than in the species used in standard toxicity testing. Attempts should be made as early as possible in the drug development process to identify differences in drug metabolism between animals used in nonclinical safety assessments compared to humans. It is important to identify “unique” metabolites as early as possible to allow for timely assessment of potential safety issues and avoid delays in drug development. This will also allow for selection of the most appropriate animal models for toxicological testing. For example, an animal species not normally used in drug development might be recommended for toxicology testing if it had similar metabolism to humans.

The scope of this guidance is limited to metabolite(s) identified in human plasma which represent >10% of drug-related material which are not present in standard nonclinical animal studies at sufficient levels to permit adequate characterization. However, based on safety concerns there may be cases where metabolites present at lower levels may need to be characterized. The rationale for setting the greater than 10% limit for characterization of metabolites reflects consistency with other FDA and EPA regulatory documents and is supported by a number of examples listed in the guidance. For example, N-acetyl-p-benzoquinone imine (NAPQI), the reactive intermediate of acetaminophen, detected as urinary thioether metabolite, was found to constitute approximately 9% of a therapeutic dose of acetaminophen. Thus NAPQI, at approximately 10% of the administered dose, has been shown to be responsible for acetaminophen-induced hepatotoxicity. However, the issue of when a “unique” human metabolite constitute a safety concern should be handled on a case by case basis regardless of how “major” metabolite is defined. We recommend that sponsors contact the agency early in the drug development process to discuss “unique” metabolite(s) characterization. When designing nonclinical studies with “unique” metabolite(s), it is important to consider physicochemical characterization (solubility, permeability, absorption), route of administration and exposure, indicated patient population, duration of use, exposure at the therapeutic dose, and potential biotransformation in animals and presence of impurities in synthesized metabolites.

The presence of a unique human metabolite(s) can be determined by in vitro studies using liver slices, microsomes, or hepatocytes from animals and humans. In vivo metabolic profiles in the nonclinical test species are also generally available early in drug development. Results from these studies may reveal significant quantitative and/or qualitative differences in metabolite formation across species. However, a unique metabolite may only be recognized after completion of in vivo metabolic profiling in humans. Therefore, we recommend this evaluation be performed as early as feasible. Generally, systemic exposure is assessed by measurement of compound concentration in serum or plasma. However, there may be circumstances where exposure is assessed by measurements in other biological matrices such as urine, feces, or bile. We recommend consulting the ICH S3A guidance with regard to the development of analytical methods for measurement of the metabolite in the selected matrices.

In general, products of Phase I metabolic pathways (e.g., oxidation, reduction) may require toxicological characterization, while products of Phase II pathways (e.g., glucuronidation, sulfation) may not. Although the conjugated metabolites from Phase II reactions are generally pharmacologically inactive, more water soluble, and readily eliminated from the body, not all conjugated metabolites are nontoxic. Sulfate and some glucuronide metabolites (e.g., acyl glucuronides of carboxylic acids)
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may retain pharmacological activity as well as toxicity of the parent drug and may require proper toxicological characterization. If the unique metabolite is suspected to contain a reactive functional group, it is important to assess the toxicological profile of these reactive metabolites. Chemically reactive intermediates are rarely detectable due to their short half-life, although stable products (i.e., glutathione conjugates) resulting from such intermediates can provide some indication of exposure to these potentially toxic species.

If needed, a general toxicity study with direct dosing of the metabolite can range from a minimum duration of 14 days to a maximum duration of 90 days. The clinical route of administration is recommended; however, other routes (i.e., intravenous, intraperitoneal) may be necessary to achieve sufficient exposure. It is recommended that the maximum dose either elicit frank toxicity without causing excessive incidence of morbidity/death or be the maximum feasible dose (2000 mg/kg/day). Identification of dose-dependent toxicity is an important objective. The draft guidance also recommends performing an assessment for QT prolongation potential. Toxicokinetics data to ensure adequate exposure should also be provided. If the metabolites are more toxic than the parent and/or have delayed toxicity, different target organs, or non-monitorable toxicity, toxicology studies of 6 months for rodents, and 9 months for non-rodents may be requested on a case-by-case basis. Mechanistic studies to assess specific toxicity endpoints may be warranted based on the results of the general toxicity studies. It is recommended that the minimal genotoxicity screen, consisting of two in vitro assays to detect point mutations and chromosomal aberrations, be conducted with the metabolite(s). It is important that these assays be conducted in accordance with ICH S2A and S2B. The complete standard battery of genotoxicity studies may need to be performed if one or both of the in vitro tests are equivocal and/or positive. Carcinogenicity studies may be requested on a case-by-case basis for metabolites of drugs that are administered continuously >3 months or used intermittently in the treatment of chronic or recurrent conditions, present with positive genotoxicity findings, display genotoxic or carcinogenic structural alerts, and provide evidence of tissue proliferative effects (i.e., hyperplasia, pre-neoplastic lesions) identified in general toxicology studies. A single 2-year rodent bioassay is recommended, but the addition of a metabolite dose group to the oncogenicity study for the parent drug will also be considered. Embryo-fetal development assessment may be necessary when the parent drug is used in a population that includes women of childbearing potential. Other reproductive toxicity studies may be requested on a case-by-case basis depending upon results of the general toxicity and embryo-fetal developmental studies. Reproductive toxicity studies may be conducted in accordance with the guidances ICH S5A and S5B.

If independent toxicological characterization of a human metabolite is warranted, we recommend these studies be completed and the study reports be submitted prior to commencement of large-scale Phase III trials. However, in some cases, it may be appropriate to conduct nonclinical studies earlier, for example, if the metabolite belongs to a chemical class with known toxicity, if the metabolite has positive structural alerts for genotoxicity, carcinogenicity, or reproductive toxicity, if clinical findings with the metabolite or related products have indicated special clinical safety concerns, such as QT prolongation. To optimize and expedite development of drugs for serious or life-threatening diseases without effective therapy, these nonclinical studies may be limited on a case-by-case basis.

The draft guidance is expected to be published soon. Comments on the document are encouraged and the method for communicating these will be given in the Federal Notice of publication. We take all comments into consideration and always appreciate them.

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