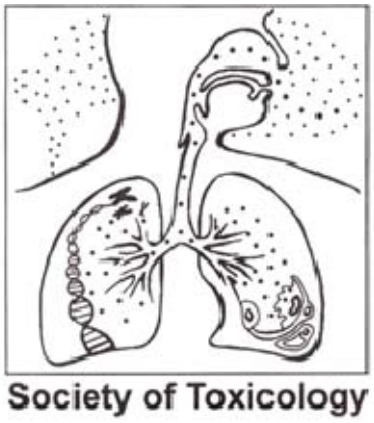
Inhalation and Respiratory Specialty Section



INHALATION AND RESPIRATORY SPECIALTY SECTION (ISS) NEWSLETTER — FEBRUARY/MARCH 2008

Dear IRSS Member:

The 47th Annual SOT Meeting and Toxicology Expo is fast approaching. It will be held at the Washington State Convention and Trade Center in Seattle Washington from the 16th to the 20th of March, 2008. Just browsing through the program, suggests that there will be more than enough information to satisfy most Inhalation, Respiratory and Pulmonary Toxicologists from Sunday to close of business on Thursday. These include Continuing Education of *"Dose Response Modeling for Occupational and Environmental Risk Assessment"* on Sunday, to poster sessions on *"Inhalants"* and *"Inhalation Toxicology"* on Monday and Tuesday. On Monday the Historical Highlight Session will review *"Ozone Toxicology"*, and Tuesday will provide a workshop entitled *"The role of chemicals in the increasing prevalence of allergy and asthma"* and a platform session of *"Mechanism of Hypersensitivity"*. On Wednesday a symposium session will be held on the *"Developmental Basis of Health and Disease: Persistent Effects of Tobacco Smoke Exposure"* and poster sessions on *"Nanoparticle Inhalation and Respiratory Cell Injury"* as well as on *"Respiratory and Skin Hypersensitivity"*. The meetings will conclude on Thursday morning with a workshop session on *"Pulmonary Toxicology Testing of Nanoparticles"* and an Informational Session on REACH the new European Community Regulation on chemicals and their safe use. (REACH- Registration, Evaluation, Authorization and Restriction of Chemical substances).

Also of importance to the IRSS is the Business Meeting of the Specialty Section to be held on Tuesday, March 18th at 6:00-7:30 PM in room 602 of the Convention Center and the Technical Committee Meeting which will be held Tuesday, March 18th at 7:30-9:00 AM in room 204 of the Convention Center.

At this time, we will discuss the current status of the OECD Acute Inhalation Guidelines (TG 403, TG 433, TG 436 and GD 39) with John Whalan, and an update of the TRAC Program and 2007 Workshop will be presented by George Woodall. See messages from both Whalan and Woodall in this newsletter.

The main purpose of the newsletter prior to the upcoming meeting, is to refresh your memory of what occurred at the 46th Annual Meeting of SOT in Charlotte, Virginia.

Also included in this Newsletter are the duties of our officers that were prepared by Mary Jane Selgrade during her term as President.

We look forward to seeing you in Seattle and wish you a safe trip and a warm and rewarding experience at these meetings.

Harry Salem

President's Message:

PRESIDENT'S 2008 FEBRUARY/ MARCH MESSAGE.

Dear Members of Inhalation and Respiratory Specialty Section:

Greetings and Happy New Year. By the time you receive this newsletter, we all would be busy with the last minute preparations for the SOT Annual Meeting in Seattle. We had an outstanding array of IRSS-endorsed activities at the last meeting in Charlotte, and we expect another year of exciting events at the upcoming meeting in Seattle.

This past year IRSS Executive Committee attended to several issues of interest to the membership. These included review of proposals for presentation at the upcoming meeting, recommendations to SOT regarding service on NIH Study Sections, endorsement of Mary Amdur Endowment Fund and last but not least selection of individuals for various awards given by the SS on an annual basis. These awards recognize the outstanding contributions of our colleagues and students.

Last year IRSS Executive Committee endorsed a proposal to establish Mary Amdur Student Endowment Fund to recognize a pioneer in the field and promote student interests. As of early February, a total contribution of $12,108 was received. This was matched with the "SOT 50th Anniversary Match" to bring the Mary Amdur Fund balance to $24,216. This included a combined contribution of $1,300 by the IRSS Executive Committee. Total assets of $25,000 are required for the Fund to become a "Permanently Restricted Net Asset Fund". We are close to the $25,000 mark, and hope to reach this goal before the SOT annual meeting in Seattle.

Last year IRSS also had an opportunity to review and endorse several outstanding proposals for presentation at this year's annual meeting in Seattle. A total of five scientific sessions with primary endorsement from IRSS have been scheduled for presentation. These include a Historical Highlight – *"Ozone Toxicology: Historical Perspectives of the Science that shaped regulatory standards"*, an Informational Seminar – *"NIEHS outstanding New Environmental Scientists (ONES) Awardees"*, two Symposia – *"Endothelial Dysfunction: More than just a 'No No' phenomenon"* and *"Particle interactions with biomaterials: Beyond opsonization",* and a Round Table – *"Biofuel combustion: An emerging health problem"*. In addition, three symposia proposals with secondary endorsement from IRSS were also accepted. I hope you will have a chance to enjoy all of these sessions during your visit to Seattle.

This newsletter serves an important function of updating the membership on the ongoing activities of the SS. It is also a valuable resource for you to utilize for disseminating your suggestions or important information for our membership, such as job openings, graduate scholarships etc. Please contact one of the officers if you have a news item. I also urge you to encourage your students and colleagues who are not SS members to join and participate in IRSS activities.

This year I will complete my term as the IRSS President. It was my pleasure to serve this SS and work with an exceptional group of SS officers who contributed their time with passion and dedication. We have enjoyed success with the SS activities in the past and I expect the tradition of excellence to continue in the able hands of the incoming President Lun Chi Chen, VP Jean Clare Seagrave and a team of outstanding officers.

I look forward to seeing you in Seattle. Please join us at the IRSS reception on Tuesday, March 18 from 6 to 7:30 PM in Room 602, Convention Center. This is a great time to socialize with your colleagues, learn about the SS activities and applaud the award winners. I wish you all a productive meeting, happy reunion with colleagues and safe trip.

Deepak Bhalla

LAST YEARS AWARDS

The following awards were presented at our annual business meeting in Charlotte:

1. ACHIEVEMENT AWARD

Bob Devlin, Ph. D., USEPA

Don Costa (L)
presenting Career Achievement Award

Bob Devlin
accepting Career Achievement Award

2. PAPER OF THE YEAR AWARD

N. J. Kenyon, M. S. Last, J. P. Eiserich, B. M. Morrissey, L. M. Temple and J. A. Last (2006). "Differentiation of the roles of NO from airway epithelium and inflammatory cells in ozone-induced lung inflammation." Toxicol Appl Pharmacol 215(3): 250-9.

3. STUDENT AND POST-DOCTORAL AWARDS

Post Doc Award: Amie K. Lund, Ph.D, Lovelace Respiratory Research Institute

IRSS Student Award: Valerie Mitchell, UC Davis

IRSS Student Travel Award: Kymberly Gowdy, NC State University

Lung Chi presenting to Kymberly Gowdy,
NC State University

IRSS Student Taylor and Francis, Book Award: Elizabeth Vancza, NYU

4. AMDUR STUDENT AWARD

Patricia Gillespie, NYU.

Rudy Yaeger and Daughter
presenting Amdur Award
to Patricia Gillespie, NYU

This past year also brought a name change for the Specialty Section from Inhalation Specialty Section (ISS) to Inhalation and Respiratory Specialty Section (IRSS) to reflect the evolving interests and breadth of our membership. The motion for the name change, initiated by Mary Jane Selgrade and brought to conclusion by Mike Foster, was approved by an overwhelm-

ing majority of the membership.

In the coming year we hope to continue the progress. The Specialty Section has received several proposals for presentation at the 2008 SOT annual meeting. Lung Chi Chen, the current Vice President and the Councilors, Ilona Jaspers, James McDonald, Jim Wagner and Jeffrey Tepper, are in the process of reviewing these proposals and making recommendations to the SOT Program Committee. We hope to bring you another set of exciting presentations at the next year's meeting in Seattle. At our annual business meeting in Charlotte John Morris, a member of the Program Committee, discussed some of the points for improving the chances of success with your submissions. Although the guidelines for submission are available at the SOT Website, we make every effort to bring to your attention the important details for preparing a successful proposal and we encourage the prospective presenters to contact the officer in charge for making recommendations to the SOT program committee. The contact person for the current year is the Vice President, Lung Chi Chen and the responsibilities for the next year's submissions will shift to Jean Clare Seagrave, the VP elect. I should also take a moment to bring to your attention that the time to nominate your colleagues and students for annual awards will be here before you know it. Please consult the SOT Website for all the available awards and deadlines. It is not too early to start thinking of nominating a highly deserving student or a colleague.

John Morris providing advice on developing programs for SOT

UPDATE FROM TECHNICAL COMMITTEE

At the OECD meeting held in the Netherlands on June 18, 2007, the guidance and recommendations of the Inhalation Experts who met in Washington, DC, in November 2006, was not upheld.

The Dutch developers of the CxT protocol explained their new protocol which the US representatives felt was insufficient to address the numerous issues. The argument, vigorously put forth, was that the upcoming computer simulations would prove the CxT protocol superior to the standard TG 403 in that it would yield LC_{50} values for a variety of durations using fewer animals than TG 403.

Although TG 403 was not discussed at the June 2007 meeting, a UK position paper was provided to the US 2 weeks prior to this meeting. In it they decided to retain "evident toxicity" as the TG 433 endpoint, instead of "death" as agreed upon by all countries at the Washington meeting in November 2006.

Apparently some of our members have already discussed doing a "proof of principle for this new suggested CxT protocol, and compare it with the other OECD proposals.
This is probably the time for some of our Technical Committee Members to volunteer to prepare another Information Paper to compare and evaluate all of these new and proposed protocols, TG 403, TG 433, TG 436 and the new CxT.

Many of you may recall, our last position paper of 1991 entitled "Recommendations for the Conduct of Acute Inhalation Limit Tests," made a significant worldwide impact on the field of Inhalation Toxicology.

If you are interested in participating in this new proposed project, please send an e-mail (harry.salem@us.army.mil) or call me at: (410) 436-3034.

DUTIES OF OFFICERS

Past-President

The immediate Past-President serves as a councillor, as chairperson of the Nominating Committee and as the Section's nominee for the national SOT Nominating Committee. With the approval of the President, the Past-President appoints a Nominating Committee of 3-6 individuals, representing broad interests of

the ISS. The Nominating Committee selects two candidates for each open office, obtains their agreement to run for that office, and submits biographical information to the SOT Headquarters by December 1 of each year. SOT prepares and sends the ballot to the ISS members. The Past-President first notifies the President and Vice President of the winners. The Past-President then notifies all individuals, whose names were on the ballot, of the outcome of the election. This must be completed before the annual national SOT meeting. The term of this office is one year and it concludes at the Business meeting at the annual national SOT ISS meeting. The Past-President announces the election results at the Business meeting and prepares a summary of the results for the ISS newsletter.

President

The President oversees all activities of the ISS, appoints chairpersons and approves members of the standing committees, which includes the Technical Committee, the Nominating Committee, the Program Committee and the Awards Committee, and oversees the arrangements for the ISS Business meeting, the Executive Committee meeting, and the Technical Committee meeting. The meeting arrangements are made with the aid of the SOT national office personnel who will contact the President and provide the necessary forms. The term of office is one year. The President assumes the position at the end of the ISS Business meeting at the annual national SOT meeting, and chairs (including preparation of the agenda) the Executive Committee meeting which is typically held on the morning following the Business meeting. The President prepares and submits the Annual Report to SOT by June 1. The President prepares the agenda for, and presides over the Business meeting that is held at the subsequent national SOT meeting (and turns over the gavel to the next President at that meeting). The President prepares a message for each ISS newsletter during her/his term.

Vice President

The Vice President assumes the position at the ISS Business meeting at the annual national SOT meeting. The term of office is one year. The Vice President chairs the Program Committee which is composed of the Councillors and herself/himself. The Program Committee is charged with submitting proposals to the national SOT for Symposia, Workshops, Roundtables and/or CE Courses for the subsequent annual meeting. This material is typically due on April 15. The time-line for this activity is very short, particularly in those years when the annual national SOT meeting is in mid- to late-March. The Vice President may make arrangements for a speaker at the ISS Business meeting; however, this has not been done over the past 4-5 years. The ISS would provide support for travel costs and meeting registration for the speaker. The Vice President also arranges for the dinner to which are invited: the ISS officers and councillors, the chair of the Technical Committee, the award winners and the speaker (if applicable). Since the Vice President is unaware of the identities of newly elected officers/councillors and the awardees, the Past-President and Vice President-Elect must contact the Vice President with this information so that dinner invitations may be extended in a timely manner. Also, if there are multiple authors on the Paper of the Year, only the first author is invited to dinner. The winner of the Mary Amdur Student Award will also be invited to dinner. The Vice President summarizes the activities of the Program Committee for the ISS membership at the Business meeting and also prepares a summary of the program at the annual national SOT meeting for the ISS newsletter.

Vice President-Elect

The Vice President-Elect assumes the office at the annual ISS Business meeting that immediately follows her or his election. The term of office is one year. The Vice President-Elect serves as chairperson of the Awards Committee. In the early summer, the Vice President-Elect prepares a request for nominations, which includes a written description of the awards. The national SOT office will send a form requesting the listing/description of awards and the deadline for nominations (typically early December for the ISS). This information, as submitted by all specialty sections, will be published in the fall issue of the SOT *Communique*. Additionally, the distribution of this information may be accomplished via a direct mailing to the ISS members, which will be done by the national SOT office. Other options include email announcements (contact: Rita Rose of the national SOT office),

publication in the ISS newsletter (contact: Harry Salem of the ISS) or inclusion in the electronic newsletter of Rudy Jaeger (ISS member). Multiple, repeated approaches are recommended in order to maximize responses from the ISS membership. The Councillors of the ISS serve on the Awards Committee, under the leadership and direction of the Vice President-Elect. The Vice President-Elect is responsible for distributing the names, letters, curricula vitae, etc. of all nominees to the other members of the Awards Committee. This should be done shortly after the December deadline. The Vice President-Elect may distribute copies of those articles which have been nominated as "Paper of the Year" or may provide the appropriate citations so that each Awards Committee member may have sufficient time to retrieve and review the articles. The Vice President-Elect schedules several teleconferences (in the early part of the new year) to discuss the nominations. In the absence of adequate nominations, the Awards Committee may exercise several options. If time permits, one option is to extend the deadline for nominations. This option should be discussed with the ISS President and with the national SOT office. Information regarding an extended deadline is communicated to ISS members, by the national SOT office. As a second option, the Awards Committee may, in itself, identify nominees for the "Paper of the Year" and for the Student Awards. The Awards Committee should consult with the ISS President in this situation. The Vice President-Elect may want to keep records of all eligible papers that are published in Toxicology and Applied Pharmacology or Toxicological Sciences, if it becomes necessary for the Awards Committee to identify nominees. Similarly, the Vice President-Elect may want to keep a record of eligible students. Based upon the nominees, the Awards Committee selects the awardees for the "Paper of the Year" and for the Student Awards. For the Career Achievement Award, the Awards Committee may select a nominee from previous (submitted within the last 3 years), as well as present, nominees. The Awards Committee, in itself, may not make nominations for this award. Note that not all awards need to be given every year. The Vice President-Elect provides the Secretary-Treasurer with the award information at the earliest possible date, so that plaques, checks, certificates, etc. may be obtained. The Vice President-Elect should also consult with the Vice President so that dinner invitations may be extended in a timely manner. The Vice President-Elect announces the names of the Award winners at the annual Business meeting and presents the winners with their awards. The Vice President-Elect also prepares a synopsis of the awards and awardees for the ISS newsletter.

Secretary-Treasurer

The Secretary-Treasurer assumes the office at the ISS Executive Committee meeting which follows the annual Business meeting. The term of office is two years. The Secretary-Treasurer reports on the state of the budget at the subsequent annual Business meeting, and takes minutes at the Technical Committee meeting, the Business meeting and the Executive Committee meeting that take place during the annual national SOT meeting. Budget information is provided by the national SOT office. Minutes of the meetings may be distributed electronically to the ISS officers/councillors. The minutes are reviewed by the ISS officers/ councillors and revisions/additions/deletions are made by the Secretary-Treasurer. The revised minutes are distributed electronically to the newsletter editor for inclusion in/ attachment to the newsletter. In years when a new Secretary-Treasurer has just been elected (odd years), the current Secretary-Treasurer reports on the budget and takes minutes at the Executive Committee meeting that typically takes place on the morning following the Business meeting. The Secretary-Treasurer purchases the awards to be given at the annual Business meeting and obtains signatures, engraving, etc., as necessary. This includes certificates of appreciation for outgoing officers/councillors, a gavel to be given to the outgoing President, and plaques/checks to be given to ISS award winners. As noted above, the Vice President-Elect should notify the Secretary-Treasurer of the award winners at the earliest possible time to facilitate preparation of the awards. The Secretary-Treasurer forwards requests for reimbursement for expenses to SOT for payment. The Secretary-Treasurer also serves as the historian of the ISS and maintains ongoing records of all activities of the section. The Secretary-Treasurer prepares a budget report for the ISS newsletter.

Deepak thanking John Hotchkiss for service as Councilor in 2006

Status Report to the SOT IRSS on OECD Projects

April 23, 2007

John E. Whalan

The OECD is developing guidance and guidelines for toxicity studies that will be used worldwide. The testing of chemicals is labor-intensive and expensive. Often the same chemical is tested and assessed in several countries. To relieve some of this burden, 30 countries, including the United States, agreed to a Mutual Acceptance of Data (MAD) principle. This means that data generated in a member country in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP) shall be accepted in other Member countries for assessment purposes and other uses related to the protection of human health and the environment. Some of these guidelines are already in use.

The past year saw a great deal of activity in the development of OECD acute inhalation toxicity guidance and guidelines. An OECD Inhalation Expert Consultation Meeting was held in Berlin, Germany on February 22-24, 2006. Participants represented France, Germany, Sweden, the Netherlands, the United Kingdom, the United States, PETA Europe, and FRAME (Fund for the Replacement of Animals in Medical Experiments).

Three acute guidelines were discussed in Berlin—TG 403, a revision of the traditional LC_{50} study developed by the US, and two alternative guidelines which use fixed concentrations. The first alternative guideline—TG 433—was developed by the UK. TG 433 tests only females and uses "evident toxicity" as an endpoint instead of death. The second alternative guideline—TG 436—was developed by Germany. This guideline tests both sexes and uses death as an endpoint. The alternative guidelines can only be used for classification and labeling. Whenever possible, the alternative guidelines should be employed because they use fewer animals than TG 403. For example, TG 433 allows for a highly toxic chemical to be classified as Toxicity Category I if a single animal dies. Agreements reached during the Berlin meeting include:

1. Aerosol MMAD should be 1-4 μm with a GSD of ≤1.5.
2. The limit concentration for liquid and solid aerosols will be lowered from 5 mg/L to 2 mg/L for humane and scientific reasons.
3. Gas concentrations will be expressed in units of "mg/L" (instead of "ppm"), and the limit concentration for gases will be 20 mg/L.
4. Testing in excess of the limit concentration will not be allowed unless there is a compelling reason to do so.
5. Individual or group housing may be used in recovery rooms.
6. Nose-only chambers are preferred, but whole-body chambers may be used when there is a good reason for using them.
7. Measurements for chamber concentration and particle sizing will be performed hourly.
8. Two types of equipment will be required for sampling aerosols, e.g., a cascade impactor and a gravimetric filter.
9. When a TG 433 or TG 436 study classifies a test article as Toxicity Category 1, a TG 403 study must be performed to further characterize its potency and toxic nature.
10. TG 403 must be used for testing dilutions of corrosives, unless there is a compelling reason for not testing.
11. A "Cxt" protocol proposed by Josje Arts of the Netherlands will be included as a testing option in TG 403.
12. The number of animals to be tested at each concentration level in the alternative guidelines (TGs 433 and 436) needs further consideration by statisticians and modelers. A Performance Assessment Group (PAG) was established to accomplish this task.
13. A guidance document (GD 39) should be

drafted that provides detailed information for the performance of all acute inhalation toxicity studies. A Guideline Document Drafting Group (GDDG) lead by Juergen Pauluhn (Germany) was organized to accomplish this task. This group met during a meeting in Berlin on July 11-12, 2006.

A second OECD Inhalation Expert Consultation Meeting was held in Washington, D.C. on November 7-9, 2006. The purposes of this meeting were to further refine TG 403 (including the Cxt protocol), and to discuss issues relevant to TG 433, TG 436, and GD 39. A major point of discussion was the use of "evident toxicity" in TG 433. This term, which is not commonly used or understood by toxicologists, refers to a sublethal toxic response and can be interpreted in many ways. It was agreed that it is not reasonable for chemicals to be classified and labeled using a sublethal endpoint (evident toxicity) for TG 433 and a lethal endpoint for TGs 403 and 436. This disparity in endpoints would lead to some overclassification when using TG 433.

Upon further discussion, it was determined that "evident toxicity" is equivalent to "moribundity," a term used and understood by all toxicologists. Because moribundity is virtually equivalent to death, this would eliminate the overclassification problem. It was agreed that TG 433 should be revised using "moribundity" in place of "evident toxicity."

The United Nation's GHS classification scheme (see below) was discussed at the first and second OECD Inhalation Expert Consultation meetings. This classification scheme is not based on sound scientific principles, but rather is the result of a political compromise. Consequently, it conflicts with OECD guidelines and guidance. Major problems are as follows:

1. The use of units of **ppm** for gases and **mg/L** for vapours. This is illogical because gases and vapors are both gases. The preferred unit for all physical states is mg/L, which allows for direct comparison regardless of physical state.

2. Each physical state (gas, vapor, aerosol) has its own classification cutoffs. There is no scientific basis for this. There should be one set of cutoffs that applies to all inhaled chemicals whether they are gases, vapors, or aerosols. This is a particular problem for volatile liquids which generally exist in two physical states (vapor and liquid aerosol).

3. The GHS limit concentrations are 20,000 ppm for gases, 20 mg/L for vapors, and 5 mg/L for aerosols. The OECD Inhalation Experts have selected more realistic limit concentrations of 20 mg/L for gases, 20 mg/L for vapors, and 2 mg/L for aerosols. It is difficult to generate a respirable (MMAD of 1-4 µm) aerosol for most chemicals at concentrations greater than 2 mg/L. The GHS limit concentration for aerosols should be lowered from 5 mg/L to 2 mg/L for scientific and humane reasons.

The current GHS inhalation bands between cutoffs are arbitrary and not equivalent. Some bands are narrow and some are wide, which makes for uneven classification and increased animal usage. The easiest way to overcome this problem is to select cut-offs on a log basis.

	LC_{50}		
GHS Class	**Vapors (mg/L)**	**Dusts and mists (mg/L)**	**Gases (ppm)**
1	≤ 0.5	≤ 0.05	≤ 100
2	> 0.5 and ≤ 2	> 0.05 and ≤ 0.5	> 100 and ≤ 500
3	> 2 and ≤ 10	> 0.5 and ≤ 1	> 500 and ≤ 2500
4	> 10 and ≤ 20	> 1 and ≤ 5	> 2500 and ≤ 20,000

The third OECD Inhalation Expert Consultation Meeting will be held in De Bilt in the Netherlands on June 18 and 19, 2007. The purposes of this meeting are as follows:

1. Continue discussions on TG 403, particularly with regards to two Cxt protocols proposed by Josje Arts of the Netherlands and Juergen Pauluhn of Germany.
2. Discuss the revision of two additional guidelines—a subacute inhalation toxicity guideline (TG 412) and a subchronic inhalation toxicity guideline (TG 413). The

Status Report to the SOT IRSS on OECD Projects

February 25, 2008

John E. Whalan

This is a report on the progress made in developing guidelines and guidance for OECD inhalation toxicity studies since the 2007 SOT IRSS meeting in Charlotte, North Carolina.

Inhalation toxicity studies are labor-intensive and expensive, and the same chemicals are often tested and assessed in several countries. To relieve some of this burden and minimize animal usage, 30 countries, including the United States, agreed to a Mutual Acceptance of Data (MAD) principle. This means that data generated in a member country in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP) shall be accepted in other Member countries for assessment purposes and other uses related to the protection of human health and the environment. The OECD is currently in the process of revising its guidelines, and some of these guidelines are already in use.

Revised toxicity guidelines (TG) and a guidance document (GD) for inhalation toxicity studies are being developed and will likely be accepted during 2008 or 2009. These include TG 403 and TG 436 (acute toxicity studies), TG 412 (14 and 30 day studies), TG 413 (90 day study), and GD 39 (an acute inhalation toxicity testing guidance).

An OECD Inhalation Expert Consultation Meeting was held in De Bilt, The Netherlands on June 18 and 19, 2007. Participants represented France, Germany, Japan, Sweden, the Netherlands, the United Kingdom, the United States, and the UK ICAPO (International Council on Animal Protection in OECD Programmes).

The first day of the De Bilt meeting was a discussion of TG 403. The revised TG 403 gives study directors a choice of two protocols—a traditional LC_{50} study and a "C x t" study developed by The Netherlands—depending on the regulatory need for a given test article. Most of the discussion centered on how a C x t study should be conducted and the number of animals needed to yield robust data. In this protocol, groups of one male and one female (or one of the sensitive sex) are exposed for five different durations (e.g., ranging from 15 to 360 minutes). One or more concentrations may be tested. Experts from several countries would prefer to have more animals in each group because this would yield a range of partial mortality outcomes (i.e., 10%, 20%, etc.) which are better suited for statistical evaluation than absolute mortality outcomes (i.e., 0% or 100%). Action items for TG 403 are to 1) characterize C x t databases from the Netherlands TNO and the US EPA, 2) perform a statistical analysis of these databases, and 3) perform a statistical simulation.

The second day of the De Bilt meeting was a discussion of TG 412 and TG 413. A draft of TG 413 (90 day study), developed by the US, was discussed line-by-line with an emphasis on clinical pathology and histopathology. A second pass through TG 413 was done to see which items should be included or modified in TG 412 (14 & 30 day studies). The US was asked to revise TG 413 and The Netherlands was asked to draft a TG 412 based on the results of this meeting. There will not be a distinct TG for chronic inhalation toxicity studies, so TG 413 will likely be used as a reference for pathologic evaluation in chronic studies.

TRAC PROGRAM

"Risk Assessment Data Repository: An Inter-Agency Collaboration"

George Woodall

George Woodall(EPA) is hosting a meeting which is a continuation of a dialogue on coordinating efforts across multiple agencies (US EPA, ATSDR, FDA, OSHA, et cetera) which use data from dose-response studies to develop assessments of health risks and associated reference values (RfCs, RfDs, MRLs, PELs, et cetera). Other interested stakeholders that have been involved in these discussions include agencies from other nations, the National Libraries of Medicine, and a number of organizations supporting information management and development of risk assessments. This meeting is open to anyone interested in these topics, and will be held in the Aspen Room at the Sheraton Hotel 11:30 to 1:30. More details will be presented by George at the Technical Committee Meeting.