Regulatory and Safety Evaluation Specialty Section—Newsletter

of the Society of Toxicology

Spring 2008

President's Message

RSESS President—Jim Green

On behalf of RSESS Councilors and Officers, I would like to extend best wishes to all members for the upcoming New Year. I know for myself personally, 2008 has been extremely busy already and the recent holiday season is but a blurred memory! This will be a short note because most of our activities were addressed in our winter newsletter and our planning activities are well underway for the RSESS business meeting at the upcoming annual meeting. Separately in this newsletter, Dr. Frank Sistare provides an update regarding our planned "Great Debate", which promises to be very provocative this year.

As I indicated in our winter newsletter, because our finances are in good shape the leadership team has decided that committee funds will be made available to the section membership for their use in supporting non-SOT sponsored activities, e.g., scientific meetings. To date, we have only received one request to access these funds. I would like to reiterate the process to have a proposal considered for funding.

If you are interested in having a proposal considered, please follow the steps outlined below:

1 – Proposal sponsor will notify RSESS President of proposal and funding request.

2 – RSESS president will circulate proposal information, requested funding amount to executive committee and scientific advisory committee chairman for review. Reviewers will be asked to respond to RSESS president whether or not they approve, disapprove or require further information.

3 – Within one week of proposal being circulated to reviewers, the RSESS president will schedule a one hour telecom in which the proposal request can be discussed if necessary.

4 – Based upon majority consensus as determined by the RSESS president, a decision will be made to support or not support the proposal. If the proposal is supported, SOT-HQ will be notified so that the requested funds can be made available. The RSESS president will notify the sponsor of the committee's decision.

This process will help RSESS membership access funds and assure a timely and objective review.

I am also pleased to announce the results of our recently completed officer election. Please join me in congratulating Dr. Brian Short to the position of Vice President – Elect and Dr. Cindy Afshari to the position of Councilor. I look forward to working with each of you in furthering the committees work.

Finally, on behalf of me and the current RSESS leadership team we look forward to hearing from you on any ideas that you may have regarding RSESS activities. We hope to see you all in Seattle.

Jim Green

President

Inside this issue:

President's Message	1
Mission Statement	2
Great Debate—MTD Testing	2
ICH Updates	3
Risk Assessments	4-5
REACH	5-7
Computational Toxicology	7-9
Value in the term "Nanotoxicology"?	9-11

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RSESS MISSION

The mission of the Regulatory and Safety Evaluation Specialty Section (RSESS) of SOT is to promote the development of sound governmental policies and regulations based on contemporary scientific knowledge arising from the disciplines encompassed by toxicology. RSESS provides a forum for the interaction of SOT members to discuss the impact of regulations, guidelines, and guidances on the practice of toxicology and the safety evaluation of food additives, nutraceuticals, therapeutic drug products and environmental, industrial and household chemicals, and other products of concern.

Great Debate- MTD Testing- Is testing to the MTD unnecessary animal use or necessary to assure human safety?

As in prior years, RSESS will again sponsor a "Great Debate" at the 2008 Annual Meeting after our business meeting. The topic for this year's debate is: "MTD: Is testing to the MTD unnecessary animal use or necessary to assure human safety?" The meeting, reception, and debate will be held on Tuesday, March 18, 2008, 6:00 PM - 7:30 PM, Rooms 612-614, Seattle State Convention and Trade Center.

The program introduction and debate moderation will be handled by our current section Vice President, Dr. Frank Sistare, Merck, Inc.

The Pro MTD Position will be presented by Dr. Jack Reynolds, current President, JAReynold Associates and former Global Head of Safety Sciences at Pfizer where he had been employed for approximately 18 years. Dr. Reynolds has over 30 years of experience in the pharmaceutical industry. The position against the need for always defining the MTD, that a margin-based exposure approach may be taken in toxicology study testing for pharmaceutical development, will be presented by Dr. Robert Osterberg, former Supervisory Pharmacologist at FDA, and currently at Aclairo Consulting. Bob has over 34 years of experience with the FDA. Both Drs. Reynolds and Osterberg have also been past presidents of the RSESS.

The debaters have graciously volunteered to develop their extreme positions for the purpose of this debate. It should not be assumed that either debater truly holds the opinions that will be expressed. Their goal is to surface the complexities of the two opposing stances to stimulate and provoke greater attention to this important topic. Opposing societal forces exist today, demanding on the one hand that animal study dosing must be driven in all studies to levels beyond the MTD that will provoke target organ injury, while other societal forces lobby for the elimination of any harmful and inhumane treatment of very valuable test animals. As drug development sponsors and regulatory review scientists find themselves in the middle of these opposing viewpoints, a prudent path forward with specific and transparent guidelines is needed to promote improved treatment of our test animals while ensuring the protection of the safety of our clinical trial patients. Please join Jack, Bob, Frank and the entire RSESS membership for this important evening as we seek to spur action and progress through lively and entertaining debate.

Frank Sistare
Merck

ICH UPDATES

The Expert Working Group (EWG) for ICH S9, Preclinical Guideline on Oncology Therapeutic Development, initiated discussions in October, 2007, in Yokohama, Japan. The Business Plan and Concept paper for the developing the S9 Guidance, with proposed timelines for completion, are available from the ICH website (http://www.ich.org/cache/html/3558-272-1.html#S9). Members of the EWG from the EU, Japan and the US FDA provided draft and finalized guidances as a framework for discussion and developing a unified working document. Both biological and drug anticancer agents will be subject to the guidance, but certain product categories, such as gene therapy, somatic cell therapy, radiopharmaceuticals, and vaccines will not be included. An observer from the Biotechnology Industry Organization, invited for input on biological anticancer drug development, was unable to attend. .

The Yokohama discussions were wide-ranging. It was agreed that the FDA document, the most comprehensive provided to the EWG, would serve as the primary basis of discussion. Areas of agreement and those requiring further input from colleagues and data collection were identified. Among the areas requiring further data collection were the use of non rodents to set an initial start dose and the duration of long term studies to be provided for product registration. The discussion also took into account the ICH principles of reduction, refinement and replacement of animals in toxicology testing. Discussions are ongoing on monthly teleconferences to continue dialogue on topic areas that were deferred, such as biologicals, those requiring additional information, and topics that were not discussed in Yokohama due to time constraints. The next face-to-face meeting for S9 is scheduled for June, 2008.

ICHM3R1

Major topics in revisions to ICHM3R1 include new exploratory IND proposals, use of embryofetal dose-ranging studies to support small clinical studies, and the duration of chronic studies in nonrodents. The new exploratory IND proposals cover two microdosing scenarios and several subtherapeutic and therapeutic dosing scenarios.

Databases covering the past 7 years were compiled for several hundred drugs and reviewed in the area of predictivity of embryofetal dose-ranging studies for the definitive studies and the need for 9 or 12-month nonrodent studies. Tentative conclusions are that the dose-ranging embryofetal toxicity studies can be used to support studies in < 100 treated women for 3 months or less and that for chronic indications, 9-month, but not 6-month or 12-month, studies are generally needed in nonrodents. Wording to address the timing during drug development for studies of combination drug products, juvenile studies, immunotoxicology studies, and phototoxicology studies is also being considered.

ICHS2(R)

Significant changes have been proposed for the basic battery of tests. The primary driver for change is that there were too many positives in the *in vitro* mammalian cell assay systems that may not be relevant to human risk. The EWG also took into consideration the 3Rs principle for genotoxicity studies, whenever possible without impacting on the scientific value of the tests and the evaluation of human risk. The major change in the revision will give sponsors the option of choosing an in vitro mammalian cell assay or a second in vivo endpoint.

In vitro mammalian cell assays:

Addition of in vitro micronucleus assay as third option to the in vitro cytogenetics assay and mouse lymphoma gene mutation assay. The upper concentration limit will be changed to 1 mM or the first dose in which precipitate is visible. The upper limits of toxicity will be reinforced, i.e. 50% for in vitro chromosome aberrations and micronucleus and 80% RTG for mouse lymphoma.

In vivo genotoxicity assays

Concurrent positive control animals will not be required for every in vivo assay if a lab is experienced with the method for that species, assay type, endpoint and protocol. The new guideline will expand advice on interpretation of in vivo data and potential false positives through mechanisms such as disturbances in erythropoesis. Integration of genetox assays into toxicology studies when justifiable will be encouraged.

David Jacobson-Kram
FDA

RISK ASSESSMENT

The ILSI-HESI project on weight of evidence in risk assessment was initiated in 2004 as a subgroup of the existing Risk Assessment Methodologies (RAM) technical committee, with the goal of building consensus on practical approaches to clearly define and implement weight of evidence-based approaches to risk assessment. Weight of evidence (WoE) is a term commonly used in risk assessment to describe the complex approaches necessary to integrate available data, consider margins of safety, incorporate variability, and various other factors. However, the definition of WoE is often unclear and the methodologies behind its use are highly variable among scientists and decision makers. A core element in risk assessment is the need to assess all available scientific information using a WoE process that is consistent, comprehensive, balanced, reproducible, and transparent.

The ILSI-HESI project began by commissioning a literature review of WoE concepts and methodologies, (Weed, 2005), which concluded that the evaluation process associated with WoE analysis is rarely defined, and the criteria underlying the evaluation are often vague. The review stressed that risk assessors should provide a definition of what is meant by the use of the term WoE when it is used, and that a research agenda for evaluating improvements in both qualitative and quantitative WoE methodologies should be developed.

As a follow-up to the 2005 literature review, the committee held an international, multi-sector workshop in December, 2006 to provide a public forum for the exchange of information on various approaches to WoE analysis within the context of risk assessment. The goals of the meeting were to identify and characterize the current uses of WoE analysis in human health risk assessment associated with regulatory policy or decision making, and to explore commonalities and differences in the application or understanding of WoE analysis. The meeting included panelists from several government agencies and programs in the US, Canada, and Europe, who were asked to provide perspectives in regards to their programs' approach with WoE analysis. All of the agencies and programs represented had the challenge of examining evidence in a rigorous and transparent manner to support specific regulatory and programmatic decisions, and were committed to considering a broad database, rather than individual contributing data points. The general principles of transparency, clarity, consistency, and reasonableness (TCCR – highlighted in the EPA's risk characterization handbook; USEPA, 2000) were embraced by all of the organizations, with the ultimate goal of communicating the lines of reasoning to increase understanding and promote consistency and convergence. Although the represented agencies and programs shared these and other common themes, it was recognized that there was no explicit guidance on the definition or use of the term WoE from any of the organizations. However, it was noted and discussed that several well-developed tools are currently in use that facilitate a WoE approach, including uncertainty & variability analysis, sensitivity analysis, value of information analysis, probabilistic methodologies, guidance on peer engagement and expert elicitation, and the mode of action/ human relevance framework (MOA/HRF).

For the remainder of the workshop, the participants were divided into breakout groups tasked with addressing barriers to a systematic WoE analysis – e.g., areas where WoE is currently effective and where it is not effective, and with developing recommendations for a research agenda to improve WoE analysis in risk assessment. Several common themes emerged as a result of these discussions. Underlying every aspect of the workshop discussions were two points. First, it was recognized that there is an essential need to implement greater transparency and documentation of the decision process. Second, it was emphasized that a single, prescriptive approach to WoE analysis would not be effective.

Despite the lack of explicit WoE guidance (as mentioned by the panelists), there exist numerous documents in both the peer-reviewed literature as well as within agency/program guidance that outline strategies and methodologies that can be integrated into a WoE approach, and therefore currently available literature and guidance should be reviewed. All of the participants highlighted the need to develop new WoE methodologies, largely drawing from and expanding upon existing risk assessment methods (e.g., probabilistic methodologies, MOA/HRF), with the ultimate goal of utilizing case-studies to illustrate these new approaches. Lastly, it was emphasized that effective communication and education is vital.

The HESI RAM committee plans to publish a summary of the workshop proceedings in early 2008, is working on developing a plan for the next phase of the project, and will present a symposium at the 2008 Eurotox Congress in October. The committee has initiated work on a critical examination of the issue of transparency in risk assessment, which will include the distillation of several transparency "principles" that should be considered. Additionally, the committee aims to begin work on improving the integration of the MOA/HRF (Butterworth 2006; Meek et al. 2003; Ruden 2002; Seed et al. 2005; Sonich-Mullin et al. 2001) into risk assessment through development of case studies to examine multiple modes of action, multiple endpoints and dose-response. Extension of the principles incorporated within the framework is also being considered as a basis to draw more effectively on the weight of evidence of dose-response data in assessing risk.

To learn more about this project, or other ILSI-HESI committees, please contact Dr. Michelle Embry (membry@ilsi.org).

RISK ASSESSMENT—cont.

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Michelle Embry
ILSI

REACH – Recent Developments and Progress on Implementation

Introduction

REACH (Registration, Evaluation and Authorization of Chemicals) is the European Union's new strategy for the management of risk to human health and the environment posed by chemical substances. REACH is a single regulatory framework that will replace over 40 existing EU directives and introduces the concept of "*no data no market"*. It came into force on the 1st of June 2007. Since then, the various stakeholders involved have been actively working to meet its provisions and timetable.

While it is known that most major producers and importers of chemical substances are actively preparing for REACH and beginning to compile the necessary information to enable them to submit a registration dossier, there is some concern that many smaller producers, chemical formulators and overseas producers are ill-equipped or unaware of their obligations under REACH.

Providing Information on Chemical Substances

At its core, REACH requires producers and users of chemical substances to register these uses in a volume-triggered system by a specific date. It demands the submission of detailed dossiers on their manufactured substances and intermediates where appropriate.

A major component of this dossier is the chemical safety assessment report (CSR) containing information on the hazards, exposures and risks associated with the uses of chemical substances. This report is based on a comprehensive chemical safety assessment (CSA) the requirements for which are set out in Annex I of the REACH Regulation. The outcome of this process will be not just to provide data for subsequent evaluation of the substance; it will also be used to demonstrate safe use of the substances contained in products and to develop updated material safety data sheets (SDS) for downstream users.

Guidance on the REACH Implementation

To assist the implementation of REACH and ensure that industry (including downstream users), regulators and other stakeholders can work effectively to meet the new legal requirements, various stakeholder expert working groups have been charged to develop the necessary guidance and support tools via REACH Implementation Projects or RIPs. These processes have thus far produced 50% of the guidance documents which are officially published on the website of the European Chemicals Agency (ECHA). They cover issues ranging from pre-registration and registration to guidance on data sharing and intermediates. There is also guidance published mainly for use by regulatory authorities which includes guidance on the preparation of Annex XV for classification and labeling purposes as well as guidance on how the Agency will develop its priorities for authorization of certain substances.

Despite the progress made, there are still some significant delays in finalizing a number of critical guidance documents – specifically guidance on the methodology. Critically from the point of view of manufacturers and importers of substances there is still no finalized guidance on how to prepare a chemical safety report (RIP 3.2) nor with respect to filling data gaps (guidance on information requirements RIP 3.3). Discussions in the relevant stakeholder groups for the development of both of these guidance documents have been difficult principally as they touch on a range of issues for which there are different views. For instance, with respect to RIP 3.3, there has been specific focus on the identification of the toxicological data requirements as specified in Annexes VII to X of REACH and the role of alternative methodologies such as in vitro testing, (Q)SARs (structural activity relationships) and read-across.

REACH – Recent Developments and Progress on Implementation—cont.

The role of alternative methodologies to animal testing is seen as a priority to avoid excessive cost on the one hand and excessive use of vertebrate testing on the other. Moreover, the possibilities of using chemical grouping and the application of 'weight of evidence' approach to justify data waiving, and the methodological approaches applied to characterize risks associated with the use of chemical substances are being strongly pushed by some Member State regulatory authorities and the European Commission.

The ECHA is already preparing contingency plans to take over the process of developing the guidance documents (including those mentioned above) in case the European Commission is unable to complete them by the end of June 2008 – the start of the pre-registration period.

Substance Evaluation

Substance evaluation is unlikely to begin before 2011 and will be on the basis of a rolling programme drawn up by the ECHA. Individual Member States will act as rapporteurs for the substances much in the same way as they do now under the existing EU risk assessment and classification and labeling legislation. The process will focus on the registration dossier submitted for the substance and will concentrate on data robustness, the CSR and classification. The outcome of this process could be changes or proposals for re-classification and/or a recommendation for authorization of that substance. The ECHA envisages evaluating some five percent of registration dossiers per year. However, this is seen as optimistic by many observers.

Substance Authorization

Any existing substance which is currently classified as CMR (Carcinogenic, Mutagenic and Reprotoxic) category 1 or 2, is a PBT (Persistent, Bioaccumulative and Toxic), a vPvB (very Persistent, very Bioaccumulative) or is designated a substance of "equivalent concern" (substances such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties, which do not fulfil the criteria of points (d) and (e) and for which there is scientific evidence of probable serious effects to humans or the environment which give rise to an equivalent level of concern to those listed in points (a) to (e) and which are identified on a case by case basis….) will need to be authorized under REACH in order for the producer/importer to continue to place it on the market. The process leading to authorization involves a number of steps which will be initiated in January 2009 with the publication of what is known as the "Candidate List" of substances requiring authorization. Substances on this list will then be prioritized for authorization via a committee procedure overseen by the European Commission the results of which will become Annex XIV of REACH at the end of June 2009. Manufacturers and importers of these substances must then formally apply for authorization within eighteen months or withdraw their substance from the market.

When submitting an application for authorization, the manufacturer should also submit all relevant information on the substance as well as a socio-economic assessment of its importance. A substitution plan must also be submitted and/or a research and development plan where no existing substitutes are available. After consideration by the Risk Assessment Committee and the Socio-economic Assessment Committee, the ECHA forwards a draft authorization to the Commission for a final decision via a regulatory committee made up of representatives of the EU Member States. The validity of the authorization will be for a period of five years. Where there is a refusal to authorize, the manufacturer must withdraw the substance from the market.

Next Steps

For manufacturers and importers of chemicals into the EU the next immediate step is clear: pre-register (from June 1st 2008) all of those substances they wish to continue placing on the market after the 1st of January 2009 and avail of the various registration deadlines thereafter. In parallel with this, manufacturers and importers need to start building their registration dossiers on those substances despite the absence of definitive guidance for the preparation of CSRs at this point in time. For those manufacturers who are not present in the EU but export to it, consideration can be given to the appointment of EU-based representatives to act on their behalf. Where manufacturers are producing an existing substance which is currently classified under the EU Dangerous Substances Directive as a CMR category 1 or 2, decisions have to be made with respect to the continued manufacturing of this substance and/or preparation for authorization.

June 2008 will see the beginning of what could turn out to be the most ambitious experiment in data sharing ever undertaken in order to minimize testing and avoid duplication of effort by producers of the same substances. REACH requires that manufacturers, importers, downstream users and third parties who have submitted information to the agency about a substance are obliged to participate in a substance information exchange forum (SIEF). While the objective of the exercise is certainly laudable, its execution is going to be fraught with difficulty in terms of legal and anti-trust issues. There will certainly not just be a need for toxicological and other scientific experts in the room. There will also be a need for lawyers and arbitrators to sort out tricky data sharing issues – particularly where significant amounts of money have been expended by one party but not the other.

Conclusions

REACH represents a long-term EU social policy decision whose outcome is the preferential treatment of technologies.

REACH – Recent Developments and Progress on Implementation—Cont.

The fundamental architecture and the basic decision making processes have been defined, though there remain significant uncertainties about the technical details. While the toxicological profile of a substance should determine whether an authorisation will be granted based on a risk assessment or a clear demonstration that the benefits outweigh the risks, this is not guaranteed due to the inherent political nature of the final decision making process.

[1]Regulation (EC) No. 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No. 793/93 and Commission Regulation (EC) No. 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2001/21/EC

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Computational Toxicology: Emerging to Meet the Testing Needs of the 21st Century

Computational (*in silico*) toxicology is the computer based analysis of the relationship of chemical structure and toxicological activity (SAR) and can be considered an extension of the Ashby and Tennant (1) concept of structural alerts. Structural alerts are chemical features that are associated with toxicity and are predictive of toxicity. Structural alerts have historically been identified by human experts but in recent years computational software programs have been developed that can analyze large chemical data sets and identify structural alerts statistically correlated with toxicity. Most of the *Salmonella* positive mutagenic compounds with structurally alerting molecular features identified by Ashby and Tennant were correctly predicted as high risk mutagens by MDL-QSAR (2) and Multicase MC4PC (3) software. The emergence of computational toxicology is due in large part to: a) the availability of increased computer power, b) chemoinformatics, the conversion of chemical structure into computer readable and searchable formats (MDL-Molfile or Simplified Molecular Input Line Entry System [SMILES] code), c) the availability of large digital and "modelable" toxicology databases and quantitative structure activity relationship (QSAR) software algorithms that can statistically correlate chemical structural and toxicological activity (4).

Identifying serious potential toxicity early in the drug development process before significant investments in time and resources are expended is a major goal of the FDA Critical Path Initiative (5) and the pharmaceutical industry. Computational toxicology software programs and database modules have been developed and validated by the FDA Center for Drug Evaluation and Research (CDER) Informatics and Computational Safety Analysis Staff (ICSAS) (6,7,8,9,10,11) under Cooperative Research and Development Agreements (CRADA) with software developers. The software are commercially distributed by CRADA partners (MultiCASE, Inc. (www.multicase.com); MDL Information Systems, Inc. (www.MDL.com) and Leadscope Inc (www.leadscope.com.) for use by the pharmaceutical and chemical industry as well as other regulatory agencies.

Computational toxicology software can be thought of as automated, virtual experts, and, as with human experts, conclusions and opinions may vary due to many factors such as experience, training, and differing points of view. Final human decisions are often made by consensus after assessing how each expert arrived at a particular conclusion. The same process applies to consensus in silico predictions obtained by multiple software platforms with different defined algorithms, domains of applicability, training data sets, decision rules, and predictive performance parameters. The increased availability of computational toxicology software programs with different predictive algorithms has led to the emergence of consensus predictions (11,12,13). In consensus predictions, test compounds are run using several different QSAR programs and there is evidence that compounds predicted to be carcinogenic or genotoxic by two or more QSAR programs employing different predictive algorithms have a higher probability of being carcinogenic or genotoxic than those predicted positive by only one QSAR program (11,13). The consensus approach can also be used to stratify potential carcinogenic risk. Using two QSAR programs, compounds that are positive in two or more software platforms would be ranked as highest risk, those found positive in only one platform would be considered of moderate risk, and consensus negative compounds would be considered the lowest risk compounds.

Genetic toxicity and rodent carcinogenicity studies are required for the marketing of most pharmaceuticals and food additives, and are an important component of environmental regulatory policy. Two-year rodent carcinogenicity studies are the most costly of the required toxicology studies in both time and resources, and the outcome of these studies can seriously impact the marketability of a product. Early screening of chemicals for genetic toxicity and carcinogenic potential using predictive models can reduce the likelihood of developing compounds that are genotoxic or carcinogenic, and this can result in substantial savings in time and resources for both industry and regulatory agencies. In the pharmaceutical industry, computational toxicology is now being used as a sentinel tool for the early toxicological assessment of candidate mole-

Computational Toxicology: Emerging to Meet the Testing Needs of the 21st Century—cont.

cules in lead selection and drug discovery applications (14,15,16,17) and it has become a pivotal component of food safety and environmental regulatory policy (18,19). The identification of structural alerts is an important factor for the qualification of impurities in pharmaceuticals and computational toxicology is being used as a decision support tool for the qualification of contaminants, degredants and impurities in drug products (20,21,22).

Although the need for rodent carcinogenicity test data is great, relatively few chemicals have been tested for carcinogenicity because the cost and resources required are considerable. The Danish EPA (23) has estimated that there are more than 175,000 chemicals currently in commerce and thousands more are added each year, yet less than 5% of these chemicals have been evaluated in any kind of animal toxicology test. From a resource, cost and timeliness perspective, it is not feasible to experimentally test the millions of chemicals in industry combinatorial databases. It has been stated that "of the 2000 chemicals that are evaluated for their potential hazard each year by the Environmental Protection Agency (EPA), the vast majority are assessed in the absence of experimental toxicity data" (24, 25). The European Union REACH (Registration, Evaluation and Authorisation of CHemicals) (26) legislation requires toxicological hazard and risk assessment for all new and existing chemicals, and the 7th Amendment for Cosmetics (27) requires eliminating animal testing. Computational toxicology (QSAR) will play a major role in this endeavor (28). To support these initiatives the EU Organization for Economic Cooperation and Development (OECD) has developed a guidance on the validation of (quantitative) structure-activity relationship (QSAR) models (29).

It is unlikely that any single QSAR model can meet all the needs and priorities of regulatory agencies or the pharmaceutical and chemical industries. Depending on the objectives of the user, greater emphasis may be placed on predictive models with high sensitivity and low false negative rates or high specificity and low false positive rates. Regulators may have a lower risk tolerance and favor high sensitivity at the expense of a higher false positive rate. In contrast, those applying QSAR as an early screen in drug discovery and development may not wish to prematurely discard a potentially promising candidate compound and may favor a QSAR model with high specificity and a low false positive rate.

Computational toxicology applies knowledge derived from decades of toxicology studies to identify and prioritize potentially hazardous substances. Equally important, it can efficiently identify new molecular entities with structural features not adequately represented in toxicology databases. Such compounds can be given a higher priority for animal testing than compounds that are well represented in the training data set. This would free resources for testing compounds that are truly new molecular entities with unknown toxicological properties. With increased experience and confidence in predictive software it may be possible to reduce or eliminate carcinogenicity testing for compounds that have molecular structures that are highly represented in the carcinogenicity database. This would reduce animal testing and free resources for testing compounds that are truly new molecular entities that are poorly represented in the carcinogenicity database.

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Value in the term "nanotoxicology"?

Is there a "there" there when we use the word nanotoxicology in a regulatory context? Over the last several years science policy discussions across agencies and governments have been wrestling with the concept of whether there is practical utility for regulatory purposes in definitions of scale in the nanometer range as an area of hazard. Does it really make sense to think of nanotoxicology as an area of focus from a risk management policy sense? Is it more usefully thought of primarily as a science communication construct, to facilitate grant writing and literature searches? Risk management policies in development at regulatory agencies are evolving to come to terms with this need to consider whether and how to draw lines in the sand for separating science communication from risk management for nanotechnology, and there is a risk communication need to make sure that this separation is understood. Toxicology and policies about uncertainty regarding it form the core of that risk communication.

Value in the term "nanotoxicology"? - cont.

What is nano?
Last summer a Task Force of FDA scientists and policy analysts delivered a report to the FDA Commissioner about risk management needs for nanotechnology.

http://www.fda.gov/nanotechnology/taskforce/report2007.html

The Commissioner had asked that the Task Force examine the state of the science and to evaluate the effectiveness of regulatory approaches, in light of the science, with respect to FDA's obligations to manage risks of nanotechnology. The Task Force was further charged to:

> "*...identify and recommend ways to address any knowledge or policy gaps that exist to better enable the agency to evaluate safety aspects of FDA-regulated products that contain nanoscale materials*."

The report made a number of recommendations for consideration by the Commissioner regarding needs to support FDA's regulatory mission. Given that the document was, potentially, an indication of policy direction and could influence not only FDA thinking but also thinking elsewhere in US government, it went through substantial review prior to release. One thing that raised eyebrows and initial smirks of "here's a fatal flaw" from seasoned reviewers in that process was the fact that a report about nanotechnology implications could be issued without defining nanotechnology, or any other term related to products derived from manipulation of matter on the nanoscale. The Task Force wrote a report but did not define what it was writing about.

There were two main reasons for this lack of a definition. First was the general state of the science and the lack of clear indication of where to place lines for size boundaries or whether to set conditions for intentional production. There were no bright lines and there was not a reason to stop attention based on whether someone intended to manipulate matter at small scales. Second was a realization that definition of distinct boundaries and conditions may not be necessary in most cases of the routine application of FDA regulatory function, and in fact such definition could do more to confuse risk management than aid it.

In fact the Task Force deliberated long and hard about whether to use a definition for nanotechnology products while developing the report, and whether to include one in the final release of the report. Furthermore, as those deeply immersed in the risk management policy of the topic are aware, the discussion of whether and how to define the products of nanotechnology is a frequently revisited and hotly debated topic. What the debate often fails to address however is that the science communication and the risk management needs for a definition are different, and a definition for one does not necessarily serve the other.

Size is relevant, but not sufficient
In the section of the FDA Task Force report titled "Definitions for Nanotechnology and Related Terms" the Task Force started by simply referring to scale in the nanometer range, and then said

> "*The Task Force has not adopted a precise definition for "nanoscale materials," "nanotechnology," or related terms to define the scope of its work. The Task Force concluded that it would be most productive to take a broadly inclusive approach in identifying potentially relevant studies, data, and other information*."

A key addition to this broadly inclusive approach, that comes through reading the rest of the report, is that the Task Force also concluded that size is a relevant variable to consider in evaluation of safety. For example, the text states:

> "*…consideration of the basic science of how materials interact with biological systems does indicate that a material's properties can change when size is increased or decreased into, or varied within, the nanoscale range."*

So while the text does not define nanotechnology or nanoscale or nanotoxicology, it does say that there is support for the conclusion that nanoscale changes can affect toxicity. We simply did not specify what the size range was. Instead, it is the change up or down or relationally in dimensions measured in nanometers that is important to note in evaluations across substances for toxicology.

It is not particularly groundbreaking to realize that size and tertiary structure are relevant to biological interaction. However, it was important to realize that drawing distinct lines may not, when generally speaking for all FDA products, be necessary to achieving greater regulatory clarity. Instead, nanotechnology is teaching us to pay greater attention to dimensional changes at the nanoscale, and our approaches to testing and to evaluation should appropriately address this new knowledge.

Value in the term "nanotoxicology"?—cont.

Furthermore, in addition to saying that size is a relevant variable to consider in evaluation of toxicity, the report also discusses the concept that size alone is not sufficiently informative for many risk management decisions. This is because size does not appear to be a definitive predictor of hazard. The report came to the conclusion that there is not now a clear basis for saying that crossing a line from 101 to 100 nanometers, or from 80 to 120 nanometers for that matter, would make something clearly more or less hazardous. Therefore, some proportion of materials that cross that line will be benign. In fact there are certain examples cited in the report where increases in size create toxicity, and citations of studies that show that attributes like surface functionalization are much more relevant determinants of risk than size, for some classes of materials. These are examples, not proof, but the realization that perhaps had the greatest effect was that there did not seem to be a basis for assigning hazard to a class defined as broadly as simply being within two dimensions of scale.

> "*…if all nanoscale materials are compared to all non-nanoscale materials, whether larger or smaller, it is not apparent that the nanoscale materials as a group would have more inherent hazard*."

This uncertainty of the predictive value of size alone has implications for some risk management decisions such that it is not known whether an action will have a net benefit or risk to health. For example, product labeling defined by a size range alone would not necessarily differentiate risk across products and so we do not know whether warning people away from the products (and toward other products) would either decrease or increase the likelihood of adverse health effects across populations that differentially respond to the labeling. Further information is needed to make a prediction of sufficient certainty or practical utility to the risk management decisions that the report writers were considering. Therefore, a data need we have for risk management application of nanotoxicology is a clearer understanding of whether there are predictors of toxicity that, in conjunction with manipulation of matter on the nanoscale, would make likelihood of adverse health risk more certainly understood. As this information is generated we will be able to define specific applications or even general classes of materials with nanoscale elements that should be managed differentially, similar to our understanding that some classes of molecules have greater risks than others.

Some information along these lines of predictive nanotoxicology is being developed and there are growing discussions of collecting data and building models of biological interaction, and even some initial modeling. The National Cancer Institute's Nanotechnology Characterization Laboratory (NCL **http://ncl.cancer.gov/**) is one place where such modeling is showing progress. NCL has developed data on a number of nanoparticles intended for imaging or cancer therapeutics and has through this investigation begun to elicit some generalizations for specific types of nanoscale materials.

Can we find it even if we know what is risky?

However, being able to predict risk based on a property of a given material is only one of the challenges, and maybe not even the most important challenge that will be faced as nanotechnology progresses and more complex nanomaterials are produced in greater volumes. Another challenge facing us, as we are able to identify determinants of risk that go with nanoscale dimensions, will be finding those elements when we need to find them outside of the laboratory conditions that create them.

For example, if size alone were the primary determinant of risk for a material that has been released to the environment, then we would be able to simply screen for size and run assays on fractionated samples of environmental media. If chemistry alone were the determinant then we could use standard mass spectroscopy methods to find the materials in samples. But if characteristics like shape, surface area, aspect ratio, surface charge, surface functionalization, specific configurations of chemistry on surfaces of particles, or aggregation of particles, to name a few, are the critical determinants of risk then we will need methods to measure those characteristics that are as reliable and widespread as mass spectroscopy in order to have the same measurement capacity we do for standard chemicals.

We will need to have analytic methods to measure the important attributes, assays to screen for those attributes, models to extrapolate findings from one assay to another and to the prediction of adverse effects for those attributes in particles, not just in chemistry.

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