Teratology Society
50th
Annual Meeting
June 26–30, 2010
This event has been accredited by
the McGill Center for Continuing Health
Professional Education.
Louisville
KENTUCKY
Marriott Louisville Downtown
23rd International Conference of the Organization
of Teratology Information Specialists (OTIS)
June 26–29, 2010
and the
34th Annual Meeting of the Neurobehavioral
Teratology Society (NBTS)
June 26–30, 2010
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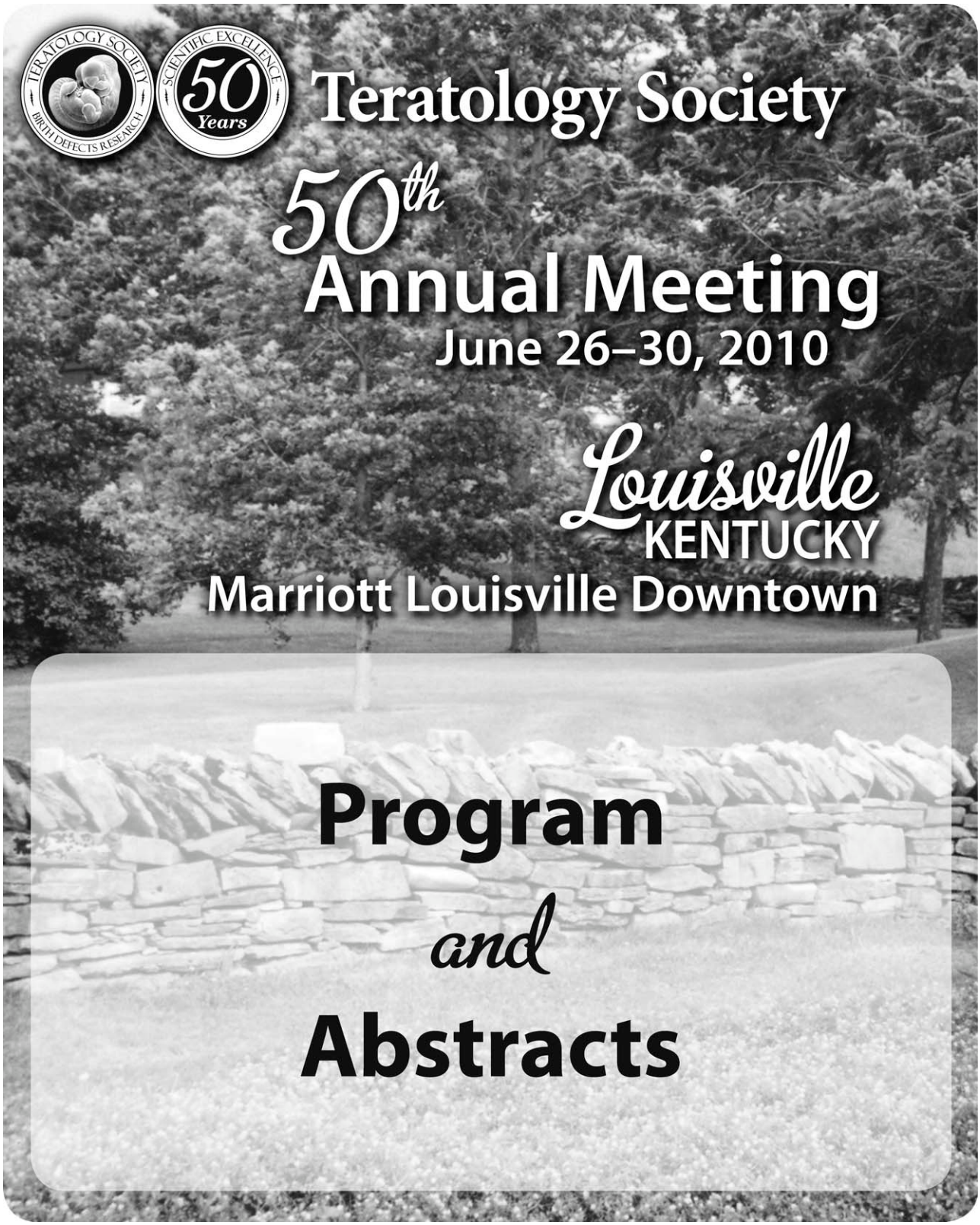
Teratology Society
50th
Annual Meeting
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Louisville
KENTUCKY
Marriott Louisville Downtown
Program
and
Abstracts

Program Overview

FRIDAY, JUNE 25, 2010

3:00 PM–6:00 PM
Council IA Meeting

4:00 PM–6:00 PM
Registration

SATURDAY, JUNE 26, 2010

7:00 AM–6:00 PM
Registration

7:30 AM–8:00 AM
Education Course: Coffee and Continental Breakfast

8:00 AM–11:30 AM
Education Course
Session I: Prenatal Drug Disposition and Teratogenesis

12:00 NOON–1:00 PM
F. Clarke Fraser and Distinguished Service Awards Committee Meeting

12:30 PM–5:30 PM
TS/OTIS Joint Pregnancy Registry Workshop

1:30 PM–4:45 PM
Education Course
Session II: Postnatal Drug Disposition and Teratogenesis

6:00 PM–8:00 PM
Student/Postdoctoral Fellow Mixer

6:30 PM–9:30 PM
Council IB Meeting and Committee Reports

SUNDAY, JUNE 27, 2010

8:00 AM–7:00 PM
Registration

8:00 AM–8:15 AM
President's Welcome

8:15 AM–9:15 AM
Josef Warkany Lecture
50 Years of Progress in Understanding the Causes of Three Common Birth Defects

9:15 AM–11:45 AM
Student/Postdoctoral Fellow Platform Session I
Wilson Presentation Award Competition

11:45 AM–12:00 NOON
Box Lunch Pick-Up

12:00 NOON–1:00 PM
TS/OTIS Joint Robert L. Brent Lecture
Ionizing Radiation Exposure to the Fetus and Infant from Medical Imaging: A Radiologist's Perspective

1:00 PM–1:30 PM
F. Clarke Fraser Award
Gastroschisis: A Journey to Discover the Pieces of the Puzzle

1:30 PM–2:00 PM
James G. Wilson Publication Award
Regulations of Folate Receptor 1 Gene Expression in the Visceral Endodem

2:00 PM–3:00 PM
TS/ETS Joint Exchange Lecture
Pros and Cons of the Extended One-Generation Study Protocol

3:15 PM–5:45 PM
Vitamin B_{12} and Neural Tube Defects: Is It Time to Fortify Food with B_{12} Symposium

6:00 PM–8:00 PM
TS/NBTS Joint Welcome Reception and Exhibits Open

MONDAY, JUNE 28, 2010

7:00 AM–8:00 AM
BDRB Editorial Board Meeting

7:30 AM–6:00 PM
Registration

8:00 AM–7:00 PM
Exhibit Hall Open

8:00 AM–9:00 AM
TS/OTIS Joint State of the Art Lecture
Palate Development: Molecular Perspectives and Current Understanding

9:15 AM–11:45 AM
TS/NBTS/OTIS Joint Symposium
Reproductive Psychiatry

9:15 AM–11:45 AM
Platform Session II
Mechanisms and Models

11:45 AM–1:15 PM
Past Presidents' Luncheon

11:45 AM–12:45 PM
Web Site Committee Meeting

1:15 PM–2:15 PM
TS/OTIS Joint Special Lecture
Human Teratogens: Update 2010

2:15 PM–5:00 PM
Update on Thalidomide Symposium

5:00 PM–7:00 PM
TS/NBTS/OTIS Joint Poster Session and Exhibits Open

7:30 PM–9:30 PM
MARTA Student and Postdoctoral Fellow Career Event

TUESDAY, JUNE 29, 2010

7:00 AM–5:00 PM
Registration

7:00 AM–8:20 AM
Sunrise Mini Course
Imaging Tools for Structural and Functional Teratogenesis Analyses

8:00 AM–2:00 PM
Exhibit Hall Open

8:30 AM–9:15 AM
TS/NBTS/OTIS Joint Special Lecture
Children's Environmental Health: A Good Start Lasts a Lifetime

9:30 AM–12:00 NOON
March of Dimes/Public Affairs Committee Symposium
Herbal Supplement Usage during Pregnancy

9:30 AM–12:00 NOON
TS/NBTS Joint Symposium
Advancing Neurodevelopmental Evaluation in Children: An Interdisciplinary Approach

12:00 NOON–2:00 PM
TS/NBTS Joint Poster Session and Exhibits Open

2:00 PM–4:30 PM
Platform Session III
Hazard Assessment and Screening

2:00 PM–4:15 PM
TS/OTIS Joint Platform Session IV
Common Conditions in Pregnancy: Treatment of Mental Health and Asthma

4:45 PM–6:30 PM
50th Anniversary Meeting Celebration

WEDNESDAY, JUNE 30, 2010

6:30 AM–7:30 AM
Teratology Society XXIX Annual Volleyball Game

7:00 AM–8:00 AM
Public Affairs Committee Meeting

7:00 AM–8:00 AM
Student Affairs Committee Meeting

8:00 AM–2:00 PM
Registration

8:00 AM–10:30 AM
Platform Session V
Epidemiology and Clinical Studies

8:00 AM–10:30 AM
Wiley-Blackwell Symposium
Teratology Society: 50 Years Then to Now

10:30 AM–11:00 AM
Warkany Tea

11:00 AM–12:00 NOON
TS/NBTS Joint Update on the National Children's Study/Panel

12:30 PM–1:30 PM
Education Committee Meeting

12:30 PM–1:30 PM
Membership Committee

1:30 PM–4:30 PM
ILSI HESI Symposium
21st Century Developmental Toxicology

4:30 PM–6:00 PM
Business Meeting and Reports from *BDR* Editors

6:30 PM–7:30 PM
Banquet Reception

7:30 PM–10:00 PM
Banquet

THURSDAY, JULY 1, 2010

7:00 AM–10:00 AM
Council II Meeting

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General Information

Registration

The Teratology Society Annual Meeting registration is located in the Marriott Ballroom Foyer.

Hours: Friday, 4:00 PM–6:00 PM
Saturday, 7:00 AM–6:00 PM
Sunday, 8:00 AM–7:00 PM
Monday, 7:30 AM–6:00 PM
Tuesday, 7:00 AM–5:00 PM
Wednesday, 8:00 AM–2:00 PM

Hotel Map

To assist you in locating the hotel registration desk, meeting rooms, and Exhibit Hall there is a map of the Ballroom Level located on page 304.

Photography and Recording Policy

Photography, video, and/or audio recording of scientific presentations is prohibited without advance specific consent of the presenter(s)/author(s). Session Chairs are asked to strictly enforce this policy and individuals who do not comply will be asked to leave the session. In addition, cameras and recording devices are prohibited in the Exhibit Hall.

Teratology Society Annual Meeting registrants grant the Teratology Society permission to reproduce, copy, and publish photographs taken at the Annual Meeting unless written notification by the registrant, stating otherwise, is submitted to the Teratology Society headquarters office prior to the Annual Meeting or while registering on-site.

First Aid and Security

The Marriott Louisville Downtown has equipped each meeting room with a house phone for use in case of an emergency. If you need medical or security assistance pick up the house phone and dial 0, the hotel operator will connect you to the correct department.

Award/Lectures

Narsingh Agnish Fellowship

This award recognizes Narsingh Agnish's contributions to the Teratology Society, and particularly the implementation of the Education Course. The Narsingh Agnish Fellowship facilitates the continuing participation of senior Teratology Society members at the Annual Meeting. The 2010 recipient of this award is Thomas H. Shepard, who will present on Saturday, June 26 at 1:30 PM.

Robert L. Brent Lecture

This award recognizes Robert L. Brent's contributions to the Teratology Society, and particularly to the implementation of the "Teratogen Update." The purpose of the Robert L. Brent Lecture is to facilitate the discussion of new and old teratogens during the Annual Meeting. The 2010 recipient of this award is Donald P. Frush, who will present on Sunday, June 27 at 12:00 NOON.

F. Clarke Fraser Award

This award honors F. Clarke Fraser, one of the founding members of the Teratology Society, for his many contributions to the field of developmental toxicology. This year's award recipient is Marcia L. Feldkamp, who will present on Sunday, June 27 at 1:00 PM.

Distinguished Service Award

To coincide with our 50th Anniversary celebrations, the Teratology Society has established the Distinguished Service Award. This award honors an individual who has provided distinguished service to the Teratology Society. The first recipient of this award is F. Clarke Fraser. The award will be presented during the 50th Anniversary Meeting Celebration session on Tuesday, June 29 at 4:45 PM.

Josef Warkany Lecturer

This award recognizes Josef Warkany's contributions to the Teratology Society. Dr. Warkany was the first person to demonstrate that exposures to environmental chemicals are responsible for production of congenital malformation. His early studies culminated in the formulation of the scientific principles of teratology. This award recognizes a scientist who has significantly contributed to the field of teratology over his/her career. This year's lecture will be presented by Diana M. Juriloff, on Sunday, June 27 at 8:15 AM.

James G. Wilson Publication Award

This annual award is presented in recognition of the best paper accepted or published in the journal *Birth Defects Research*. The dual purpose of the award is to provide recognition to the authors of the best paper and to encourage authors trained in various disciplines to submit high quality papers to *Birth Defects Research*. The paper selected for this year's award is *Regulations of Folate Receptor 1 Gene Expression in the Visceral Endodem*. J. Michael Salbaum will present the data on Sunday, June 27 at 1:30 PM.

James C. Bradford Memorial Student Poster Award

This is an award for the best poster presentation by a student at the annual meetings of the Teratology Society and Neurobehavioral Teratology Society (NBTS). It is jointly sponsored by the Middle Atlantic Reproduction and Teratology Association (MARTA) and sanofi-aventis. These awards are presented to awardees during the Banquet on Wednesday, June 30 at 7:30 PM.

Continuing Medical Education (CME)

The Teratology Society is offering a CME Program to clinicians and trainees for many of the scientific sessions held during the 50th Annual Meeting. The CME Program is available on the Teratology Society Web site at **www.teratology.org**.

This is the Society's third year offering CME credits in an effort to broaden the audience at our scientific sessions, while enhancing the professional development of clinicians who integrate the outcome of the research into everyday practice. Talks designated as part of the CME Program are identified by the CME icon CME in the agenda.

Teratology Society CME Program

This event is approved for up to 26 credits by the Center for Continuing Health Professional Education (CCHPE). The Center for CCHPE, Faculty of Medicine, McGill University is fully accredited by the Committee on Accreditation of Canadian Medical Schools and through the (CACMS) is accredited to award AMA PRA category 1 credits.

This event is an Accredited Group Learning Activity as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada.

Through a reciprocal agreement between the American Medical Association and the Royal College of Physicians and Surgeons of Canada, the Center for CCHPE, Faculty of Medicine, McGill University designates this activity for AMA PRA Category 1 credit(s) up to the maximum number of credit hours noted above.

Each physician should claim only those hours of credit that he/she actually spent at the educational activity.

Daily Breakdown on CME Credits

The following is the daily breakdown of credits available. Each attendee is responsible for claiming credit commensurate with the extent of your participation in the scientific activities.

Saturday, June 26: 4 credits
Sunday, June 27: 5.5 credits
Monday, June 28: 7 credits
Tuesday, June 29: 4.5 credits
Wednesday, June 30: 5 credits

Required CME Program—Intent to Participate

Teratology Society Annual Meeting attendees who wish to receive CME credits must complete the CME participation form, which is available on-line on the Society's Web site and at the registration desk for on-site participants.

Required Daily Sign-In Sheets

Teratology Society Annual Meeting attendees who wish to receive CME credits are responsible for signing the attendance sheet each day of participation. The sign-in sheets will be located at the registration desk during registration hours. Only the current day's sign-in sheet will be available at the registration desk.

CME Certificates of Participation

Certificates of CME participation, based on the daily sign-in sheets, will be available at the registration desk. Attendees are required to state the number of CME credits they are claiming and sign the certificate prior to departure. Certificates will be issued until 2:00 PM on Wednesday, June 30. Certification of Continuing Medical Education credits is the responsibility of the attendee.

ACCME Accreditation

Disclosure of Faculty and Industry Relationships

In accordance with ACCME policy, all faculty members have signed a conflict of interest statement in which they have disclosed any significant financial interests or other relationships with industry relative to topics they will discuss at this program. At the beginning of the program, faculty members are expected to disclose any such information to participants. Such disclosure allows you to evaluate better the objectivity of the information presented in lectures. Please report on your evaluation form any undisclosed conflict of interest you perceive.

Highlights

Welcoming Reception

The Welcoming Reception will be held in the Marriott Ballroom I on Sunday, June 27 at 6:00 PM. The reception is open to registered attendees of the Teratology Society and NBTS Annual Meetings. Please wear your badge to gain entrance to the reception. This year the reception will feature a Silent Auction with certificates for local dining and attractions and much more! Come prepared to support the Teratology Society.

Exhibits

Exhibits will be open in Marriott Ballroom I to attendees Sunday evening through Tuesday afternoon featuring companies offering products and services relating to teratology. Scientific posters will be displayed in the Exhibit Hall and complimentary coffee breaks will take place in the hall Monday through Tuesday morning.

Exhibit Hall Hours:
Sunday, 6:00 PM–8:00 PM
Monday, 8:00 AM–7:00 PM
Tuesday, 8:00 AM–2:00 PM

Poster Sessions

The Poster Sessions will be held in the Marriott Ballroom I on Monday, June 28 and Tuesday, June 29. The TS/NBTS/OTIS Joint Poster Session will take place on Monday. The posters for this session will be on display starting at 12:30 PM. The authors will be present for discussion from 5:00 PM–7:00 PM. The TS/NBTS Joint Poster Session will take place on Tuesday. The posters for this session will be on display starting at 8:00 AM. The authors will be present for discussion from 12:00 NOON–2:00 PM.

Celebrating 50 Years and More…

To celebrate 50 years of success, we offer a session on Tuesday afternoon full of history and honors, a look forward and a bit of levity as well. The session will begin with a tribute to Dr. Josef Warkany, a founder and first President of the Teratology Society, by the pediatrician, geneticist and Warkany historian, Dr. Wladimir Wertelecki. A second founder, Dr. James Wilson, will be celebrated in a talk by Dr. Robert Brent, a charter member of the Society, Past President and Dr. Wilson's first graduate student. Then, Dr. F. Clarke Fraser, the third founder of the Society, will receive the first Teratology Society Distinguished Service Award. Having honored our history and all three of our founding fathers, we will then get a forward-looking perspective from our students and postdoctoral fellows—where they see the field and the Society heading in the coming decades. We will finish the session with a rousing game of Teratology Society jeopardy. Students will be recruited to play this Q&A game based on the History of the Teratology Society. Answers to most questions will be found on displays and in events throughout the meeting—prizes will be offered. Rumor has it that a few door prizes will be given to attendees as well! You won't want to miss this special session!

Banquet and Award Presentations

Plan to stay for the grand finale of the 50th Annual Meeting celebration on Wednesday, June 30—the Banquet. A reception (no host bar) will be held in the Marriott Ballroom Foyer beginning at 6:30 PM. Seating for dinner will begin at 7:30 PM in the Marriott Ballroom I. Join your colleagues in a celebratory champagne toast and dancing as this memorable year draws to a close.

The Banquet is included with your Teratology Society meeting registration. Tickets, which are distributed with your registration materials, are required for this event and are not transferable. Guest tickets can be purchased at the registration desk. Teratology Society Awards presented during the banquet are as follows:

Travel Awards
James C. Bradford Memorial Student Poster Award
Wilson Presentation Awards
Marie Taubeneck Award

XXIX Annual Volleyball Game

Come one, come all and join in the fun! The 29th Annual Volleyball Game is scheduled for Wednesday, June 30, from 6:30 AM–7:30 AM at the Baxter Jack's Volleyball Club. This is an event that you will not want to miss. Stop by the registration desk for more information on how to participate in this match—it is free and open to all attendees. If you don't play, come out and cheer!

Student/Postdoctoral Fellow Activities

Special events for student and postdoctoral attendees will occur throughout the Teratology Society meeting. These events were planned with you in mind and allow you to meet other students, postdoctoral fellows, and scientists in our field. The following special events are scheduled.

Saturday Mixer—Come get acquainted or reacquainted with your fellow student and postdoctoral attendees before the start of the meeting. Students and postdoctoral attendees are encouraged to meet at the Champions Sports Bar at 6:00 PM on Saturday, June 26.

Student and Postdoctoral attendees should plan to gather in groups of at least 6 to redeem coupons for a free drink and appetizer for the group to share. Your coupon will be in your registration materials. The coupons are only good for Saturday evening.

Annual Volleyball Game—Come out and show the "seasoned players" how it is done! The 29th Annual Volleyball Game is scheduled for Wednesday, June 30, from 6:30 AM–7:30 AM. If you don't play, come out and cheer!

Student/Postdoctoral Fellow Platform Session—Wilson Presentation Award Competition

This year's Student/Postdoctoral Platform Session showcases the work of eight students and postdoctoral fellows. The participants in this session were selected by the Student Affairs Committee from submitted abstracts. The presenters in this session will compete for the Wilson Presentation Award. This award was established in honor of James G. Wilson, one of the founding members of the Teratology Society and recognizes the work of students and postdoctoral fellows in the field of teratology. It is awarded based on the content and quality of the oral presentations. The two award winners will be announced during the Society Banquet on Wednesday, June 30. Make plans to support the Society's student and postdoctoral members by attending this session on Sunday, June 27 at 9:15 AM.

MARTA Student and Postdoctoral Fellow Career Event

Please be our guest for dinner, conversation, and networking at the Student/Postdoctoral Career Event on Monday, June 28, from 7:30 PM–9:30 PM. This popular event, hosted by the Middle Atlantic Reproduction and Teratology Association (MARTA), is for students and postdoctoral fellows attending the joint annual meetings of the Teratology Society, Neurobehavioral Teratology Society, and the Organization of Teratology Information Specialists. As you prepare for the next phase in your professional career, we offer you this opportunity to meet your fellow students and postdoctoral fellows and to interact with scientists from academia, government, and industry. This is also an opportunity for you to discuss your future and the various career paths available to you. This event has been overwhelmingly well received in the past and we hope to see you there.

While in Louisville

Conference Site

The Marriott Louisville Downtown is a smoke-free hotel featuring plush accommodations, Blu Italian Grille, Champions Sports Bar, and Starbucks Café. Located in the heart of downtown, the Louisville Marriott is adjacent to the 4th Street Live dining and entertainment district and within blocks of many of Louisville's museums and attractions like the Muhammad Ali Center, Louisville Slugger Museum, Louisville Glassworks, and a short drive to Churchill Downs.

The hotel has a full service business center open 24 hours to hotel guests, full service concierge, 24-hour guest room dining, local restaurant delivery, laundry/dry cleaning services, coin operated laundry, newsstand and gift shop, indoor pool, and has a 24-hour complimentary fitness center, featuring cardiovascular equipment and free weights.

Stay Connected While You Travel

The Teratology Society appreciates how important it is for attendees to stay connected to daily responsibilities while attending the meeting. The Teratology Society will provide Internet Café which will be open during the posted registration hours. The hotel will provide complimentary wireless Internet access in the meeting registration area for attendees who bring their own computers. Stop by the Teratology Society registration desk to obtain the access information.

If you would like to access the Internet in your guest room, the Marriott Louisville Downtown offers high-speed wireless Internet access for a daily rate of $12.95.

Ground Transportation

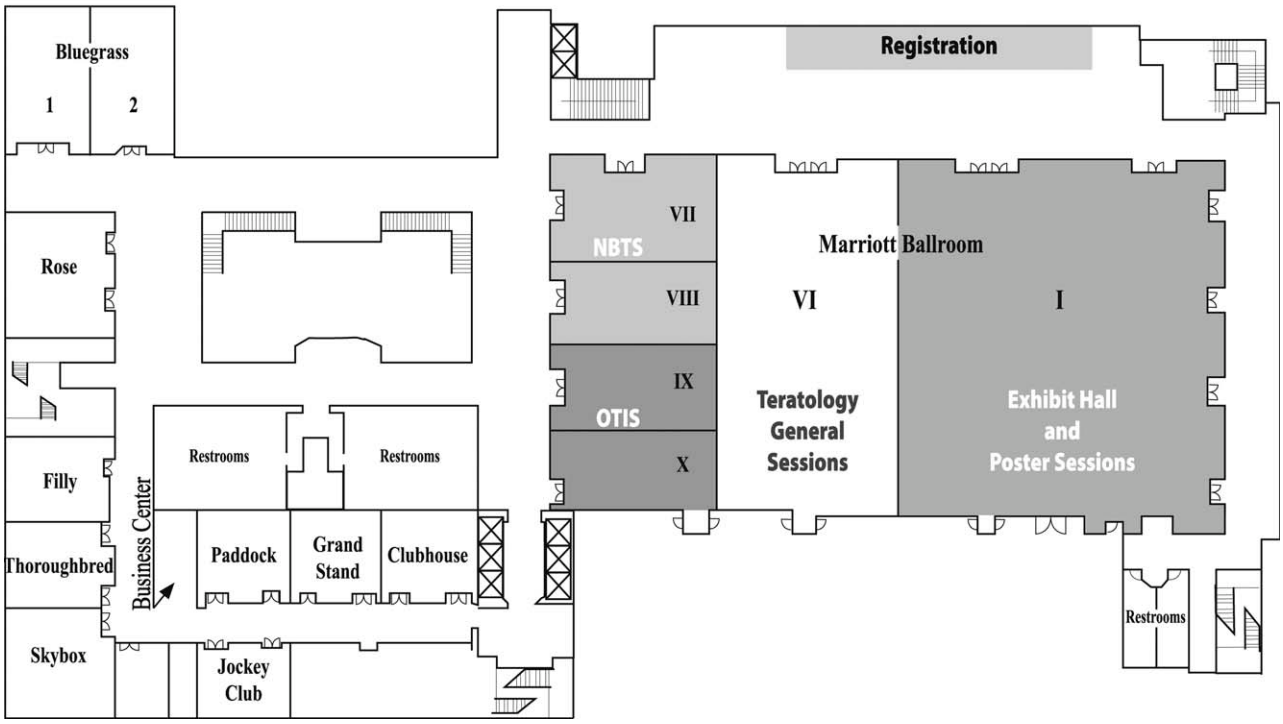
The estimated one way taxi fare from the Louisville International Airport to the hotel is $20. Bus service is available for approximately $2.50 each way. If you will be arriving by train or bus, the Greyhound bus terminal is located .8 miles from the hotel while Louisville Union Station is .4 miles southwest.

Hotel Parking

The Marriott Louisville Downtown offers both self parking and valet parking. Self parking is offered at $21 per day and valet parking is $25 per day. Off-site parking is also available for $8 per day. All prices are subject to change.

Marriott Louisville Downtown Map

Second Floor



Program Agenda

FRIDAY, JUNE 25, 2010

3:00 PM–6:00 PM	COUNCIL IA MEETING—Skybox Meeting Room
4:00 PM–6:00 PM	REGISTRATION—Marriott Ballroom VI Foyer

SATURDAY, JUNE 26, 2010

7:00 AM–6:00 PM	REGISTRATION—Marriott Ballroom VI Foyer
7:30 AM–8:00 AM	EDUCATION COURSE: COFFEE AND CONTINENTAL BREAKFAST—Marriott Ballroom VI
8:00 AM–11:30 AM	EDUCATION COURSE *(Separate Registration Required)*—Marriott Ballroom VI

Session I: Prenatal Drug Disposition and Teratogenesis
Organized by the Education Committee, Chairperson, Louise M. Winn, Queen's University

8:00 AM–8:10 AM	**Welcome** CME *Barbara F. Hales, Teratology Society President*
8:10 AM–8:15 AM	**Course Overview** CME *Education Committee Chairperson, Louise M. Winn, Queen's University*
8:15 AM–9:00 AM	**The Role of Biotransformation in Developmental Toxicology** CME *Craig Harris, University of Michigan*
9:00 AM–9:45 AM	**Stage- and Species-Specific Disposition of Toxicants during Pregnancy** *Edward W. Carney, The Dow Chemical Company*
9:45 AM–10:00 AM	**Break**
10:00 AM–10:45 AM	**Prenatal Ontogeny and Capabilities of Phase I and Phase II Enzymes** CME *J. Steven Leeder, Children's Mercy Hospitals and Clinics*
10:45 AM–11:30 AM	**Repair Capabilities in the Embryo** CME *Peter G. Wells, University of Toronto*

11:30 AM–1:30 PM	LUNCH ON YOUR OWN
12:00 NOON–1:00 PM	F. CLARKE FRASER AND DISTINGUISHED SERVICE AWARDS COMMITTEE MEETING—Skybox Meeting Room

12:30 PM–5:30 PM **TS/OTIS JOINT PREGNANCY REGISTRY WORKSHOP—Marriott Ballroom IX**

Moderators: Christina D. Chambers, University of California, San Diego and Lewis B. Holmes, MassGeneral Hospital For Children

12:30 PM–12:40 PM		**Introduction**
12:40 PM–1:10 PM	**W1**	**Classifying Birth Defects in Reproductive Research** *Lewis B. Holmes, MassGeneral Hospital for Children*
		Point/Counterpoint
1:10 PM–1:30 PM	**W2**	**Methodological Challenges in Surveillance of Spontaneous Abortion As a Reproductive Health Endpoint** *David A. Savitz, Mt. Sinai School of Medicine*
1:30 PM–1:50 PM	**W3**	**Studying Miscarriage Using Pregnancy Registries** *De-Kun Li, Kaiser Permanente Medical Group*
1:50 PM–2:10 PM	**W4**	**Organizing Pregnancy Registries during an Emergency Response** *Ava Marie S. Conlin, Naval Health Research Center*
2:10 PM–2:30 PM	**W5**	**The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS): Launch of a New System for Post-Marketing Surveillance** *Christina Chambers, University of California, San Diego*
2:30 PM–3:15 PM		**Panel Discussion: FDA Pregnancy Registry Guidance Document Revisions** *Moderator: Melissa S. Tassinari, U.S. Food and Drug Administration*
3:15 PM–3:30 PM	**W6**	**Universal Call Center for Medicine Use in Pregnancy** *Michael McDonagh, CKR Consulting*
3:30 PM–3:45 PM		**Break**
3:45 PM–4:00 PM	**W7**	**Birth Defect Categorization Systems Employed by Pregnancy Registries** *Covington DL, McKain LR, Hurst N. Pharmaceutical Product Development Inc., Wilmington, NC, United States.*
4:00 PM–4:15 PM	**W8**	**Pregnancy Drug Safety Labeling and Surveillance at the Time of Product Approval** *McKain LE, Covington DL. Pharmaceutical Product Development, Inc., Wilmington, NC, United States.*
4:15 PM–4:30 PM	**W9**	**Comparative Safety of Topiramate during Pregnancy** *Hernandez-Diaz S[1], Mittendorf R[2], Holmes LB[3]. [1]Harvard School of Public Health, Boston, MA, United States, [2]Loyola University Chicago, Chicago, IL, United States, [3]MassGeneral Hospital for Children, Boston, MA, United States.*
4:30 PM–4:45 PM	**W10**	**UCB Antiepileptic Drug Pregnancy Registry** *Scheuerle A[1], Harden C[2], Alekar S[3], Leppik I[4], Montouris G[5]. [1]Tesserae Genetics, Dallas, TX, United States, [2]University of Miami School of Medicine, Miami, FL, United States, [3]UCB, Inc., Raleigh, NC, United States, [4]University of Minnesota, Minneapolis, MN, United States, [5]Boston University School of Medicine and Boston Medical Center, Boston, MA, United States.*

4:45 PM–5:00 PM **W11** **Medication Exposure in Pregnancy Risk Evaluation Program**
Li DK[1], Andrade S[2], Scott P[3], Cheetham C[4], Cooper W[5], Davis R[6], Dublin S[7], Pawloski P[8], Raebel M[9], Smith D[10], Toh D[11]. [1]Kaiser Permanente Northern California, Oakland, CA, United States, [2]Meyers Primary Care Institute, Worcester, MA, United States, [3]U.S. Food and Drug Administration, Silver Spring, MD, United States, [4]Kaiser Permanente Southern California, Los Angeles, CA, United States, [5]Vanderbilt University School of Medicine, Vanderbilt University School of Medicine, United States, [6]Kaiser Permanente Georgia, Atlanta, GA, United States, [7]Group Health Center for Health Studies,, Seattle, WA, United States, [8]HealthPartners Research Foundation, Bloomington, MN, United States, [9]Kaiser Permanente Colorado, Denver, CO, United States, [10]Kaiser Permanente Northwest, Portland, OR, United States, [11]Harvard Medical School and Harvard Pilgrim Health Care, Boston, MA, United States.

5:00 PM–5:30 PM **Poster Session**
Posters WP1–WP4

1:30 PM–4:45 PM **EDUCATION COURSE** *(Separate Registration Required)*—**Marriott Ballroom VI**

Session II: Postnatal Drug Disposition and Teratogenesis
Organized by the Education Committee, Chairperson, Louise M. Winn, Queen's University

1:30 PM–1:45 PM **Narsingh Agnish Fellowship**
Thomas H. Shepard, University of Washington

1:45 PM–2:15 PM **Lactational Transfer of Drugs**
Sue Marty, The Dow Chemical Company

2:15 PM–3:00 PM **Postnatal Metabolic Systems** CME
Ronald N. Hines, Medical College of Wisconsin

3:00 PM–3:15 PM **Break**

3:15 PM–4:00 PM **Toxicity Profile Differences between Adults and Juveniles** CME
Melissa J. Beck, WIL Research Laboratories, LLC

4:00 PM–4:45 PM **Environmental Influences** CME
Carl L. Keen, University of California, Davis

6:00 PM–8:00 PM **STUDENT/POSTDOCTORAL FELLOW MIXER—Champions Sport Bar**

6:30 PM–9:30 PM **COUNCIL IB MEETING AND COMMITTEE REPORTS—Skybox Meeting Room**

SUNDAY, JUNE 27, 2010

8:00 AM–7:00 PM **REGISTRATION—Marriott Ballroom VI Foyer**

8:00 AM–8:15 AM **PRESIDENT'S WELCOME—Marriott Ballroom VI**

8:15 AM–9:15 AM **JOSEF WARKANY LECTURE—Marriott Ballroom VI**

50 Years of Progress in Understanding the Causes of Three Common Birth Defects CME
Diana M. Juriloff, University of British Columbia

9:15 AM–11:45 AM **STUDENT/POSTDOCTORAL FELLOW PLATFORM SESSION I—Marriott Ballroom VI**

Wilson Presentation Award Competition
Chairpersons: Meredith S. Rocca, Elan Pharmaceuticals, Jeffrey H. Charlap, Charles River and Jane F. Rasco, University of Alabama

Organized by the Student Affairs Committee

9:15 AM–9:30 AM **Introduction**

9:30 AM–9:45 AM **1** **Exposure of Organogenesis Stage Mouse Embryos to Hydroxyurea Induces Nuclear 4-hydroxy-2-nonenal Protein Adducts**
Schlisser AE, Hales BF. McGill University, Montreal, QC, Canada.

9:45 AM–10:00 AM	**2**	**Maternal DNA Hypomethylation, Methionine Pathway Metabolites, Lifestyle Factors and Congenital Heart Defects** *Chowdhury S, Cleves MA, MacLeod SL, Zhao W, Hobbs CA. University of Arkansas for Medical Sciences, Arkansas Children's Hospital Research Institute, Little Rock, AR, United States.*
10:00 AM–10:15 AM	**3**	**A Toxicity Signature for Species-Specific Disruption of Embryonic Vasculogenesis Derived from ToxCast™ *In Vitro* Profiling Data** *Kleinstreuer N[1], Dix D[1], Judson R[1], Kavlock R[1], Sipes N[1], Reif D[1], Chandler K[1,3], Rountree M[1], DeWoskin R[2], Singh A[4], Spencer R[4], Knudsen T[1]. [1]NCCT, ORD, U.S. EPA, Research Triangle Park, NC, United States, [2]NCEA, ORD, U.S. EPA, Research Triangle Park, NC, United States, [3]NHEERL, ORD, U.S. EPA, Research Triangle Park, NC, United States, [4]Lockheed Martin, Research Triangle Park, NC, United States.*
10:15 AM–10:30 AM	**4**	**Exposure to 2-methoxyacetic Acid Induces Limb Malformations and Histone 4 Hyperacetylation *In Vitro*** *Dayan C, Hales BF. McGill University, Montreal, QC, Canada.*
10:30 AM–10:45 AM		**Break**
10:45 AM–11:00 AM	**5**	**High-Throughput Screening of ToxCast™ Phase I Chemicals in an Embryonic Stem Cell Assay Reveals Potential Disruption of a Critical Developmental Signaling Pathway** *Chandler K[1,2], Hunter S[1], Jeffay S[1], Nichols H[1], Hoopes M[1], Barrier M[1], Habig J[3], Knudsen T[2]. [1]Integrated Systems Toxicology Division, U.S. EPA, Research Triangle Park, NC, United States, [2]National Center for Computational Toxicology, U.S. EPA, Research Triangle Park, NC, United States, [3]Endogenics, Eagle, ID, United States.*
11:00 AM–11:15 AM	**6**	**Valproic Acid Disrupts Chondrocyte Differentiation and Increases Apoptosis *In Vitro* in Murine Limb Buds** *Paradis FH, Hales BF. McGill University, Montreal, QC, Canada.*
11:15 AM–11:30 AM	**7**	**Dissecting the Action of Bisphenol-A on Germline Maintenance Using *C. elegans*** *Allard P, Colaiacovo M. Harvard Medical School, Genetics, Boston, MA, United States.*
11:30 AM–11:45 AM	**8**	**Transfer of Dendrimers in the Perfused Human Placental Lobule *In Vitro*: Prospects for Use As Drug Carriers during Pregnancy** *Rinderknecht AL[1], Menjoge AR[2,3], Kannan RM[2,3], Kim CJ[3], Romero R[3], Faridnia M[1], Miller RK[1]. [1]University of Rochester, Rochester, NY, United States, [2]Wayne State University, Detroit, MI, United States, [3]National Institute of Child Health and Human Development, Detroit, MI, United States.*

11:45 AM–12:00 NOON **BOX LUNCH PICK-UP**

12:00 NOON–1:00 PM **TS/OTIS JOINT ROBERT L. BRENT LECTURE** *(A Box Lunch Session)*—**Marriott Ballroom VI**

Ionizing Radiation Exposure to the Fetus and Infant from Medical Imaging: A Radiologist's Perspective (L1)
Donald P. Frush, Duke University Medical Center

1:00 PM–1:30 PM **F. CLARKE FRASER AWARD—Marriott Ballroom VI**

Gastroschisis: A Journey to Discover the Pieces of the Puzzle (L2)
Marcia L. Feldkamp, University of Utah

1:30 PM–2:00 PM **JAMES G. WILSON PUBLICATION AWARD—Marriott Ballroom VI**

Regulations of Folate Receptor 1 Gene Expression in the Visceral Endodem
J. Michael Salbaum, Pennington Biomedical Research Center

2:00 PM–3:00 PM **TS/ETS JOINT EXCHANGE LECTURE—Marriott Ballroom VI**

Pros and Cons of the Extended One-Generation Study Protocol

Teratology Society
The Cons of the Extended One-Generation Study Protocol (L3) CME
Paul M.D. Foster, National Institute of Environmental Health Sciences

European Teratology Society
The Extended One-Generation Reproduction Toxicity Study: Improving Hazard Assessment and Saving Animals? (L4) CME
Aldert H. Piersma, National Institute for Public Health and the Environment (RIVM), Bilthoven

3:00 PM–3:15 PM **BREAK**

3:15 PM–5:45 PM **VITAMIN B_{12} AND NEURAL TUBE DEFECTS: IS IT TIME TO FORTIFY FOOD WITH B_{12} SYMPOSIUM—Marriott Ballroom VI**

Chairperson: James L. Mills, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH

3:15 PM–3:40 PM **S1** **Vitamin B_{12} Deficiency and NTDs: Is There a Causal Relationship?** CME
James L. Mills, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH

3:40 PM–4:05 PM **S2** **Normal Vitamin B_{12} Physiology, the Pathophysiology of B_{12} Deficiency, and Their Relevance to Treatment and Fortification** CME
Ralph Carmel, New York Methodist Hospital and Weill Medical College of Cornell University

4:05 PM–4:30 PM **S3** **Should FDA Require Vitamin B_{12} Fortification of Enriched Flour? Yes** CME
Godfrey P. Oakley, Emory University

4:30 PM–4:55 PM **S4** **Should We Fortify Food with B_{12} Now? No** CME
Ralph Green, University of California Davis Medical Center

4:55 PM–5:45 PM **Panel Discussion and Response to Questions from the Audience** CME

6:00 PM–8:00 PM **TS/NBTS JOINT WELCOME RECEPTION AND EXHIBITS OPEN—Marriott Ballroom I**

Silent Auction

MONDAY, JUNE 28, 2010

7:00 AM–8:00 AM ***BDRB* EDITORIAL BOARD MEETING—Filly Meeting Room**

7:30 AM–6:00 PM **REGISTRATION—Marriott Ballroom VI Foyer**

8:00 AM–7:00 PM **EXHIBIT HALL OPEN—Marriott Ballroom I**

8:00 AM–9:00 AM **TS/OTIS JOINT STATE OF THE ART LECTURE—Marriott Ballroom VI**

Palate Development: Molecular Perspectives and Current Understanding (L5) CME
Robert M. Greene, Director, Birth Defects Center, University of Louisville

9:00 AM–9:15 AM **BREAK**

9:15 AM–11:45 AM **TS/NBTS/OTIS JOINT SYMPOSIUM—Marriott Ballroom VI**

Reproductive Psychiatry
Chairpersons: Katherine L. Wisner, University of Pittsburgh Medical Center and Adrienne Einarson, The Motherisk Program

9:15 AM–9:20 AM		**Introduction** CME
9:20 AM–9:50 AM	**S5**	**Prenatal SRI Exposure: Where Does Neonatal Behavioral Syndrome End and Neurobehavioral Teratogenicity Begin?** CME *Tim F. Oberlander, University of British Columbia*
9:50 AM–10:20 AM	**S6**	**Messages from the Womb: Maternal Antidepressant Use and Fetal Neurobehavior** CME *Amy L. Salisbury, Alpert Medical School of Brown University*
10:20 AM–10:50 AM	**S7**	**An Update on Lithium Treatment during Pregnancy and Lactation** CME *Adele C. Viguera, Neurological Institute, Cleveland Clinic*
10:50 AM–11:20 AM	**S8**	**Effects of Developmental Exposure to Methylphenidate on Brain Areas Involved in Cognition, Motivated Behaviors, Appetite and Stress** CME *Teresa Ann Milner, Weill Cornell Medical College*
11:20 AM–11:45 AM		**Discussion: How Do We Incorporate These Data into Human Risk Assessment?** CME *Katherine L. Wisner, University of Pittsburgh Medical Center*

9:15 AM–11:45 AM **PLATFORM SESSION II—Marriott Ballroom VII**

Mechanisms and Models
Chairpersons: Barbara D. Abbott, U.S. Environmental Protection Agency and Peter G. Wells, University of Toronto

9:15 AM–9:30 AM	**9**	**Peroxisome Proliferator-Activated Receptor Alpha (PPARγ), Beta (PPARβ), and Gamma (PPARβ) Expression in Human Fetal Tissues** *Abbott BD, Wood CR, Watkins AM, Das KP, Lau CS. Developmental Biology Branch, Toxicity Assessment Div., NHEERL, U.S. EPA, Research Triangle Park, NC, United States.*
9:30 AM–9:45 AM	**10**	**Modulation of Adenosine Receptor A_1 Signaling Results in Inhibition of Calvarial Ossification in Mice** *Bushdid PB, Gibbard A, Pagana JM, White TE. GlaxoSmithKline, King of Prussia, PA, United States.*
9:45 AM–10:00 AM	**11**	**Akt1 Mediates Mammary Gland Growth and Development *In Vivo*** *LaRocca J, Hixon M. Brown University, Providence, RI, United States.*
10:00 AM–10:15 AM	**12**	**Role of Mitogen-Activating Protein Kinase Signaling in the Developmental Toxicity of Hydroxyurea** *Banh S, Hales BF. McGill University, Montreal, QC, Canada.*
10:15 AM–10:30 AM	**13**	**Ethanol Teratogenesis, Oxidative Stress and Protection by a Free Radical Spin Trapping Agent** *Miller L[1], Wells PG[1]. [1]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada, [2]Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada.*
10:30 AM–10:45 AM	**14**	**Advantages and Challenges of Dietary Developmental Toxicity Studies in the Rabbit** *Rasoulpour RJ, Brooks KJ, Saghir SA, Billington R, Carney EW. The Dow Chemical Company, Midland, MI, United States.*
10:45 AM–11:00 AM	**15**	**Cigarette Smoke Exposure: Alterations in the Metabolome of the Gravid and Non-Gravid Mouse Uterus** *Neal RE[1,2], Chen J[1], Birtles T[2], Greene RM[2], Pisano MM[2]. [1]EOHS, SPHIS, University of Louisville, Louisville, KY, United States, [2]Birth Defects Center, University of Louisville, Louisville, KY, United States.*

11:00 AM–11:15 AM	**16**	**Altered Liver Proteome Profiles in a Mouse Model of "Developmental" Cigarette Smoke Exposure** *Canales L[1], Chen J[1], Birtles T[2], Greene RM [2], Pisano MM[2], Neal R[1,2]. [1]University of Louisville, Louisville, KY, United States, [2]Birth Defects Research Center, University of Louisville, Louisville, KY, United States.*
11:15 AM–11:30 AM	**17**	**Proteome Profiling of Mouse Embryonic Stem Cells to Define Markers for Cell Differentiation and Embryotoxicity** *Osman A[1,2], van Dartel DAM[1,2], Zwart E[1], Blokland M[1], Pennings J[1], Piersma AH[1,3]. [1]RIVM Lab for Health Protection Research, Bilthoven, Netherlands, [2]GRAT-NUTRIM-Maastricht University, Maastricht, Netherlands, [3]IRAS-Utrecht University, Utrecht, Netherlands.*
11:30 AM–11:45 AM	**18**	**Development of a Computational (*In Silico*) Model of Ocular Teratogenesis** *Sipes NS[1], Rountree MR[1], Kleinstreuer NC[1], Dix DJ[1], Judson RS[1], Kavlock RJ[1], Swat M[4], Glazier JA[4], DeWoskin RS[2], Singh AV[3], Spencer RM[3], Knudsen[1]. [1]NCCT, ORD, U.S. EPA, Research Triangle Park, NC, United States, [2]NCEA, ORD, U.S. EPA, Research Triangle Park, NC, United States, [3]Lockheed Martin, Research Triangle Park, NC, United States, [4]The Biocomplexity Institute, Dept. of Physics, Indiana University, Bloomington, IN, United States.*

11:45 AM–1:15 PM **LUNCH ON YOUR OWN**

11:45 AM–1:15 PM **PAST PRESIDENTS' LUNCHEON** *(By Invitation Only)*—**Bluegrass 1 Meeting Room**

11:45 AM–12:45 PM **WEB SITE COMMITTEE MEETING—Filly Meeting Room**

1:15 PM–2:15 PM **TS/OTIS JOINT SPECIAL LECTURE—Marriott Ballroom VI**

Human Teratogens: Update 2010 CME
Lewis B. Holmes, MassGeneral Hospital for Children

2:15 PM–5:00 PM **UPDATE ON THALIDOMIDE SYMPOSIUM—Marriott Ballroom VI**

Chairperson: Lewis B. Holmes, MassGeneral Hospital for Children

2:15 PM–2:20 PM		**Introduction** CME *Lewis B. Holmes, MassGeneral Hospital for Children*
2:20 PM–2:30 PM		**Thalidomide Epidemic and the Founding of the Teratology Society** CME *F. Clarke Fraser, McGill University*
2:30 PM–3:15 PM	**S9**	**Thalidomide Embryopathy: Ophthalmologic Findings and a Few Surprises** CME *Marilyn Miller, University of Illinois College of Medicine*
3:15 PM–3:30 PM		**Break**
3:30 PM–4:15 PM	**S10**	**Recent Advances in Understanding the Developmental Basis of Phocomelia** CME *Patrick Allard, Harvard Medical School*
4:15 PM–5:00 PM	**S11**	**Lessons Learned from the Thalidomide Epidemic and the Current Hypotheses of the Possible Mechanisms of Action** CME *Trent Stephens, Idaho State University*

5:00 PM–7:00 PM **TS/NBTS/OTIS JOINT POSTER SESSION AND EXHIBITS OPEN—Marriott Ballroom I**

Teratology Society Posters: P1–P28A
NBTS Posters: 1–6
OTIS Posters: 1–11

7:30 PM–9:30 PM **MARTA STUDENT AND POSTDOCTORAL FELLOW CAREER EVENT—Bluegrass 1 Meeting Room**

Open to TS/NBTS/OTIS Students and Postdoctoral Fellows

TUESDAY, JUNE 29, 2010

7:00 AM–5:00 PM **REGISTRATION—Marriott Ballroom VI Foyer**

7:00 AM–8:20 AM **SUNRISE MINI COURSE** *(Separate Registration Required)*—**Marriott Ballroom VI**

Imaging Tools for Structural and Functional Teratogenesis Analyses
Organized by the Education Committee, Chairperson, Louise M. Winn, Queen's University

7:00 AM–7:40 AM **Imaging Tools for Structural Analysis** CME
William Slikker, Jr., National Center for Toxicological Research, U.S. FDA

7:40 AM–8:20 AM **Imaging Tools for Functional Analysis** CME
Julia M. Stephen, University of New Mexico

8:00 AM–2:00 PM **EXHIBIT HALL OPEN—Marriott Ballroom I**

8:30 AM–9:15 AM **TS/NBTS/OTIS JOINT SPECIAL LECTURE—Marriott Ballroom VI**

Children's Environmental Health: A Good Start Lasts a Lifetime CME
Linda S. Birnbaum, Director, National Institute of Environmental Health Sciences, NIH

9:15 AM–9:30 AM **BREAK**

9:30 AM–12:00 NOON **MARCH OF DIMES/PUBLIC AFFAIRS COMMITTEE SYMPOSIUM—Marriott Ballroom VI**

Herbal Supplement Usage during Pregnancy
Chairpersons: Patricia M. Bittner, U.S. Consumer Product Safety Commission, Chair, Public Affairs Committee and Richard K. Miller, University of Rochester Medical Center

Organized by the Public Affairs Committee

9:30 AM–10:00 AM **S12** **Herbal Usage during Pregnancy: Teratology Society White Paper** CME
Richard K. Miller, University of Rochester Medical Center

10:00 AM–10:30 AM **S13** **Herbal Preparations Usage and Pregnancy** CME
Henry M. Hess, University of Rochester Medical Center

10:30 AM–11:00 AM **S14** **Herbal Products: Are They What They Claim to Be?** CME
William R. Obermeyer, ConsumerLab.com

11:00 AM–11:10 AM **S15** **Herbal Drugs in Pregnancy: A Canadian Perspective** CME
Gideon Koren, The Hospital for Sick Children

11:10 AM–11:20 AM **S16** **Traditional Chinese Medicine: Herbal Medicine Origins and Utilization in China** CME
Robert L. Brent, Alfred I. duPont Hospital for Children

11:20 AM–11:30 AM **S17** **Herbal Preparations: Are We at the Beginning of Regulations? The Situation in Europe and the Eastern Mediterranean Region** CME
Asher Ornoy, Hebrew University Hadassah Medical School and Israeli Ministry of Health

11:30 AM–12:00 NOON **Panel Discussion of Position Paper and Topic** CME
Patricia M. Bittner, U.S. Consumer Product Safety Commission, Chair, Public Affairs Committee

9:30 AM–12:00 NOON **TS/NBTS JOINT SYMPOSIUM—Marriott Ballroom VII**

Advancing Neurodevelopmental Evaluation in Children: An Interdisciplinary Approach
Chairperson: Susan Makris, U.S. Environmental Protection Agency and William Slikker, Jr., National Center for Toxicological Research, U.S. FDA

9:30 AM–9:55 AM	**S18**	**The Use of Neurodevelopmental Data in Children for Risk Assessment of Environmental Chemicals** CME *Susan Makris, U.S. Environmental Protection Agency*
9:55 AM–10:20 AM	**S19**	**A Multidisciplinary Approach to Advancing the Science of Neurodevelopmental Testing in Cohorts of Infants and Young Children** CME *Judy S. LaKind, LaKind Associates, LLC*
10:20 AM–10:45 AM	**S20**	**Getting the Biggest Bang for Your Buck: Choosing Neurodevelopmental Tests That Maximize Power** CME *Lauren Kenworthy, George Washington University School of Medicine*
10:45 AM–11:10 AM	**S21**	**Threats to Study Validity: The Flynn Effect, Examiner Drift, Confounders, Lost in Translation, and Other Important Considerations** CME *Laura Gutermuth Anthony, George Washington University School of Medicine*
11:10 AM–11:35 AM	**S22**	**Weight-of-the-Evidence Assessment in Neurodevelopmental Epidemiology: A Plea for Consistency** CME *Michael Goodman, Emory University*
11:35 AM–12:00 NOON		**Panel Discussion** CME

12:00 NOON–2:00 PM **TS/NBTS JOINT POSTER SESSION AND EXHIBITS OPEN—Marriott Ballroom I**

Teratology Society Posters: P29–P58
NBTS Posters: 7–11

2:00 PM–4:30 PM **PLATFORM SESSION III—Marriott Ballroom VI**

Hazard Assessment and Screening
Chairpersons: Michael G. Narotsky, U.S. Environmental Protection Agency and Rochelle W. Tyl, RTI International

2:00 PM–2:15 PM	**19**	**Effects of *In Utero* Exposure to Mono-2-ethylhexylphthalate (MEHP) on the Adult Female Mouse** *Moyer BJ, Hixon ML. Brown University, Providence, RI, United States.*
2:15 PM–2:30 PM	**20**	**Micro-CT and Alizarin Red Evaluations of Fetal Rat and Rabbit Skeletal Abnormalities Induced by All-Trans-Retinoic Acid** *Wise LD[1], Xue D[2], Winkelmann CT[2]. [1]Toxicological Sciences, Merck Research Laboratories, West Point, PA, United States, [2]Imaging Department, Merck Research Laboratories, West Point, PA, United States.*
2:30 PM–2:45 PM	**21**	**Effects of Bisphenol A and Diethylstilbestrol on the Adult Male Reproductive System Following Oral Administration to Pregnant C57BL6 Mice on Gestational Days 10 through 16** *Hixon ML, LaRocca J, Boyajian A, Brown C, Duncan Smith S. Brown University, Providence, RI, United States.*
2:45 PM–3:00 PM	**22**	**Gonadal Responses to Vinclozolin Administered Orally to Han Wistar Rats** *Tyl RW[1], Seely JC[2], Marr MC[1], Myers CB[1], Youn VY[1], Browning DB[1], Bishop JB[3]. [1]RTI International, Research Triangle Park, NC, United States, [2]Experimental Pathology Laboratories, Inc., Research Triangle Park, NC, United States, [3]National Toxicology Program/NIEHS/NIH, Research Triangle Park, NC, United States.*
3:00 PM–3:15 PM		**Break**

3:15 PM–3:30 PM **23** **Maternal Diet Modulates the Rate of Neural Tube Defects in Diabetic Pregnancies**
Kappen C, Kruger C, MacGowan J, Salbaum JM. Pennington Biomedical Research Center, Baton Rouge, LA, United States.

3:30 PM–3:45 PM **24** **Mammary Gland Development As a Sensitive Indicator of Early Life Exposures: Recommendations from an Interdisciplinary Workshop**
Fenton SE[1], Rudel RA[2], Euling SY[3], Makris SL[3]. [1]National Institute of Environmental Health Sciences, National Toxicology Program, Research Triangle Park, NC, United States, [2]Silent Spring Institute, Newton, MA, United States, [3]NCEA, U.S. EPA, Washington, DC, United States.

3:45 PM–4:00 PM **25** **Assessment of Reproductive and Developmental Toxicity of Mixtures of Regulated Drinking Water Chlorination By-Products in a Multigenerational Rat Bioassay**
Narotsky MG[1], Klinefelter GR[1], Goldman JM[1], Strader LF[1], Suarez JD[1], Pressman JG[2], Miltner RJ[2], Speth T [2], Teuschler LK[3], Rice GE[3], Richardson SD[4], Best DS[1], McDonald A[1], Murr AS[1], Hunter ES[1], Simmons JE[1]. [1]National Health and Environmental Effects Research Laboratory, ORD, U.S. EPA, Research Triangle Park, NC, United States, [2]National Risk Management Research Laboratory, ORD, U.S. EPA, Cincinnati, OH, United States, [3]National Center for Environmental Assessment, ORD, U.S. EPA, Cincinnati, OH, United States, [4]National Exposure Research Laboratory, ORD, U.S. EPA, Athens, GA, United States.

4:00 PM–4:15 PM **26** **A Fishy Solution to Reproductive Toxicity Screening or Just a Red Herring? Zebrafish in Developmental Toxicity: Value within Pharmaceutical Development**
Van den Bulck K[1], Hill A[2], Jones M[2], Dodd A[2], Mesens N[1], Bailey GP[1], De Schaepdrijver L[1], Lammens L[1]. [1]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium, [2]Evotec AG, Hamburg, Germany.

4:15 PM–4:30 PM **27** **Establishment of a Statistical Prediction Model and Abbreviated Assay Design for Teratogenicity Screening of Compounds Using Rat Whole Embryo Culture**
Zhang CXZ, Cao JC, Panzica-Kelly JPK, Stock DS, Augustine-Rauch KAA. Bristol Myers Squibb, Pennington, NJ, United States.

2:00 PM–4:15 PM **TS/OTIS JOINT PLATFORM SESSION IV—Marriott Ballroom IX**

Common Conditions in Pregnancy: Treatment of Mental Health and Asthma
Chairpersons: Ludmila Bakhireva, University of New Mexico and Myla Moretti, The Hospital For Sick Children

2:00 PM–2:15 PM **28** **Patterns of Psychotropic Drug Use in Pregnancy and Lactation: The MotherSafe Experience 2000–2007**
Eamus M[1], Oei J[1,2], Hill M[3], Taylor T[3], Kennedy D[1,3]. [1]School of Women's and Children's Health, University of NSW, Kensington, NSW, Australia, [2]Dept. of Neonatology, Royal Hospital for Women, Randwick, NSW, Australia, [3]MotherSafe, Royal Hospital for Women, Randwick, NSW, Australia.

2:15 PM–2:30 PM **29** **Birth Defects, Preterm Birth and Intrauterine Growth in the Offspring of Women Prescribed Citalopram during Pregnancy**
Colvin L[1,2], Slack-Smith L[2], Stanley FJ[1], Bower C[1]. [1]Centre for Child Health Research, Telethon Institute for Child Health Research, The University of Western Australia, West Perth, Australia, [2]School of Dentistry, The University of Western Australia, West Perth, Austria.

2:30 PM–2:45 PM **30** **The Safety of Escitalopram in Pregnancy: A Prospective Cohort Study**
Klieger-Grossmann C[1], Weitzner B[1], Einarson T[2], Koren G[1], Einarson A[1]. [1]The Motherisk Program, Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [2]Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada.

2:45 PM–3:00 PM **31** **Neurodevelopment of Children Exposed *In Utero* to Venlafaxine: Preliminary Results**
Nulman I[1,2], Barrera M[1,2], Pulver A[1], Streiner D[2,3], Feldman B[1,2], Koren G[1,2]. [1]The Hospital for Sick Children, Toronto, ON, Canada, [2]The University of Toronto, Toronto, ON, Canada, [3]Baycrest Centre, Toronto, ON, Canada.

3:00 PM–3:15 PM **Break**

3:15 PM–3:30 PM **32** **Impact of Changing the Dose of Inhaled Corticosteroids during Pregnancy on the Risk of Maternal Asthma Exacerbations**
Blais L[1,2], Kettani F[2], Ducharme FM[3], Lemière C[1,2], Beauchesne M-F[1], Bérard A[1]. [1]Université de Montréal, Montréal, QC, Canada, [2]Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada, [3]CHU Ste-Justine, Montréal, QC, Canada.

3:30 PM–3:45 PM **33** **Congenital Anomalies in Asthmatic Women Using Corticosteroids during Pregnancy: A Meta Analysis from Published Data**
Namazy JA[1], Murphy VE[2,3], Powell H[2,4], Gibson PG[2,4], Chambers CD[5], Schatz M[6]. [1]Scripps Clinic, San Diego, CA, United States, [2]University of Newcastle, Newcastle, NSW, Australia, [3]Hunter Medical Research Institute, Newcastle, NSW, Australia, [4]John Hunter Hospital, Newcastle, NSW, Australia, [5]University of California San Diego, La Jolla, CA, United States, [6]Kaiser Permanente Medical Center, San Diego, CA, United States.

3:45 PM–4:00 PM **34** **Risk of Perinatal Mortality Associated with the Use of Inhaled Corticosteroids for the Treatment of Asthma during Pregnancy**
Breton MCB[1], Beauchesne MFB[1,2], Lemière CL[2], Rey ER[3], Amélie AF[2], Blais LB[1,2]. [1]Universite de Montreal, Montreal, QC, Canada, [2]Research Center, Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada, [3]Obstetric and Gynecology Department, CHU Ste-Justine, Montreal, QC, Canada.

4:00 PM–4:15 PM **35** **Perception of Teratogenicity among Pregnant Women with Asthma or Diabetes Mellitus**
Sarangarm P[1], Liu S[1], Young BN[1], Phelan ST[2], Nawarskas J[1], Rayburn WF[2], Bakhireva LN[1]. [1]University of New Mexico, College of Pharmacy, Albuquerque, NM, United States, [2]University of New Mexico, Department of Obstetrics and Gynecology, Albuquerque, NM, United States.

4:45 PM–6:30 PM **50TH ANNIVERSARY MEETING CELEBRATION—Marriott Ballroom VI**

Chairpersons: Barbara F. Hales, McGill University and John M. Rogers, U.S. Environmental Protection Agency

Organized by the 50th Anniversary Planning Committee

4:45 PM–4:50 PM **Introduction**
John M. Rogers, U.S. Environmental Protection Agency

4:50 PM–5:10 PM **S23** **Josef Warkany: Then and Now**
Wladimir Wertelecki, University of South Alabama

5:10 PM–5:30 PM **S24** **James G. Wilson, Embryologist, Teratologist, Founding Member of the Teratology Society, Superb Researcher, Teacher and Human Being**
Robert L. Brent, Alfred I. duPont Hospital for Children

5:30 PM–5:45 PM **Distinguished Service Award**
Presented by Barbara F. Hales, McGill University and Terence R.S. Ozolins, Queen's University

5:45 PM–6:00 PM **Students' Viewpoints on the Future of the Teratology Society**

6:00 PM–6:30 PM **Let's Play Jeopardy! History of the Teratology Society**

WEDNESDAY, JUNE 30, 2010

6:30 AM–7:30 AM **TERATOLOGY SOCIETY XXIX ANNUAL VOLLEYBALL GAME—Baxter Jack's Volleyball Club**

7:00 AM–8:00 AM **PUBLIC AFFAIRS COMMITTEE MEETING—Skybox Meeting Room**

7:00 AM–8:00 AM **STUDENT AFFAIRS COMMITTEE MEETING—Filly Meeting Room**

8:00 AM–2:00 PM **REGISTRATION—Marriott Ballroom VI Foyer**

8:00 AM–10:30 AM **PLATFORM SESSION V—Marriott Ballroom IX**

Epidemiology and Clinical Studies

Chairpersons: Sonja A. Rasmussen, Centers for Disease Control and Prevention and Robert Felix, University of California, San Diego

8:00 AM–8:15 AM **36** **Maternal Exposure to Venlafaxine and Risk for Birth Defects**
Duwe K[1], Rasmussen S[1], Louik C[2], Colarusso T[1], Reefhuis J[1]. [1]NCBDDD, CDC, Atlanta, GA, United States, [2]Slone Epidemiology Center, BU, Boston, MA, United States.

8:15 AM–8:30 AM **37** **Maternal Occupational Exposure to Organic Solvents and Congenital Heart Defects: Results from the National Birth Defects Prevention Study, 1997–2002**
Gilboa SM[1], Correa A[1], Desrosiers T[2], Lupo P[3], Lawson C[4], Riehle-Colarusso T[1], Stewart P[5], van Winjgaarden E[6]. [1]National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, GA, United States, [2]North Carolina Birth Defects Monitoring Program, Raleigh, NC, United States, [3]University of Texas Health Sciences Center, Houston, TX, United States, [4]National Institute for Occupational Safety and Health, CDC, Cincinnati, OH, United States, [5]Stenzel Exposure Assessments, LLC, Arlington, VA, United States, [6]University of Rochester, Rochester, NY, United States.

8:30 AM–8:45 AM **38** **No Effect of Perchlorate on Serum Thyroxine for Pregnant Women with Low Urine Iodine**
Lamm SH[1,2], Robbins S[1], Lu J[4], Chen R[3], Hollowell JG[5]. [1]CEOH, LLC., Washington, DC, United States, [2]Johns-Hopkins University Bloomberg School of Public Health, Baltimore, MD, United States, [3]Georgetown University, Washington, DC, United States, [4]American University, Washington, DC, United States, [5]University of Kansas, Kansas City, KS, United States.

8:45 AM–9:00 AM **39** **Genital Tract Infections during Pregnancy and the Risk of Selected Birth Defects**
Carter TC[1], Olney RS[2], Mitchell AA[3], Romitti PA[4], Bell EM[5], Druschel CM[6]. [1]National Institute of Child Health and Human Development, NIH, Bethesda, MD, United States, [2]Centers for Disease Control and Prevention, Atlanta, GA, United States, [3]Slone Epidemiology Unit, Boston University, Boston, MA, United States, [4]University of Iowa, Iowa City, IA, United States, [5]State University of New York at Albany, Albany, NY, United States, [6]New York State Department of Health, Albany, NY, United States.

9:00 AM–9:15 AM **40** **Maternal Plasma Folate, Dihydrofolate Reductase Genotype and Risk of Isolated Cleft Lip with or without Cleft Palate: Findings from a Population-Based Study**
Munger RG[1], Mansilla MA[3], Tamura T[4], Feldkamp M[2], Johnson K[4], Botto LD[2], Murray JC[3]. [1]Utah State University, Logan, UT, United States, [2]University of Utah, Salt Lake City, UT, United States, [3]University of Iowa, Iowa City, IA, United States, [4]University of Alabama-Birmingham, Birmingham, AL, United States.

9:15 AM–9:30 AM **41** **An Electronic Medical Record (EMR) System-Based Referral Facilitating Access to Teratogen Risk Counseling for Health Care Providers and Their Patients**
Felix R[1], Chambers CD[1,2], Cobian V[1], Prince L[1], Kao K[1], Alvarado S[1], Jones KL[1]. [1]University of California, San Diego, Department of Pediatrics, La Jolla, CA, United States, [2]University of California, San Diego, Department of Family and Preventative Medicine, La Jolla, CA, United States.

9:30 AM–9:45 AM **42** **The Contribution of Chromosomal Abnormalities to Congenital Heart Defects: A Population-Based Study**
Hartman RJ[1,2], Rasmussen SA[1], Riehle-Colarusso T[1], Botto L[3], Correa A[1]. [1]National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, GA, United States, [2]Oak Ridge Institute for Science and Education, Oak Ridge, TN, United States, [3]Division of Medical Genetics, University of Utah, Salt Lake City, UT, United States.

9:45 AM–10:00 AM **43** **Thalidomide Embryopathy Mimics Idiopathic Congenital Vascular and Skeletal Dysmorphologies**
Hootnick DR. Upstate Medical University, Syracuse, NY, United States.

10:00 AM–10:15 AM **44** **Factors Associated with the Occurrence of Vascular Disruption Defects and Their Relationship with Heavy Metals: Case-Control Study in Cali, Colombia (South America) 2007–2009**
Pachajoa H, Ariza Y, Suarez M, Aguilar C, Isaza C, Méndez F. Universidad del Valle, Cali, Colombia.

10:15 AM–10:30 AM **45** **Maternal Dietary Fat Intake As a Potentially Preventable Cause of Gastroschisis**
Jones KL[1], Hagey LR[2], Gonzalez V[1], Benirschke K[3], Chambers CD[1,4]. [1]University of California, San Diego, Department of Pediatrics, La Jolla, CA, United States, [2]University of California, San Diego, Department of Internal Medicine, La Jolla, CA, United States, [3]University of California, San Diego, Department of Pathology, La Jolla, CA, United States, [4]University of California, San Diego, Department of Family and Preventative Medicine, La Jolla, CA, United States.

8:00 AM–10:30 AM **WILEY-BLACKWELL SYMPOSIUM—Marriott Ballroom VI**

Teratology Society: 50 Years Then to Now
Organized by the Publications Committee

Chairperson: Michael A. Schellpfeffer, Medical College of Wisconsin

8:00 AM–8:30 AM **S24** **A Personal Perspective of Historical Events That Affected the Development and Maturation of the Society in the Past 50 Years** CME
Robert L. Brent, Alfred I. duPont Hospital for Children

8:30 AM–9:15 AM **S25** **Clinical Teratology** CME
Kenneth Lyons Jones, CTIS

9:15 AM–10:00 AM **S26** **Experimental Teratology: Scenes from the Last Fifty Years** CME
William J. Scott, Jr., Cincinnati Children's Hospital Medical Center

10:00 AM–10:30 AM **S27** **Fast Forward to the Future: Where Will We Be?** CME
Barbara F. Hales, McGill University

10:30 AM–11:00 AM **WARKANY TEA**

11:00 AM–12:00 NOON **TS/NBTS JOINT UPDATE ON THE NATIONAL CHILDREN'S STUDY/ PANEL—Marriott Ballroom VI**

Chairperson: Elaine M. Faustman, University of Washington

12:00 NOON–1:30 PM **LUNCH ON YOUR OWN**

12:30 PM–1:30 PM **EDUCATION COMMITTEE MEETING—Filly Meeting Room**

12:30 PM–1:30 PM **MEMBERSHIP COMMITTEE—Thoroughbred Meeting Room**

1:30 PM–4:30 PM **ILSI HESI SYMPOSIUM—Marriott Ballroom VI**

21st Century Developmental Toxicology
Chairpersons: Edward W. Carney, The Dow Chemical Company and George P. Daston, Procter & Gamble Company

1:30 PM–1:35 PM		**Introduction** *George P. Daston, Procter & Gamble Company*
1:35 PM–2:00 PM	**S28**	**Of Babies and Their Bathwater: Strengths to Maintain and Limitations to Overcome in Transitioning Developmental Toxicology to Meet 21st Century Needs** *Edward W. Carney, The Dow Chemical Company*
2:00 PM–2:30 PM	**S29**	**Exposure Assessment in the 21st Century: Increased Reliance on Biomonitoring** CME *Sean Hays, Summit Toxicology*
2:30 PM–2:45 PM		**Break**
2:45 PM–3:15 PM	**S30**	**Pathway Profiling and Tissue Modeling Using ToxCast™ HTS Data** CME *Thomas B. Knudsen, National Center for Computational Toxicology*
3:15 PM–3:45 PM	**S31**	**Computational Toxicology: From Data to Analyses to Applications** CME *Ivan Rusyn, University of North Carolina at Chapel Hill*
3:45 PM–4:30 PM	**S32**	**Future Strategies for Developmental Toxicity Safety Assessment** CME *Thomas Hartung, Johns Hopkins University Center for Alternatives to Animal Testing*

4:30 PM–6:00 PM **BUSINESS MEETING AND REPORTS FROM *BDR* EDITORS—Marriott Ballroom VI**

6:30 PM–7:30 PM **BANQUET RECEPTION—Marriott Ballroom Foyer**

7:30 PM–10:00 PM **BANQUET—Marriott Ballroom I**

Travel Awards
James C. Bradford Memorial Student Poster Award
Wilson Presentation Awards
Marie Taubeneck Award

THURSDAY, JULY 1, 2010

7:00 AM–10:00 AM **COUNCIL II MEETING—Skybox Meeting Room**

Annual Meeting Exhibitors

(as of March 26, 2010)

The Teratology Society thanks the following organizations for their participation as Exhibitors at the 2010 Annual Meeting:

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Exhibitor Information

(as of March 26, 2010)

Exhibits and Posters are located in Marriott Ballroom I and will be open at the following times:

Sunday, June 27, 2010 ..... 6:00 PM–8:00 PM
Monday, June 28, 2010 ..... 8:00 AM–7:00 PM
Tuesday, June 29, 2010 ..... 8:00 AM–2:00 PM

All information printed in this exhibitor section is listed in alphabetical order and was submitted by the exhibiting company.

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TERATOLOGY SOCIETY

LECTURE ABSTRACTS

(Presenter designated by underlined author.)

L1

FRUSH D. Duke Medical Center, Durham, NC, United States. Ionizing Radiation Exposure to the Fetus and Infant from Medical Imaging: A Radiologist's Perspective

Radiation exposure from medical imaging during pregnancy and to young children is an increasing public concern, including recent articles in *NEJM* (Aug 2009), *Archives of Internal Medicine* (Dec 2009), and the *NY Times* (Jan 2010). This exposure is a source of great anxiety to parents and other caregivers, healthcare providers, and radiologists as well as other imaging experts. Therefore, it is important to understand several aspects of medical radiation exposure from medical imaging. These include the individual and population radiation doses for imaging examinations, especially CT. For example, the radiation exposure from medical imaging to the U.S. population in the past 30 years has increased six fold and now accounts for 48% of the total exposure, the majority of the remainder accounted for by background radiation. In addition, practice patterns, especially those factors driving imaging, should be recognized. These go beyond "indicated" examinations, and include influences such as industry marketing, pressures resulting in defensive medicine, and public expectations. In addition, it is essential to understand the debate over the risks to both fetus/embryo and young child from medical radiation. In pregnancy, for example, there is essentially no risk of abortion, major organ malformation, or cognitive impairment from a single or even up to a few abdomen/pelvis CT examinations. The risk of cancer development once the child is born is debatable, is potentially zero, but no more than a very small increase. In the young child, the vulnerability is increased compared with the adult. It is difficult to assign an exact number to the risk however discussion about the range of risks in the literature and the strategies for discussing these risks with parents/caregivers will be provided. Finally, it is helpful to review strategies for managing radiation dose, especially from CT, during pregnancy and young childhood. Strategies that can be adopted by imaging specialists and some of the recent technical improvements and educational efforts (www.Imagegently.org) will be discussed. With the above information, an informed discussion can ensue between healthcare providers and patients and parents/caregivers fostering confidence in the delivery of healthcare, and optimizing diagnostic yield while minimizing risks.

L2

FELDKAMP ML. Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, UT, United States. Gastroschisis: A Journey to Discover the Pieces of the Puzzle

Introduction: Gastroschisis remains an epidemiologic and pathogenetic dilemma. Epidemiologically, gastroschisis is unique among birth defects for its strong association with very young maternal age and its increasing occurrence in recent decades. Many competing pathogenetic views have been proposed. Two paths of inquiry emerge that in the future may converge: recent evidence suggesting infection/inflammation as playing a role and the evidence from animal models suggesting a genetic predisposition. In this talk, I will provide an overview of the existing knowledge of gastroschisis in the context of this recent evidence and our genetic analyses. Methods: We analyzed data from the statewide population-based Utah Birth Defect Network (UBDN). The UBDN is an active birth defect surveillance system that monitors all pregnancy outcomes for any identified major structural birth defect. This study included clinically well-characterized case-infants meeting strict criteria for gastroschisis born between 1997 and 2008. Gastroschisis cases were linked with the Utah Population Database to determine the relatedness within the case group using the familial standardized incidence ratio. Results: Over the 12-year period, the prevalence of gastroschisis has increased 26%. Of the 284 cases of gastroschisis, 245 (86.3%) were isolated defects and 39 (13.7%) were multiple (unrelated defects). Among all cases, two (0.7%) infants had the amyoplasia/arthrogryposis association and one infant had a paracentric inversion of chromosome 5 with a unique split hand malformation. From these data, we observed a total of seven (2.5%) families with more than one affected family member: three families with two affected siblings each; a distant cousin; a paternal uncle; a maternal half-uncle; and a paternal cousin. After linkage, we detected unrelated pedigrees each with their own common founder: two large kindreds with five cases, several with four and many with three cases of gastroschisis. Discussion: These findings suggest that gastroschisis is etiologically heterogeneous and has a higher occurrence in families than previously documented. We posit that genetic susceptibility may be a more significant factor in gastroschisis and requires further investigation.

L3

FOSTER PMD. National Toxicology Program, NIEHS, Research Triangle Park, NC, United States. The Cons of the Extended One - Generation Study Protocol

A new design for the evaluation of the reproductive toxicity of pesticides and chemicals (the extended 1-generation study) is currently being evaluated for adoption by OECD to replace the multigeneration reproduction study (OECD 416). This new design is based on a paper[1] that incorporates several cohorts of animals to evaluate reproduction, developmental immuno- and neurotoxicity. The current version (# 28) of the draft guideline has attempted to address many of the criticisms voiced in the 2008 Teratology Society debate, but still has a number of weaknesses compared to OECD 416, particularly the use of triggers to produce the F_2 generation. One of the major drivers for the change arises from the number of animals employed to fulfill current testing requirements under REACH legislation in Europe. The current 416 guideline needs improvement to ensure that it has sufficient power to detect post-natal developmental effects and animals are used more effectively and efficiently in the protection of public health. The NTP recently modified its default approach for the rat cancer bioassay by incorporating a perinatal exposure period (gestation, lactation and puberty) into the 2-year design that starts treatment with animals at 5-6 weeks of age. A cancer bioassay would normally require a prior sub-chronic toxicity study with the same exposure paradigm, for basic toxicity information and dose level setting that can stand alone, or be adapted for a reproductive study. This NTP alternate design focuses evaluations on the F_1 animals with continuous exposure during the study. The design commences with timed pregnant animals, routinely breeds the resulting F_1 offspring and also incorporates cohorts of F_1 animals for examination of other developmental toxicities. This approach would maximize the use of animals produced, maintain a 10 week pre-breed period, to ensure that male germ cell effects could be noted as a functional change, and increases the power to detect potential developmental effects on the reproductive system. The total number of animals used would be considerably less than a multigeneration study and similar to the OECD proposal, but produces more information on developmental outcomes. [1]Cooper, R. L., *et al* (2006). Crit Rev Toxicol 36, 69-98.

L4

PIERSMA AH[1,2]. [1]RIVM, Bilthoven, Netherlands, [2]IRAS, Utrecht, Netherlands. The Extended One-Generation Reproduction Toxicity Study: Improving Hazard Assessment and Saving Animals?

For three decades the two-generation reproductive toxicity study (OECD416) has been the standard protocol of choice in the assessment of reproductive hazards of chemicals. This is the only globally agreed protocol assessing effects throughout the entire reproductive cycle. The F2 generation enables the study of functional fertility of the F1 generation which has been exposed from conception onwards. VanderJagt calculated that over 35% of experimental animals in REACH would be spent on this study protocol. Cooper published an extended one-generation study design, presented as an alternative to the two-generation study without reducing the information level essential for risk assessment. The protocol included additional assessment of developmental immunotoxicity and neurotoxicity, enhancing data collection efficiency and including novel end points of concern. This alternative design reduces animal use around 40%, and cost and time, the latter being of importance in view of the timelines of REACH. Janer (RIVM) published a study of the impact of the second generation offspring (F2) on the conclusions of the two-generation study, based on a retrospective analysis of available data of 176 two-generation studies. Surprisingly, in none of these studies the F2 generation had an impact on Classification & Labelling or on Risk Assessment. Our analysis could be biased by the limited availability of studies. In a similar study, USEPA came to similar conclusions (Martin). In 2008, an OECD Expert Group discussed the extended one- generation protocol and decided that a comprehensive analysis of past experience with the two-generation study should be performed before general conclusions on the necessity of studying the F2 generation could be made. This comprehensive analysis is currently ongoing as a collaborative effort between NL, US, DE and CA using the US-EPA ToxRef database as the central repository. The outcome will impact on the choice between principle *versus* pragmatic approaches in reproductive toxicology hazard assessment. Van der Jagt, *et al*., Report EU21405EN, 2004. Cooper, *et al*., *Crit.Rev.Toxicol*. 36: 69-98, 2006. Janer, *et al*., *Reprod. Toxicol*. 24: 97-102, 2007. Martin *et al*., *Tox Sci.* 110(1), 181-190, 2009.

L5

Greene RM. University of Louisville Birth Defects Center, Department of Molecular Cellular and Craniofacial Biology, ULSD, Louisville, KY, United States. Palate Development: Molecular Perspectives and Current Understanding

When compared with the development of other organs, development of the secondary palate appears deceptively simple—which is why a naive graduate student of Dave Kochhar's decided that the 'palate' and not the "far more complex" limb bud would be the experimental system he would study… little did I know! While genetic predisposition contributes significantly, the complex morphogenetic events that coordinate the development of the orofacial region account, in large measure, for the sensitivity of this region to malformation. Indeed, 1% (≈1 million) of the infants born worldwide each year exhibit some form of facial dysmorphology. Such complexity is underscored by the current recognition that normal development of the palate involves the interactions of numerous cell populations, and the coordinate integration of multiple cellular signal transduction pathways. These include the cAMP/PKA/CREB axis, and FGF, BMP, MAPK, TGFß, Wnt and Rb signaling pathways. A variety of genetic approaches involving both human populations and animal models have identified numerous genes critical to orofacial development. Moreover, it is understood that an interplay between genetic and environmental factors contributes to the etiology of developmental abnormalities including those of the orofacial region. It is now recognized that the intrauterine environment of the developing embryo/fetus, via acquired epigenetic 'marks,' plays a critical role in the determination of predisposition to many adult diseases. DNA methylation, remodeling of chromatin, and the function of miRNAs represent the means by which epigenetics transforms genetic homogeneity of the organism into functional cellular and tissue diversity. Recent studies have enabled the emergence of the concept that miRNAs, regulators of over 30% of protein coding genes, play a key role during orofacial development by regulating multiple signal transduction pathways. Using miRNA microarray technology, unique expression signatures of hundreds of miRNAs in embryonic orofacial tissue have been defined. Gene targeting and functional analysis revealed that the expression of numerous protein-encoding genes, crucial to normal orofacial ontogeny, may be regulated by specific miRNAs. Moreover, genes governing cell cycle progression, metabolism of extracellular matrices, epithelial–mesenchymal transformation, apoptosis and cell migration—all processes critical to normal development of the palate—appear to be regulated by specific differentially expressed miRNAs in embryonic palatal tissue. Thus, this "deceptively simple" system has turned out to be far more complex than most anyone imagined. The currency of science is originality in ideas. Over the years many investigators have expended this currency to provide us with an enlargement of our understanding of the molecular events attendant to normal as well as abnormal development of the palate. Their efforts have provided us with insight into the fascination that is the developing embryo. Supported in part by NIH grants DE018215, HD053509, and P20 RR017702 from the COBRE program of the NCRR.

L6

HOLMES LB. MassGeneral Hospital for Children, Boston, MA, United States. Human Teratogens: Update 2010

Background: Unfortunately "new" human teratogens continue to be identified. To recognize these, the health care professional needs good sources of information and a working knowledge of the characteristics of a teratogen. Methods: A teratogen is defined as an exposure during pregnancy which has a harmful effect on the fetus. The characteristics include: 1) a significant increase in a specific outcome; 2) a dose-response relationship; 3) a period of greatest sensitivity during pregnancy; 4) a biologically plausible mechanism of action, which may be based on experimental studies; 5) theoretically, a genetically more susceptible group of exposed individuals. Results: The information sources include published literature, textbooks and reference books, such as TERIS, Reprotox, Shepard's Catalog and Drugs in Pregnancy and Lactation. Telephone based services, like OTIS and ENTIS Centers, provide valuable counseling for the concerned woman and her health care providers. There are several current unresolved concerns about potential teratogenicity that require further study, such as the potential fetal effects of SSRIs, assisted reproductive technologies and tumor necrosis factor-alpha. Some exposures, like misoprostol and mycophenolate mofetils, are recognized teratogens, but the risk of a fetal effect from an exposure has not been established. For most teratogens, there are major deficiencies in the information available: 1) the cellular and molecular basis of the fetal effect is not known; 2) the genetic basis for susceptibility has not been established. For potential airborne or dermal exposures of concern, there is too little information available. Pregnancy registries are a new source of information on fetal risks, which would benefit from the formation of a national resource center for standards and guidance. One major problem in counseling is the serious inaccuracy of the Drug Categories A, B, C, D and X in the Physicians' Desk Reference and the fact that most physicians and nurses are not aware of this inaccuracy. The new narrative summaries, promised by FDA, will be very helpful. Conclusions: There is a need for better use of the information available on human teratogens in the counseling of pregnancy women. Too little teaching is provided to physicians, nurses, and counselors in training.

TERATOLOGY SOCIETY

SYMPOSIUM ABSTRACTS

(Presenter designated by underlined author.)

Vitamin B_{12} and Neural Tube Defects: Is It Time to Fortify Food with B_{12} Symposium

S1

MILLS JL. Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD, United States. Vitamin B_{12} Deficiency and NTDs: Is There a Causal Relationship?

More than 20 studies have examined the relationship between maternal vitamin B_{12} levels and the risk for neural tube defects (NTDs). The majority have found that low maternal B_{12} is associated with an increased risk. Most studies, however, have serious limitations. These include that the women were not studied during pregnancy, that the number of subjects was too small to answer the question, that folate levels (a major risk factor) were not adjusted for, that samples were collected in case and control subjects at different time intervals from neural tube closure, that obesity and mendelian defects were not considered, and that prenatal vitamins were started between the time of neural tube closure and the time of sample collection. Few studies avoided all or even most of these problems. The best studies provide some support for the claim that women who have low B_{12} levels are more likely to have affected babies and that women in the deficient range are at greatest risk. This is biologically plausible because vitamin B_{12} interacts with folate, a well documented risk factor, as a cofactor for methionine synthase in the conversion of homocysteine to methionine. Insufficient B_{12} leads to the trapping of folate as 5 methyl-folate and functional deficiency of folate in all pathways. It is also noteworthy that only a small amount of B_{12} is required for this function, hence women with low or frankly deficient levels would be the most likely to be affected. Nonetheless, it is premature to assume that a causal relationship between low B_{12} levels and NTDs has been established. Low B_{12} levels may be a marker for generally poor nutrition and low folate may be the true causal factor. B_{12} may only be important in societies where B_{12} in the diet is limited or in populations at high risk for poor B_{12} status such as vegans who do not take supplements. In summary, there is insufficient evidence to recommend fortifying food with B_{12} in the USA and a randomized trial is needed to resolve the issue if such a trial is feasible. Funded by the Intramural Research Program, NICHD.

S2

CARMEL R[1,2]. [1]New York Methodist Hospital, Brooklyn, NY, United States, [2]Weill Medical College of Cornell University, New York, NY, United States. Normal Vitamin B_{12} Physiology, the Pathophysiology of B_{12} Deficiency, and Their Relevance to Treatment and Fortification

The unusual physiology of cobalamin (vitamin B_{12}) imposes both advantages and disadvantages that, unsurprisingly, create complex pathophysiologies of B_{12} deficiency. Few parallels and little guidance are available from the simpler physiology of folic acid. The following narrative of B_{12} physiology, pathophysiology, and their consequences is arranged to provide context for thinking about fortification. (1) B_{12} physiology and bioavailability: Because daily losses are <0.1% of body stores, only years, not months, of unwaveringly poor intake of animal-related foods can achieve even modest depletion. Absorption, reabsorption, transport, and cellular uptake depend virtually exclusively on specific carrier-receptor systems. Gastric intrinsic factor (IF) and its intestinal receptors assure high bioavailability (approximately 50%) for normal B_{12} doses. However, capacity and flexibility are limited, and bioavailability falls toward 1% when intake exceeds 1-2 ug even in normal persons (eg, supplements). (2) Clinical deficiency: Bioavailability virtually disappears whenever disease inactivates any part of the IF-receptor dyad [eg, pernicious anemia (PA), which affects 1.9% of the elderly]. Usually, only such severe malabsorption can guarantee progression of depletion to anemia or neurocognitive dysfunction. It explains 94% of all clinically apparent B_{12} deficiencies. (3) Subclinical B_{12} deficiency: This deficiency, typically featuring mild biochemical changes without anemia or symptoms, in contrast, affects 10-20% of the elderly (ie, >5 times the frequency of PA). Because it usually features normal absorption or only partial malabsorption (eg, limited to food-bound B_{12}), subclinical B_{12} depletion fluctuates or progresses very slowly, if at all, to clinical deficiency. Moreover, neurologic progression in the face of high folic acid intake has been described only in PA and is undocumented in subclinical deficiency. (4) B_{12} supplementation and fortification: Whereas serum B_{12} improves after small oral B_{12} doses in normal persons with normal B_{12} absorption (who do not need B_{12}), persons with severe malabsorption (>94% of clinical deficiencies) or mild malabsorption (30-40% of elderly with subclinical deficiency) who require B_{12} are unlikely to respond without several-hundredfold higher doses. Moreover, the health consequences of subclinical deficiency, its likelihood to progress to clinical deficiency, its susceptibility to neurologic risks from high folic acid intake, and its benefits from B_{12} treatment are untested.

S3

OAKLEY, JR. GP. Rollins School of Public Health of Emory University, Atlanta, GA, United States. Should FDA Require Vitamin B_{12} Fortification of Enriched Flour? Yes

Twenty year ago a study of the Framingham cohort found that forty per cent of the participants over 60 years of age had biochemically defined vitamin B_{12} deficiency. For those not taking a vitamin supplement, the percentage was 50 percent and it was reduced to 17% for those taking a vitamin supplement with a median B_{12} content of 6 micrograms. Many studies have been published to show biochemically defined B_{12} deficiency to be high in people 60 and over and to show that consuming a low dose of vitamin B_{12} in supplements markedly reduces the biochemically defined B_{12} deficiency. These findings led the Institute of Medicine/Food and Nutrition Board to recommend all persons 50 and over consume 2.4 micrograms of synthetic vitamin B_{12} from vitamin supplement pills or from fortified foods. Since the recommendations, bread made from flour with low doses of vitamin B_{12} has been shown to increase serum vitamin B_{12} concentration in persons 60 and over with biochemical deficiency. Folic acid fortification of flour has shown flour fortification to be a proficient way to have the total population consume a similar amount of a B vitamin. FDA should require vitamin B_{12} fortification now. When vitamin B_{12} fortification is done, it will prevent/cure 70 per cent of biochemically defined B_{12} deficiency and is likely to improve our ability to find people with early or preclinical pernicious anemia-a cause of B_{12} deficiency that may progress to serious clinical disease if not diagnosed early and treated for life with much higher doses of vitamin B_{12} than would be consumed from products made with fortified flour.

S4

GREEN R. University of California Davis Medical Center, Sacramento, CA, United States. Should We Fortify Food with Vitamin B_{12} Now? No

Introduction: Folic acid fortification of the diet was introduced in the US in 1998 to reduce the incidence of neural tube defect (NTD) pregnancies. This initiative was based on primary interventional studies linking improved folate status to reduced NTD incidence. This program has been highly successful although NTD pregnancies have not been eradicated. More recently, an initiative to consider fortifying flour with vitamin B_{12} (B_{12}) has gained momentum. The impetus for this stems from evidence that some NTD pregnancies may be the result of B_{12}rather than folate deficiency. Other reasons put forward for B_{12} fortification include the high prevalence of B_{12} deficiency among the elderly and in some countries, among pregnant women and the young as well. The question is unanswered as to whether B_{12} fortification will further reduce NTD incidence or ameliorate any morbidity associated with B_{12} deficiency. Discussion: Unlike folic acid, there is no evidence showing efficacy of B_{12} supplementation or fortification in the prevention of NTD pregnancies. Much of the apparent deficiency of B_{12} is subclinical and not associated with manifest morbidity. Moreover, individuals affected by clinically evident B_{12} deficiency associated with morbidity would not benefit from practical levels of B_{12} fortification that are under consideration. This is because deficiency is generally not a consequence of inadequate intake of B_{12} but results from malabsorption of the vitamin due to dysfunction of the normally efficient physiological mechanism for B_{12} absorption. Efficiency of absorption of B_{12} in the form of supplements, or added to food in fortification programs is poor (ca 1%) under these conditions. While reported toxic effects of supplemental vitamin B_{12} are rare and a safe upper limit for the vitamin has not been defined, recent data suggests that B_{12} may undergo partial degradation in the gastrointestinal tract with the generation of B_{12} analogues, the effects of which have not been fully characterized. Additionally, there is some evidence that as in the case of folic acid, supplemental B_{12} may result in progression of cancers. Consequently, at this time it is reasonable to conclude that fortification of the food supply with B_{12} may be premature.

Joint TS/NBTS/OITS Symposium
Reproductive Psychiatry

S5

OBERLANDER TF. University of British Columbia, Vancouver, BC, Canada. Prenatal SRI Exposure: Where Does Neonatal Behavioral Syndrome End and Neurobehavioral Teratogenicity Begin?

Prenatal exposure to depressed maternal mood and serotonin reuptake inhibitor [SRI] antidepressants may be one of the earliest adverse life events. Both are associated with neonatal behavior disturbances. While symptoms are typically self-limited, the underlying mechanisms and long-term sequelae are unknown. While, SRI-exposure related risk may differ from the effects of maternal depression alone and appear to be modified by genotype for the serotonin transporter gene (SLC6A4), it remains unclear whether adverse outcomes also reflect increased drug levels, suppressed monoamine neurotransmitter levels, or reflect long term gestational changes in brain development related to altered central serotonergic tone. This session will focus on recent data illustrating how we might begin to distinguish neonatal behavioral disturbances from SRI related neurobehavioral teratogenicity.

S6

SALISBURY AL. Women and Infants Hospital, Alpert Medical School of Brown University, Providence, RI, United States. Messages From the Womb: Maternal Antidepressant Use and Fetal Neurobehavior

Major Depressive Disorder (MDD) occurs in at least 10-15% of pregnant women, with greater than 30% of affected women choosing to take antidepressant medications for treatment. Although some data exists about the effects of these medications in the newborn, little is known about fetal behavior during the exposure. Data from 158 pregnant women, ages 18 to 40 will be presented examining neurobehavioral development of fetuses prenatally exposed to maternal MDD and/or antidepressant medications. Women were interviewed for current and past psychiatric history using a semi-structured interview (SCID-IV-NP). The timing of exposure to medication and psychiatric illness as well as drug doses of SRIs was recorded on a graphic timeline. Fetal neurobehavior was recorded at 26 and 36 weeks gestational age (GA) using ultrasound and fetal actocardiograph monitoring for 60 minutes (40 min baseline, 3 sec stimulus, 20 min post-stimulus). Ultrasound video recordings were played back in the lab and scored in 10 second epochs for the presence of fetal behaviors (Salisbury et al 2005) using the Mangold Interact coding software (Germany). Newborn neurobehavior was then examined at 24-48 hours after delivery. Analyses were conducted using 2 (SRI) X 2 (MDD) ANCOVA's, forming 4 groups: a no-exposure control group, a SRI-exposed, no MDD group, a Major Depression/No SRI group and a group with both exposures (SRI+MDD). This talk will discuss results of this study for fetal and infant data. These findings will be discussed in terms of the larger dataset from this study including fetal heart rate and infant neurobehavioral measures.

S7

VIGUERA AC. Cleveland Clinic, Cleveland, OH, United States. An Update on Lithium Treatment during Pregnancy and Lactation

Background: Challenges for the clinical management of bipolar disorder (BD) during pregnancy are multiple and complex and include competing risks to mother and offspring. Method: In this oral presentation, we will review research findings on the reproductive safety data of lithium as well as recent data on its use during lactation. Results: Pregnancy, and especially the postpartum period, are associated with a high risk for recurrence of BD. This risk appears to be limited by mood-stabilizing treatments like lithium and the risk is markedly increased by the abrupt discontinuation. Medications used to treat or protect against recurrences of BD vary markedly in teratogenic potential: there are low risks with typical neuroleptics, moderate risks with lithium, higher risks with older anticonvulsants such as valproic acid and virtually unknown risks with other newer-generation anticonvulsants and atypical antipsychotics (ATPs). We will focus our discussion on lithium, one of the oldest and best know teratogens, and review changes in teratogenic risk estimates over past 50 years as well as discuss recent nursing data. Conclusions: Clinical management of BD through pregnancy and postpartum calls for balanced assessments of maternal and fetal risks and benefits. Lithium should be considered a first line treatment option during pregnancy and should not be viewed as an absolute contraindication during nursing.

S8

MILNER TA[1,2], TORRES-REVERON A[4], EINHEBER S[3]. [1]Weill Cornell Medical College, New York, NY, United States, [2]The Rockefeller University, New York, NY, United States, [3]Hunter College, New York, NY, United States, [4]NOVA Southeastern University, Ponce, Puerto Rico. Effects of Developmental Exposure to Methylphenidate on Brain Areas Involved in Cognition, Motivated Behaviors, Appetite and Stress

Introduction: Methylphenidate (MPH; Ritalin) is commonly prescribed to children to relieve symptoms of attention deficit/hyperactivity disorder (ADHD). Methods: To model exposure to MPH during early development, male rats were injected with MPH (5mg/kp, I.P.) or saline twice daily from postnatal day (PND) 7-35. At the end of administration (PND35) or in adulthood (PND135), sections through the entire brain were analyzed for transmitters or cytological markers implicated in MPH effects and/or ADHD etiology. Results: At PND35, (1) the distribution of catecholamine fibers was altered in the medial prefrontal cortex, hippocampus and striatum, (2) the density of neuropeptide Y was increased in hypothalamus, (3) the processes of newly generated cells were expanded in the hippocampus and (4) the numbers of myelinated fibers were reduced in the corpus callosum. At PND135, these brain differences were no longer apparent; however, the MPH rats had decreased anxiety levels in behavioral tests. A separate cohort of rats was exposed to stressful conditions during the 2003 New York City blackout on PND76 and similarly studied at PND135. This cohort was slower in regaining weight the week following the blackout and, at PND135, had more ectopic granule cells in the hippocampus and elevated systolic arterial pressure. Discussion: These findings indicate that early postnatal exposure to MPH can have long lasting effects in brain regions involved in cognition, motivated behaviors, appetite and stress and can affect reactivity to stress in adulthood.

Update on Thalidomide Symposium

S9

MILLER MT. University of Illinois at Chicago, Department of Ophthalmology and Visual Sciences, Chicago, IL, United States. Thalidomide Embryopathy: Ophthalmological Findings and a Few Surprises

Introduction: Thalidomide is a very potent teratogen capable of causing severe systemic malformations in the embryo when exposed during the sensitive period. Although structural anomalies of the eye can occur from thalidomide exposure, the most frequent eye complication is secondary to damage to the cranial nuclei in the brain stem, resulting in aberrant neurological connections causing a condition of abnormal ocular movement, Duane Syndrome. Less frequent anomalous neurologic complication is tearing when eating (paradoxical gustolacrimal tearing, "crocodile tears"). Involvement of the 6th and 7th cranial nerves is common in these patients. Methods: Two studies were performed in Sweden to describe the ophthalmologic and systemic association noted in individuals with known thalidomide embryopathy born in the years 1959-1962. The first study (1987-1989) was a prospective study of 86 of an estimated 100 known thalidomide-affected patients living in Sweden. The diagnosis of thalidomide embryopathy had usually been made when they were children. A general history, a superficial systemic evaluation and a complete ophthalmologic evaluation were performed as the study focused on eye anomalies. The second study (2006, 2007) was a multidiscipline study of a subset of patients from the original study and a few identified later. Results: The common ophthalmologic findings were abduction deficit, usually Duane Syndrome (44%), facial nerve palsy in 17 (20%), and aberrant tearing in 17 (20%). Only a few structural eye malformations were noted (coloboma in 4 patients and microphthalmia in 3 patients). An unexpected finding was autism in 4 individuals and the large number (17) of individuals with aberrant tearing. By comparing the observed malformations and dysfunctions in the study patients to the timetable of sensitive periods available in the literature of malformations, it was concluded that Duane Syndrome, aberrant tearing, autism, and facial nerve palsy all occurred in the early sensitive period (day 20-24) followed by structural malformations of the eye at a slightly later time. Discussion: The early part of the sensitive period for thalidomide embryopathy is characterized by cranial nerve involvement, ear and thumb anomalies or dysfunction. The ocular problems were primarily ocular motor disturbances and aberrant tearing.

S10

ALLARD P, GALLOWAY JL, TABIN CJ. Harvard Medical School, Genetics, Boston, MA, United States. Recent Advances in Understanding the Developmental Basis of Phocomelia

Phocomelia is a devastating, rare congenital limb malformation in which the long bones are shorter than normal, with the upper portion of the limb being most severely affected. In extreme cases, the hands or fingers are attached directly to the shoulder and the most proximal elements (those closest to the shoulder) are entirely missing. This disorder, previously known in both autosomal recessive and sporadic forms, showed a dramatic increase in incidence in the early 1960's due to the tragic toxicological effects of the drug thalidomide, which had been prescribed as a mild sedative. This human birth defect is mimicked in developing chick limb buds exposed to X-irradiation. Both X-irradiation induced and thalidomide-induced phocomelia have been interpreted as patterning defects in the context of the Progress Zone Model for proximodistal patterning. Indeed, studies of X-irradiation induced phocomelia have served as one of the two major experimental lines of evidence supporting the validity of the Progress Zone Model. Here, using a combination of molecular analysis and lineage tracing, we show that X-irradiation-induced phocomelia is fundamentally not a patterning defect, but rather results from a time-dependent loss of skeletal progenitors. As skeletal condensation proceeds from the shoulder to finger tips (in a proximal to distal direction), the proximal elements are differentially affected in the limb buds exposed to radiation at early stages. This conclusion changes the framework in which one must consider the effect of thalidomide and other forms of phocomelia, suggesting that the etiology lies not in a defect in the patterning process, but rather in progenitor cell survival and differentiation. Moreover, molecular evidence that proximodistal patterning is unaffected following X-irradiation directly contradicts the predictions of the Progress Zone Model.

S11

STEPHENS TD. Idaho State University, Pocatello, ID, United States. Lessons Learned from the Thalidomide Epidemic and the Current Hypotheses of the Possible Mechanisms of Action

Before the thalidomide disaster, it was clear that environmental factors, including drugs, could cause congenital defects. The scope and scale of such effects, however, had not been previously appreciated. Sydney Gellis stated in the 1964-1965 *Year Book of Pediatrics*, "Stimulation provided by recent events will cause more interest in congenital malformations and their possible environmental causes." Another major lesson learned from the thalidomide disaster, perhaps one of the most important, is the value of one person in recognizing a developing epidemic of birth defects and preventing the disaster from becoming even greater: people like the German attorney Karl-Hermann Schulte-Hillen who first brought the epidemic in Germany to the attention of Dr. Widukind D. Lenz who made the connection between the epidemic and thalidomide; people like Dr. William McBride, in Australia, who had also made the same connection; and people like Dr. Frances Kathleen Oldham Kelsey, who single-handedly prevented a far greater disaster by keeping thalidomide off the US market. Another important set of lessons to be learned from the disaster is that neither thalidomide nor its victims have gone away. Although thalidomide has a relatively simple chemical structure its actions are numerous and diverse. There are numerous current hypotheses of the possible mechanisms of action. It appears very likely that the birth defects were the result of several mechanisms working synergistically.

March of Dimes Symposium
Herbal Supplement Usage during Pregnancy
Organized by the Public Affairs Committee

S12

MILLER RK[1], BITTNER P[1]. [1]University of Rochester, Rochester, NY, United States, [2]U.S. Consumer Product Safety Commission, Washington, DC, United States. Herbal Usage during Pregnancy: Teratology Society White Paper

Herbal products have been widely marketed in the United States and internationally by many manufacturers and distributors. The usage of herbal products has grown to be a multi-billion-dollar enterprise. Many pregnant women are consuming these herbals in hope that there is benefit to themselves and their babies in these "natural" products. Unfortunately, there is marginal to no evidenced based medicine associated with many of these preparations. Further, regulation of purity and exact amounts of active ingredients are often lacking or may be inaccurate. Because pregnant women are being exposed to not only variable amounts of the herbals but in a number of preparations to heavy metal and other contaminants, the Teratology Society has developed a white paper on this subject to encourage appropriate usage of these herbal products during pregnancy. As in the 1987 Teratology Society White Paper on Vitamin A Usage During Pregnancy (*Teratology*, 1987), it is hoped that manufacturers, governmental regulatory agencies, and the medical community will cooperate to provide women who are pregnant or plan to be the opportunity to make well informed and safe decisions about the usage of herbal preparations in their multiple forms. Guidelines and Recommendations from the Teratology Society White Paper on Herbal Usage during Pregnancy will be presented for discussion. (This White Paper is developed through the efforts of the Teratology Society Drafting Committee, Public Affairs Committee, and the many consultants asked to share their insights and recommendations. We thank all of these dedicated individuals for their collective efforts in bringing this White Paper to reality.) (This paper has not been reviewed or approved by and does not reflect the views of the US Consumer Product Safety Commission.)

S13

HESS H, MILLER R. University Of Rochester, Rochester, NY, United States. Herbal Preparations Usage and Pregnancy

Surveys show that nearly 50% of women use herbals prior to and during pregnancy. They take herbals to ensure that they are healthy before and during their pregnancies. But data are limited concerning the efficacy and especially the safety of these preparations in general, but especially for mother and fetus. Healthcare providers do not have sufficient authoritative resources to advise pregnant women who take herbals. The difficulties in evaluating the safety of herbals are enhanced in pregnant women because the risks are even more difficult to evaluate. The problems of determining the safety of herbals in pregnant women or in women intending to conceive are examined. A complete review of the medical as well as traditional literature was performed to assess the best evidence available to counsel pregnant patients concerning their use of herbals. Limitations on evidenced-based data are detailed. Based on the best evidence available on the commonly used herbals during pregnancy, these herbals are divided into five categories to enhance understanding the safety of herbals during pregnancy, and to assist the provider to better counsel a pregnant woman. The five groups are: 1. Herbs used as foods. 2. Essential oils considered safe during pregnancy. 3. Herbs frequently used during pregnancy which are considered safe. 4. Herbs controversially used during pregnancy. 5. Herbs contraindicated during pregnancy. Herbs in each of these groups that are commonly used during pregnancy are listed, their common usage, doses, and evidence regarding safety is presented. There are other significant differences between herbal preparations and pharmaceuticals. The form of the herb [teas or infusions, capsules, dried extracts, and tinctures] the dose of the contents and the integrity of the dose and other contents of the preparations - as well as its purity and certification of purity, are all extremely important. Recommendations to deal with these issues are offered for the pregnant and potentially pregnant and provider. The importance of selecting safe brands is discussed. The importance of increased awareness for the pregnant consumer in assessing the risks of herbal preparations during pregnancy is stressed.

S14

OBERMEYER WR. ConsumerLab.com, White Plains, NY, United States. Herbal Products: Are They What They Claim to Be?

Recently published survey data indicated that ~10% of US women have used herbal products just prior to or during pregnancy. While the general public assumes that "natural" is good, scientific literature and the popular press continually highlight instances of poor quality control, misidentification, and the presence of contaminants in herbal/dietary supplements. Moreover, very little is known about the risks associated with herbal product consumption during pregnancy. Even with the recently implemented Good Manufacturing Practices (GMP) specific to dietary supplements, consumers cannot be assured that they are purchasing safe dietary supplements that have been properly identified, provide the quality or ingredient levels declared on the label, or are free of contamination. Finished product testing has shown mixed trends in product quality with respect to heavy metal, pesticide, and/or microbial contamination, along with herbal misidentification and adulteration. There is a clear need for independent testing and product vigilance to educate health care providers and consumers of the potential risks associated with herbal/dietary supplement products during pregnancy.

S15

Koren G. Motherisk Program, Toronto, ON, Canada. Herbal Drugs in Pregnancy: A Canadian Perspective

Similar to other developed countries, large numbers of women use complementary-alternative medicine (CAM), with herbal products topping the CAM practice in Canada. Every year thousands of pregnant and planning mothers are counseled in pregnancy about these products by us. While safety of several leading herbals have been studies by us (including Echinacea, Ginger, St John's Wort), little has been done on the use of herbals during labor, as emenagogues. In 2004 Health Canada inaugurated a new Branch dealing with the regulation of Natural Products, setting criteria for the process, putting safety as its first objective. Yet, similar to medicinal drugs, very little emphasis on safe use in pregnancy has been demanded at this time. This presentation will highlight the major trends of these initiatives in Motherisk, and in Canada in general.

S16

BRENT RL. Jefferson Medical College and DuPont Hospital for Children, Wilmington, DE, United States. Traditional Chinese Medicine: Herbal Medicine Origins and Utilization in China

In mainland China, medical schools that teach traditional Chinese medicine and allopathic medicine continue to thrive. In the traditional schools there is more of an emphasis on the prescribing of herbal medicines. Not all herbal medicines are herbal. i.e. bile from a reptile's gall bladder or Antelope horns which are used in traditional Chinese medicine as an aphrodisiac. Traditional Chinese medicine focuses on restoring a balance of energy, body, and spirit to maintain health rather than treating a particular disease or medical condition. Because of the large number of Chinese herbs used and the different uses recommended by practitioners, it is difficult to comment on Chinese herbal medicine as a whole. There may be some individual herbs or extracts that play a role in the prevention and treatment of cancer and other diseases when combined with conventional treatment. However, more research is needed to determine the effectiveness of these individual substances. Chinese herbal medicine uses a variety of herbs in different combinations to restore balance to the body, such as astragalus, ginkgo, ginseng, green tea, and eleuthero. Herbal preparations are said to prevent and treat hormone disturbances, infections, breathing disorders, and a vast number of other ailments and diseases. Some practitioners claim herbs have the power to prevent and treat a variety of types of cancer. Most Chinese herbalists do not claim to cure cancer. In China, more than 3,200 herbs and 300 mineral and animal extracts are used in more than 400 different formulas. Herbal formulations may consist of 4 to 12 different ingredients, to be taken in the form of teas, powders, pills, tinctures, or syrups. During a one month visit to China regulatory agencies and both types of medical schools were visited. There was intense interest on the part of the foreign visitors concerning the process of approval of a new preparation which turned out to be a combination of academic politics and science. Efficacy and safety are not emphasized, probably because the multiple contents of each preparation are frequently present in homeopathic concentrations. Finally, displays of symptoms and therapies that are presented for educational purposes in the medical schools will be presented.

S17

ORNOY A. Hebrew University Hadassah Medical School and Israeli Ministry of Health, Jerusalem, Israel. Herbal Preparations: Are We at the Beginning of Regulations? The Situation in Europe and the Eastern Mediterranean Region

In contrast to drugs, where dose and purity are always known, herbal products are only partially quantified, and there is little reinforcement of rules regarding their exact composition, quantity, effectiveness and safety. Hence, the WHO suggested in 1978 to create special rules for the use of herbal products, as done with drugs, and in 1991 published their recommendations. In 2005, the WHO published a global survey on the state of herbal medicines. There are large differences in the use of herbal products among different European countries. For example, there is widespread use of such products in Germany and France, where health insurance subsidizes some of the costs, while in the UK there is little use of herbal products as there is no reimbursement by health insurances. The European Community also published in 1999 its Food and Drug Law on commercial herbals, recommending the same regulations as for drugs, but coincidently approving the preparations for which there are data that demonstrate they are harmless and efficient. Only a few European countries tried to implement these recommendations. Overall in Europe, herbal products are considered food additives, with "loose" regulations. However, in several of the Eastern Mediterranean region countries (i.e. Egypt, Jordan) there is a commitment for research and for the development of strict rules regarding comparisons with regulated drugs, and in these countries many of these preparations also appear in the pharmacopoeia and are prescribed mainly by doctors. Even there, herbal products are mainly sold over the counter (OTC). In other countries (i.e. Afghanistan, Bahrain) there are no regulations. In Israel, herbal products are treated as food additives and sold OTC. Pregnant women tend to use herbal products because they are thought to be safe, although their safety for the developing embryo and fetus or for the pregnant mother has not been established. The "easy" escape is to avoid their use in pregnancy and lactation. However, this is difficult since herbal preparations are used widely by pregnant women and they are perceived to be effective.

Joint TS/NBTS Symposium
Advancing Neurodevelopment

S18

MAKRIS SL, BALE AS, RAFFAELE KC. U.S. EPA, ORD, NCEA, Washington, DC, United States. The Use of Neurodevelopmental Data in Children for Risk Assessment of Environmental Chemicals

A number of environmental chemicals are known to target the nervous system, with the potential to elicit perturbations during critical windows of nervous system development. A review of the US EPA Integrated Risk Information System (IRIS) database was conducted to evaluate the impact that studies assessing neurodevelopmental endpoints in children have had on the characterization of hazards resulting from early life stage exposures to specific environmental toxicants. The IRIS program generates publicly available hazard and dose response evaluations of environmental chemicals for human health risk assessment. IRIS assessments include consideration and analysis of epidemiology and animal toxicology data. For non-cancer outcomes, chronic oral and inhalation reference values (RfVs) are derived in accordance with EPA policy, which includes principles and practices described in Agency risk assessment guidelines. Rigorous evaluation of available epidemiological data, including neurodevelopmental assessments in children, is critical to the process of hazard characterization in IRIS documents. Whether such data are used in the final determination of RfVs depends upon a number of factors, such as the relative placement of the study results in the overall toxicological and dose-response profile of the chemical, and an analysis of confidence in the data. To assess the impact of these neurodevelopmental studies, the database of approximately 550 IRIS chemical assessments was surveyed to identify chemicals with data indicating neurotoxic potential. For those assessments that included epidemiological data relevant to neurotoxicity, an analysis was conducted of the characterization and use in risk assessment of any neurodevelopmental evaluations in children. Criteria that were found to qualitatively affect the disposition of the studies in the final hazard assessment included (e.g.) sample size, selection of appropriate testing procedures, and adequate consideration of confounding factors in data assessment. This effort demonstrated that critical consideration of study designs commonly used in neurodevelopmental testing of children for epidemiological research has the potential to improve and refine the assessment of risk for environmental toxicants. The views expressed are those of the authors and do not necessarily reflect the views or policies of the U.S.EPA.

S19

LAKIND JS[1,2], YOUNGSTROM E[4], GOODMAN M[5], SQUIBB K[2], LIPKIN PH[6], ANTHONY LG[7], KENWORTHY L[7], MATTISON DR[8]. [1]LaKind Associates, LLC, Catonsville, MD, United States, [2]University of Maryland School of Medicine, Baltimore, MD, United States, [3]Penn State College of Medicine, Hershey, PA, United States, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [5]Emory University School of Public Health, Atlanta, GA, United States, [6]Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [7]Children's National Medical Center, George Washington University School of Medicine, Rockville, MD, United States, [8]Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, HHS, Bethesda MD, United States. A Multidisciplinary Approach to Advancing the Science of Neurodevelopmental Testing in Cohorts of Infants and Young Children

With published research suggesting that growing numbers of children are affected by an array of neurodevelopmental disorders, questions regarding etiology will continue to be raised. These questions can be addressed in part by well-designed epidemiological studies. The uses of neurodevelopmental function tests in studies of environmental chemicals and pediatric neurodevelopmental disorders have been reviewed, but a comprehensive critical examination of methodologies commonly used in past studies has not been conducted. There are limitations associated with currently used tests; in addition, many available neurodevelopmental tests have not been used in the environmental chemical study arena. In addition, differences in methods for conducting neurodevelopmental epidemiologic studies of environmental chemicals can lead to difficulties in performing weight-of-evidence assessments. Our research team critically reviewed commonly used neurodevelopmental tests in epidemiological studies of associations between environmental chemical exposure and adverse health effects, identified tests that should be considered for use in future studies, and developed guidelines and/or criteria for selection, administration, and interpretation of neurodevelopmental tests in studies of environmental chemical exposures. We developed a series of recommendations to move the field of neurodevelopmental environmental epidemiology forward, including a proposed set of guidelines that can be used to help the design of future studies (similar to what has been done with clinical trials, studies of diagnostic assessment tools, and medical epidemiological studies). Improvements and consistency in study design, test selection, and reporting of results are needed in order for these types of studies to be useful as part of regulatory weight-of-evidence assessments.

S20

KENWORTHY L[1], ANTHONY LG[1], GOODMAN M[2], LAKIND JS[7,8], LIPKIN PH[5], MATTISON DR[6], SQUIBB K[3], YOUNGSTROM E[4]. [1]Children's National Medical Center, Center for Autism Spectrum Disorders; Depts. of Pediatrics and Psychiatry, George Washington University School of Medicine, Washington, DC, United States, [2]Dept of Epidemiology, Emroy University School of Public Health, Atlanta, GA, United States, [3]Dept of Medicine, University of Maryland School of Medicine, Baltimore, MD, United States, [4]Depts of Psychology and Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [5]Center for Development and Learning, Kennedy Kreiger Institute, Dept of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [6]Eunice Kennedy Shriver National Institute of Child Health and Human Dev, Bethesda, MD, United States, [7]LaKind Associates, LLC, Catonsville, MD, United States, [8]Dept of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, United States. Getting the Biggest Bang for Your Buck: Choosing Neurodevelopmental Tests That Maximize Power

Introduction: Review of neurodevelopmental measures used to investigate the effects of polychlorinated biphenyls (PCBs) in children revealed limitations of currently used tests that compromised the power of specific studies to detect potential neurodevelopmental effects of environmental chemicals. We present here test selection criteria for maximizing power to detect effects. Methods: We conducted a critical review of the environmental epidemiology literature on neurodevelopmental effects of PCBs and a needs assessment workshop attended by a multi-disciplinary team of international experts from the public sector and academia. The panel was asked to identify areas where improvements are needed to strengthen the core methodological elements of neurodevelopmental epidemiological studies; and develop recommendations for meeting those needs. Results: Our review of the literature and workshop discussion produced several recommendations, including emphasizing enhancement of power of individual studies to detect effects. For increased power, the following specific test properties are particularly important: Test-retest reliability, or the extent to which tests scores are reproducible when the same person is administered the same test on two different occasions; Inter-rater reliability, or the extent to which scores are reproducible when the same test is administered or scored by different individuals; Concurrent predictive validity or diagnostic efficiency; Exposure sensitivity; Developmental sensitivity, or a well distributed range of scores in typically developing children in the age range to be assessed; For neurocognitive constructs which are poorly operationalized in the laboratory (eg executive function), ecological validity, or the ability for a measure to relate to real world functioning; Breadth or narrowness of the measure in relationship to the neurocognitive function in question. Discussion: The power of investigations in environmental epidemiology to detect effects of exposures on children can be increased through the consideration of the specific tests administered in relation to key criteria.

S21

ANTHONY LG[1], YOUNGSTROM EA[2], KENWORTHY LE[1], LAKIND JS[3], GOODMAN M[4], SQUIBB KS[5], LIPKIN PH[6], MATTISON DR[7]. [1]Children's National Medical Center, GWU, Rockville, MD, United States, [2]University of North Carolina, Chapel Hill, Chapel Hill, NC, United States, [3]LaKind Associates, LLC, Catonsville, MD, United States, [4]Emory University School of Public Health, Atlanta, GA, United States, [5]University of Maryland School of Medicine, Baltimore, MD, United States, [6]Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [7]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Washington, DC, United States. Threats to Study Validity: The Flynn Effect, Examiner Drift, Confounders, Lost in Translation, and Other Important Considerations

Introduction: Concerns regarding the negative impact of environmental factors on neurodevelopment have lead to a large number of epidemiological studies examining associations between *in utero* and neonatal exposures and pediatric neurodevelopmental disorders. A review of specific neurodevelopmental tests used in these studies has identified some limitations in the chosen tests and difficulties with their interpretation. An examination of threats to validity for studies using neurodevelopmental testing to evaluate effects of environmental exposures is essential. Methods: We first conducted a critical review of the environmental chemical exposure literature, which brought several important methodological considerations to the forefront. A needs assessment workshop was held with our interdisciplinary team and invited international experts from the public sector and academia with recognized research experience in experimental neurodevelopmental biology, neurology, neuropsychology, psychology, pediatrics, epidemiology, statistics/methodology, and chemical risk assessment. The panel was asked to identify areas where improvements are needed to strengthen the methodological elements of neurodevelopmental epidemiological studies; and to develop recommendations for meeting those needs. Results: Based on the review of the literature and workshop discussions, the panel recommended developing study design methodological standards to minimize the following threats to validity: The use of tests with outdated norms (accounting for the Flynn Effect); the powerful effects of different examiners, and differences in each examiner over time (e.g., intermittent reliability reviews of administration/scoring standards); the selection of risk and protective factors in environmental studies going beyond demographics and selected confounders. Inclusion of other covariates (e.g., IQ) that are highly correlated with the dependent variable (e.g., language) would further improve estimation of toxicant effects; uncertainties in the degree of measurement equivalence when tests are transported into different languages and cultures; the influence of normal developmental brain changes on the domain of functioning and the stability and predictive validity of test scores. Conclusion: The field of environmental epidemiology is nearing a stage where a formal set of methodological and reporting guidelines could be developed to help in the design of future studies, as has been done with clinical trials, studies of diagnostic assessment tools, and medical epidemiological studies. Supported by Cefic-LRI.

S22

GOODMAN M[1], LAKIND J[2,3], SQUIBB K[3], YOUNGSTROM E[4], ANTHONY L[5], KENWORTHY L[5], LIPKIN P[6], MATTISON D[7]. [1]Emory University, Atlanta, GA, United States, [2]LaKind Associates, LLC, Catonsville, MD, United States, [3]University of Maryland, Baltimore, MD, United States, [4]University of North Carolina, Chapel Hill, NC, United States, [5]Children's National Medical Center, Rockville, MD, United States, [6]The Johns Hopkins University, Baltimore, MD, United States, [7]National Institute of Child Health and Human Development National Institutes of Health, Bethesda, MD, United States. Weight-of-the-Evidence Assessment in Neurodevelopmental Epidemiology: A Plea for Consistency

Introduction: Judgment about the presence or absence of a causal relation between an exposure to a specific toxicant and a particular outcome is generally based on the weight of evidence, because even well-designed studies are subject to methodological limitations that are unavoidable in observational research. To provide a methodological framework for a review of the association between *in utero* and early-life exposures to environmental chemicals and neurodevelopmental outcomes in children we considered epidemiologic cohort studies that focused on prenatal and neonatal exposure to polychlorinated biphenyls (PCBs). Methods: We retrieved and reviewed relevant publications to assess: (i) the consistency of study methods; and (ii) the feasibility of conducting a systematic weight-of-the-evidence assessment (e.g., in a form of a meta-analysis). Information extracted from each study was classified according to cohort description, exposure categorization, timing of each neurodevelopmental testing, specific tests used to define the endpoints of interest, methods of data analysis and reporting of results. This characterization of the cohort studies allowed us to identify reasonably homogeneous groups of articles that could then be included in a systematic analysis. Results: The published literature includes 11 cohort studies of children for whom pre- or neonatal PCB exposures were measured or estimated, and who underwent neurobehavioral testing at different ages. The most consistently used tests included Brazelton's Neonatal Behavioral Assessment Scale and the neurologic optimality score in the neonatal period, the Bayley Scales of Infant Development at 5-8 months of age, and the McCarthy Scales of Children's Abilities in 5-year olds. Despite administering the same tests at essentially the same ages, the studies were too dissimilar to allow a meaningful systematic examination of results across cohorts. Discussion: Our evaluation of the PCBs neurodevelopmental epidemiology literature found a lack of uniformity in data collection, analysis and reporting. Even for age intervals examined by several research groups a meta-analysis of results is not possible at this time. The data on PCBs were used here as an example to highlight the need for improved inter-study consistency. Future studies of chemical exposures and neurodevelopmental outcomes must build on previous research with the aim of facilitating weight-of-evidence assessments.

50th Annual Meeting Symposium

S23

WERTELECKI W. University of South Alabama, Mobile, AL, United States. Josef Warkany - Then and Now

Josef Warkany was a humanist, etcher, scientist, physician, and pediatrician, whose integrity, convictions, and courage were obvious to those who knew him. In 1950, in the leading Pediatrics text by Graeme Mitchell and Waldo E. Nelson, Warkany stressed that "genetically determined abnormalities can be imitated by environmental disturbances" and that "nutritional constituents of the maternal diet may result in defective offspring ... ". Yet, he was reluctant to endorse the creation of a society of Teratology because "the premature formalization of an emerging discipline could stunt its growth ...". Even so, a decade later Warkany accepted the honor of becoming the first President of the Teratology Society, perhaps because he realized that the discoveries in genetics were capturing the imagination of many. Of his meetings with Basil O'Connor, then leader of the National Foundation - March of Dimes and a specially-appointed committee of science who judged studies of genetic problems of greater interest than studies of structural malformations, he remarked, "how is one to convince virologists of the importance of malformations?". In 1986, the duality Genetics-Teratology was symbolically bridged when Warkany became the first recipient of the Basil O'Connor Award. That was then. Regarding now, perhaps he would remind us that prevention of malformations is the central task of Teratology and urge investigations of "long chains of causative factors ... (that can be) interrupted at their weak links." - already one victory, the prevention of neural tube defects by folic acid supplements, stands as perhaps the greatest achievement of Preventive Medicine of the last century. Warkany's legacy is rich in facts and allusions to what T. Dobzhansky called "ultimate concerns". His frequent gentle admonition to his "younger mentors" was to "keep me alive", meaning his "ultimate concerns". Now is the turn for younger minds of Teratologists to know and enliven Warkany's ideals and confront his concerns about Teratology.

S24

BRENT RL. Jefferson Medical and Alfred I. duPont Hospital for Children, Wilmington, DE, United States. James G. Wilson, Embryologist, Teratologist, Founding Member of the Teratology Society, Superb Researcher, Teacher and Human Being.

James G. Wilson was born in Clarksdale, Mississippi on April 2, 1915. His parents were fine people: hardworking, independent southern Democrats. Jim's family and cultural heritage were important contributors to his active interest in racial tolerance, fair play, and the importance of human dignity. He graduated in 1936 from Mississippi College. He spent time at the Woods Hole Marine Biological Laboratory and then he entered Brown University in the fall of 1938. He transferred to the Department of Anatomy at Yale and completed his Ph.D. in 1942. A faculty position became available at the University of Rochester Medical School. It was suggested that he give some lectures on the subject of embryology. He decided to demonstrate rather than try to describe certain complicated embryonic processes. It became possible by means of models that he prepared from clay so that the students could actually visualize the changes and relationships. At the University of Rochester he began his embryological research dealing with the effects of irradiation on embryonic development. In 1955, he accepted the position of professor and chairman of the new Department of Anatomy at the University of Florida. It was in Florida that the first teratology workshop was conceived by Dr. Warkany and Dr. Wilson. He was one of the founding members of the Teratology Society and its second president. His major contributions were in the development of approaches to animal testing and he was one of the earliest workers in the field of primate teratology. His first love was his family, his wife, Harriet, his three children; Mary, Jay, and Arthur, and his grandchildren along with his summer home in the highlands of North Carolina. His many students and colleagues will remember many personal anecdotes about their relation with him. R. Wilson was one of the three founding membersw of the Teratology Society and its 2nd President. He made important contributions to the field of teratology and he was a lovely human being, which is really the most important of all.

Wiley-Blackwell Symposium
Teratology Society: 50 Years Then to Now

S25

BRENT RL. duPont Hospital for Children, Wilmington, DE, United States. A Personal Perspective of Historical Events That Affected the Development and Maturation of the Teratology Society in the Past 50 Years

Drs. Warkany, Wilson and Fraser were the founding members of the Teratology Society and these fine scientists convened a meeting at the Sloan-Kettering Institute in New York City in the spring of 1960. There were approximately forty five attendees, many of whom eventually became the charter members of the new Society. There was a scientific program, but much of the time was spent in developing the guidelines for creating a research society, since Dr. Warkany was a faculty member at the University of Cincinnati and his laboratory was housed in the Children's Hospital Research Foundation. The first meeting of the Society was held in Cincinnati in the spring of 1961 at the Children's Hospital. Dr. Warkany was elected President and had worked hard to obtain a document that registered the Society as a non-profit scientific organization in the state of Ohio. Each of the founding members was very different in training and expertise. Dr. Warkany was trained in Vienna and was a Pediatrician. He had a wonderful sense of humor. Although he came to the USA as an adult, he spoke with Viennese accent. But his English was perfect and his manuscripts in English were superb. His early research dealt with nutritional deficiencies as a cause of birth defects and he described the etiology of a puzzling disease, "acrodynia". Dr. Wilson was a "southerner", but obtained his Ph.D. in physiology at Yale and came to the University of Rochester as an assistant professor in the Anatomy department. He had a wonderful speaking voice and was a superb lecturer. He was also a talented artist and made sculptures of the developing heart and brain. His early research dealt with the effects of x-ray on the developing embryo. Dr. Clarke Fraser was a Canadian and was a faculty member at McGill University. Although he was a respected geneticist, he was also an experimental teratologist and was the first to describe the teratogenicity of cortisone when administered to pregnant mice. All three of these scientists were very important in the history of the Teratology Society.

S26

JONES KL. Department of Pediatrics, Division of Dysmorphology/Teratology, University of California, San Diego, School of Medicine, La Jolla, CA, United States. Clinical Teratology

Although the field of teratology has been arbitrarily divided over the years into a variety of different disciplines, one of the most exciting developments has been the awareness that the greatest strength of our Society is that we represent a group of seemingly diverse individuals who have come together to solve problems of extraordinary importance to individual families as well as to the public health in general. Although in the earliest years of our Society, discussions were primarily focused on basic science, it was always within the context of better understanding the causes of birth defects in humans with the ultimate goal of prevention. In 1984, the 24th Annual Meeting of the Teratology Society met in conjunction with the David W. Smith Workshop in Boca Raton, Florida with the purpose of melding individuals focused on children with birth defects with those involved primarily with basic science questions. Arguably the first of our annual meetings to focus on clinical teratology came in 1986 in Boston, MA. At that meeting, hosted by Lew Holmes, there were two sessions devoted exclusively to Clinical Teratology and two sessions devoted to Epidemiology. In recent years our annual meeting has successfully included in each of the sessions basic science, clinical teratology, epidemiology and regulatory issues. The purpose of my presentation is to highlight the advances that have been made by members of our Society in clinical teratology, but I will focus my discussion on the extent to which clinicians, basic scientists, and epidemiologists have informed each other in gaining new information that will help us better understand the etiology of birth defects and ultimately to develop strategies to prevent them.

S27

SCOTT W. Children's Hospital Research Fdn, Cincinnati, OH, United States. Experimental Teratology:Scenes from the Last Fifty Years

A variety of topics will be used to highlight some of the accomplishments and luminaries since the establishment of the Society.

S28

HALES BF. McGill University, Montreal, QC, Canada.
Fast Forward to the Future: Where Will We Be?

In the 50 years since the organizational meeting of the Teratology Society in New York our basic question has not changed. What causes the majority of birth defects? Since 1960, researchers have focused on the roles of genes, nutrition and the environment. We now know that genes, viruses, nutritional deficiencies and excesses, and chemical exposures each enhance the risk of birth defects. Vaccinations and folic acid supplementation have taught us that prevention is possible. It is unlikely that our founders foresaw the growing armament of powerful tools that are available today to propel us from describing phenomena to understanding underlying mechanisms and discovering novel approaches to protection from insult. Genome-wide association studies identify common genetic factors that influence the incidence of birth defects. The analyses of chemicals and their metabolites in a mother's hair reveal her exposures. High-throughput technologies, such as transcriptomics, proteomics and metabolomics, screen environmental chemicals for early signals of developmental toxicity. Emerging genome-wide epigenetic tools, such as ChIP-sequencing and ChIP-on-Chip, enable the assessment of gene-environment interactions. Systems biology teaches us that embryogenesis depends on self-regulatory interactions between spatially separated signaling centres. We can "engineer" a healthy conceptus by selecting the best spermatozoa and oocytes. Stem cells are everywhere. Where will we be in 50, or even 10, years from today? Can we dream "big enough" to fast forward to the future? Networking will remain important if we want to answer the basic question that drove our founders to unite as members of the Teratology Society 50 years ago. In the near future, we will be able to analyze the complete genome and epigenome of every "future" person, from a single cell, for a few dollars. Perhaps farther into the future, this analysis will reveal not only their genotype and phenotype but also their lifetime potential and susceptibility for disease. Since in this future vision development will take place "*ex utero*", our concern will be not with exposures *in utero* but with those of previous generations. Will we be ready?

ILSI HESI Symposium
21st Century Developmental Toxicology

S29

CARNEY EW. The Dow Chemical Company, Midland, MI, United States. Of Babies and Their Bathwater: Strengths to Maintain and Limitations to Overcome in Transitioning Developmental Toxicology to Meet 21st Century Needs

Developmental toxicity testing protocols have changed very little since their inception shortly after formation of The Teratology Society 50 years ago. These tests have served as the principle basis for countless public health decisions concerning the potential development hazards of numerous chemical agents, and the incredible longevity of these protocols is a tribute to their designers. Nonetheless, it is clear that developmental toxicology must adapt if it is to remain vibrant and useful into the future. This talk will discuss the drivers in the call for change, including technical advances in computational biology and high throughput assay development, corresponding improvements in our fundamental understanding of normal development and its control processes, as well as societal pressures to reduce animal use, expand the number of chemicals evaluated and enhance public confidence in the safety assessment system. While we all can agree that developmental toxicology must embrace new science and respond to current societal demands, how we get there is not quite as obvious. Playing on the old adage, "don't throw the baby out with the bathwater", this presentation will seek to objectively examine the strengths and weaknesses inherent in the current developmental safety testing paradigm, and then identify those strengths which should be retained ("the baby") *vs*. the weaknesses which can be relinquished ("the bathwater"). This analysis can serve as a guide in the design and implementation of future developmental toxicity testing strategies.

S30

HAYS S[1], AYLWARD L[1]. [1]Summit Toxicology, L.L.P., Allenspark, CO, United States, [2]Summit Toxicology, L.L.P., Falls Church, VA, United States. Exposure Assessment in the 21st Century: Increased Reliance on Biomonitoring

As advances in toxicology are moving towards a new paradigm in toxicity testing, exposure assessment is likewise undergoing a shift towards increased reliance on biomonitoring to assess children's and adult's exposures to chemicals from the environment and consumer products. Exposure assessment *via* biomonitoring provides many advantages. It is able to account for many factors that have to be assumed in a conventional exposure assessment, like frequency and duration of exposures, and also is able to capture issues associated with pharmacokinetic variations. As a result, biomonitoring has been called the 'gold standard' of exposure assessment and will be an integral part of the exposure assessment being employed in the National Children's Study. However, biomonitoring data usually represents a snapshot in time, which can result in uncertainties for evaluation of exposure to chemicals with short half-lives or when exposures are infrequent. Currently, biomonitoring data cannot generally be interpreted directly in terms of existing risk assessments and conventional exposure assessments. Because new toxicity testing methods often rely on *in vitro* techniques, new ways of thinking about exposure, namely how to assess internal dose rather than applied dose, will be required, and biomonitoring data can be valuable in this effort. This talk will describe advantages and limitations of biomonitoring, how biomonitoring is currently being used in risk assessment, and discuss future challenges that biomonitoring data will pose to the field of teratology.

S31

KNUDSEN TB. U.S. EPA, Research Triangle Park, NC, United States. Pathway Profiling and Tissue Modeling Using ToxCast™ HTS Data

High-throughput screening (HTS) and high-content screening (HCS) assays are providing data-rich studies to probe and profile the direct cellular effects of thousands of chemical compounds in commerce or potentially entering the environment. *In vitro* profiling may compare unknown bioactivities against reference compounds of well-characterized activity or else be interrogated in different ways, looking for novel and predictive signatures of *in vivo* toxicities. EPA's ToxCast™ project has generated HTS and HCS data on 309 environmental chemicals across over 467 *in vitro* assays. Proof-of-principle (Phase-I) addressed mostly pesticidal and anti-microbial chemicals with rich *in vivo* animal testing data culled from EPA's ToxRefDB database. The assays cover diverse biochemical activities, receptor binding activities, reporter gene activation and gene expression profiles, stress-response indicators, and perturbation in cell state and cellular function. In addition, the Phase-I assay space was expanded to monitor susceptibility in zebrafish embryos and pathways of differentiation in mouse embryonic stem cells. Machine-learning is used to identify patterns of biological activity and build predictive signatures of toxicity for chemical prioritization. A key aspect to this strategy is the integration of HTS/HCS data into canonical pathways for developmental signaling and cellular regulation. Several challenges face technology development such as correlating *in vitro* concentration-response with internal dose-response kinetics *in vivo*, understanding how *in vitro* bioactivity profiles extrapolate from one cell-type or technology platform to another, and linking individual targets of *in vitro* bioactivity into pathways of developmental toxicity. Computer simulators that reconstruct an emergent morphogenetic series of events can help extrapolate predictive signatures to different tissues, stages, doses, species, and exposures. Such multicellular models are a goal of EPA's Virtual Embryo. The project aligns with the federal Tox21c consortium ramping up to test ~10,000 chemical compounds by *in vitro* profiling. [This work is approved by EPA but does not reflect official Agency policy.]

S32

RUSYN I. University of North Carolina, Chapel Hill, NC, United States. Computational Toxicology: From Data to Analyses to Applications

The toxicology testing world is undergoing a major transformation as raised social and political expectations for a better environment and a healthier life are demanding that the industry, the regulators and the academia deliver more evidence on safety or harm by environmental chemicals. Computational toxicology is a sub-discipline of toxicology that aims to use the mathematical, statistical, modeling and computer science tools to better understand the mechanisms through which a given chemical induces harm and, ultimately, be able to predict adverse effects of the toxicants on human health and/or the environment. There are two major foci in the field of computational toxicology: (i) the appearance of novel data streams amenable to computational modeling and data mining; and (ii) the need for unconventional data analysis and modeling tools. Even though it is widely believed that the success and progress in computational toxicology is critical to the future of environmental health sciences and regulatory decisions in public health, it is also clear that many challenges remain to be addressed before the findings from high-throughput screens and *in silico* models may be considered sufficiently robust and informative.

S33

HARTUNG T[1,2]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [2]University of Konstanz, Konstanz, Germany. Future Strategies for Developmental Toxicity Safety Assessments

Developments on both sides of the Atlantic have created an atmosphere of departure in toxicology: The European REACH legislation for chemicals is the biggest investment into consumer product safety ever but challenges at the same time the available testing resources. This has prompted an integrated use of novel approaches in testing strategies. In the US, the NAS report on a toxicology for the 21st century (Tox-21c) calls to change toward modern non-animal methods. This has led to an alliance of federal agencies pursuing this new paradigm. It appears that essentially Tox-21c offers some answers to the problems posed by the REACH effort. A reanalysis of the REACH testing plan identified testing needs, which cannot be met with current capacities. Noteworthy, 70% of costs and 90% of animal use would be in the field of reproductive toxicology. It is therefore suggested to explore whether the area offers opportunities for the Tox-21c approach. Furthermore, it has been suggested to subject current approaches to a review process similar to Evidence-based Medicine, coining the term Evidence-based Toxicology (EBT). This promises a quality assurance in an objective manner to determine needs and opportunities for integration of new tools as well as refinement of replacement of traditional approaches. This might include refinements such as the extended one-generation study, embryonic stem cell models, information-rich omics and image analysis methods as well as high-throughput testing technologies. Similar to systems biology, data mining using existing scientific knowledge and computational tools is envisaged. A key goal must be the mapping of pathways of toxicity or the covering of the different elements of the reproductive cycle. Beside technical developments of novel tests, conceptual steering for their standardization, quality assurance, validation and implementation will be necessary. Though it is not at all clear, how the goals of higher throughput, better predictivity and reduced animal use can achieved, the ongoing activities promise to renew the toxicological toolbox and create a momentum for meaningful risk assessment.

TERATOLOGY SOCIETY

PLATFORM ABSTRACTS

(Presenter designated by underlined author.)

Student/Postdoctoral Fellow Platform Session I

1

SCHLISSER AE, HALES BF. McGill University, Montreal, QC, Canada. Exposure of Organogenesis Stage Mouse Embryos to Hydroxyurea Induces Nuclear 4-hydroxy-2-nonenal Protein Adducts

Exposure of mouse embryos to hydroxyurea (HU) increases the presence of a lipid peroxidation end-product, 4-hydroxy-2-nonenal (4-HNE); 4-HNE forms protein adducts resulting in aberrant protein function and signaling a cellular stress response. We have identified several proteins that are modified by 4-HNE in the caudal, malformation sensitive, tissues of embryos exposed to HU; these include glyceraldehyde-3-phosphate dehydrogenase (GAPDH), albumin, and heat shock proteins. Interestingly, GAPDH was found in the nucleus in HU exposed embryos; GAPDH translocation to the nucleus is associated with apoptosis. The goal of this study was to test the hypothesis that proteins with HU-induced 4-HNE adducts are transported from the cytoplasm to the nucleus. To test this hypothesis, CD1 mice were treated on GD9 with saline (Control) or HU (Low: 400mg/kg or High: 600mg/kg). Mice were euthanized at 3, 6, and 12h; embryos were excised and either separated into head, body, and tail regions or fractionated to purify the cytoplasmic and nuclear fractions. At 3, 6, or 12h post HU challenge, GAPDH protein concentrations remained constant in all body regions. In control embryos, 4-HNE-modified GAPDH was found in the nucleus; HU treatment did not significantly affect the amount of nuclear GAPDH protein (Control: 2.90, Low: 3.09, High: 2.94; densitometric ratio of 4-HNE/GAPDH, normalized to Ac-histone H3). Interestingly, at 3h, three 4-HNE tagged proteins that were present in control embryos in equal proportions in the cytoplasm and nucleus were enhanced within the nucleus of HU-treated embryos. The molecular weights and relative nuclear contents of these proteins were: ~60kDa (Control: 0.21, Low: 0.69, High: 0.57); ~70kDa (Control: 0.16, Low: 0.74, High: 0.38); and ~75kDa (Control: 0.11, Low: 0.54, High: 0.63). We propose that the trafficking of these 4-HNE-modified proteins into the nucleus is involved in stress response signaling; the identification of these proteins and elucidation of their function in the nucleus will help to reveal their role in mediating hydroxyurea induced malformations. Supported by CIHR.

2

CHOWDHURY S, CLEVES MA, MACLEOD SL, ZHAO W, HOBBS CA. University of Arkansas for Medical Sciences, Arkansas Children's Hospital Research Institute, Little Rock, AR, United States. Maternal DNA Hypomethylation, Methionine Pathway Metabolites, Lifestyle Factors and Congenital Heart Defects

Introduction: Congenital heart defects (CHDs) are the most prevalent and serious of recognized birth defects. Multiple factors including genetic susceptibilities, epigenetic mechanisms, and environmental influences are thought to contribute to the development of non-syndromic CHDs. Maternal DNA methylation, which is dependent on folate metabolism, has yet to be studied as a contributor to CHD risk. Our study was designed to determine whether differences in maternal DNA methylation are associated with an increased risk of CHDs in offspring. Methods: Using a case-control study design, we measured LINE-1 methylation among mothers whose pregnancies were affected by non-syndromic CHDs (N=181) and mothers of unaffected pregnancies (N=187). The study builds on the infrastructure of the National Birth Defects Research and Prevention Study (NBDPS). Blood was collected from Arkansas NBDPS participants who delivered a singleton live birth with a non-syndromic CHD and women who had a live birth without a major defect. Utilizing the LINE-1 repetitive element, a Methylight assay was developed to assess DNA methylation levels. Plasma concentrations of metabolites involved in folate metabolism were determined, and their association with CHDs and DNA methylation were analyzed. In addition, quantitative trait locus analysis of 1536 single nucleotide polymorphisms (SNPs) in candidate genes involved in folate metabolism are used to test for possible associations with LINE-1 methylation and folate pathway metabolites. Results: LINE-1 DNA methylation was significantly lower in cases when compared with controls ($p= 0.017$). After adjustment for age, body mass index, multivitamin supplementation, alcohol, and smoking, LINE-1 hypomethylation was still significant in cases when compared to controls ($p= 0.012$). Case mothers had significantly higher levels of homocysteine and SAH and lower levels of methionine, SAM, and SAM/SAH ($p <0.001$ for all metabolites) after covariate adjustments. Regression analysis identified homocysteine and methionine as the biomarkers most predictive of DNA methylation status. Discussion: Our findings indicate maternal DNA hypomethylation is associated with an increased risk of CHDs. Aberrations in maternal DNA methylation converge with previous evidence that indicates folate-dependent genetic and metabolic susceptibilities increase the risk of CHDs. These results suggest that further investigation into maternal epigenetic mechanisms as they affect CHD risk is warranted.

3

KLEINSTREUER N[1], DIX D[1], JUDSON R[1], KAVLOCK R[1], SIPES N[1], REIF D[1], CHANDLER K[1,3], ROUNTREE M[1], DEWOSKIN R[2], SINGH A[4], SPENCER R[4], KNUDSEN T[1]. [1]NCCT, ORD, U.S. EPA, Research Triangle Park, NC, United States, [2]NCEA, ORD, U.S. EPA, Research Triangle Park, NC, United States, [3]NHEERL, ORD, U.S. EPA, Research Triangle Park, NC, United States, [4]Lockheed Martin, Research Triangle Park, NC, United States. A Toxicity Signature for Species-Specific Disruption of Embryonic Vasculogenesis Derived from ToxCast™ *In Vitro* Profiling Data

Blood vessel formation is crucial for normal embryo development and is sensitive to disruption by diverse teratogens. Recent studies have begun to reveal the cell signaling networks underlying vasculogenesis and angiogenesis and how these pathways might be perturbed by specific chemicals. For example, vascular endothelial growth factor (VEGF) and platelet-derived growth-factor receptor (PDGFRb) pathways are sensitive to thalidomide and perturbation may disrupt vascular cell recruitment and proliferation at key stages of embryogenesis. An initial analysis of ToxCast™ high-throughput screening (HTS) data from 467 assays and 309 environmental chemicals revealed measureable effects on multiple *in vitro* assays for molecular targets or cellular processes important to vasculogenesis and angiogenesis. A predictive signature was built around statistical associations to *in vivo* developmental endpoints derived from EPA's ToxRefDB database. This analysis revealed a strong connection between developmental defects and a network of pathways consisting of pro-inflammatory / anti-angiogenic cytokine signaling, VEGF signaling, and the plasminogen activating system (PAS) network of enzymes and growth factors mediating matrix remodeling and local signaling during blood vessel growth. From these inferred associations, we hypothesize that embryonic microvascular networks are targets for the teratogenic activity of a number of environmental chemicals. Furthermore, relatively robust patterns emerge from the *in vitro* profiling data linked to species-specific *in vivo* developmental toxicity in either rats or rabbits. The strongest pattern reflects a differential response in the up- or down- regulation of specific elements in the proposed vascular signature. This implies a systematic response that foreshadows perturbations with species-specific impacts on developmental toxicity.

4

DAYAN C, HALES BF. McGill University, Montreal, QC, Canada. Exposure to 2-methoxyacetic Acid Induces Limb Malformations and Histone 4 Hyperacetylation *In Vitro*

Exposure to 2-methoxyacetic Acid (2-MAA), a primary metabolite of the ethylene glycol ethers used as fuel system deicing additives, induces skeletal malformations. The molecular mechanism of 2-MAA teratogenicity is not known although disturbances in maternal circulation, folate-dependent one-carbon transfer reactions, apoptosis and chondrogenesis have been implicated. The goal of this study was to examine the relationship between 2-MAA induced limb malformations and histone hyperacetylation since 2-MAA is also a histone deacetylase (HDAC) inhibitor. Timed pregnant CD-1 mice were euthanized on gestation day 12, forelimbs excised, and cultured with vehicle or 2-MAA (3mM, 10mM, or 30mM). Limb differentiation was scored with a morphogenetic scoring system on day 6 of culture. Histone H4 acetylation (H4Ac) was assessed by Western blotting after 3h of culture. The morphology of limbs exposed to 3mM 2-MAA did not differ from controls, whereas those exposed to 10mM or 30mM 2-MAA exhibited significantly impaired limb development, with severely damaged carpals and an increase in the number of missing digits. The morphogenetic scores for limbs exposed to 10 or 30mM 2-MAA were dramatically reduced (control: 212±13; 3mM: 198±7; 10mM: 143±35; 30mM: 98±53). Western blotting revealed that H4Ac was upregulated (1.8 to 2.5 fold) in limbs exposed to all 2-MAA concentrations examined. Thus, exposure to 3mM 2-MAA induced a greater than 2-fold increase in H4Ac in the absence of any overt effect on limb pattern formation. These results suggest that 2-MAA induced histone 4 hyperacetylation is not sufficient to disrupt limb development *in vitro*. Further studies will be necessary to elucidate the mechanisms by which this chemical induces limb malformations. This study was supported by the CIHR.

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CHANDLER K[1,2], HUNTER S[1], JEFFAY S[1], NICHOLS H[1], HOOPES M[1], BARRIER M[1], HABIG J[3], KNUDSEN T[2]. [1]Integrated Systems Toxicology Division, U.S. Environmental Protection Agency, Research Triangle Park, NC, United States, [2]National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC, United States, [3]Endogenics, Eagle, ID, United States. High-Throughput Screening of ToxCast™ Phase I Chemicals in an Embryonic Stem Cell Assay Reveals Potential Disruption of a Critical Developmental Signaling Pathway

Little is known about the developmental toxicity of the expansive chemical landscape in existence today. Significant efforts are being made to apply novel methods to predict developmental activity of chemicals utilizing high-throughput screening (HTS) and high-content screening (HCS) approaches. Several *in vitro* models, such as the embryonic stem cell test (EST), are used to evaluate the effects of xenobiotics and as predictive models of developmental toxicity. An Adherent Cell Differentiation and Cytotoxicity (ACDC) J1 mouse embryonic stem cell (mESC) assay was used to interrogate the well-characterized ToxCast™ Phase I chemical library for potential developmental activity. Differentiation and cytotoxicity were measured by In-Cell Western™ analysis of Myosin Heavy Chain (MHC), a cardiomyocyte marker, and DRAQ5™/Sapphire700™, respectively. Chromosome and MHC analysis of J1 mESCs through passage 27 showed the line remained euploid and maintained consistent levels of cardiomyocyte differentiation in control conditions. A dose-response curve was generated between 0.0125-12.5 μM for each of 309 ToxCast™ chemicals and half-maximal activity (AC50) was computed by curve-fitting methods. This analysis revealed an AC50 for MHC expression in 45 of 309 chemicals. The majority of these actives (41/45) inhibited cardiomyocyte differentiation. Comparison with 467 ToxCast™ assays revealed significant correlations between the inhibition of cardiomyocyte differentiation and perturbation of transcription factor signaling such as POU2F1/OCT1 (p=0.01), JUN (p=0.01), and EGR1 (p=0.03) as well as BMPR2 transcription (p=0.002). The BMP signaling pathway, which includes EGR1, JUN, and BMPR2, has been shown to play an important role in mESC self-renewal, embryonic development, cardiomyocyte differentiation, and cardiopulmonary function. These findings suggest this subset of ToxCast™ Phase I chemicals perturbs developmental signaling in pluripotent mESCs. [This work is approved by EPA but does not necessarily reflect official Agency policy.]

6

PARADIS FH, HALES BF. McGill University, Montreal, QC, Canada. Valproic Acid Disrupts Chondrocyte Differentiation and Increases Apoptosis *In Vitro* in Murine Limb Buds

In utero exposure to valproic acid (VPA), an anticonvulsant and antidepressant, can induce neural tube and skeletal malformations. Although VPA was identified as a teratogen in the 1980s, its molecular mechanism of action remains unsolved. Using a limb bud culture system, we showed that VPA induced a concentration-dependant decrease in limb growth and differentiation. Chondrogenesis and apoptosis are critical during limb pattern formation. Chondrogenesis is regulated by Sox family transcription factors, comprised of Sox9 and its downstream targets, Sox5 and Sox6. Sox9 also regulates the expression of collagen type II (Col2a1), present in the cartilaginous matrix. Apoptosis sculpts the digits during limb development and is regulated by the activation of caspases; cleaved caspase 3 is a marker of apoptotic cells. The present study investigated the effects of VPA on chondrogenesis and apoptosis during limb differentiation. Timed-pregnant CD1 mice were euthanized on gestation day 12, their embryos explanted, and the embryonic forelimbs excised. Forelimbs were cultured in the absence or presence of VPA (0.6, 1.8 or 3.6 mM) for 1, 3, 6, 12 or 24h. Total mRNA was isolated; Sox9, Sox5, Sox6 and Col2a1 transcripts were quantified by qRT-PCR and normalized to 18S rRNA. Cleaved-caspase 3 was analyzed in limbs cultured for 6 or 12h using Western blot analysis. All concentrations of VPA induced a significant decrease in Sox9 transcripts as early as 1h after exposure. The Sox9 downstream targets, Sox5 and Sox6, were downregulated by 3h; Col2a1 expression was decreased by 6h. Cleaved caspase 3 was detected in 1.8 and 3.6mM VPA-treated limbs at 12h. Although Sox5 and Sox6 expression returned to control by 12h, Col2a1 remained downregulated up to 24h after VPA exposure in the two highest concentration groups. Thus, VPA inhibits limb development through a sequential disruption of the expression of markers responsible for chondrocyte differentiation and an increase in cellular apoptosis. These studies were supported by CIHR and FRSQ.

7

ALLARD P, COLAIACOVO M. Harvard Medical School, Genetics, Boston, MA, United States. Dissecting the Action of Bisphenol-A on Germline Maintenance Using *C. elegans*

Although previous work in mice indicated that Bisphenol-A (BPA) disrupts normal germline function and meiosis in particular, the dissection of the affected molecular pathways has been particularly challenging. We propose to use the classic model organism *Caenorhabditis elegans* to investigate the genetic mechanisms of meiotic disruption following BPA exposure. Assessment of *C. elegans* fertility following BPA exposure revealed a dramatic increase in embryonic and larval lethality as well as a decrease in the total number of eggs laid compared to control (exposed to vehicle). Measurement of internal BPA levels indicated that BPA impairs *C. elegans* fertility at internal levels within the range of concentrations previously described in mammals. A two-fold increase in germ cell apoptosis is detected in BPA-exposed worms suggesting the activation of a DNA damage checkpoint that may stem from a defect in DNA double-strand break repair (DSBs). We also observed aberrant chromosome morphologies in pachytene nuclei indicative of chromosome fragmentation. Consistent with these results, following BPA exposure, we observed a dramatic redistribution of RAD-51 foci, a marker of DSB repair progression, and an up-regulation of the DNA-damage checkpoint protein ATL-1 in nuclei at the pachytene stage. Altered progression of meiotic DSB repair can lead to a delay in the maturation/remodeling of chromosomes during late Prophase I. In oocytes at late diakinesis, 3-D chromosome morphology analysis revealed the presence of decondensed bivalents and the appearance of chromatin bridges in BPA-treated gonads. Furthermore, series of events which are a hallmark of late meiotic prophase I such as the disassembly of the synaptonemal complex, the loading of the Aurora B kinase and the detection of pH3 on chromosomes, were also affected and delayed. Finally, following fertilization, live imaging of 1-cell embryos of BPA exposed worms revealed aberrant chromosome number, morphologies and behavior. Taken together, these data demonstrate that exposure to BPA specifically disrupts meiotic DSB repair in *C. elegans* which impedes proper progression through Prophase I and leads to embryonic inviability. The development of high-throughput screening strategies for endocrine disruption of meiosis in *C. elegans* will also be discussed.

8

RINDERKNECHT AL[1], MENJOGE AR[2,3], KANNAN RM[2,3], KIM CJ[3], ROMERO R[3], FARIDNIA M[1], MILLER RK[1]. [1]University of Rochester, Rochester, NY, United States, [2]Wayne State University, Detroit, MI, United States, [3]National Institute of Child Health and Human Development, Detroit, MI, United States. Transfer of Dendrimers in the Perfused Human Placental Lobule *In Vitro*: Prospects for Use as Drug Carriers during Pregnancy

Nanoscale medicines continue to be a powerful factor in the advancement of clinical therapy. The benefits and safety of this technology to the pregnant woman and the unborn are yet to be studied. Dendrimers are emerging as promising nanoscale delivery vehicles for targeted delivery of drugs and imaging agents. The objectives of this study were to evaluate the transplacental transport, kinetics and biodistribution of PAMAM dendrimers across the human placenta in comparison with antipyrine, a freely diffusible molecule, using *in vitro* dually perfused recirculating term placental lobules, as has been previously described (Miller *et al*., 1985, 2003). The transplacental transfer of fluorescently tagged (Alexa 488) dendrimer (Mw = 16 kDa) and antipyrine were measured using HPLC/dual UV and fluorescent detector with a sensitivity of 0.1 μg/mL and 10 ng/mL, respectively. C_{max} for the dendrimer-Alexa (DDA) in maternal perfusate was 13 times higher than in the fetal perfusate, and the fetal DDA concentrations were 4% and 6% of the maternal DDA by 2 and 6 hours of perfusion, respectively (n=4). Immunofluorescence for Alexa 488 confirmed that the biodistribution of dendrimer in the perfused placental lobule was relatively small and principally seen on the syncytiotrophoblast surface of the chorionic villi. These results suggest that the DDA is crossing from mother to fetus in concentrations similar to that noted for immunoglobulin G (Miller *et al*., 2003; Schneider and Miller, 2010). Further, the perfused placentae functioned normally with steady production of human chorionic gonadotropin and progesterone, net fetal O_2 transfer, flow rates and fetal perfusion pressure. In conclusion, the PAMAM dendrimers (5.6 nm; Mw = 16 kDa), did demonstrate the ability to slowly transfer across the placenta and reach significant and measurable concentrations without accumulating in the placenta. This demonstrates the potential for these dendrimer nanoparticles to play a role in fetal drug delivery. {Supported by Eunice Kennedy Shriver NICHD Perinatology Research Branch (Wayne State) and NIH R03HD059027 (Rochester).}

Platform Session II: Mechanisms and Models

9

ABBOTT BD, WOOD CR, WATKINS AM, DAS KP, LAU CS. Developmental Biology Branch, Toxicity Assessment Div., NHEERL, U.S. EPA, Research Triangle Park, NC, United States. Peroxisome Proliferator-Activated Receptor Alpha (PPARα), Beta (PPARβ), and Gamma (PPARγ) Expression in Human Fetal Tissues

Peroxisome proliferator-activated receptors (PPARs) regulate lipid and glucose homeostasis, are targets of pharmaceuticals, and are also activated by environmental contaminants. Almost nothing is known about expression of PPARs during human fetal development. This study uses qPCR and Western blot to examine expression of PPARα, β, and γ mRNA and protein in gestation day 54-125 human fetal liver, heart, lung, kidney, stomach, intestine, adrenal, spleen, and thymus. Fetal tissues were obtained from the Birth Defects Research Laboratory at the University of Washington, Seattle. Fetal PPAR mRNA expression was compared to that of adult samples (First Choice Human Total RNA, Ambion, Inc). With increasing fetal age, mRNA expression of PPARα and β increased in liver, but PPARβ decreased in heart and intestine, and PPARγ decreased in adrenal. Adult and fetal mean expression of PPAR mRNAs did not differ in intestine, but fetal expression of PPAR mRNAs was lower in stomach and heart compared to adult levels. PPARγ in liver and PPARβ in thymus were expressed at higher levels in fetal tissues. PPARα and β mRNA expression was lower in fetal kidney and spleen compared to the adult, and PPARγ was lower in fetal lung and adrenal compared to adult expression. PPARα, β, and γ protein did not change with age in liver, heart, stomach, spleen, or thymus. PPARα protein increased with age in intestine and decreased in lung, kidney and adrenal. PPARβ decreased with age in adrenal and PPARγ decreased in kidney. This study provides new information on expression of PPAR isoforms during human development and will be important in evaluating the potential for the developing human to respond to PPAR agonists. This abstract does not necessarily reflect EPA policy.

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BUSHDID PB, GIBBARD A, PAGANA JM, WHITE TE. GlaxoSmithKline, King of Prussia, PA, United States. Modulation of Adenosine Receptor A_1 Signaling Results in Inhibition of Calvarial Ossification in Mice

Adenosine receptor A_1 (A_1AR) agonists are potential therapies for cardiac arrhythmias, neuropathic pain and dyslipidemia. An A_1AR agonist (Cpd-A) caused skeletal defects in a rabbit embryo-fetal development (EFD) study, including enlargement of the anterior fontanelle, misshapen frontal bones, unossified orbital margins and other non-cranial defects. The pattern of malformations was similar to several human disorders that affect calvarial, cranio-facial and axio-skeletal formation. Conversely, Cpd-A did not cause developmental toxicity in rats (dosed on Days 6 to 17 *postcoitum*; pc). However, in mice, 4 different A_1AR agonists caused varying degrees of skeletal defects (ossification defects of the skull, ribs, sternebrae and vertebrae) when administered on Days 8 to 17 pc. Incomplete or no ossification of the frontal, parietals or interparietal were the most common skull findings. Therefore, mouse was considered a good model for evaluating skull defects. In order to establish an *in vitro* model for the skull defects, a mouse calvarial culture system was employed. Calvaria from Day 15 pc mouse embryos were dissected and cultured on filter platforms at the air/media interface and incubated with 4 different A_1AR agonists (Cpds A-D), or the adenosine analogs 2-chloro-N^6-cyclopentyladenosine (CCPA) or 8-cyclopentyl-1,3-dimethylxanthine (CDMX). Qualitative assessment using alizarin red staining showed a dose dependent inhibition of calvarial ossification with all 4 A_1AR agonists, CCPA (agonist), CDMX (antagonist) and the positive control TGF-β3. Incomplete ossification of the inner edges of the frontals and parietals resulting in an enlarged anterior fonticulus was the most common finding, similar to the skull defects noted *in vivo* in rabbits and mice. Moreover, treatment of calvaria with one compound resulted in a ~50% reduction in Runx-2 and Osteocalcin expression by RT-PCR. These data demonstrate that modulation of A_1AR signaling can inhibit ossification of the developing calvarium in mice and that calvarium organ culture was able to replicate *in vivo* effects of A_1AR agonism.

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LAROCCA J, HIXON M. Brown University, Providence, RI, United States. Akt1 Mediates Mammary Gland Growth and Development *In Vivo*

Mammary gland development is an intricate process controlled by steroid and peptide hormones that is highly conserved in mammals. Pubertal and post-natal mammary gland growth is largely controlled by the hormones estrogen, progesterone, and growth hormone. Akt1 is a serine-threonine protein kinase member of the Akt proto-oncogene family, which is involved in a number of cellular processes including cell proliferation, survival, and apoptosis. Akt1 has been found to be involved in lactation and involution in the mammary gland, as well as being implicated in the development of mammary tumors. We have previously reported that Akt1-null females have delayed vaginal opening, delayed estrous cycles, and are sub-fertile. This study focuses on the role of Akt1 in mammary gland development during post-natal, pre-pubescent, and pubescent time points. Akt1-wild type and Akt1-null mice were used to examine mammary glands at post-natal days 11, 25, 50, and 70. Inguinal mammary glands were dissected for whole mount and histological analysis and thoracic mammary glands were flash frozen for gene expression. The loss of Akt1 resulted in severely delayed mammary gland development. Terminal end bud number was significantly reduced in Akt1-null mice at PND 25 ($p<0.001$). Ductal outgrowth was significantly reduced up to and including PND 50 ($p<0.01$). At adulthood (PND 70), Akt1-null mammary glands occupied the same space in the fat pad, but contain less aleveolar buds than Akt1-wild type mammary glands. Early gene expression analysis indicates a number of differentially expressed genes in the PND 70 Akt1-null mammary glands. We hypothesize that Akt1-ablation alters gene and protein expression in the mammary gland, causing a delay in development. Experiments are ongoing.

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BANH S, HALES BF. McGill University, Montreal, QC, Canada. Role of Mitogen-Activating Protein Kinase Signaling in the Developmental Toxicity of Hydroxyurea

Hydroxyurea (HU), an anti-neoplastic drug, has been studied extensively as a model teratogen. Exposure of timed-pregnant CD1 mice to HU on gestation day 9 stimulated oxidative stress and activated mitogen-activating protein kinase (MAPK) signaling, increasing the phosphorylation of p38 and JNK MAPKs. The inhibition of p38 or JNK activation increased fetal deaths or hindlimb malformations, respectively, demonstrating that these MAPK family members play distinct roles in protecting the conceptus from insult. The goal of this study was to investigate the role of MEK 4, an upstream MAPKK that has been reported to activate JNKs. Timed-pregnant CD1 mice were treated with vehicle (saline) or HU (low dose: 400mg/kg; high dose: 600 mg/kg) by i.p injection on gestation day 9 and euthanized 0.5, 3, or 6h post-treatment. Embryos were explanted and whole tissue lysates prepared. MEK 4 and phospho-MEK-4 protein expression levels were quantified by Western blot analysis and normalized to β-Actin. HU treatment did not affect MEK 4 protein expression at any time. Phospho-MEK-4 was not affected by HU exposure at 0.5h; however, at 3h phospho-MEK-4 was significantly increased, to 130% of the control, in HU treated embryos. Thus, MEK-4 is activated by HU exposure, suggesting that this upstream kinase plays a role in coordinating the embryonic response to this teratogen. Supported by CIHR.

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MILLER L[1], WELLS PG[1,2]. [1]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada, [2]Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada. Ethanol Teratogenesis, Oxidative Stress and Protection by a Free Radical Spin Trapping Agent

Consumption of alcohol (ethanol) during pregnancy can cause a spectrum of structural, cognitive and behavioural anomalies termed the Fetal Alcohol Spectrum Disorder (FASD). Although the underlying mechanisms are not fully understood, there is evidence suggesting that reactive oxygen species (ROS) are involved in the teratogenic mechanism. To determine the extent to which ROS are involved in FASD, CD-1 dams were dosed on gestational day (GD) 9 (plug = GD 1) and exposed to ethanol (4, 6 g/kg low and high dose, respectively) or its vehicle, with or without pretreatment with phenylbutylnitrone (PBN), a free radical spin trapping agent previously shown to reduce embryonic ROS formation and embryopathies caused by teratogens like phenytoin and thalidomide. Ethanol caused dose-dependent teratogenesis that was reduced by pretreatment with PBN. Exposure to 4 g/kg ethanol alone decreased crown-rump length ($p < 0.05$), while exposure to 6 g/kg ethanol alone decreased fetal weight and crown-rump length, and increased the incidences of resorptions, microcephaly and nasal defects ($p < 0.05$). Pretreatment of dams with PBN (40 mg/kg) followed by ethanol (4 or 6 g/kg) was protective, evidenced by increases in fetal weight and crown rump-length, as well as decreases in the incidences of microcephaly and nasal defects ($p < 0.01$) compared to dams exposed to ethanol alone. The reduction in ethanol teratogenesis by PBN pretreatment in mice suggests that ROS may contribute to the FASD. (Support: CIHR)

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RASOULPOUR RJ, BROOKS KJ, SAGHIR SA, BILLINGTON R, CARNEY EW. The Dow Chemical Company, Midland, MI, United States. Advantages and Challenges of Dietary Developmental Toxicity Studies in the Rabbit

Gavage, the default route of oral exposure for developmental toxicity studies, often produces an oscillating daily pharmacokinetic profile characterized by short-lived high Cmax, and low Cmin values. Our lab has been exploring the use of dietary administration for these studies to avoid large fluctuations and ensure consistent exposure across all critical periods of development. We compared gavage *versus* dietary administration of a new developmental compound (X11422208) in pregnant New Zealand White rabbits. In probe studies, X11422208 was administered at 0, 10, 15, 20, or 25 mg/kg/day by gavage or 0, 500, or 1000 ppm (0, 21.7, or 36.6 mg/kg/day) in feed on gestation days (GD) 7-28. Gavage of 20 or 25 mg/kg/day exceeded a maximum tolerated dose (MTD), while maternal toxicity was similar between gavage at 15 mg/kg/day and diet at 1000 ppm. Plasma concentrations of X11422208 in the dietary groups were constant, compared to a three-fold difference between Cmax and Cmin by gavage, while plasma AUC_{24h} of the test material, which is not metabolized, was greater than two-fold higher for dietary *vs*. gavage at the respective MTDs,. Based on these findings, the dietary route was chosen for the definitive study at 0, 30, 150, or 750 ppm on GD 7-28. Animals in the 750 ppm dose group had decreased body weight (12%, GD 7-28) and body weight gain (55%, GD 7-13), relative to controls. There was no treatment-related maternal toxicity in the 30 or 150 ppm dose groups and no treatment-related developmental toxicity in any dose group, resulting in maternal and developmental toxicity no-observed effect levels (NOEL) of 150 ppm and 750 ppm (the highest level tested), respectively. The daily systemic dose of X11422208 on GD 27-28 was dose-proportional to the dose-corrected AUC_{24h} values of 18-19 µg X11422208/h/kg^{-1} for animals in the 30, 150 and 750 ppm dose groups. In comparison to gavage administration, the dietary route allowed a more than two-fold greater top dose level, regarding both dose and systemic exposure, with the dietary route providing stable, consistent exposure throughout all stages of fetal development. The study also demonstrated the first successful use of dietary administration in rabbits.

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NEAL RE[1,2], CHEN J[1], BIRTLES T[2], GREENE RM[2], PISANO MM[2]. [1]EOHS, SPHIS, University of Louisville, Louisville, KY, United States, [2]Birth Defects Center, University of Louisville, Louisville, KY, United States. Cigarette Smoke Exposure: Alterations in the Metabolome of the Gravid and Non-Gravid Mouse Uterus

A murine model of gestational cigarette smoke exposure-induced low birthweight (LBW), developed in our laboratory, exhibits susceptibility during the peri-implantation period of development. In the current study, metabolome profiles of uterine tissue from cigarette smoke exposed (CSE) non-pregnant *vs* pregnant mice were examined to elucidate differences in tissue biochemical homeostasis. C57BL/6J mice were mated (GD 0) and all plug-positive females were exposed to mainstream/sidestream smoke for 6 hours/day for 5 days (serum cotinine levels >50 ng/dL) to model active maternal smoking during the peri-implantation period. Directly after the final exposure, animals were euthanized by CO_2 asphyxiation and uterine tissue was collected from both pregnant and non-pregnant females for analysis. Methanol-extracted metabolites were subjected to direct inject nano-ESI-MS (Advion Nanomate interfaced to ThermoElectron LTQ-FT-ICR-MS; positive polarity; 100,000 resolving power). Duplicate positive polarity uterine methanolic extract metabolome profiles were collected for CSE exposed females (non-pregnant, n=8; pregnant, n=5). Nine mass features of interest ($p<0.05$, 2-fold difference) were found in the comparison of metabolome differences between groups. Preliminary identification of mass features of interest was based on accurate mass agreement with metabolites present in HMDB or METLIN-structural validation of identification is ongoing. The candidate chemical compound classes that were tentatively identified as altered in the uterine tissue of pregnant *vs*. non-pregnant CSE mice includes lipid species such as sphingomyelins and phosphatidylcholines. A decreased abundance of phosphatidylcholines containing 46 carbons was noted in the pregnant *vs*. non-pregnant uterus, which is similar to the trend noted when comparing the uterine metabolome profiles from CSE vs. sham exposed non-pregnant mice. This may indicate a chemical class specific deficit of phosphatidylcholines in uterine tissue for CSE mice with a furtherance of effect in pregnant mice. It should be noted that not all phosphatidylcholines exhibit the same trend-indeed a phosphatidylcholine comprised of shorter acyl chains with a total of 42 carbons exhibited increased abundance in pregnant *vs.* non-pregnant cigarette smoke exposed mice. This may indicate a pregnancy related increase in acyl-chain specific lipid synthesis/transport in uterine tissue. Research Support: NIH grants DA027466, HD053509 and P20 RR017702.

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CANALES L[1], CHEN J[1], BIRTLES T[2], GREENE RM[2], PISANO MM[2], NEAL R[1,2]. [1]University of Louisville, Louisville, KY, United States, [2]Birth Defects Research Center, University of Louisville, Louisville, KY, United States. Altered Liver Proteome Profiles in a Mouse Model of "Developmental" Cigarette Smoke Exposure

Cigarette smoke (CS) is composed of over 4000 chemicals many of which are strong oxidizing agents and known chemical carcinogens. The liver is a primary site of exogenous compound detoxification and lipid synthesis/storage. Various models of CS exposure have identified alterations in liver histology indicative of mild tissue toxicity, though it is not known whether "developmental" CS exposure results in alterations in the global proteome profile of the liver. Thus, the goal of the present study was to determine whether "developmental" CS exposure alters liver protein expression and the activity of enzymes associated with chemical detoxification. Utilizing a mouse model of "developmental" CS exposure which simulates active smoking and which demonstrates offspring low birth weight and neurocognitive deficits, we collected liver tissue following maternal/pup exposure to CS from gestational day 1 through postnatal day (PD) 21 (maternal/pup cotinine>50 ng/mL). On PD21, pups were euthanized by CO_2 asphyxiation and liver tissue was harvested and stored at -80°C until analysis. 350 micrograms of liver protein was subjected to 2D SDS-PAGE with protein spot detection by colloidal Coomassie blue staining. Densitometric analysis of relative protein spot abundances was performed with Progenesis SameSpots Software and ANOVA for statistical analysis ($p<0.05$ and a Power>0.6). Preliminary results indicate that 37 protein spots from the liver of CS exposed pups were up-regulated while 2 protein spots were down-regulated. Identification of proteins is ongoing. In addition, measurement of the activities of lactate dehydrogenase (LDH; marker of tissue hypoxia and damage) and glutathione-S-transferase (GST; detoxification enzyme) in livers from smoke- and sham-exposed pups demonstrated no impact of CS on enzymatic activity. These preliminary data support the presence of significant alterations in liver protein expression resulting from "developmental" CS exposure without attendant alterations in enzymatic activity indicative of tissue damage or impairment of detoxification pathways. Research Support: NIH grants DA027466, HD053509 and P20 RR017702.

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OSMAN A[1,2], VAN DARTEL DAM[1,2], ZWART E[1], BLOKLAND M[1], PENNINGS J[1], PIERSMA AH[1,3]. [1]RIVM Lab for Health Protection Research, Bilthoven, Netherlands, [2]GRAT-NUTRIM-Maastricht University, Maastricht, Netherlands, [3]IRAS-Utrecht University, Utrecht, Netherlands. Proteome Profiling of Mouse Embryonic Stem Cells to Define Markers for Cell Differentiation and Embryotoxicity

In search for alternative methods for developmental toxicity testing, we investigated whether embryonic stem cell (ESC) differentiation and its modulation by toxic exposure could be monitored by proteome profiling. We compared the proteomes of mouse ESC, differentiating ESC (DIF) and differentiating ESC exposed to the embryotoxicant monobutyl phthalate (MBP). The identified proteins were quantified using a label-free quantitative method based on counting the observed peptides as an index of protein abundance. Fifty seven proteins were upregulated in DIF relative to ESC, whereas 42 proteins were downregulated. Most of the upregulated proteins could be correlated with cardiomyocyte functionality. In contrast, the downregulated proteins were principally pluripotency markers, chaperones and ribosomal proteins. Higher expression levels of enzymes involved in DNA mismatch repair (MSH6) and in methylation reactions (MAT2A, AHCY) were also detected in the ESC, suggesting that these processes are more active in the ESC. In addition, the detection of gluthatione S-transferase alpha 4 (GSTA4) and Park7 DJ-1 protein (antioxidant) in ESC indicates that these cells have potential detoxification mechanisms. Furthermore, MBP affected the expression of 33 proteins, including MYH6, a cardiomyocyte specific protein, which was significantly downregulated. MBP also affected the expression levels of chaperones, metabolic enzymes and chromatin modulating proteins, suggesting that MBP alters the differentiation process. Western blot analysis of MYH6 and HSPB1 confirmed the proteomic data. In addition, a favorable correlation was observed between protein expression and published changes in the expression of related genes at the transcriptomics level. Together, the results reveal potential protein markers that may be used as endpoints in an ESC based animal free alternative test for embryotoxicity.

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SIPES NS[1], ROUNTREE MR[1], KLEINSTREUER NC[1], DIX DJ[1], JUDSON RS[1], KAVLOCK RJ[1], SWAT M[4], GLAZIER JA[4], DEWOSKIN RS[2], SINGH AV[3], SPENCER RM[3], KNUDSEN TB[1]. [1]NCCT, ORD, U.S. EPA, Research Triangle Park, NC, United States, [2]NCEA, ORD, U.S. EPA, Research Triangle Park, NC, United States, [3]Lockheed Martin, Research Triangle Park, NC, United States, [4]The Biocomplexity Institute, Dept. of Physics, Indiana University, Bloomington, IN, United States. Development of a Computational (*In Silico*) Model of Ocular Teratogenesis

EPA's ToxCast™ project is profiling the *in vitro* bioactivity of chemical compounds to assess pathway-level and cell-based signatures that are highly correlated with observed *in vivo* toxicity. *In silico* models provide a framework for interpreting the *in vitro* results and for simulating the toxicity pathways. One such model is being developed to predict the potential of chemical compounds and classes to disrupt embryonic development. The embryonic eye was initially used as a prototype for embryonic target organ systems modeling. Early eye development is broadly susceptible to mechanistically diverse teratogens. We hypothesize that cell signaling pathways underlying eye development are primary targets for diverse environmental chemicals that disrupt ocular formation and have combinatorial effects on cellular functions. To test this hypothesis, we are building an integrative cell-based model of early eye development based on *in vitro* high-throughput screening (HTS) and high-content screening (HCS) data from EPA's ToxCast™ project, and *in vivo* developmental toxicity data from ToxRefDB. Initial analysis of *in vitro* profiles for several microphthalmia-inducing teratogens revealed pathway disruption of microtubule stability, mitotic inhibition, mitochondrial dysfunction, and perturbation of pro-inflammatory/anti-angiogenic factors (VCAM1, HLA-DRA, CXCL10, MMP1, and uPAR). Optic cup development, for example, is known to be sensitive to mitochondrial dysfunction. Three of the six ToxRefDB ocular teratogens tested *in vitro* disrupted mitochondrial function and also induced microphthamia *in vivo*. Studies are underway to investigate the linkages between eye morphogenesis, cellular effects, and the identified pathways in a virtual embryo using CompuCell3D modeling software. [This work is approved by EPA but does not reflect official Agency policy.]

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MOYER BJ, HIXON ML. Brown University, Providence, RI, United States. Effects of *In Utero* Exposure to Mono-2-ethylhexylphthalate (MEHP) on the Adult Female Mouse

Mono-2-ethylhexylphthalate is the primary metabolite of the ubiquitous plasticizer di-2-ethylhexylphthalate (DEHP) and is a known reproductive toxicant in both male and female rodents. In this study, pregnant C57/BL6 mice were exposed *via* oral gavage to 500 or 1000 mg/kg MEHP or vehicle control at gestational days 17, 18, and 19. Offspring were then allowed to age to early adulthood. Body weights were similar between vehicle-treated and MEHP exposed females (mean body weight of vehicle treated = 19.25 +/- 0.9; mean body weight of 1000 mg/kg = 17.6 +/- 2.5 g). The date of vaginal opening, a marker of sexual maturity, was also similar between treated and control mice (mean date of vaginal opening in vehicle treated = 29.85 +/-1.3 days; mean date of vaginal opening in 1000 mg/kg and 500 mg/kg at 30.75 +/-2.54 and 30.0 +/- 2.20 days, respectively). Ovary weights were not statistically different with mean combined ovary weights of 12.5 +/- 2.3 mg in control and 12.0 +/- 2.0 mg in 1000 mg/kg group. *In utero* exposed female offspring had a delayed onset of estrous in both the 500 and 1000 mg/kg MEHP treated groups relative to controls (Mean onset in vehicle treated animals at PND 35 +/- 1.9; mean onset in 1000 mg/kg at PND 39.8 +/- 1.6; mean onset in 500 mg/kg PND 39.0 +/- 3.7). Exposed females displayed abnormal cyclicity marked by a prolonged estrus stage. (Mean duration of estrus stage in vehicle treated, 1.44 +/- 0.53 days; mean duration of estrous in 1000 mg/kg treated 2.9 +/- 0.64 days; mean duration in 500 mg/kg 2.80 +/- 0.84 days). Gene expression of LHCGR was down regulated 7-fold in the 1000 mg/kg group relative to vehicle controls. Serum levels of FSH were significantly elevated at 1000 mg/kg (mean serum FSH in control = 3.69 +/- 2.01; 1000 mg/kg = 7.58 +/- 3.10). Our results suggest that *in utero* exposure to MEHP leads to the onset of adult reproductive abnormalities.

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WISE LD[1], XUE D[2], WINKELMANN CT[2]. [1]Toxicological Sciences, Merck Research Laboratories, West Point, PA, United States, [2]Imaging Department, Merck Research Laboratories, West Point, PA, United States. Micro-CT and Alizarin Red Evaluations of Fetal Rat and Rabbit Skeletal Abnormalities Induced by All-Trans-Retinoic Acid

During safety assessment studies the evaluation of fetal skeletal morphology is routinely based on staining with alizarin red. X-ray micro-computed tomography (micro-CT) produces high-resolution images of skeletal structures and we have been investigating it as a high-throughput replacement to staining (BDRB 86:214-226). The present study examined the malformations produced by all-trans-retinoic acid (atRA). Five mated Crl:CD(SD) rats per group were administered 0 (vehicle only) or 2.5 to 50 mg/kg atRA orally on GD 10. Four mated Dutch Belted rabbits per group were administered 0 or 6.25 to 25 mg/kg atRA orally on GD 9. Cesarean sections were performed on GD 21 and 28, respectively. All litters were scanned by micro-CT and subsequently stained by routine methods with alizarin red. Skeletal morphology was evaluated without knowledge of treatment group using routine manual methods and Amira® software. In rats there were dose-related increases in the incidence of extra lumbar vertebrae and a dose-independent increase in supernumerary ribs at all dose levels. There were increased incidence of skull bone malformations in rats at ≥10 mg/kg, and decreases in mean number of ossified sacrocaudal vertebra (SCV) at ≥5 mg/kg. Rabbits were less sensitive on a mg/kg basis since skeletal malformations were observed only in the 25-mg/kg group, along with a decrease in mean number of ossified SCV. Micro-CT evaluation detected essentially the same incidence of skeletal abnormalities as seen by the staining method. Additional micro-CT-derived quantitative parameters (e.g., bone mineral content) were also affected by treatment. These results add further support to our findings that micro-CT imaging can effectively assess rat and rabbit fetal skeletal morphology.

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HIXON ML, LAROCCA J, BOYAJIAN A, BROWN C, DUNCAN SMITH S. Brown University, Providence, RI, United States. Effects of Bisphenol A and Diethylstilbestrol on the Adult Male Reproductive System Following Oral Administration to Pregnant C57BL6 Mice on Gestational Days 10 through 16

Bisphenol A (BPA) is an estrogenic compound and the building block of polycarbonate plastic. Using the C57BL6 mouse as a model, we investigated whether or not male reproductive parameters were at particular risk following *in utero* exposure to moderate to high doses of BPA. This study was limited to the measurement of sex-organ weights, anogenital distance, and testis histopathology in the adult offspring of pregnant female mice exposed orally to the EPA reference dose (50mg/kg/day) or a high dose (1000mg/kg/day) of BPA on gestation days 10-16. An additional group of dams was dosed orally with 2mg /kg/day of diethylstilbestrol (DES) as a positive control. In the 1000mg/kg BPA exposure group, dam weight was significantly reduced relative to the other exposure groups. Anogenital distance (AGD) was not significantly altered in any of the BPA exposure groups; however, DES exposure significantly increased AGD in male offspring. At postnatal day 56, testes exposed to BPA exhibited normal histology and produced testosterone at levels that were similar to controls. In summary, *in utero* exposure to a moderate dose of BPA (50 mg/kg) had no effect on the male reproductive parameters measured. At the higher dose of BPA (1,000mg/kg) decreased testis weight was observed.

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TYL RW[1], SEELY JC[2], MARR MC[1], MYERS CB[1], YOUN VY[1], BROWNING DB[1], BISHOP JB[3]. [1]RTI International, Research Triangle Park, NC, United States, [2]Experimental Pathology Laboratories, Inc., Research Triangle Park, NC, United States, [3]National Toxicology Program/NIEHS/NIH, Research Triangle Park, NC, United States. Gonadal Responses to Vinclozolin Administered Orally to Han Wistar Rats

Introduction: RTI recently completed an NTP Reproductive Assessment by Continuous Breeding (RACB) study with an orally administered androgen receptor (AR) antagonist, vinclozolin, at 0, 10, 30, or 100 mg/kg/day (in corn oil) to Han Wistar rats over 3 generations (F0 females and F1 and F2 males and females; 25-75 animals/sex/group). Methods: All of the appropriate parameters were assessed for all animals in all generations in-life and at necropsy. Results: During the histopathologic evaluation of tissues/organs of interest, interstitial cell hypertrophy and/or hyperplasia were observed in the ovaries and testes of adult F1 and F2b rats. F0 parental females (purchased timed mated) did not exhibit these effects. Dose-related increases in incidence at 0, 10, 30, and 100 mg/kg/day in males were, respectively, F1 nonparental: 0, 0, 55.6, and 100.0%; F1 parental: 0, 0, 79.2, and 100.0%; F2b: 0, 0, 31.2, and 100.0%; and in females were, respectively, F1 nonparental: 0, 0, 40.0, and 66.7%; F1 parental: 0, 4.4, 100.0, and 94.7%; and F2b: 0, 0, 64.6, and 100.0%. Discussion: ARs are located in the Leydig cells, in the peritubular myloid cells (precursors to fetal Leydig cells), pituitary, hypothalamus and ovary. The ovarian responsive cells are the theca cells in the interstitial stroma just outside the follicle, responsible for steroidogenesis of testosterone and androstene-dione (for transport into the granulosa cells within the follicle to synthesize estrogen). The testicular responsive cells are the Leydig cells, which reside outside the seminiferous tubules and are responsible for testosterone biosynthesis. We propose that reduced sex steroid biosynthesis in the gonads from exposure to vinclozolin, which binds to AR receptor and affects downstream AR-dependent gene activations for steroid biosynthesis, results in reduced blood levels of sex steroids. This causes increased synthesis of hypothalamic gonadotrophin releasing hormone. In turn, this causes increased synthesis and release of luteinizing hormone (and follicle stimulating hormone) from the anterior pituitary, which then stimulates growth (increased sizes and numbers) of the steroidogenic cells in the gonads (ovaries or testes) to produce more androgen for synthesis of testosterone or 17β-estradiol. Alternatively, the mechanism may be local and direct in the gonads.

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KAPPEN C, KRUGER C, MACGOWAN J, SALBAUM JM. Pennington Biomedical Research Center, Baton Rouge, LA, United States. Maternal Diet Modulates the Rate of Neural Tube Defects in Diabetic Pregnancies

Pregnancies complicated by maternal diabetes have long been known to carry a higher risk of adverse outcomes in the offspring, including congenital malformations, such as neural tube defects. Using the FVB inbred mouse strain and the Streptozotocin-induced diabetes model, we have found that the incidence of neural tube defects in diabetic pregnancies in the mouse can be modulated by maternal diet. In a comparison of two widely used commercial mouse diets, we observed that maternal consumption of the adverse diet was associated with a more than three-fold higher rate of neural tube defects. Although both diets are considered nutritionally replete and vary only slightly in vitamin and amino acid composition, the most notable differences are in the amounts of calories derived from fat *versus* protein. To our knowledge, this is the first demonstration that macronutrient composition of the diet affects the risk for developmental defects in genetically wildtype inbred mice, compounding the detrimental effects of maternal diabetes on embryonic susceptibility for neural tube defects.

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FENTON SE[1], RUDEL RA[2], EULING SY[3], MAKRIS SL[3]. [1]National Institute of Environmental Health Sciences, National Toxicology Program, Research Triangle Park, NC, United States, [2]Silent Spring Institute, Newton, MA, United States, [3]NCEA, U.S. Environmental Protection Agency, Washington, DC, United States. Mammary Gland Development As a Sensitive Indicator of Early Life Exposures: Recommendations from an Interdisciplinary Workshop

Development of the mammary gland (MG), particularly the timing and extent of epithelial growth and ductal branching, can be affected after developmental exposure to a number of endocrine disrupting chemicals. Few guideline studies for testing chemicals include pre- or postnatal dosing or MG endpoints. Some current toxicity testing protocols evaluate indirect endpoints such as pup weight and nursing behaviors as surrogates for altered maternal lactation. MG assessments can include clinical and macroscopic observations, as well as comprehensive or triggered histopathology evaluation of mammary tissue. The MG whole mount assay can demonstrate morphological changes in the timing and completion of development and differentiation yet there are no standardized procedures. The goals of the 2009 Mammary Gland Evaluation and Risk Assessment Workshop were to initiate MG whole mount assay standardization and identify current consensus regarding the use of the MG assay among a multidisciplinary group of scientists. To address assay standardization, experts from seven laboratories performed an evaluation of MG whole mounts collected on postnatal days (PND) 4, 21, and 45 from mice and rats treated *in utero* with vehicle or chemical. Similar findings were reported in PND 45 mice MGs among all labs, and in PND 21 rat and mice MGs for most labs. Agreement was reached on a number of study design aspects, and thus, this assay, with additional validation efforts, could be added to existing chemical testing protocols or those under development at EPA and OECD. A majority of the workshop participants agreed that 1) rodent MG development is a reasonable surrogate for human breast development; 2) in some cases, MG changes (e.g., altered branching, extent of growth, relative proportion of terminal end buds, lobules, and/or terminal ducts) have been observed at lower doses than other endpoints of endocrine disruption; 3) these changes in MG development are abnormal, and further, could be interpreted as adverse because they represent alterations in growth and development, and may reflect altered susceptibility to carcinogenesis and/or lead to effects on lactation. Disclaimer: The views expressed are those of the authors and do not necessarily reflect the views or policies of the USEPA or NIEHS.

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NAROTSKY MG[1], KLINEFELTER GR[1], GOLDMAN JM[1], STRADER LF[1], SUAREZ JD[1], PRESSMAN JG[2], MILTNER RJ[2], SPETH TF[2], TEUSCHLER LK[3], RICE GE[3], RICHARDSON SD[4], BEST DS[1], MCDONALD A[1], MURR AS[1], HUNTER ES[1], SIMMONS JE[1]. [1]National Health and Environmental Effects Research Laboratory, ORD, U.S. EPA, Research Triangle Park, NC, United States, [2]National Risk Management Research Laboratory, ORD, U.S. EPA, Cincinnati, OH, United States, [3]National Center for Environmental Assessment, ORD, U.S. EPA Cincinnati, OH, United States, [4]National Exposure Research Laboratory, ORD, U.S. EPA, Athens, GA, United States. Assessment of Reproductive and Developmental Toxicity of Mixtures of Regulated Drinking Water Chlorination By-Products in a Multigenerational Rat Bioassay

Epidemiological and animal toxicity studies have raised concerns regarding possible adverse reproductive and developmental effects of disinfection by-products (DBPs) in drinking water. To address these concerns, we provided mixtures of the regulated trihalomethanes (THMs; chloroform, bromodichloromethane, chlorodibromomethane, bromoform) and haloacetic acids (HAAs; chloroacetic, dichloroacetic, trichloroacetic, bromoacetic, and dibromoacetic acids) as drinking water to Sprague-Dawley rats in a multigenerational reproductive toxicity bioassay. Mixtures were prepared in 0.25% (v/v) Alkamuls® EL-620, in reverse-osmosis-purified water, at 0, 500×, 1000×, and 2000× of EPA's maximum contaminant levels (MCLs) for THMs and HAAs. Chemical proportions were based on analyses at a water utility. Timed-pregnant females (P_0 generation; 25 per group) were exposed from gestation day 0 until weaning of the F_1 litters. Litter sizes were reduced to 10 pups on postnatal day (PD) 6. Litter examinations on PD 0, 6, 21, and 26 revealed no treatment effects on pre- or postnatal survival; however, pup weights were reduced at 2000× on PD 6-21and at ≥1000× on PD 26. Anogenital distance, examined on PD 0 in 15 randomly selected control and high-dose litters, was unaffected. On PD 13, eye opening was unaffected, but there was an increased incidence of retained nipples in males at 2000×. At weaning (PD 26), three females and two to four males per litter were maintained at least through puberty with continued exposure in their respective treatment groups. Both vaginal opening (VO) in females and preputial separation (PPS) in males (indicators of puberty) showed significant, dose-related delays at 1000× and 2000×. The mean ± SE age at PPS was 45.5 ± 0.3, 46.8 ± 0.3, 48.4 ± 0.6, and 51.2 ± 0.5 days at 0, 500×, 1000×, and 2000×, respectively. For VO, the respective values were 34.0 ± 0.4, 34.9 ± 0.3, 35.5 ± 0.4, and 39.8 ± 0.7. F_1 estrous cycles, breeding, and fertility were unaffected and their F_2 litters showed no effects on pup weight, or prenatal or neonatal survival. Thus, although exposure did not affect F_1 animals' ability to reproduce, puberty was delayed for both sexes at DBP concentrations ≥1000× the MCLs. [This abstract does not necessarily reflect EPA policy.]

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VAN DEN BULCK K[1], HILL A[2], JONES M[2], DODD A[2], MESENS N[1], BAILEY GP[1], DE SCHAEPDRIJVER L[1], LAMMENS L[1]. [1]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium, [2]Evotec AG, Hamburg, Germany. A Fishy Solution to Reproductive Toxicity Screening or Just a Red Herring? Zebrafish in Developmental Toxicity: Value within Pharmaceutical Development

The *in vivo* zebrafish embryotoxicity/teratogenicity assay is described as a useful alternative screening model to evaluate the effect of drugs on embryofoetal development. It enables the study of the complete developmental period of a vertebrate embryo in a simple and fast culture system but has some limitations when compared to mammalian *in vivo* test systems, i.e. the lack of a placenta or a different metabolism capacity. Fifteen compounds of the Johnson & Johnson portfolio with teratogenic (8) and non-teratogenic (7) potential, as demonstrated in rat and rabbit embryofoetal developmental toxicity studies, were tested in this model. Fertilized eggs (n=14) from adult Tuebingen zebrafish were exposed to different concentrations of the test articles from the 2-cell stage until 96 hours post-fertilization (hpf). Lethality, defined as lack of heartbeat, circulating blood, motility and the presence of necrotic tissue was assessed daily. At 96 hpf, anaesthetized larvae were observed for motility and screened for 28 morphological endpoints using a dissecting stereomicroscope. The exposure of the larvae at EC50 and LC50 was measured. Retinoic acid and saccharin were included as positive and negative controls, respectively. For the drugs testing positive in the traditional *in vivo* testing, the majority produced a similar result in the zebrafish. In most cases however the pattern of abnormalities didn't correlate between the zebrafish and mammals. For this model, a sensitivity of 75% was obtained, indicating that this might be useful in aiding drug candidate selection. For compounds testing negative in the mammalian tests, the findings were more interesting and are currently being investigated. The final conclusion will be presented at the meeting. At present the specificity has not been determined. Based on the above results, the zebrafish assay shows some potential as a screening tool for developmental toxicity within Johnson & Johnson drug development, however a more profound interpretation of the data or a larger data set might be needed. Since there is no clear correlation between the pattern of abnormalities observed in zebrafish or mammals, the anticipated results of the mammalian testing and the relevance to humans is difficult to predict.

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ZHANG CXZ, CAO JC, PANZICA-KELLY JPK, STOCK DS, AUGUSTINE-RAUCH KAA. Bristol Myers Squibb, Pennington, NJ, United States. Establishment of a Statistical Prediction Model and Abbreviated Assay Design for Teratogenicity Screening of Compounds Using Rat Whole Embryo Culture

The rat whole embryo culture (rWEC) system is a well established model for identifying and characterizing teratogenic properties of test compounds. However, the method validated by the European Center for the Validation of Alternative Methods (ECVAM) is labor intensive, requiring evaluation of a series of test concentrations and a comprehensive morphological evaluation using the Brown and Fabro score system. The objective of this study was to generate a statistical prediction model as a means to develop an abbreviated rWEC assay that requires less test concentrations and morphological score endpoints. In a separate study, a novel morphological score system was generated (the Dysmorphology-Based Score System) where crown rump length and somite count were recorded as stage/growth endpoints and the primary structures and organ systems in the gestational day 11 rat embryo were assessed and assigned a score from 1 (severely malformed) through 5 (normal morphology). In a preliminary assessment, 25 compounds (definitive teratogens and non teratogens) were evaluated at 0.1, 1 and 10 mM concentrations using Linear Discriminant analysis. The 1 mM concentration score data was found to have the best potential for separating teratogens from non teratogens by statistical modeling. Subsequently, a total of 19 non-teratogenic and 26 teratogenic compounds were tested. All compounds were assessed in multiple experiments including different laboratories. The inter-experimental data was averaged and used for building the prediction models. Among the 11 scored endpoints, heart, pharyngeal arches, rotation, presumptive spinal cord and number of somites were identified as the most promising endpoints to discriminate teratogens from non teratogens. The IC50 cytotoxicity values measured in murine D3 stem cell cultures were also included as a potential discriminator. Currently, two promising prediction models were generated. One model was based upon Recursive Partitioning analysis using heart, pharyngeal arch morphology scores, and somite number with a cross-validated error rate of 18%. The second model was based on two algorithms - Linear Discriminate and Recursive Partitioning analyses using morphological endpoints and IC50 values with similar error rates to the first model. Both models have potential value for improving throughput and results-turnaround for supporting *in vitro* teratogenicity screen assessment.

Joint TS/OTIS Platform Session IV

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EAMUS M[1], OEI J[1,2], HILL M[3], TAYLOR T[3], KENNEDY D[1,3]. [1]School of Women's and Children's Health, University of NSW, Kensington, NSW, Australia, [2]Dept. of Neonatology, Royal Hospital for Women, Randwick, NSW, Australia, [3]MotherSafe, Royal Hospital for Women, Randwick, NSW, Australia. Patterns of Psychotropic Drug Use in Pregnancy and Lactation: The MotherSafe Experience 2000-2007

Aim: The aim of this study was to analyse calls to MotherSafe regarding psychotropic medication exposures during pregnancy and lactation and to document patterns of use of these drugs in Australian women as well as to identify any trends or changes in their use during the 8 years between 2000 and 2007 MotherSafe is the largest TIS in Australia and receives over 80 calls daily regarding exposures from both women and health professionals. Methods: Retrospective analyses of Mothersafe call data (Access database) from 2000 through 2007. Records of calls regarding psychotropic medications were retrieved and analysed to establish the most frequently reported class of medication as well as individual agents. Results: Between 2000 and 2007, 7953 calls (10% total, n=79467) were made to Mothersafe regarding psychotropic medications. There was an 8-fold increase between 2000 (n=227) and 2007 (n=1716) in these calls. SSRIs were the most common group of psychotropic medications (>25% of calls were regarding sertraline). Calls regarding paroxetine decreased three-fold, from 23.8% in 2000 to 7.8% in 2007 ($p < 0.001$), as did calls about fluoxetine (17.1% in 2000 to 7.2% in 2007, $p<0.001$). Conversely, calls regarding citalopram almost doubled from 5.7% in 2000 to 10.8% in 2007 ($p = 0.04$). Calls regarding antipsychotic agents increased significantly during the study period, notably from the rural areas of NSW (metropolitan: 13.3% (n=161) pre-2004 to 15.7% (n=528), $p = 0.04$; rural antipsychotic: 7.2% (n=49) pre-2004 to 16.5% (n=334, $p< 0.001$). Conclusions: Our study shows that demand for Mothersafe's services has increased significantly, especially regarding the use of psychotropic medications. Trends in patterns of use may reflect perceptions of safety and social issues such as resource and service availability. Further work should be focused on assessing the impact of such influences on prescribing patterns and use of medication so as to improve dissemination of appropriate information to women and their health care providers and thereby optimise prescribing and use of psychotropic medications in the perinatal period.

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COLVIN L[1,2], SLACK-SMITH L[2], STANLEY FJ[1], BOWER C[1]. [1]Centre for Child Health Research, Telethon Institute for Child Health Research, The University of Western Australia, West Perth, Australia, [2]School of Dentistry, The University of Western Australia, West Perth, Australia. Birth Defects, Preterm Birth and Intrauterine Growth in the Offspring of Women Prescribed Citalopram during Pregnancy

Background: The safety of citalopram use during pregnancy remains uncertain. Linkable health datasets enable the use of large study sizes and extended periods of follow-up. Methods: In this study state-based health datasets were linked to prescription data. For women who were dispensed citalopram (cases) we compared their pregnancy outcomes to these outcomes for all other births in Western Australia (controls) from 2002-2005. Maternal socio-demographic characteristics, pregnancy and delivery information were included as well as birth outcomes such as registered birth defects (BD), birth weight and length, and gestational age. A novel approach was to include hospital admissions in the first two years of life. Results: There were 4,777 dispenses of citalopram during 1,136 pregnancies resulting in 1,157 births out of a total of 96,698 pregnancies resulting in 98,325 births. The case children were more likely to require resuscitation at birth, have a birth length < 50 cm, weigh < 2500g, be born prematurely, and have a registered BD. There were 68 (5.9%) of the case children and 4,697 (4.8%) of the control children with a registered BD (OR 1.2; 95% CI: 1.0-1.6). With first trimester exposure, a significantly increased risk was found for patent ductus arteriosus (N=5; OR 5.3; 95% CI: 2.2-13.0) and vesico-ureteric reflux (N=5; OR 8.3; 95% CI: 3.6-19.2). The mean birth admission was longer for the case children: 5.3 days *vs* 4.9 days with a median of 4.0 days in both groups. The mean number of admissions was greater for the case children even when the birth admission was excluded: 2.2 *vs* 1.8 admissions (p-value <0.0001). The case children were also more likely to be admitted to intensive care: OR 1.3; 95% CI: 1.1-1.6. Conclusions: The higher than expected number of children with vesico-ureteric reflux requires further investigation as this has not previously been reported. Through data linkage, we have demonstrated that there is an excess of non-birth hospital admissions per child before the age of 2 years in this group.

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KLIEGER-GROSSMANN C[1], WEITZNER B[1], EINARSON T[2], KOREN G[1], EINARSON A[1]. [1]The Motherisk Program, Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, the Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [2]Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada. The Safety of Escitalopram in Pregnancy: A Prospective Cohort Study

Background: Escitalopram (Lexapro®) is a 5-HT reuptake inhibitor prescribed for its antidepressant and anxiolytic activity. To date, no prospective studies documenting fetal outcome following exposure to escitalopram during pregnancy have been reported. Objectives: Primary objective: to determine whether the use of escitalopram during pregnancy is associated with an increased risk of major malformations; Secondary objective: to determine the rates of spontaneous abortions, therapeutic abortions, stillbirths, mean birth weight, low birth weight and prematurity. Methods: A prospective, observational cohort study involving pregnant and planning women who contacted the Motherisk Program in Canada and other TISs in Italy and Switzerland, between January 2003 and August 2009 requesting information on the safety of escitalopram in pregnancy. Data was collected by telephone *via* standardized questionnaire including details of exposure and fetal outcomes. Two comparison groups of pregnant women exposed to other antidepressant medications (N=213) as well as non-teratogenic exposures (N=213) were matched for maternal age and gestational age at call. Statistical analysis was performed using Fishers exact test and Chi Square statistics. Results: To date, 639 patients have completed the study. Among the 213 escitalopram exposed, 38 (17.6%) reported spontaneous abortion, 3 (1.41%) reported still birth, 19 (8.9%) reported premature birth, and 6 (2.8%) described a major malformation. Mean birth weight of exposed infants was 3198 g while low birth weights were reported in 17 (8%). Comparison group results are pending. Conclusion: Preliminary results reveal that escitalopram exposure during pregnancy does not increase the risk of major malformation above the baseline and does not appear to affect fetal survival rates, mean birth weights or duration of pregnancy.

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NULMAN I[1,2], BARRERA M[1,2], PULVER A[1], STREINER D[2,3], FELDMAN B[1,2], KOREN G[1,2]. [1]The Hospital for Sick Children, Toronto, ON, Canada, [2]The University of Toronto, Toronto, ON, Canada, [3]Baycrest Centre, Toronto, ON, Canada. Neurodevelopment of Children Exposed *In Utero* to Venlafaxine: Preliminary Results

Introduction: Venlafaxine (VLF) is widely used to control depression in women of childbearing age. VLF crosses the placenta and its effects on fetal central nervous system development have not been studied.We aim to identify the long-term neurodevelopment of children exposed to VLF during pregnancy using standardized psychological tests, and to compare the outcome to those of children exposed to SSRIs, to children of mothers with depression no medication, and to healthy children exposed to non-teratogens. Methods: Cohort study using a prospectively collected database. Four groups of children (Group 1 n=62: exposed to VLF, Group 2 n=62: exposed to SSRIs, Group 3 n=32: exposed to depression no medication, Group 4 n=62: exposed to non-teratogens). The main outcome measure was children's Full Scale IQ. Statistical analysis included descriptive statistics, ANOVA, ANCOVA, and multiple regression. Results: Children exposed to antidepressant medication achieved significantly lower scores on Full Scale IQ than children exposed to non-teratogens. Maternal IQ, group affiliation, and severity of maternal depression in pregnancy were significant predictors for child's Full Scale IQ. Severity of maternal depression during pregnancy and CES-D scores at testing were significant predictors for child's behavior (Child Behavior Checklist). VLF dose and duration of exposure during pregnancy were not found to be significant predictors for the outcomes. Discussion: Maternal depression should be balanced against the potential teratogenic effects of antidepressant medication, higher levels of stress hormones associated with depressive symptoms, and the child's long-term neurodevelopment. If indicated, the benefits of treatment should be weighed against the risk associated with uncontrolled maternal depression. Genetic and environmental factors related to maternal psychopathology are strongly associated with children's intelligence and behavior. Children of mothers with depression may be at risk for future psychopathology. More studies are needed to separate the effect of the antidepressant drug from the effect of maternal depression.

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BLAIS L[1,2], KETTANI F[2], DUCHARME FM[3], LEMIÈRE C[1,2], BEAUCHESNE M-F[1], BÉRARD A[1]. [1]Université de Montréal, Montréal, QC, Canada, [2]Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada, [3]CHU Ste-Justine, Montréal, QC, Canada. Impact of Changing the Dose of Inhaled Corticosteroids during Pregnancy on the Risk of Maternal Asthma Exacerbations

Introduction: Asthmatic women tend to reduce their use of inhaled corticosteroids (ICS) during pregnancy, but little is known on the impact of a reduction of these controller medications on the mother's health. The objective of this study was to investigate the effect of change in ICS dose during pregnancy on the risk of maternal asthma exacerbations. Methods: A cohort of 4920 pregnancies from asthmatic women who delivered between 1990 and 2002 and used ICS prior to pregnancy was selected from the Quebec administrative databases. The average daily dose of ICS taken in the 9 months preceding and during pregnancy was compared, and the relative exposure was categorized as discontinuation (decrease ≥75%), reduction (26-75% decrease), no change (± 25% change), or increase (increase ≥25%). The primary outcome was maternal asthma exacerbation, defined as an emergency department visit or a hospitalization for asthma or the use of oral corticosteroids during pregnancy. Generalized Estimation Equation models were used to estimate the association between change in ICS dose and asthma exacerbations. Results: In the cohort, 29.5% of women discontinued, 19.0% reduced, 22.7% did not change, and 28.8% increased their dose of ICS during pregnancy. The average daily dose of ICS was lower than 145 µg in fluticasone-equivalent for all women during pregnancy. The proportion of women who had an exacerbation during pregnancy was 8.2%, 21.7% and 28.8% among those who discontinued, reduced, and increased their use of ICS, respectively, while it was 20.6% for those who did not change their ICS dose. Compared to those who did not change ICS dose, women who discontinued ICS during pregnancy were less likely to have an exacerbation (OR=0.42; 95%CI: 0.33-0.54), while the opposite was observed for those who increased ICS dose (OR=1.42; 1.17-1.72). Discussion: These results suggest that women discontinued ICS because their asthma appeared sufficiently controlled without the medication, while those who were uncontrolled increased their dose of ICS to avoid an exacerbation. Despite ICS increase for some women, the observed average daily dose was quite low and the rate of exacerbation too high, indicating a need for closer monitoring of asthma during pregnancy.

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NAMAZY JA[1], MURPHY VE[2,3], POWELL H[2,4], GIBSON PG[2,4], CHAMBERS CD[5], SCHATZ M[6]. [1]Scripps Clinic, San Diego, CA, United States, [2]University of Newcastle, Newcastle, NSW, Australia, [3]Hunter Medical Research Institute, Newcastle, NSW, Australia, [4]John Hunter Hospital, Newcastle, NSW, Australia, [5]University of California San Diego, La Jolla, CA, United States, [6]Kaiser Permanente Medical Center, San Diego, CA, United States. Congenital Anomalies in Asthmatic Women Using Corticosteroids during Pregnancy: A Meta Analysis from Published Data

Introduction: There have been reports that exposure to oral corticosteroids during the first trimester may be associated with increased risk of congenital anomalies such as oral clefts. Most of these studies were not specifically conducted in women with asthma. It has also been reported that asthmatic women who experience severe exacerbations in the first trimester of pregnancy are at significantly increased risk of congenital anomalies relative to asthmatic women who do not experience exacerbations. This meta-analysis was conducted to investigate whether oral or inhaled corticosteroid use during the first trimester or history of exacerbations among pregnant asthmatics is associated with an increased risk of any (major or minor) congenital anomalies. Methods: Electronic databases were searched for the following search terms: (asthma or wheeze and (pregnan * or perinat * or obstet *)). Cohort studies that were considered for inclusion were those conducted between 1975 and 2009 in which pregnancy outcomes in women with asthma using corticosteroids during pregnancy or experiencing exacerbations of asthma (emergency treatment, emergency room visits, hospitalizations, or unscheduled visits to the doctor) were compared with asthmatic women not using corticosteroids or not experiencing exacerbations respectively. Eleven of 103 identified articles were included in this meta-analysis. Results: Corticosteroid use during pregnancy was not significantly associated with congenital malformations: inhaled (RR 0.98, 95% CI [0.90,1.07]); oral (1.19, 95% CI [0.76,1.84]); inhaled or oral (RR 0.97, 95% CI [0.87,1.08]). There was a non-significant trend towards an increased risk of congenital anomalies in infants of asthmatic women with exacerbations during pregnancy compared to infants of asthmatic women with no exacerbations (RR 1.32, 95% CI [0.95,1.82]). Discussion: Pregnant asthmatic women who experience exacerbations during pregnancy may have an increased risk of congenital anomalies compared to well-controlled asthmatic women. Oral corticosteroids are frequently used as treatment for asthma exacerbations. These data suggest that corticosteroid use (inhaled or oral) during pregnancy is not independently associated with an increased risk of congenital anomalies. Therefore, previously reported associations between oral or high dose inhaled corticosteroids and congenital anomalies may be confounded by poor asthma control.

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BRETON MCB[1], BEAUCHESNE MFB[1,2], LEMIÈRE CL[2], REY ER[3], AMÉLIE AF[2], BLAIS LB[1,2]. [1]Universite de Montreal, Montreal, QC, Canada, [2]Research Center, Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada, [3]Obstetric and Gynecology Department, CHU Ste-Justine, Montreal, QC, Canada. Risk of Perinatal Mortality Associated with the Use of Inhaled Corticosteroids for the Treatment of Asthma during Pregnancy

Introduction: Four studies reported no significant increased risk of perinatal mortality associated with the use of inhaled corticosteroids (ICS) during pregnancy. These studies must be interpreted with caution because they have insufficient statistical power and suffer from lack of adjustment for potential confounders. The aim of this study was to evaluate whether or not the use as well as the dose of ICS are associated with an increased risk of perinatal mortality among pregnant asthmatic women. Methods: A cohort including 13 004 single pregnancies from asthmatic women who delivered between 1990 and 2002 was constructed from the linkage of three administrative databases from Québec (Canada). We used a two-stage sampling cohort design to obtain information on cigarette smoking and history of stillbirth in preceding pregnancies from the medical chart of 487 selected mothers. The final estimate of the OR of perinatal mortality comparing asthmatic women exposed to those not exposed to ICS during pregnancy was estimated with a logistic regression model adjusted for maternal characteristics, pregnancy and asthma related variables. Logistic regression was also used to estimate the adjusted final OR of perinatal mortality associated with the mean daily dose of ICS. Results: The cohort was formed from 4 140 women who used 1-250 ug/day of ICS (beclomethasone-CFC-equivalent), 1 140 women who used >250 ug/day of ICS and 7 724 women who did not use ICS during pregnancy. Women exposed to ICS (any dose) were not found to be more at risk of perinatal mortality than women not exposed during pregnancy (OR=1.07: 95% CI: 0.70 -1.61). However, the use of >250 ug/day of ICS during pregnancy was associated with a non-significant 52% increased risk of perinatal mortality (OR=1.52: 95% CI: 0.62-3.76). Conclusion: The risk of perinatal mortality was not found to be associated with ICS use during pregnancy when the dose was not considered, but women taking higher doses might be at increased risk. Larger studies are needed to confirm or infirm this potential increased risk, and to investigate the relative role of a pharmacologic effect and confounding by indication in the association.

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SARANGARM P[1], LIU S[1], YOUNG BN[1], PHELAN ST[2], NAWARSKAS J[1], RAYBURN WF[2], BAKHIREVA LN[1]. [1]University of New Mexico, College of Pharmacy, Albuquerque, NM, United States, [2]University of New Mexico, Department of Obstetrics and Gynecology, Albuquerque, NM, United States. Perception of Teratogenicity among Pregnant Women with Asthma or Diabetes Mellitus

Background: The safety of medications during pregnancy is a challenge for both healthcare providers and patients. An incorrect or exaggerated perception of teratogenicity by patients may result in apprehension of medication use during pregnancy and sub-optimal control of chronic conditions or result in inadvertent exposure to medications which might be contraindicated in pregnancy. Methods: The data for this cross-sectional analysis are derived from a multi-clinic cohort study "Safety of Medications and Perception of Teratogenicity (SMART)". Pregnant women (n=405) recruited from 5 prenatal care clinics in Albuquerque, NM were interviewed about their medication use and perception of teratogenicity. Patients ranked perceived 'harmfulness' of each medication they took and the risk from uncontrolled chronic condition on a Likert-type 5-point scale with higher scores indicating higher degrees of perceived risk. The analysis was limited to 104 subjects who had a physician diagnosis of asthma or diabetes. Patients' perception of teratogenicity was determined for each major therapeutic drug class and uncontrolled maternal condition. Results: The majority of the study participants were Latina (76%), had a ≤high school education (54.8%) and had public insurance (51.9%). In the overall study population, 20% of patients had pre-existing or gestational diabetes and 8.6% had asthma. Among patients with diabetes, 78.3% indicated that uncontrolled hyperglycemia will cause birth defects or other serious problems always or very often (mean perception score 4.2±1.1). Among patients with asthma, only 33% ranked uncontrolled asthma as a serious problem (mean score 3.1±1.1). Mean perception of teratogenicity scores for major classes of anti-diabetes (insulin: 1.4±0.6; sulfonylureas: 1.8±0.8; biguanides: 1.6±0.8) and asthma medications (inhaled corticosteroids: 1.5±1.0; short-acting beta-agonists: 1.8±0.6) were quite low. We did not have enough subjects on oral corticosteroids and long-acting beta-agonists to estimate perception of teratogenicity for these classes. Conclusions: These data indicate that most patients in our population accurately ranked the risk of uncontrolled maternal chronic conditions higher than the risk from taking prescription medications which are not considered teratogenic. Further research should examine patients' perception about risks and benefits of medications with a potential teratogenic effect.

Platform Session V: Epidemiology and Clinical Studies

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DUWE K[1], RASMUSSEN S[1], LOUIK C[2], COLARUSSO T[1], REEFHUIS J[1]. [1]NCBDDD, CDC, Atlanta, GA, United States, [2]Slone Epidemiology Center, BU, Boston, MA, United States.

Maternal Exposure to Venlafaxine and Risk for Birth Defects

Few epidemiologic studies have investigated the safety of the antidepressant venlafaxine (Effexor®) during pregnancy. To examine whether use of venlafaxine during pregnancy is associated with any specific birth defect or class of defects, we analyzed data from the National Birth Defects Prevention Study (NBDPS), a multi-site population-based case-control study. We included mothers of children with birth defects (cases) and mothers of unaffected children (controls) for birth years 1997-2005 who completed the maternal interview and reported no other antidepressant use or prepregnancy diabetes. Exposure was defined as any venlafaxine use from 1 month preconception through month 3 of pregnancy. We calculated adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the 29 birth defect categories with at least 400 interviewed case mothers, controlling for maternal age, race/ethnicity, obesity, education, parity, tobacco use, and folic acid use. Among the 6,661 control mothers, 7 (0.11%) reported any use of venlafaxine from 1 month preconception through month 3 of pregnancy; among the 16,241 case mothers included, 55 (0.34%) reported any use of venlafaxine. Statistically significant adjusted associations were found for cleft palate (4 exposed cases, aOR 4.2 [95% CI 1.2-14.5]), limb defects (3 exposed cases, aOR 4.3 [95% CI 1.1-16.8]), gastroschisis (4 exposed cases, aOR 11.5 [95% CI 2.9-45.3]), and heart defects (33 exposed cases, aOR 4.2 [95% CI 1.8-9.4]). Our data suggest associations between prenatal use of venlafaxine and some birth defects, but sample sizes were small. Because we examined a large number of birth defects categories, we would expect at least one category to be significant by chance. Additional studies are needed to confirm these results.

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GILBOA SM[1], CORREA A[1], DESROSIERS T[2], LUPO P[3], LAWSON C[4], RIEHLE-COLARUSSO T[1], STEWART P[5], VAN WINJGAARDEN E[6]. [1]National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, GA, United States, [2]North Carolina Birth Defects Monitoring Program, Raleigh, NC, United States, [3]University of Texas Health Sciences Center, Houston, TX, United States, [4]National Institute for Occupational Safety and Health, CDC, Cincinnati, OH, United States, [5]Stenzel Exposure Assessments, LLC, Arlington, VA, United States, [6]University of Rochester, Rochester, NY, United States.

Maternal Occupational Exposure to Organic Solvents and Congenital Heart Defects: Results from the National Birth Defects Prevention Study, 1997-2002

Introduction: Early epidemiologic studies reported inconsistent associations between occupational exposure to organic solvents during pregnancy and congenital heart defects (CHD). Data from the National Birth Defects Prevention Study (NBDPS), an ongoing, population-based case-control study, were used to examine the association between 31 CHD subtypes in children and maternal occupational exposure to six chlorinated solvents - carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, trichloroethane, and trichloroethylene, three aromatic solvents - benzene, toluene, and xylene, and Stoddard solvent from the month before conception through the end of the first trimester (B1-P3). Methods: Mothers of cases with CHD and live-born infants without birth defects who participated in the NBDPS between 1997 and 2002 and reported working outside the home during pregnancy were eligible for this study. Industrial hygienists determined whether each mother-job was exposed to a solvent. Potential confounders included in multivariable logistic regression models were maternal age, race-ethnicity, education, smoking during B1-P3, and folic acid supplement use during B1-P3. Results: There were 3,121 CHD case mothers and 2,951 control mothers available for analysis. Overall 8.1% of control mothers and 9.5% of case mothers were exposed to any organic solvent. Considering all heart defects combined, there were no statistically significant associations with any of the six chlorinated solvents, three aromatic solvents, or Stoddard solvent. Left ventricular outflow tract obstruction defects were associated with benzene (OR=2.54; 95% CI=1.04-6.35), an association driven by aortic stenosis (OR=5.48; 95% CI=1.52-19.75). Right ventricular outflow tract obstruction (RVOTO) defects were associated with Stoddard solvent (OR=1.74; 95% CI=1.06-2.85), an association driven by pulmonary valve stenosis (OR=1.86; 95% CI=1.07-3.22). RVOTO defects were also associated with carbon tetrachloride (OR=3.47; 95% CI=1.02-11.76), perchloroethylene (OR=1.61; 95% CI=1.03-2.49), and trichloroethane (OR=1.63; 95% CI=1.07-2.19). Discussion: There is limited evidence of an association between exposure to organic solvents and CHD. The few significant associations, although noteworthy, should be interpreted with caution. To date, this is the largest epidemiologic study of maternal occupational exposure to organic solvents and CHD.

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LAMM SH[1,2], ROBBINS S[1], LU J[4], CHEN R[3], HOLLOWELL JG[5]. [1]CEOH, LLC., Washington, DC, United States, [2]Johns-Hopkins University Bloomberg School of Public Health, Baltimore, MD, United States, [3]Georgetown University, Washington, DC, United States, [4]American University, Washington, DC, United States, [5]University of Kansas, Kansas City, KS, United States. No Effect of Perchlorate on Serum Thyroxine for Pregnant Women with Low Urine Iodine

Introduction: Blount (2006) found perchlorate was a significant negative predictor of serum thyroxine (T4) for women with urine iodine < 100 ug/L, using data from NHANES 2001-2002. Pregnant women are a population of particular concern because of the potential risk to the fetus from a lowered maternal serum thyroxine (Trumbo, 2010). Previous analyses using pregnancy as a regression variable (Blount, 2006; Steinmaus, 2007) could not examine the relationship between perchlorate and thyroxine in pregnant women. We have examined these questions using specifically the NHANES 2001-2002 data on pregnant women. Methods: NHANES 2001-2002 contains a complex multistage probability sampling of the US population and includes data on serum thyroxine levels and on urinary levels of iodine and of the iodine uptake inhibitors (IUI) - nitrate, perchlorate, and thiocyanate. We have conducted multivariate analyses of IUI levels on serum thyroxine levels for pregnant women (N = 104) stratified by urinary iodine terciles (< 100 ug/L, 100-199 ug/L, and 200+ ug/L). Results: No association (p = 0.96) was found between serum thyroxine levels and log urinary perchlorate levels for pregnant women with urine iodine levels < 100 ug/L. Similarly, none was found for women with urine iodine 100-199 ug/L (p = 0.94), for women with urine iodine 200+ ug/L (p = 0.47), or for all pregnant women (p = 0.86). Models had been adjusted for log urinary nitrate, thiocyanate, creatinine, cotinine, and c-reactive protein. Log urinary creatinine was suggestively associated. Log urinary thiocyanate and log c-reactive protein were significant predictors at high urine iodine but not at low urine iodine. Discussion: Analysis of the NHANES 2001-2002 data for pregnant women finds no association between serum thyroxine and perchlorate exposure whether urine iodine level was low (< 100 ug/L), medium (100-199 ug/L), or high (200+ ug/L). The absence of this association in pregnant women with urine iodine < 100 ug/L has been reported for low iodine areas (Pearce, 2008) and high iodine areas (Gibbs 2008), but this is the first demonstration in a statistical sample of a normal iodine population.

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CARTER TC[1], OLNEY RS[2], MITCHELL AA[3], ROMITTI PA[4], BELL EM[5], DRUSCHEL CM[6]. [1]National Institute of Child Health and Human Development, NIH, Bethesda, MD, United States, [2]Centers for Disease Control and Prevention, Atlanta, GA, United States, [3]Slone Epidemiology Unit, Boston University, Boston, MA, United States, [4]University of Iowa, Iowa City, IA, United States, [5]State University of New York At Albany, Albany, NY, United States, [6]New York State Department of Health, Albany, NY, United States. Genital Tract Infections during Pregnancy and the Risk of Selected Birth Defects

Introduction: Genital tract infections are common during pregnancy and can result in adverse outcomes including preterm birth and neonatal infection. This hypothesis-generating study examined whether these infections are associated with selected birth defects. Methods: We conducted a case-control study that included 5,913 non-malformed controls and 10,547 cases with an estimated delivery date between 1997 and 2004 from the National Birth Defects Prevention Study. Maternal interviews provided data on genital tract infections that occurred from one month before pregnancy through the end of the first trimester. Infections were grouped as a single overall exposure or considered as a subgroup of three clinically-related infections: chlamydia/gonorrhea/pelvic inflammatory disease. Twenty-one case groups, each having at least 60 subjects with isolated birth defects, were considered. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression, adjusting for confounding variables. Mothers were also questioned about treatments used for reported infections; this permitted performance of sub-analyses to calculate effect estimates for treated and untreated infection. Results: Genital tract infections in the exposure period of interest were reported by 2.35% (139/5,913) of control mothers and 2.47% (260/10,547) of case mothers. Reports included group B streptococcus, chlamydia, gonorrhea, pelvic inflammatory disease, genital herpes, genital warts, trichomoniasis, bacterial vaginosis, and unspecified vaginal infections. Overall, these infections were associated with bilateral renal agenesis/hypoplasia (OR: 3.02; 95% CI: 1.18, 7.72), transverse limb deficiency (OR: 1.86; 1.06, 3.27), and full-term hydrocephaly births (OR: 2.38; 1.02, 5.57). Chlamydia/gonorrhea/pelvic inflammatory disease was associated with cleft lip only (OR: 2.54; 1.26, 5.14). Information on treatment was limited; untreated genital tract infections overall were associated with transverse limb deficiency (OR: 2.69; 1.20, 6.02) but no association was observed with treated infections (OR: 1.41; 0.65, 3.08). None of the observed associations was statistically significant after adjustment for multiple comparisons. Discussion: Concerns about possible detection bias and misclassification of infection, together with limited information on treatment require caution in interpreting the results. While these data do not provide strong evidence for an association between genital tract infections and some birth defects, additional research based on confirmed diagnoses of infections and details of treatment is needed.

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MUNGER RG[1], MANSILLA MA[3], TAMURA T[4], FELDKAMP M[2], JOHNSON K[4], BOTTO LD[2], MURRAY JC[3]. [1]Utah State University, Logan, UT, United States, [2]University of Utah, Salt Lake City, UT, United States, [3]University of Iowa, Iowa City, IA, United States, [4]University of Alabama-Birmingham, Birmingham, AL, United States. Maternal Plasma Folate, Dihydrofolate Reductase Genotype and Risk of Isolated Cleft Lip with or without Cleft Palate: Findings from a Population-Based Study

Introduction: Increased folic acid (FA, pteroylglutamic acid) intake has reduced the risk of neural tube defects but its effect on oral clefts is uncertain. FA must be metabolized to tetrahydrofolate by dihyrofolate reductase (DHFR) to yield active forms of folate. The association between total plasma folate concentrations, DHFR genotype and risk of oral clefts was examined in a population-based case-control study in Utah. Methods: Participants included 178 mothers of children with isolated cleft lip, with or without cleft palate (CL/P cases), identified from the population-based registry of the Utah Birth Defect Network, and 356 mothers of children without birth defects (controls), selected randomly from birth certificates. Cases with multiple congenital anomalies and syndromes were excluded. Maternal blood samples were collected one year or more after birth of the index child and assayed for plasma folate and genotyped at DHFR rs1643638 (common allele T and minor allele C). Results: Risk of CL/P was 65% lower in the highest *vs*. lowest quartile of plasma folate (odds ratio (OR) = 0.35; 95% confidence interval (CI) = 0.21-0.57). Overall there was no significant association between DHFR genotype and CL/P risk. However, when stratified by DHFR genotype, the highest *vs*. lowest plasma folate quartile had a stronger protective effect in the TT genotype (OR = 0.19; 95% CI = 0.09-0.38) and no protective effect in the CC genotype (OR = 1.25; 95% CI = 0.25-6.24). Further analyses revealed that DHFR genotype had a protective effect among mothers in the lowest quartile of plasma folate (TC *vs*. TT genotype OR = 0.67, 95% CI = 0.34-1.30; CC *vs*. TT genotype OR = 0.33, 95% CI = 0.09-1.18) and an adverse effect among mothers in the highest quartile of plasma folate (TC *vs*. TT genotype OR = 2.32, 95% CI = 1.07-5.05); CC *vs*. TT genotype OR = 2.22, 95% CI = 0.66-7.45). Discussion: In the current era of high FA intake due to food fortification and supplement use, DHFR genotype may interact with plasma folate level to modify risk of oral clefts. Replication studies are needed with analyses of additional biomarkers, DHFR variants and their interactions.

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FELIX R[1], CHAMBERS CD[1,2], COBIAN V[1], PRINCE L[1], KAO K[1], ALVARADO S[1], JONES KL[1]. [1]University of California, San Diego, Department of Pediatrics, La Jolla, CA, United States, [2]University of California, San Diego, Department of Family and Preventative Medicine, La Jolla, CA, United States. An Electronic Medical Record (EMR) System-Based Referral Facilitating Access to Teratogen Risk Counseling for Health Care Providers and Their Patients

Background: The California Teratogen Information Service (CTIS) and Clinical Research Program offers a free phone-based and email service to provide pregnancy health education and risk-assessments regarding preventable birth defects. Although there is a demonstrated need for CTIS services, there are barriers to practitioners making referrals. Objective: As electronic medical record systems (EMR) are being adopted in numerous health systems, CTIS sought to pilot test an enhanced method of access to services by health care providers and their patients by implementing an automated electronic method within UCSD Medical Center's EMR system, EPIC. Methods: Software programming modifications were made to the EPIC EMR system to support EPIC referral and information exchange with CTIS, and training for providers was initiated. Subsequently, during each office visit with a pregnant patient, the participating clinician who enters the EPIC system may receive an automated Teratogen Best Practice Alert prompt (TBPA), depending on predetermined criteria including the patient's problem list, past medical history, and encounter diagnosis list. If the clinician deems the referral appropriate and "accepts," the referral is included in the after visit summary provided to the patient. Within 24 hours, CTIS counselors receive the TBPA referral *via* EPIC and patient contact is initiated. A comprehensive patient interview is conducted and risk assessment and education provided. This information is then summarized and returned to the referring clinician *via* EPIC. Results: In the six completed months of the pilot phase of this system, CTIS has received over 100 EPIC referrals, primarily for high-risk diagnoses including drug exposure, and maternal diabetes. Patient counseling and clinician education has been successfully completed for 96% of those referrals, and upon completion, summary counseling has been uploaded into the EPIC record within 5 business days.Conclusion: EMRs have the potential to improve delivery of health care services. Through use of an enhanced CTIS referral system, using EPIC, clinicians can overcome barriers to referral of their patients and improve quality of care. The EMR-based partnership between obstetric health care providers and CTIS within UCSD provides a cost-neutral team-based approach to healthcare quality improvement.

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HARTMAN RJ[1,2], RASMUSSEN SA[1], RIEHLE-COLARUSSO T[1], BOTTO L[3], CORREA A[1]. [1]CDC's National Center on Birth Defects and Developmental Disabilities, Atlanta, GA, United States, [2]Oak Ridge Institute for Science and Education, Oak Ridge, TN, United States, [3]Division of Medical Genetics, University of Utah, Salt Lake City, UT, United States. The Contribution of Chromosomal Abnormalities to Congenital Heart Defects: A Population-Based Study

Chromosome abnormalities have long been observed in infants with congenital heart defects (CHDs). Recent advances in cytogenetic technology have allowed for improved evaluation of the types of chromosomal disorders associated with CHDs in the clinical setting. Our objective was to evaluate the frequency of chromosomal abnormalities among live born infants and fetal deaths with CHDs on a population basis. We reviewed data on CHD cases delivered from 1994-2005 and registered in the Metropolitan Atlanta Congenital Defects Program, a population-based birth defects surveillance system that uses active methods of case ascertainment and multiple data sources to identify infants with birth defects born to mothers who reside in the central five-county metropolitan Atlanta area. CHD phenotypes were classified based on an adaptation of the Society of Thoracic Surgeons nomenclature and classification system. We identified 4,430 cases with CHDs, for a birth prevalence of 7.9 per 1,000 live births. Among cases with CHDs, 546 (12.3%) had a chromosomal abnormality. The most common chromosomal abnormalities among infants with CHDs were trisomy 21 (53%), trisomy 18 (13%), 22q11.2 deletion (12%), and trisomy 13 (5.7%). CHDs most likely to be associated with a chromosomal abnormality were interrupted aortic arch (type B and not otherwise specified) (69%), atrioventricular septal defect (67%), and double outlet right ventricle (33%). CHDs least likely to have a chromosomal abnormality were heterotaxy (2.2%), Ebstein anomaly (2.6%) and pulmonary valve stenosis (3.3%). Our study shows that approximately 1 in 8 infants with a CHD have a chromosomal abnormality. This finding is similar to the estimated prevalence seen in most previous studies. The three most prevalent trisomies and 22q11.2 deletion make up the majority of chromosome abnormalities seen in infants with CHDs. Clinicians should have a high index of suspicion to obtain cytogenetic testing in infants with CHDs, especially for specific types of CHDs. Studies aimed at identifying non-genetic risk factors for CHDs need to consider the frequency of chromosomal abnormalities among infants with these conditions.

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HOOTNICK DR. Upstate Medical University, Syracuse, NY, United States. Thalidomide Embryopathy Mimics Idiopathic Congenital Vascular and Skeletal Dysmorphologies

Introduction: The literature recognizes a consistent and well established association between embryonic dysvasculogenesis and the pleomorphic skeletal dysmorphologies of the idiopathic congenital short limb (CSL). CSL includes all segments of the human lower limb including the femur to a variable degree. The idiopathic femoral hypoplasias studied with CT angiography has independently been associated with deficiencies and diminution of the proximal limb vasculature as well as preservation of an embryologically primitive "ischiatic artery". In the past no essential anatomic differences have been observed between ideopathic and thalidomide induced femur hypoplasias. Recent research has revealed that thalidomide embryopathy is caused by loss of the forming limb vasculature. Methods: A critical retrospective review of dysvasculogenesis demonstrated to have been associated with idiopathic CSL was initiated. We compared and contrasted documented examples of arterial dysgenesis with the theoretical changes anticipated through the mechanism of thalidomide dysvasculogenesis. Results: All segments of the idiopathic CSL including both arterial and skeletal dysmorphologies are explicable on the basis of thalidomide dysvasculogenesis: short femur, kyphotic tibia, unossified fibular anlagan and midline metatarsal dysplasia. Conclusions: Thalidomide embryopathy mimics idiopathic congenital vascular and skeletal dysgenesis. We have previously hypothesized that an "etiologically significant" relationship exists between the development of the bony and arterial abnormalities in idiopathic CSL.

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PACHAJOA H, ARIZA Y, SUAREZ M, AGUILAR C, ISAZA C, MÉNDEZ F. Universidad del Valle, Cali, Colombia. Factors Associated with the Occurrence of Vascular Disruption Defects and Their Relationship with Heavy Metals: Case-Control Study in Cali, Colombia (South America) 2007-2009

Introduction: Vascular disruption defect (VDD) refers to birth defects caused by a disturbance (disruption) of the vascular system, altering blood flow and the availability of O_2 in the tissue or organ that is being formed during a critical period, are multifactorial, with interactions between multiple maternal and environmental factors in the early weeks of gestation. Its prevalence has increased in recent decades, mainly gastroschisis. Methodology: A case control study was designed to evaluate risk factors associated to vascular disruption defect occurring in the study area. Cases were defined as newborns with VDD and normal karyotype. Controls were selected from the same hospital with conception dates +/- two weeks from those of cases. A comprehensive questionnaire was applied to all women including the following information: Demographic and socioeconomic, behavioral (smoking, marihuana and cocaine), environmental exposures (activities with high risk), diet (intake: folic acid, Zn, Fe), pregnancy and birth. Hair samples were used for heavy metal measurement (cadmium, lead and zinc) by atomic absorption spectrophotometry. Results: Smoking mothers during the first trimester had a VDD odds ratio (OR) of 2.07 (95% confidence interval (CI)= 0.7 - 5.78). Mothers exposed to secondhand smoke during the first trimester had a VDD OR: 3.76 (95% CI = 1.49 - 49.6) compared to those unexposed to secondhand smoke. Alcohol, marijuana and cocaine were not related to VDD, but paternal consumption of marijuana (OR: 4.47; 95% CI: 1.57 – 12.5) or cocaine (OR: 5.06; 95% CI: 1.54 – 16.63) was associated with VDD. Measurements of heavy metals suggested that levels of cadmium were related, but not significantly (OR: 1.17; 95% CI: 0.23 – 4.93). For zinc and lead, there was no association. Exposure to misoprostol (OR: 14.14; 95% CI: 1.29 – 703.14) as an abortifacient was associated with VDD. Discussion: This study suggests that cigarette smoke including secondhand exposure is a risk factor for VDD. Exposure to misoprostol as an abortifacient was associated with VDD. Preliminary results suggest cadmium levels adjusted by high lead and low zinc levels are positively associated to VDD.

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JONES KL[1], HAGEY LR[2], GONZALEZ V[1], BENIRSCHKE K[3], CHAMBERS CD[1,4]. [1]University of California, San Diego, Department of Pediatrics, La Jolla, CA, United States, [2]University of California, San Diego, Department of Internal Medicine, La Jolla, CA, United States, [3]University of California, San Diego, Department of Pathology, La Jolla, CA, United States, [4]University of California, San Diego, Department of Family and Preventative Medicine, La Jolla, CA, United States. Maternal Dietary Fat Intake As a Potentially Preventable Cause of Gastroschisis

Introduction: Although a number of risk factors have been identified, the etiology of gastroschisis is unknown. We have documented lipid laden molecules made up of triglycerides ester-linked to an unusual pattern of fatty acids, lacking in essential polyunsaturated fatty acids, in the amniotic epithelial cells of all newborns with gastroschisis. Methods: Based on that observation, we have begun a study to characterize the dietary habits, nutritional status, and fatty acid composition of phospholipids in pregnant women and their offspring who have gastroschisis (cases) as opposed to mothers who have normal babies (controls). Twenty-four hour dietary recall and red blood cell (RBC) phospholipids are evaluated in mothers in both groups at mid-gestation; at the time of delivery RBC phospholipids are measured in both the mother and baby in both groups as well as fatty acids in amnion epithelial cells. Results: To date, we have evaluated the fatty acids in RBC phospholipids from seven pregnant women at 22 weeks' gestation, each of whom was carrying a fetus with gastroschisis and in two controls. Both the control population of young, first time mothers, and those mothers with a gastroschisis fetus are slightly low (average 7.5%; 90% of the general population mothers) in arachidonic acid (20:4), and substantially lower (average 2.4%; 55% of the general population mothers) in docosahexanoic acid (22:6), the two most important essential polyunsaturated fatty acids. This finding was consistent with the mothers' dietary history which was deficient in essential fatty acids in both the cases and the controls. However whereas control fetuses preferentially accumulated 20:4 and 22:6 polyunsaturated fatty acids at the expense of the mother, the opposite occurred for docosahexanoic acid (22):6 in the neonates with gastroschisis. (maternal control=1.6%/neonatalcontrol=4.8% *vs* maternal gastroschisis=2.4%/neonatal gastroschisis=1.8%) Discussion: These preliminary results suggest an etiologic association between gastroschisis and maternal nutritional status and possibly the quality of maternal dietary intake. They further suggest that a specific defect in placental transfer of these essential lipids maybe an important genetic mechanism involved in the etiology of gastroschisis, explaining why only a small proportion of women nutritionally deficient in essential fatty acids give birth to a baby with gastroschisis.

TERATOLOGY SOCIETY

POSTER ABSTRACTS

(Presenter designated by underlined author.)

Monday Poster Session

P1

LACASSE-GUAY V[1], THUOT M[1], NGUYEN S[1], BRINDAMOUR D[1], COURSOL TELLIER MA[1], BEAUCHESNE MF[1,2], FILLION A[1,2], FORGET A[1,2], BLAIS L[1,2,3]. [1]Université de Montréal, Montreal, QC, Canada, [2]Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada, [3]Endowment Pharmaceutical Chair AstraZeneca in Respiratory Health, Montréal, QC, Canada.

Impact of Body Mass Index on Patterns of Asthma Medication Use in Pregnant Women

Introduction: Studies report that asthmatic women tend to reduce their use of inhaled corticosteroids (ICS) during pregnancy. However, no study has investigated the role of obesity (a co-morbidity that can potentially worsen asthma symptoms) on the use of asthma medications during pregnancy. Therefore, the primary study objective was to determine if pre-pregnancy body mass index (BMI) is associated with changes in the use of ICS and short-acting β_2-agonists (SABA) during pregnancy. Methods: Three databases from Quebec (Canada) were linked to obtain a cohort of 1100 pregnancies of asthmatic women who gave birth between 1990 and 2002 and used ICS in the year prior to pregnancy. The primary outcome was a clinically significant reduction of ICS use defined as a reduction of 25% or more in the mean daily dose throughout pregnancy, compared with the previous year. The same criterion was used to describe changes in SABA use. Following the WHO recommendations, underweight (BMI < 18.5), overweight (25.0 ≤ BMI < 30.0) and obese (BMI ≥ 30.0) were compared to normal weight (18.5 ≤ BMI < 25.0) women. Poisson regression models were used to obtain relative risks of ICS or SABA use reduction in association with the BMI, adjusted for socio-demographics and pregnancy characteristics. Results: In 44.5% (n=489) of the pregnancies, mothers reduced by 25% or more their use of ICS. Comparatively, in 34.8% (n=383) of the pregnancies, mothers significantly reduced their use of SABA. Among women who used ICS during pregnancy, the mean daily dose was low in all four study groups, ranging from 248 to 347µg in beclomethasone-CFC equivalents. On the other hand, users of SABA took high doses, ranging from a mean of 10 to 12 doses per week. The BMI was not found to be significantly associated with changes in ICS use (underweight: RR=1.040; 95% CI=0.774-1.398, overweight: RR=0.932; 95%CI=0.739-1.177, obese RR=0.882; 95%CI=0.687-1.133) nor was it associated to changes in SABA use. Conclusion: The pre-pregnancy BMI was not found to be associated with changes in the use of asthma medications during pregnancy. However, many women decreased their use of ICS and SABA during pregnancy.

P2

THUOT M[1], NGUYEN S[1], LACASSE-GUAY V[1], COURSOL TELLIER MA[1], BRINDAMOUR D[1], BEAUCHESNE MF[1,2], FILLION A[1,2], FORGET A[1,2], BLAIS L[1,2,3]. [1]Université de Montréal, Montreal, QC, Canada, [2]Hôpital Sacré-Coeur de Montréal, Montreal, QC, Canada, [3]Endowment pharmaceutical Chair AstraZeneca in Respiratory Health, Montreal, QC, Canada.

The Impact of Obesity and Asthma During Pregnancy on Perinatal Outcomes

Introduction: One study investigated the combined effect of maternal asthma and obesity on perinatal outcomes and reported no association with mean birth weight and gestational age. It did not consider the outcome "small for gestational age" (SGA) which is a more precise measure of intrauterine growth. The purpose of our study is to investigate the combined effect of maternal asthma and obesity on the risk of SGA. Methods: A cohort formed of 1386 pregnancies from asthmatic women was reconstructed using 3 Quebec's databases from 1990 to 2002, and a mailed questionnaire. The mother's pre-pregnancy body mass index (BMI) was calculated using the height and weight she reported and categorised following the WHO recommendations. Underweight (BMI < 18.5 kg/m^2), overweight (25.0 kg/m^2 ≤ BMI < 30.0 kg/m^2) and obese women (IMC ≥ 30.0 kg/m^2) were compared to normal weight women (18.5 ≤ BMI < 25.0 kg/m^2). The primary outcome was the birth of a SGA infant defined as a birth weight below the 10th percentile for gestational age and gender, according to Canadian standards. A logistic regression model was used to obtain odds ratios of SGA as a function of the BMI, adjusted for the age of the mother, parity, maternal weight gain and use of short-acting inhaled beta$_2$-agonists during pregnancy. Results: The proportion of women categorised as underweight, normal weight, overweight and obese was 10.8%, 53.3%, 19.7% and 16.2% respectively. The crude risk of SGA was 23.5% for underweight, 16.0% for normal weight, 11.7% for overweight and 8.4% for obese women. The adjusted risk of SGA was significantly reduced for obese women (OR: 0.5, 95%IC: 0.3-0.9). Overweight women had a non significant reduction in risk (OR: 0.7, 95%IC: 0.5-1.1) and underweight women had a non significant higher risk of SGA (OR: 1.3, 95%IC: 0.8-2.1). Conclusion: Obese asthmatic women were found to be less likely to give birth to SGA infants than normal weight asthmatic women. We can conclude that there was not a negative interaction between asthma and obesity on the risk of SGA.

P3

DELRAHIM-HOWLETT K[1,2], CHAMBERS CD[1], CLAPP JD[2], DUKE K[1], XU R[1], MOYER R[2], VAN SICKLE D[2], LARSON S[2]. [1]University of California, San Diego, La Jolla, CA, United States, [2]San Diego State University, San Diego, CA, United States. Web-Based Intervention for Alcohol Use in Women of Childbearing Potential

Introduction: There is a need for more effective assessment and primary prevention programs aimed at accurately measuring and reducing alcohol consumption before conception in underserved, high-risk populations. Health Information Technology (HIT) may serve this purpose; however, the effectiveness of such tools is not known. Methods: We conducted a small-scale randomized controlled trial to test the effectiveness of an adapted web-based alcohol assessment and intervention tool among low-income, non-pregnant women of reproductive age who were receiving WIC services in San Diego County and who reported currently drinking in a binge pattern. Results: A total of 150 binge-drinking participants completed a web-based assessment and were randomly assigned to either receive a personalized feedback intervention OR general health information about alcohol consumption and Fetal Alcohol Syndrome. Follow-Up assessments on reported alcohol consumption were conducted *via* telephone at 1- and 2-months post baseline. Participants ranged in age from 18 to 44 and were predominately Hispanic/Latina (44%). At baseline, all respondents reported consuming $\geq$3 standard drinks on $\geq$1 occasion in the previous month. Outcome was available for 131 participants. The main outcome measure was reduction in number of risky drinking occasions, and did not differ significantly between treatment conditions, (OR 1.200, 95% CI 0.567-2.539, p=0.634). However, over 70% of the participants reported a reduction in risky drinking occasions regardless of treatment condition (Control 43/63, 68%; Experimental 49/68, 72%). Furthermore, after controlling for confounding in a multivariate hierarchical logistic regression model, the estimate of treatment effect reached borderline significance (OR 2.922, 95% CI 0.991-8.613, p=0.052). Discussion: The results of the present study demonstrate that web-based assessment of alcohol consumption among low-income women of reproductive age, as represented by WIC clients, is feasible and acceptable. The findings also suggest that detailed and interactive assessments of alcohol consumption may be sufficient for the reduction of risky drinking within this population and personalized feedback may be more effective for a subset of individuals.

P4

STRÖMLAND K. Gothenburg University, Gothenburg, Sweden. Worldwide Frequency of Thalidomide Embryopathy 50 Years Later

Thalidomide was taken off the market in 1961-62 after having caused severe birth defects in an estimated number of 10000 children worldwide. However, the drug has been remarketed in several countries for treatment of various diseases, mostly erythema nodosum leprosum and multiple myeloma. Despite the very strict safety precautions taken, new cases of thalidomide embryopathy (TE) have been reported. There are "three generations" of TE, the first comprising the years 1957-65, the second 1966-99 and the third generation consisting of children born during the 2000s. One report (Castilla *et al* 1996) found 34 TE cases born after 1965 in different South American countries and Schuler-Faccini *et al*. (2007) described three new cases in Brazil born since 2005. In order to find out the present frequency of individuals with TE in different ages, TE associations and individuals with TE with special knowledge in the area around the world were inquired about the number of living individuals with officially recognized TE in their country in 2009. Information on deaths of affected individuals during recent years was also asked for. Thirteen countries reported their number of individuals with TE. Only Brazil reported cases from all three generations; 317 were born 1957-65, 144 cases 1966-98, and four children with TE were born 2005-2006. Information on the number of individuals with TE alive in 2009, all belonging to the first generation (1957-1965), was received from Germany (2672), Sweden (99), Norway (12), Finland (1), Denmark (5), The Netherlands (17), United Kingdom (467), Ireland (32), Japan (296), Australia (40), New Zealand (9), and Canada (95). Some countries reported the number of deaths during recent years. The reported data show only an approximate number of alive TE cases around the world because many countries still do not officially recognize TE and some cases may be misdiagnosed. However, children are still being born with TE because of ignorance and poor information on the teratogenicity of thalidomide in its new use in treating some diseases. Continuous intense information how to avoid new cases of TE has to be given focusing on exposed populations.

P5

DZUBOW RC[1,2]. [1]Brookings Institution, Legis Congressional Fellowship, Washington, DC, United States, [2]U.S. Environmental Protection Agency, Washington, DC, United States. Legislative Initiatives in the 111th U.S. Congress Related to Early Lifestage Exposures to Chemicals

Introduction: Legislative actions can advance the federal government's ability to regulate chemicals manufactured, produced, or imported in the United States, as well as provide federal funding for relevant scientific research on exposure and adverse health effects. A concern for harmful chemical exposures during early lifestages has been one justification for recent legislative initiatives. In particular, these include actions that impact the activities of the Environmental Protection Agency, the Food and Drug Administration, the Consumer Product Safety Commission, National Institutes of Health and several other federal agencies. Methods: Legislation introduced during the 111th Congress related to chemicals and early lifestage exposure were identified using The Library of Congress' THOMAS legislative database. Results: A number of Congressional bills regarding harmful chemicals were identified that are based on a concern for early lifestage exposure and adverse health outcomes during childhood. These include bills on endocrine disrupting chemicals, bisphenol-A, mercury, and perchlorate. In addition, expected revisions to the Toxic Substances Control Act are likely to be based on concern for early lifestage exposure. Discussion: Many States are also considering and passing legislation based on concern for early lifestage exposure to chemicals, although there is broad consensus from many stakeholders that these efforts need to take place at the federal level. There is general recognition among federal legislators for the need to protect children from exposure to harmful chemicals. Disclaimer: These views are those of the author and do not represent those of the US Environmental Protection Agency or the Brookings Institution.

P6

THORSRUD BA, RESENDEZ JC, HOLDSWORTH DL, FAQI AS, BAIRD TJ. MPI Research, Mattawan, MI, United States. A Comparative Evaluation of Cardiac Parameters of the Electrocardiogram (ECG) in Juvenile Beagle Dogs and Non-Human Primates

Recent requirements by regulatory authorities to pursue juvenile preclinical testing have focused on pediatric guidelines intended to help characterize and identify potential differences in the effects of drugs in the juvenile population. Historically, therapeutic agents were limited to standard adult animal models for drug safety assessments. An important part of the evaluation of the juvenile large animal, such as the dog and non-human primate (NHP), is basic electrophysiology *via* ECG. The objective of this study was to evaluate and compare ECG datasets and telemetry profiles obtained from juvenile dogs and NHP's, and consider trends that may be species or age specific when compared to adult animals. Post-weaning beagle dogs were evaluated at 7 and 11 weeks of age using a modified 6-lead ECG system (Leads I, II, III, aVR, aVL, and aVF, recorded at 50 mm/sec). Young cynomolgus macaques approximately 7-14 months old were implanted with a pressure-sensitive catheter within the descending aorta, and a bipolar electrode implanted to record a Lead II ECG. Heart rate, blood pressure, body temperature and the ECG were collected according to a bi-weekly schedule using PoNeMah (Ver 4.1) software. Comparative data indicate distinct differences in heart rate and ECG intervals sensitive to heart rate variability in juveniles, as compared to adults. Fixed-factor QT correction procedures performed differently in adult and juvenile animals, with elevated heart rates in juveniles associated with changes in the estimation of QTc. The results obtained from these data sets confirmed maturational differences in chronotropy, and associated changes in some indices of electrocardiographic cycling.

P7

COWAN J[1], LENNOX L[1], KENFIELD J[1], ONEDA S[1], MAKORI N[1], GOLUB M[2], EYRE R[1], TSUSAKI H[1], NAGATA R[3]. [1]SNBL USA, Ltd., Everett, WA, United States, [2]University of California Davis, Davis, CA, United States, [3]Shin Nippon Biomedical Laboratories, Ltd., Kagoshim, Japan. Learning and Memory Evaluations in Infant and Juvenile Cynomolgus Monkeys

The aim of this study is to develop an object discrimination and reversal (ODR) protocol as a tool of evaluation for learning and memory for mandated postnatal developmental toxicology testing. Ten naïve animals were acclimated to the food rewards, stimulus objects, WGTA presentation board and transfer/holding box for variable adaptation periods based on age. The ODR task consisted of three consecutive phases: 1) Training phase: each animal was trained to consistently displace an object covering a well to retrieve a food reward; 2) Learning phase: each animal learned to discriminate between two objects presented simultaneously, a positive object (rewarded) and a negative object (not rewarded); 3) Reversal phase: the positive and negative objects from the learning phase were reversed so that each animal had to inhibit a learned response to select the previously negative object (now the positive object). Testing was conducted once per day for five days per week and each phase of the ODR task consisted of 20 trials in which animals had 30 seconds to respond. The number of sessions conducted during the training phase was open-ended until the animals met criterion, 18 out of 20 correct responses (retrieval of reward from fully-covered well). The total number of sessions for learning and reversal was limited to 30. Criterion for the learning and reversal phases was 23 correct responses out of 25 consecutive trials conducted over two days of testing. Additional reversals were conducted for animals that met criterion before reaching the 30-session limit. On average, the number of sessions to criterion for the training phase was 6 (range 2 to 12), 12 (range 4 to 24) for the learning phase, and 6 (range 3 to 12) for the seven animals that completed the first reversal. The number of reversals completed within the 30-session series was on average 3 (range 1 to 7). In conclusion, the object discrimination and reversal task using a modified WGTA with carefully defined end-points is suitable for use in toxicology studies in infant and juvenile cynomolgus monkeys to evaluate potential effect on learning and memory.

P8

MEYER JK, BROCKUS CW, HUFF AS, CHELLMAN GJ. Charles River Laboratories, Preclinical Services Nevada, Reno, NV, United States. Strategies for Reducing Variability of Male Reproductive Data in Nonhuman Primate DART Studies

Nonclinical development of biotherapeutics frequently involves studies in nonhuman primates (NHPs), including reproductive toxicology studies. Fertility evaluations are generally conducted before Phase III clinical trials, and in NHPs can be evaluated in stand-alone studies or incorporated into chronic toxicity studies [ICH M3(R2) and S6(R1)]. In males, these studies may include not only histopathologic evaluation of testis, but also analysis of semen parameters, testicular volume (TV), and/or testosterone (T) levels. Male reproductive data may be highly variable, therefore challenging to interpret. This abstract reviewed data from three previously-conducted male fertility studies in cynomolgus monkeys to determine if revised procedures for determination of TV and T were effective in reducing data variability. When TV was determined by ultrasound instead of conventional caliper measurements, the coefficient of variation (CV) was reduced from 20.8% to 8.4% (60% decrease in variability). Average TV for sexually mature NHPs (>5-6 years old) by ultrasound (49.0 ± 15.1 mL, n = 39) was slightly smaller than caliper (59.6 ± 21.4 mL, n = 144), as expected. In an attempt to decrease variation in T, which is secreted episodically every ~2 hours in NHPs, blood sampling was done at the same time each day (morning), and also by collecting more than one sample at each interval (i.e., 3 blood samples collected 20-40 min apart, at 4 intervals over 3 months). Unexpectedly, data analysis showed that the collection of multiple blood samples at each interval did not decrease variability. Average T values (ng/dL) calculated for 1, 2, and 3 blood samples for mature male NHPs were 673 ± 418, 726 ± 385, and 724 ± 391 (mean ± SD, n = 83), respectively. CVs were calculated for each animal over time, using each frequency of sampling (1, 2, or 3 samples), then summated by group average. Results showed comparable variability in the final derived T values regardless of blood sample frequency (CVs were 62, 53, and 54% for 1, 2, and 3 samples, respectively). These results suggest that variability of testicular volume data, but not testosterone data, were improved by modification of study procedures.

P9

LALAYEVA N[1], KENFIELD J[1], ONEDA S[1], MAKORI N[1], EYRE R[1], TSUSAKI H[1], NAGATA R[2]. [1]SNBL USA, Ltd., Everett, WA, United States, [2]Shin Nippon Biomedical Laboratories, Ltd., Kagoshima, Japan. Infant Postnatal Assessments in Developmental Toxicology Studies in Cynomolgus Monkeys

Infant developmental monitoring, following test compound administration throughout pregnancy in cynomolgus monkeys, is an integral part in the enhanced pre-/post natal developmental toxicology studies. The aim of this poster is to present infant background data, collected prior to birth and through seven months post delivery, based on the proposed revision to ICH 6S guideline. Monitored parameters included incidence of newborn losses at natural delivery, external teratological examination at birth, skeletal development at Post Natal Day (PND) 30, external morphometrics at PNDs 3, 30, and 95, behavioral monitoring (e.g. exploratory, climbing activity, release grasp, and self-clasp) at PNDs 45, 105, and 195, body weights (weekly), immunophenotyping of peripheral blood lymphocyte subsets, and TDAR (specific anti-KLH immunoglobulins) following KLH primary and secondary immunization. Incidence of stillbirths ranged from 0% to 21.4%. Average infant body weights at birth were 323.3 g (220.4 g to 441.8 g) and 404.4 g (276.0 g to 510.4 g) one month after birth. No abnormalities were observed during external or skeletal examinations. External morphometrics showed steady changes throughout the 7 month post-natal period. Similarities in behavioral development were demonstrated in >90% of infants. At PND 30, the relative percentage (of total lymphocytes) of CD3+ T-lymphocytes was 64% and that of total B-lymphocytes (CD20+ and CD40+ cells) was 29%, similar to adult females. The CD3+CD4+ T-lymphocyte percentage was 47% at PND 30 compared to 34% in adult females, while the percentage of CD3+CD8+ T-lymphocytes was 19% at PND 30 compared to 30% in adult females. The relative percentage of NK cells (CD3-CD16+) was 5% at PND 30 compared to 10% in adult females. Following primary KLH immunization, a robust immune response was evidenced by antibody production and a class switch from IgM to IgG KLH-specific antibodies. The mean IgM values increased by ~2-fold and the mean IgG values by ~5-fold after the second immunization. No KLH-related changes occurred on populations of peripheral blood lymphocytes (T, B or NK cells). In conclusion, evaluation of a combination of established parameters serves as a meaningful reference of infant development in pre-/postnatal reproductive toxicology studies.

P10

CARRUTHERS CM, STAHL K, EDEN E. Covance Laboratories Inc, Vienna, VA, United States. Amniotic Fluid Collection in Rats and Rabbits

Amniotic fluid can prove to be of great value in toxicology studies. It can be analyzed for compound and/or metabolite to indirectly determine fetal exposure, to assess the ability of the placenta to transfer compound and/or metabolite, and to determine if additional metabolism of the compound and/or metabolite by the placenta occurs. In this study, amniotic fluid was collected from untreated Sprague Dawley rats and New Zealand White rabbits on gestation day (GD) 9-20 or 9-29, respectively. The volume of fluid collected was measured and recorded. Amniotic fluid was successfully collected from rat amniotic sacs as young as GD 12. These amniotic sacs had a pooled volume of approximately 0.42 mL collected from a mean number of 14 amniotic sacs. Amniotic fluid volume peaked at GD 18 (3.18 mL) and by GD 20 the volume was markedly reduced (1.28 mL). Although attempts were made, amniotic fluid could not be collected from amniotic sacs earlier than GD 12. The earliest gestational age of clear amniotic fluid could be collected from rabbit amniotic sacs on GD 13. These amniotic sacs had a pooled volume of approximately 1.27 mL collected from a mean number of eight amniotic sacs. Amniotic fluid volume peaked on GD 25 (24.35 mL) and was markedly reduced by GD 27 (2.18 mL). Rabbit amniotic fluid collected on GDs 9-12 was cloudy and it is theorized to not be of the quality suitable for analysis; however it should be noted that fluid was present at these young gestational ages. In conclusion, amniotic fluid volumes peak at approximately GD 18 and 25 in rats and rabbits, respectively. Fluid can be collected from rat amniotic sacs as young as GD 12 and rabbit amniotic sacs as young as GD 13. The volume of fluid at this gestational age is very small; however if analysis of amniotic fluid at this early gestational age is required, additional animals may be added to the pool to enlarge the sample size to enable a qualitative analysis.

P11

TORNESI B[1], HASLBERGER T[2], CALDWELL R[1], VOGG B[2], TARCSA E[1], BLAICH G[2], SEEMANN D[2]. [1]Abbott Laboratories, Abbott Park, IL, United States, [2]Abbott GmbH & Co.KG, Ludwigshafen, Germany. Is PK Modeling an Option to Identify Optimal Dosing Regimens for Therapeutic Antibodies in Developmental Toxicity Studies in Rats?

Rodent species can be used for toxicology assessments of therapeutic antibodies if justified based upon adequate species-specific target binding, tissue cross reactivity and pharmacokinetic profiles. When enabled, the rat becomes an attractive model species to conduct reproductive and embryofetal (SEGII) toxicity studies. Monoclonal antibodies (mAbs) are well known to have long half-lives, usually > 7 days, and are often administered weekly. A dosing interval shorter than the half-life leads to accumulation of the drug until steady state is reached. Usually, this takes around five to seven half-lives. Steady state values (C_{trough}) are important in setting safety margins. During developmental toxicity studies, mAbs are only administered during the period of organogenesis, which significantly varies among species. In the cynomolgus monkey, organogenesis occurs between gestation day (GD) 20-50 resulting in five weekly injections. A similar approach in the rat (organogenesis between GD 6-17) would translate into two weekly doses. Consequently, such a dosing regimen cannot lead to the desired target drug concentration in the rat. Since our candidate drug shows tissue cross reactivity in both, monkey and rat, we decided to use modeling to help us designing the most appropriate dosing regimen for a rat SEGII study. Here, the goal was to achieve the target C_{trough} value as fast as possible with as little oscillation as possible. We describe such simulation attempts, compare them to real data sets and discuss advantages and shortcomings of such an approach.

P12

MCKEON M, FISHER B, LATIMER K, HALE S, MAKLE B, WILLIAMS C. Covance Labs Inc, Vienna, VA, United States. The Effects of Continuous Infusion Rates on Embryo/Fetal Development in Rabbits

Continuous infusion can be used for drugs with physiological characteristics (i.e., pH, osmolarity, etc) that prevent administration *via* intravenous bolus injection. This study evaluated the maternal and embryo/fetal effects of saline when administered at varying rates *via* continuous infusion to pregnant rabbits. Time-mated, femorally-cannulated, female Hra:(NZW)SPF rabbits were assigned to four groups and catheter patency was maintained during acclimation with an infusion rate of 0.35 mL/hour. From gestation day (GD) 7 through 20, rabbits were infused with 0.9% sodium chloride solution at dose volumes of 0.5 mL/hour (keep vein open rate), 60, or 120 mL/kg/24 hours. The control animals were noncannulated, untreated time-mated animals. Cesarean sections were performed on GD 29 and fetuses were examined. Treatment-related clinical observations were limited to fecal changes (few or no feces, soft feces), although the incidences of these observations were independent of the infusion flow rates. There were no flow rate effects on mean maternal body weight or food consumption. On GD 7, predose hematology, coagulation, and clinical chemistry test results were similar among rabbits in all infusion groups. Compared with untreated controls, the mean platelet count was minimally increased in rabbits in some infusion groups and mean total leukocyte count, albumin concentration, and calcium concentration were minimally decreased. Mean chloride concentration also was minimally increased in all the infusion groups. On GD 20, no differences in hematology, coagulation, and clinical chemistry test results were present between controls and infused rabbits. There were no infusion-associated changes in macroscopic findings, mean gravid uterine weights, corrected mean maternal body weights, or organ weights. Moderate to marked chronic nephropathy and increased splenic pigment deposition were present in the 120 mL/kg/day group. There were no issues regarding mating, the ability of these females to become pregnant, or preimplantation loss. Although cesarean section data were mostly unremarkable, increased mean postimplantation loss was observed in the 120 mL/kg/day group. There were no effects on covariate-adjusted mean fetal weights and no fetal anomalies attributed to changes in infusion flow rate.

P13

ISLAM A, MENON L. Northeastern University, Boston, MA, United States. Nanowire Array-Based Optical and Electrical Investigation of Embryonic-18 Day Old Rat Hippocampal Neurons

Nanowires are expected to play a fundamental role to investigate the neuronal activity at the nanoscale level in near future. Neurons are complicated and interconnected network system which features a unit size range from millimeter to micron to nanoscale regimes. We have developed arrays of gold nanowires inside the nanoporous alumina templates which are vertically aligned and arranged parallel to each other. For the investigation of nano-neuronal interactions we have cultured embryonic-18 day old rat hippocampal neurons on the surface of such nanowire arrays. The interaction between the neurons and the nanowire arrays are studied as a function of scanning electron microscopy, Keck microscopy and fluorescence microscopy studies. The cell viability on the surface of the nanowire depends on the bioconjugation material, growth factor and attachment protein applications. By utilizing such a nanobiodevice based on nanowire arrays, we investigate the nano-neuro interactions through optical and morphological studies. Using the nanowire arrays, we are also carrying out preliminary studies to measure electrical signals from stimulated neurons. This study will help us further to investigate different neuronal diseases in postnatal to adults.

P14

ROBINSON JF[1,2], YU X[1,2], HONG S[1,2], GRIFFITH WC[1,2], FAUSTMAN EM[1,2]. [1]University of Washington, Seattle, WA, United States, [2]Institute for Risk Analysis and Risk Communication, Seattle, WA, United States. Systems-Biology Approach for Characterizing and Assessing the Interaction of Developmental Disease Candidate Genes and Environmental Exposure for Risk Assessment

The complex etiology of developmental disease involves both genetic and environmental risk factors. Human and rodent genetic studies have identified multiple genetic associations with specific development diseases, such as neural tube defects (NTDs). Due to unknown genetic factors, common inbred mouse strains display differences in sensitivity to environmental toxicants during periods of early embryonic development. Using newly emerging toxicogenomic-based assessments, we evaluated metal-induced alterations in gene expression coinciding with cranial neural tube closure comparing sensitive and resistant mouse embryos. We identified toxicogenomic responses that underlie NTD development and potential mechanisms of differential sensitivity between these two strains. We propose a systems-based framework to integrate classical genetic information into toxicogenomic-based studies to characterize and assess developmental disease candidate genes in the context of variables critical for risk assessment, such as time and dose. We illustrate this approach by integrating genetic data from extensive human and mouse NTD genetic reviews and genetic linkage studies (QTL) into toxicogenomic studies assessing gene expression response associated with differential sensitivity to metals between two common inbred mouse strains (C57 and SWV). Using the combination of toxicogenomic studies and complementary bioinformatic tools, we characterize NTD candidate genes during normal development by function (gene ontology), linked phenotype (disease outcome), location and expression (temporally and strain-dependent). In addition, we show how environmental exposures (cadmium) influence expression of these genes in a strain dependent manner. Using NTDs as an example of developmental disease, we show how integration of genetic information from previous studies into the standard microarray design can accentuate analysis of gene-environment interactions to better define environmental exposure-disease pathways in sensitive and resistant mouse strains. (Supported by EPA: R826886, NIEHS:5P30ES0733, 2P01ES09601, U10ES11387 and NSF: 0CE0434087.)

P15

SLIKKER W, LIU F, ZHANG X, XOU X, PATTERSON T, PAULE M, WANG C. National Center for Toxicological Research. U.S. FDA, Jefferson, AR, United States. Genomic Response to Perinatal Anesthetic-Induced Neuronal Cell Death

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is associated with accelerated neuronal apoptosis in the developing rodent brain. In this study, postnatal day (PND) 7 rats were treated with 20 mg/kg ketamine or saline in six successive doses (sc) at 2-h intervals. Brain frontal cortical areas were collected 6 h after the last dose and RNA isolated and hybridized to Illumina Rat Ref-12 Expression BeadChips containing 22,226 probes. Many of the differentially expressed genes were associated with cell death or differentiation and receptor activity. Ingenuity Pathway Analysis software identified perturbations in NMDA-type glutamate, GABA and dopamine receptor signaling. Q-PCR confirmed that NMDA receptor subunits were significantly up-regulated. Up-regulation of NMDA receptor mRNA signaling was further confirmed by *in situ* hybridization. These observations support our working hypothesis that prolonged ketamine exposure produces up-regulation of NMDA receptors and subsequent over-stimulation of the glutamatergic system by endogenous glutamate, triggering enhanced apoptosis in developing neurons.

P16

NGALAME NNO, BEIER JI, ARTEEL GE, SRIVASTAVA S, STATES JC. University of Louisville, Louisville, KY, United States. *In Utero* Arsenic Exposure Induces Subtle Hepatic Damage And Systemic Inflammation Associated with Accelerated Atherosclerosis in ApoE$^{-/-}$ Mice

Atherosclerosis underlies most cardiovascular disease (CVD). Arsenic exposure in drinking water is associated with higher rates of CVD. We showed that *in utero* arsenic exposure accelerates atherosclerosis in the ApoE$^{-/-}$ mouse, but the mechanism is unknown. Arsenic causes liver disease, and non-alcoholic fatty liver disease is associated with increased risk of atherosclerosis. We hypothesize that prenatal arsenic exposure primes the liver to a pro-inflammatory state which worsens liver disease upon stimulation, and provides an inflammatory stimulus for atherosclerosis. To test this hypothesis, liver damage was induced in 10 week old ApoE$^{-/-}$ mice, prenatally exposed to arsenic (49 ppm) in drinking water, by intraperitoneal injection with a bolus dose of LPS (10 mg/Kg). Mice were sacrificed 24 h later. Indices of liver damage (plasma ALT and AST) and inflammatory cytokine expression (plasma TNF-α and IL-6) were analyzed. Liver sections were stained for necroinflammation and neutrophil infiltration. We had shown previously by microarray analysis and western blot that *in utero* arsenic exposure increases the expression of Hsp70 in the livers of these mice. It has been reported that Hsp70 released from cells in to circulation in membrane-bound forms (exosomes) activates macrophages, which are involved in atherogenesis. Accordingly, we also determined the effect of *in utero* arsenic exposure on the release of Hsp70 within exosomes isolated from plasmas of 10 week old mice. Arsenic exposure significantly increased plasma ALT and AST levels, which was decreased by LPS challenge. Although arsenic did not significantly increase the basal and LPS-stimulated levels of TNF-α, IL-6 and neutrophil infiltration, it however produced quite elevated responses in some mice. This mouse-to-mouse variability in very high responses was also seen in exosomal Hsp70. Lesion analysis showed no direct correlation between plasma cytokine expression and presence of vascular lesions. These results suggest that *in utero* arsenic exposure induces subtle but significant liver damage, together with systemic inflammation which might be associated with inflammatory responses that are the driving force behind the accelerated atherogenesis. Supported in part by USPHS grants ES015812 and ES014443 and U of L Competitive Enhancement Grant.

P17

AGYEKUM AK, LEBLANC L, CHMIELEWSKI R, WILLIAMS D, SMITH MA. The University of Georgia, Athens, GA, United States. Oral Administration of Yogurt Reduces *Listeria monocytogenes* Tissue Invasion and Stillbirths in Guinea Pigs

The effects of yogurt consumption on host susceptibility to *Listeria monocytogenes* infection was evaluated using a pregnant guinea pig model. A commercially available yogurt was orally administered to pregnant guinea pigs on the mornings of gd 33-36 (before 10 am) and a single oral dose of 10^9 CFU *L. monocytogenes* at 2-3 pm on gd 35. Host susceptibility was determined by isolation of *L. monocytogenes* from maternal and fetal tissues, along with fecal shedding and stillbirths. When comparing the effects of yogurt treatment on the invasion of *L. monocytogenes* in maternal tissues, the number of dams in which *L. monocytogenes* was isolated from the tissues was reduced compared to *L. monocytogenes* treatment alone in liver (56% v 100%, respectively) and the spleen (14% v 75%, respectively). Similarly, fetal tissues from dams receiving yogurt resulted in a reduction of *L. monocytogenes* isolates when compared to *L. monocytogenes* treatment alone in fetal liver (17% v. 71%, respectively) and fetal brain (21% and 71%). Importantly, stillbirths were also reduced in guinea pigs receiving treatments with yogurt and *L. monocytogenes* as compared to *L. monocytogenes* treatment alone (14% v. 75%). Stillbirths occurred in only 1 of 9 dams receiving yogurt and *L. monocytogenes*, and in that dam, *L. monocytogenes* was also isolated from her maternal tissues and fecal samples. *L. monocytogenes* was not isolated from any viable fetus in dams receiving yogurt and *L. monocytogenes*. The results suggest that consumption of yogurt decreases stillbirths after the dam is exposed to *L. monocytogenes*. Additional studies are needed to investigate the specific mechanisms of the protective effects of probiotics in listeriosis. Studies are also needed to explore cytokines and their contribution to the fetal transmission of *L. monocytogenes*.

P18

KAPRON CM, CHENG L. Trent University, Peterborough, ON, Canada. The Effect of Inhibition of c-Jun N-Terminal Kinase Phosphorylation on Micromass Cultures of Mouse Limb Bud Cells

Stress activated protein kinase pathways, such as the c-Jun N-terminal kinase (JNK) and p38 pathways, are stimulated when embryonic cells are exposed to a variety of teratogenic compounds. These pathways are also believed to play a key role in normal embryonic development. We have observed a low level of JNK phosphorylation in untreated micromass cultures of mouse embryo limb bud cells. In the present study, we investigated the role of JNK activation in normal limb development by examining the effect of manipulating the JNK pathway on limb cell survival and differentiation. Using micromass cultures of gestation day 11 mouse embryonic limb cells, we inhibited JNK phosphorylation by treatment with SP600125 in concentrations ranging from 0.01 to 4 μM. In a separate set of experiments, we reduced the amount of c-Jun, one of the main targets of phosphorylated JNK, using a c-Jun antisense oligonucleotide in concentrations ranging from 10 to 200 nM. These concentrations of inhibitors were chosen as they are known to reduce JNK and c-Jun activation after cadmium treatment. Cell numbers, viability and differentiation were analyzed after 5 days of culture. Treatment with SP600125 caused a concentration-dependent decrease in the total numbers of cells in culture compared to controls, but the viability of cells remaining on the dishes was not significantly affected. In parallel with the decrease in cell numbers there was also a concentration-dependent decrease in differentiation, as determined by Alcian blue staining. In contrast, treatment with c-Jun antisense oligonucleotides caused an increase in total cell numbers after 5 days in culture, as well as an increase in cell viability and differentiation. Thus, activated JNK appears to be necessary for cell survival in micromass cultures of limb bud cells. However, because a reduction in the amount of total and activated c-Jun had the opposite outcome, we propose that the observed effects of JNK inhibition are mediated through a separate target of this kinase.

P19

KOMADA M[1,2], FUJIYAMA F[3], YAMADA S[1,2], SHIOTA K[1,2], NAGAO T[3]. [1]Congenital Anomaly Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Institute for Bioinformatics Research and Development (BIRD), Japan Science and Technology Agency (JST), Tokyo, Japan, [3]Laboratory of Developmental Biology, Department of Life Science, Kinki University, Osaka, Japan. Methylnitrosourea Exposure Induces Apoptosis in the Dorsal Telencephalon and Microcephaly in Mouse Embryos

Prenatal exposure to methylnitrosourea (MNU), an alkylating agent, induces microcephaly in mice. The administration of this alkylating agent during gestation in mice causes the acceleration of reactive oxygen species production, resulting in cellular membrane damage, mitochondrial membrane damage, and DNA strand breaks. Furthermore, Nitroso compounds, such as MNU and ENU (ethylnitrosourea) can have teratogenic effects on laboratory animals. However, its pathogenetic mechanism has not been clarified, especially that in the development of the cerebral cortex. The purpose of the present study was to clarify the pathogenesis of microcephaly and histological changes by exposing mice to MNU. The pregnant ICR mice were treated with MNU at 10 mg/kg intraperitoneally on day 13 of gestation, and the embryos were observed histologically on embryonic day (E) 14.5, 16.5, or 18.5. A decrease in the brain size and histological abnormalities of the dorsal telencephalon, and the excessive cell death of proliferative neural progenitor/stem cells in the ventricular zone (VZ) and subventricular zone (SVZ) were noted in the MNU-treated embryos. The highest frequencies of cell death occurred at 36 hr after MNU treatment, and little or no neurogenesis was observed in the dorsal telencephalon. Abnormality of the radial migration and neuronal positioning was caused by the reduction of radial fibers in the radial glias in the VZ of dorsal telencephalon. Birth-date analysis revealed the abnormal positioning of neurons and aberrant lamination of the cerebral cortex. Observation of the prenatal exposure to MNU-treated embryos revealed the decreased proliferation and differentiation of neurons and increased cell death of neural progenitors at the neurogenesis stages. In addition, our data indicate that MNU-induced microcephaly results from the spatially and temporally aberrant cell death of neural progenitors in the SVZ/VZ at the neurogenesis stage. The most sensitive periods of MNU-induced microcephaly were from E13.5 through E15.5 in mice.

P20

YAMADA S[1,2], TSUCHIYA M[1], KAMEDA T[1], KOMADA M[1,2], SHIOTA K[2]. [1]Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Institute for Bioinformatics Research and Development (BIRD), Japan Science and Technology Agency (JST), Tokyo, Japan. Embryo Imaging: Episcopic Fluorescence Image Capture (EFIC) for Experimental Animals

During embryonic development, it is important to analyze complicated morphogenetic changes temporally and spatially. Recently, MRI (magnetic resonance imaging) and CT (computed tomography) are frequently used as three-dimensionally (3D) visualizing modalities for embryology. However, they do not yield a resolution enough for small embryos which are several millimeters. In this study, a novel 3D imaging technique named episcopic fluorescence image capture (EFIC) was used for high-resolution imaging of various experimental animals. We used staged mouse embryos, chick embryos, Xenopus laevis tadpoles, and medaka fish Oryzias latipes (larval and adult stage). Using mouse and chick embryos, the structures of the heart were clearly observed and embryonic heart anomalies such as endocardial cushion defect observed in the mutant mice were easily imaged and analyzed three-dimensionally. The fine images of the intestine in the tadpoles were obtained, and branchial structures adjacent to the heart in the medaka fish were analyzed in detail with clear 2D sectional images and 3D reconstruction. This study is the first application of EFIC for tadpoles and medaka fish, and detailed anatomical structure can be clearly observed by EFIC. This system is suitable for analyzing the various experimental animals and the phenotype screening of genetically modified animals. EFIC is a useful technology for research in embryology and teratology.

P21

URIU-ADAMS JY[1], CHAMBERS CD[2], GROSS HB[1], ENSUNSA JL[1], GREEN K[1], LE A[1], YEVTUSHOK L[3], ZYMAK-ZAKUTNYA N[4], WERTELECKI W[5]. [1]University of CA, Davis, Davis, CA, United States, [2]University of CA, San Diego, San Diego, CA, United States, [3]OMNI-NET, Rivne, Ukraine, [4]Khmelnytsky Perinatal Hospital, Khmelnytsky, Ukraine, [5]University of South Alabama, Mobile, AL, United States. Alcohol Drinking Patterns and Nutrient Status in Ukrainian Pregnant Women

Fetal alcohol spectrum disorders (FASD) account for a high frequency of growth deficiency, birth defects, and neurobehavioral impairment in infants. An ongoing study in Ukraine seeks to determine whether maternal nutrient status interacts with alcohol exposure to influence the risk for FASD. 3,736 pregnant women (mean gestational age 20.4 +/- 7.0 wks) were screened between April 2008 and December 2009 in two regions of Ukraine. 46.4% of the women were taking prenatal vitamins and/or folic acid at the time of screening. 10.9% were taking supplemental iodine. 94.8% of the women reported some alcohol consumption, a proportion that exceeds the U.S. 44.7% reported consuming alcohol in the month around conception, and 33.3% reported consuming alcohol in the most recent month of pregnancy. 9.0% reported at least one binge episode of 4 or more drinks in the month around conception, and 7.5% reported at least one binge episode of 4 or more drinks in the most recent month of pregnancy. A sample of screened women who reported frequent or binge drinking and low/unexposed comparison women were recruited into a prospective cohort study of maternal risk factors for alcohol-related pregnancy outcomes. Analysis to date of maternal baseline plasma samples shows that alcohol-exposed women (N=63) had lower Zn and Cu concentrations vs. controls (N=53). Ferritin, Fe, Mg, Ca, ceruloplasmin activity, methyl-donor nutrients (choline, betaine, DMG, folate, Vit B_{12}, and homocysteine), Vit A, E, and indices of oxidative stress and inflammation (TBARS, protein carbonyls, hsCRP) were similar between groups. Regression analyses showed that the absolute oz. of alcohol/drinking day (AADD) in the month around conception was associated with lower plasma Total Radical-trapping Antioxidant Potential (TRAP) and Vit A. AADD in the most recent month of pregnancy was associated with lower Vit B_{12} and higher ferritin (which may indicate higher body stores of Fe). The low Zn and Cu in ethanol-exposed women and the lower TRAP and higher ferritin related with alcohol consumption may increase oxidative stress and contribute to alcohol-induced teratogenesis. The association of alcohol consumption with lower Vit B_{12} and Vit A may also contribute to adverse fetal development. Supported by NIAAA-U01-AA014835-05 and HD01743.

P22

NILSSON MF[1], SCHOLZ B[1], KHAN KM[2], PIERSMA AH[3,4], DENCKER L[1]. [1]Department of Pharmacetucial Biosciences, Division of Toxicology, Uppsala University, Uppsala, Sweden, [2]Centre for Image Analysis, Uppsala University, Uppsala, Sweden, [3]Laboratory for Health Protection Research, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands, [4]Institute for Risk Assessment Sciences, Veterinary Faculty, Utrecht University, Utrecht, Netherlands. Rodent Organogenesis Toxicology Ontology (ROTO): Linking Morphology to Embryotoxicity

Introduction: The rat whole embryo culture (WEC) *in vitro* assay is used to assess developmental toxicity. Routine endpoints in the assay are a) growth b) functionality and c) morphology. The scoring methods used for morphology are generally semi-quantitative (categorical, score 1–5) and mainly associated with growth rate. Specific malformations are scored as either absent (=0) or present (=1). Organogenesis associated embryotoxicity scoring suffers from a lack of uniform terminology and a link between affected embryonic tissues/processes and known molecular mechanisms. We propose to complement existing scoring systems with 1) a structured anatomical/biological ontology that will improve embryotoxicity comparisons between labs and enable the creation of a database with cross-reference ability to molecular biology data and 2) an automated image analysis system. Methods: Anatomical/morphological and dynamical features covering mouse Theiler stages ~12-17) were linked in a structural fashion using the COBrA anatomy ontology editor. The ontology was modified from existing ontologies (EMAP and MP), and designed to be complementary to the van Maele-Fabry scoring system. MATLAB was used to design an image analysis software for the estimation of growth and functional (i.e. heart rate) properties, and morphological development (optic- and yolk sac circulatory system) from images/videos of embryos cultured *in vitro*. Results: The Rodent Organogenesis Toxicology Ontology (ROTO) structures the previously independent scoring endpoints in an anatomically/biologically interconnected system that covers embryonic growth. The result from image analysis shows that parameters such as growth, heart function and to some extent morphology of rat embryos can be captured digitally at the end of culture and estimated later on. Discussion: ROTO has the potential to provide a structured approach to the description and information storage of experimentally induced embryotoxicity. The use of ROTO terms may also serve as a standardized terminology to researchers. It enables the cross-referencing between abnormal morphology and the developmental processes in other species and relevant molecular biology data. ROTO may even be used to annotate non-typical endpoints in a decision-tree like manner. Automated image analysis, in combination with an anatomical ontology will provide a more objective approach to embryotoxicity scoring, making it more consistent and with that more informative.

P23

YING X, JI J, BARLOW N, OSWALD J, FEUSTON M. sanofi-aventis U.S., Bridgewater, NJ, United States. Micro-CT Evaluation of Alizarin Red S Stained Mouse, Rat and Rabbit Fetuses

Background: X-ray micro-computed tomography (micro-CT) technology has demonstrated its unique value in the evaluation of fetal skeletal malformations. However, micro-CT data on previously stained fetal skeletons do not appear to be available in the published literature. Since it will be useful if 3-dimensional (3D) imaging and analysis can be applied on already-stained specimens, we conducted a micro-CT study using single (alizarin red S) or double (plus alcian blue) -stained fetal specimens. Methods: To develop the micro-CT imaging protocols, stained mouse and rat fetuses were used. Specimens were stored in glycerin. A group of 7 alizarin red S stained rabbit fetuses were evaluated by the same CT method. During the micro-CT scanning, each specimen was loaded in a custom-made polystyrene holder. A micro-CT system (SkyScan 1076, SkyScan, Belgium) with 18 or 36 μm/voxel setting was used for the rabbit fetuses and another high-resolution micro-CT system (SkyScan 1172) with 8-25 μm/voxel setting was used for scanning the mouse, rat and some rabbit specimens. Special care was taken to overcome possible movement of the soft specimens during CT scanning. The 3D reconstructed CT data were reviewed and analyzed using the SkyScan CTAn/CTvol and the Amira (Visage Imaging Inc., CA) software. Results: All micro-CT scans were able to clearly image the ossified skeletal structures of the stained specimens. The CT densities of the stained ossified structures and surrounding soft tissues are significantly different. However, the alcian blue stained cartilage could not be clearly distinguished. With high-resolution CT imaging, the skeletal malformations and/or variations observed exactly matched the direct manual observations of the stained specimens. It was also possible to quantitatively measure bone microarchitecture of the stained specimens. Conclusions: This study confirmed that micro-CT can be used to accurately assess the stained fetal skeletons. In addition to skeletal structure analyses, the micro-CT makes it possible to conduct quantitative 3D measurements of skeletal ossification/ mineralization and bone microarchitecture on previously stained fetuses. This ability may contribute to the generation of new data by re-assessment of existing specimens.

P24

SILVA MH. California Environmental Protection Agency, Sacramento, CA, United States. Reproductive and Developmental Toxicology from the Pesticide Sodium Tetrathiocarbonate (STTC) and the Metabolites Carbon Disulfide (CS_2) and Hydrogen Sulfide (H_2S)

Introduction: STTC (Enzone®) was prioritized for risk assessment by the Department of Pesticide Regulation due to high use and breakdown into CS_2 (active ingredient) and H_2S. STTC is a fumigant for control of plant parasitic nematodes, fungi and citrus Phytophthora root rot. In aqueous solution it produces equal concentrations of CS_2 and H_2S. Offsite movement of CS_2 and H_2S results in ambient air exposures of workers and bystanders. CS_2 was the first reported soil fumigant in Europe during the 1870's to control the sugar beet nematode; volatility and extreme flammability make direct use impractical. It is listed in California as a Toxic Air Contaminant and under Proposition 65 (developmental and reproductive toxin). The reproductive and developmental effects of STTC are primarily due to CS_2. H_2S is generated by STTC metabolism and endogenous production from metabolism. Results: STTC showed no effects on fetuses in a rabbit developmental study while maternal toxicity was observed. CS_2 primary source of human exposure is most likely *via* inhalation, however since dietary tolerances exist for several crops treated in California oral developmental studies were also evaluated. It is evident from the studies selected for critical endpoints that there are severe developmental effects after treatment of rat and rabbit dams *via* oral gavage, intraperitoneal administration or inhalation. By these routes animals showed embryo/fetal toxicity and malformations and an increased incidence in total litter resorptions indicating a potential effect on the ability of dams to maintain a pregnancy (endocrine disruption). CS_2 has been described previously as a suspected human developmental toxicant and teratogen. Reproductive effects in humans (spontaneous abortions, premature births, birth defects, decreased sperm production, loss of libido and menstrual irregularities) have also been described. Epidemiology results with CS_2 may be confounded by co-exposure to H_2S (<5 ppm). H_2S treatment in a developmental inhalation study in rats did not indicate that H_2S is more toxic to fetuses than it is to dams. A reproductive/developmental neurotoxicity study was performed in rats and while there was maternal toxicity, there were no effects in pups or fetuses. Views expressed are the author's and not those of Cal/EPA.

P25

MILLER DL. University of Michigan, Ann Arbor, MI, United States. Update on Safety Assurance for Ultrasound in Obstetrics

Diagnostic ultrasound (DUS) is routinely used for monitoring virtually every fetus in the developed world. Considerations of safety, which arose as DUS developed in the 1970's, were resolved by a federal law enacted in 1976. This essentially assumed safety for then-existing medical ultrasound equipment and the FDA established upper limits for several examination categories based on the exposure quantities used on or before 1976. The obstetrical category has undergone substantial evolution from the initial limit of 46 mW/cm^2 spatial peak temporal average (SPTA) intensity set in 1985. Thermal and mechanical exposure indices were developed for on-screen display to inform sonographers of exposure levels. In 1992, limits for obstetrical ultrasound were relaxed both in terms of the temporal-average exposure, to a possible 720 mW/cm^2 SPTA intensity, and of the temporal-peak exposure, to a Mechanical Index of 1.9 $MPa/MHz^{1/2}$ (there is no limit on the Thermal Index). Little subsequent research has been conducted with post-1992 obstetrical DUS machines and modern biological methods to thoroughly assess potential risks to the fetus. New reasons for concern have recently emerged. Possible risks to the fetus from reported DUS bioeffects include altered migration of neurons in the brain, apoptosis of heart cells and interactions with bone growth. Furthermore, routine DUS protocols are under development for for evaluation of placental circulation using ultrasound contrast agents, and for Doppler ultrasound examination of fetal cardiac function in the first trimester, which involves relatively prolonged examination durations. Responding to these concerns, the American Institute of Ultrasound in Medicine (AIUM) and the World Federation of Ultrasound in Medicine and Biology (WFUMB) have set up safety committees to study the uses of DUS examination in the fist trimester. At this time, there are no established risks which would discourage the prudent use of DUS in obstetrics by trained professionals. However, high-quality interdisciplinary research is urgently needed to address worrisome reports of possible subtle risks to the fetus and the safety of novel DUS examinations.

P26

FOGEL P[1], SUTER H[1], KARAKOS AC[2], SCHUSTER MN[2], SUTER D[2]. [1]PDS Pathology Data Systems Ltd, Pratteln, Switzerland, [2]PDS Preclinical Data Systems Inc, Mount Arlington, NJ, United States. The Next Challenge: Tailoring Statistics to the Specificities of a GLP Study While Maintaining Productivity and Traceability

Regulatory agencies expect GLP-compliant statistical procedures to be planned and well-specified in order to ensure traceability, which helps assure unbiased analysis, reproducibility and reliability through validated calculations. As companies seek to respond to this challenge without adversely affecting productivity, they tend to "freeze" statistical procedures, which are then implemented in a software package and applied in a more or less systematical way. An obvious drawback of this approach is the lack of flexibility, which can lead to misuse of statistics that do not fit well with the experimental design of a study. For example, multiple comparison tests to a control must not be multiplicity adjusted when different treatments/endpoints are studied, by contrast with a dose-response study of a single treatment. The PDS solution developed to address this dilemma provides a number of different procedures that can be easily tailored to the specificities of each single measurement within a particular study, with respect to clearly identified characteristics such as test multiplicity strategy, type of multiple comparisons (*versus* control only, pair wise), trend type (two or one-sided), test type (automatic selection, parametric or non parametric), to cite just a few. Moreover, audit trail guarantees that all adjustments to existing procedures are defined and planned in advance of the study. Finally, productivity is enhanced, since all of the settings are stored in the database system-- a single "click" allows the automatic repeating of the same statistical procedure for each of the parameters studied.

P27

HOOTNICK DR. Upstate Medical University, Syracuse, NY, United States. Midline Metatarsal Dysplasia is the Rosetta Stone of Embryonic Dysvasculogenesis

Introduction: All segments of the congenital short limb (CSL) are abnormal to a variable degree; we have described the most frequent pattern of skeletal dysplasia involving the upper femur, fibula and midline metatarsals. Those noncontiguous skeletal segments correspond to regions of active vasculogenesis in the 6 week embryonic limb. Inosculation of the dorsalis pedis and lateral plantar arteries of the midline of the foot result in completion of vasculogenesis in the developing limb. Methods: Four specimens were dissected including limbs with congenital tibial absence and preaxial polydactyly, a congenital short limb with clubfoot and ectrodactyly, congenital tibial absence with a complete foot and a congenital short limb ectrodactyly following ankle disarticulation. Arteriography of 3 other CSL patients was obtained during the course of treatment. Results: Abnormalities of the muscles, tendons and nerves correlated with the bony abnormalities present in each limb but the abnormalities of the arteries were consistent and did not vary significantly despite the presence of different bony malformations in each limb. Discussion: Development of the arterial tree in the embryo terminates in the midline of the foot upon completion of the arterial arch. While several detailed mechanisms have been proposed to explain the formation of a normal limb model, none can account for dysplasia of a midline structure. Midline metatarsal dysplasia is consistent with degradation of a previously preexistent normal limb model, a post specification defect. Since the skeletal and vascular systems undergo rapid change at approximately the 6th week of embryonic development, the concurrent abnormal morphogenesis of both the arteries and skeletal structures appears significant. Therefore, it is possible retrospectively to interpret the mechanisms inherent in the congenital lower limb dysplasias including PFFD, clubfoot, bowed tibia and fibula dysplasia from the perspective of dysvasculogenesis.

P28

HOOTNICK DR. Upstate Medical University, Syracuse, NY, United States. Surgical Misadventures in the Treatment of Congenital Limb Dysplasia and Clubfoot Associated with Dysvasculogenesis

Introduction: Publication of the detailed complications of ischemic necrosis of 14 limbs following clubfoot surgery has codified the hypothesis that congenital arterial deficiencies put some postoperative clubfeet at risk, secondary to congenitally diminished anterior tibial and dorsalis pedis arterial flow. Surgeons who operate on congenitally short limbs (CSL) by leg lengthening have observed a 200% incidence of morbidity associated with that surgery. The current standard of treatment for CSL includes surgical lengthening as a preferred option of treatment for all varieties of CSL. Methods: A Review of the orthopedic literature and specific individual case reports involving clubfoot surgery and CSL lengthening procedures has been analyzed in regards to the known vascular alterations. Results: The reported results of excellent function following leg lengthening procedures in all varieties of CSL appear extravagant. Complications included uncontrollable hypertension, fractures, joint dislocations, and ultimately amputation after multiple prolonged operative interventions. Discussion: Our review of the comparative utility of leg lengthening in the severe forms of CSL appear to make lengthening an unattractive alternative of treatment. We suggest there is some evidence that dysvasculogenesis plays a role in the poor quality of bone regeneration which leads to recurrent fractures. The perioperative surgical difficulties in CSL surgery are analogous to those seen in clubfoot surgery. We propose the formation of a national parents' organization to enhance the awareness of families towards the morbidities of surgical intervention in severe limb dysplasia.

P28A

RENGASAMY P[1], SHAFIULLA M[1], NAGELKERKE N[1]. [1]Mercer University School of Medicine, Macon, GA, United States, [2]UAE University, Faculty of Medicine, Al Ain, Abu Dhabi, United Arab Emirates, [3]UAE University, Faculty of Medicine, Al Ain, Abu Dhabi, United Arab Emirates. Maternal Exposure to Alcohol during Gestation Augments Fetal Skeletal Defects in Diabetic Mice

Alcohol consumption during pregnancy is reported to be associated with fetal alcohol spectrum disorders in some offspring. One of the concerns of pregnancy in diabetic women is a several-fold increase in birth defects in the offspring. Thus both maternal alcohol consumption and pregnancy in diabetes mellitus (DM) constitute independent risk factors for offspring maldevelopment. DM women are reported to not differ from non DM women in the drinking and smoking behavior. We aimed to determine the effects of potential interaction between acute doses of alcohol and maternal DM during gestation on fetal skeletal development. Mice were made diabetic with streptozotocin (STZ) on gestation day (GD) 2. Single doses of 25% v/v of absolute alcohol in saline (0.03 ml/g body weight) was administered (IP) to groups of DM and non-DM animals on GD 7 or 8. One group of DM animals was treated with insulin (SC). Skeletons of GD 18 fetuses were stained with Alizarin red-S and Alcian blue. Fetuses of both ethanol and DM group of mice were observed to have a low incidence of skull bones hypoplasia and vertebral defects. Ethanol injection of DM mice on GD 7 resulted in accentuation of DM-related skeletal defects. Treatment on GD 8 resulted in defects of axial and appendicular skeletons differentially. Combination treatment induced markedly poor ossification in about 60% of animals. Alcohol also was found to augment the frequency of supernumerary ribs and sternal anomalies and poor ossification of bones of paws. These data suggest that alcohol affects the developmental processes of mesoderm of embryos of diabetic mouse resulting in augmentation of skeletal malformations. (Supported by Mercer University School of Medicine, Macon, GA & UAEU.)

Tuesday Poster Session

P29

THEUNISSEN PT[1,2], DE JONG E[1,3], VAN SCHOOTEN FJ[2], PIERSMA AH[1,3]. [1]Laboratory for Health Protection Research, National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands, [2]Department of Health Risk Analysis and Toxicology, University of Maastricht, Maastricht, Netherlands, [3]Institute for Risk Assessment Sciences, Veterinary Faculty, Utrecht University, Utrecht, Netherlands. Effects of Triazole Antifungal Compounds on Neural Differentiation of Murine Embryonic Stem Cells as Determined By Flow Cytometry

Current chemical safety legislation for reproductive and developmental toxicity requires animal testing in multiple generations, requiring high numbers of experimental animals. Alternative assays for developmental toxicity testing are highly desirable to reduce the extensive experimental animal use in this area. To screen for effects of developmental toxicants on neural differentiation, we developed a dynamic *in vitro* model which makes use of the capacity of pluripotent murine embryonic stem (mES) cells to differentiate into neural cell types. We designed a cell culture model in which differentiation to neurons and astrocytes is completed in 13 days. The model involves retinoic acid as growth factor and stage-specific serum deprivation. To test the applicability of the test system to the triazole chemical class, we tested 6 representative compounds (cyproconazole, flusilazole, hexaconazole, myclobutanil, triadimefon and triticonazole) in this model. Triazoles are widely used as fungicides in human health care and agriculture. Some compounds in this chemical class are known teratogenic compounds causing major neural and skeletal malformations. Effects of these triazoles on neural differentiation of mES cells was determined by morphological scoring of neural outgrowth and flow cytometric analysis of SSEA1 for undifferentiated cells and the key neural developmental markers, nestin and βIII-tubulin. All compounds showed a dose-dependent pattern of inhibition of neural differentiation. This *in vitro* model may be useful in ranking potency of developmental toxicants within the chemical class studied. Novel chemicals in the class could be tested in the model in order to decide on whether *in vivo* testing is warranted. Such an approach may assist in reducing animal testing in developmental toxicology.

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DE JONG E[1,2], BARENYS M[3], VERHOEF A[2], PIERSMA AH[1,2]. [1]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands, [2]National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands, [3]Toxicology Unit, Public Health Department, School of Pharmacy, University of Barcelona, Barcelona, Spain. Relative Developmental Toxicity of Triazoles in the Embryonic Stem Cell Test and the Whole Embryo Culture

The high number of animals needed for developmental toxicity testing has stimulated the search for *in vitro* alternatives. Two possible alternative assays are the mouse embryonic stem cell test (EST) and the postimplantation rat whole embryo culture (WEC). We have evaluated the relative sensitivity of both assays for a series of structurally related compounds. The chemical class of triazoles was selected as they are known developmental toxicants covering a wide range of embryotoxic potencies. Triazoles are used as fungicides in agriculture and as antifungal drugs in medicine. We compared the results of the EST and the WEC with the *in vivo* developmental toxicity of the compounds to determine their relative predictivity. Malformations in the WEC occurred primarily in the craniofacial region with malformations to the branchial bars and mandibular processes. Flusilazole was the most potent compound tested in both the WEC and the EST followed by hexaconazole in the EST. This corresponds with the known developmental toxicity potency of these compounds *in vivo*. The potency ranking of cyproconazole, myclobutanil, triadimefon, and triticonazole in both *in vitro* systems did not directly correlate with the known relative developmental toxicity from *in vivo* studies based on external exposures. In general, the EST was more sensitive than the WEC with 7-fold lower effect concentrations. Cyproconazole induced neural differentiation in the EST despite the lack of culture conditions that are optimal for neural differentiation of embryonic stem cells. Remarkably, cyproconazole was the least potent compound in the WEC, although a similar pattern of malformations was induced. In this study the triazoles tested, with the exception of cyproconazole, showed a similar potency ranking in the EST and the WEC, neither of which corresponded completely with their *in vivo* developmental toxicity ranking based on external exposures. The difference in the effects of cyproconazole in the two systems illustrates the differences in endpoints in both assays, which appear to show complementary information as regards the developmental toxicity of triazoles.

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SCHREUR DK, SHARPER VA, LEWIS EM, HOBERMAN AM. Charles River Laboratories Preclinical Services, Horsham, PA, United States. A Comparative Study of Suspension Media Characteristics for Motility Maintenance Over Time for Computer Automated Sperm Analysis (CASA) Of Crl:CD1(ICR) Mouse Sperm

Automated analysis of sperm motility requires the use of a suspension medium that provides appropriate conditions for sperm survival, which is a function of time, temperature, pH, and nutrients. Three commonly used media (M-199 and Ham's F-10 medium, both containing inorganic salts, amino acids, vitamins, and other constituents, and Dulbecco's Phosphate Buffered Saline [DPBS]) were evaluated to ascertain which would provide the best maintenance of sperm motility over time. First, each was tested for pH stability at seven time points (5, 10, 20, and 30 minutes, and 1, 2, and 3 hours). Second, sperm samples acquired from the left cauda epididymis of Crl:CD1(ICR) mice were placed in 2 mL aliquots of each medium and analyzed for motility at the same time points to correlate pH changes to sperm motility changes. The rise in pH at the 3-hour time period was similar for M-199 (Δ pH = 1.7) and Ham's F-10 (Δ pH = 1.7) as it was for the other time points evaluated, while the pH for DPBS was relatively stable (Δ pH = 0.1). When tested for maintenance of the percentage of motile sperm cells over time, the best results at 3 hours were obtained using Ham's F-10, a medium with unstable pH, while the results obtained using DPBS, a balanced salt solution with stable pH, were similar to those obtained using M-199, a medium with the same pH instability as Ham's F-10. Similar results were found for the other time points evaluated and for the percentages of rapidly-moving and progressively-moving sperm at the same time points. These results indicate that, under these circumstances, Ham's F-10 gave the best results and, while pH appears to influence sperm motility over time, the nutrient composition of the medium appears to be more significant in maintaining sperm motility.

P32

IYER PR, WU KL, KAUFMAN FL, GOLUB MS, DONALD JM. California Environmental Protection Agency, Sacramento, CA, United States. Role of Data from Emerging Technologies and Biomonitoring in Existing Regulatory Programs in California

Emerging data from methods such as gene expression studies and findings from programs such as the California Environmental Contaminant Biomonitoring Program (CECBP) may provide avenues for improving and expanding existing regulatory programs. We explored approaches for incorporating such data and findings into existing regulations that focus on developmental and reproductive toxicity (DART) in California. Currently, regulatory programs in California are based on generally accepted scientific principles and follow procedures similar to established federal guidelines. These programs include the Safe Drinking Water and Toxic Enforcement Act of 1986 (commonly known as Proposition 65), which was intended by its authors to specifically protect California's citizens and the state's drinking water sources from chemicals known to cause birth defects or other reproductive harm, and to inform its citizens about exposure to such chemicals. Endpoints currently considered in developmental toxicity studies include maternal toxicity, altered fetal survival, growth, morphological development, and functional deficits. Similarly, reproductive toxicity parameters include endpoints such as body weight and organ weights. Male-specific endpoints include histopathologic evaluations, sperm evaluations, and paternally-mediated effects on offspring; and female-specific endpoints include organ morphology and histology, oocyte production, alterations in the female reproductive cycle, mammary gland and lactation, and reproductive senescence. Emerging data from gene expression studies are being included in datasets available for DART risk assessments. Accordingly, we have explored the possible role these data may have in specific on-going regulatory programs. The limitations in the use of gene expression experiments were examined and the approaches needed for their use in DART risk assessment considered. For findings from biomonitoring programs, the detection of specific chemicals in biological samples and the use of this information in health-risk interpretation and existing regulatory programs were assessed. A systematic approach and recommendations for the inclusion of gene expression data and biomonitoring data as part of the weight of evidence is being developed. Challenges in using these data in regulatory programs are also discussed. Disclaimer: These views are those of the authors and do not reflect the policy of the California Environmental Protection Agency.

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MARSDEN EKS[1], BARROW PC[1], ELLEGAARD L[2], GANDERUP NC[2]. [1]MDS Pharma Services, Lyon, France, [2]Ellegaard Göttingen Minipigs A/S, Dalmose, Denmark. Supply of Mated Female Göttingen Minipigs for Embryo-Fetal Development Studies

Undertaking embryo-fetal development studies in the minipig can appear a challenging prospect for both the investigator and the test facility for economic, technical and scientific reasons. However, with technical and scientific know-how becoming more common place, the focus is now turning towards making the studies more economically attractive. One way of reducing cost would be to obtain mated females directly from the animal supplier and thereby avoid the procurement and housing of boars for a lengthy in-house mating phase. Four 9 to 10 month old Göttingen Minipig gilts were mated at Ellegaard Göttingen Minipigs A/S (EGM) for up to three consecutive days. The first day of mating was regarded as day 0 *post-coitum*. The animals were then delivered to our facilities, arriving on Day 6 or 8 *post-coitum* depending on their mating history. EGM provided bodyweight, food consumption and mating data so complete pre-treatment study records could be compiled. On arrival, the females were submitted to health check and transfer to the housing pens. In order to simulate a standard dosing regimen, the females were administered water, by oral gavage, from days 11 to 35 *post-coitum*, inclusive. Dosing was extended for 1 or 2 days for females with repeated copulation. Clinical observations, bodyweight and food consumption were monitored throughout the study. Caesarean section was performed on Day 55 *post-coitum*. Maternal abdominal and thoracic organs were examined together with the uterine contents. Litter parameters were recorded and fetuses were weighed and examined for external and palate defects. There were no remarkable clinical changes, including for bodyweight change or food consumption. All four females survived to terminal caesarean section and were pregnant with viable fetuses. An average litter size of 6 fetuses was comparable with our current historical control data obtained after in-house mating. Two fetuses had pentadactyly, a common variant in the Göttingen Minipig. In conclusion, mated females can be obtained directly from EGM, at least in sufficient numbers to perform dose range-finding studies. The females are delivered in time to allow a number of day's acclimatization prior to the start of uterine implantation and study dosing on day 11 *post-coitum*.

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SINGH AV[1], SIPES NS[2], KLEINSTREUER N[2], KNUDSEN TB[2], SHAH I[2]. [1]Lockheed Martin, Research Triangle Park, NC, United States, [2]National Center for Computational Toxicology US EPA, Research Triangle Park, NC, United States. Literature Mining and Knowledge Discovery Tools for Virtual Tissues Knowledgebase (VTKB)

Virtual Tissues (VTs) are *in silico* models that simulate cellular function and events in tissues to analyze complex relationships and predict multicellular behaviors in specific biological systems. Developing VT models often requires input of vast biological knowledge about the systems under investigation. EPA is developing VT models for hepatic function (v-Liver™) and embryo development (v-Embryo™) to aid in the integration and interpretation of high-throughput screening (HTS) data, such as ToxCast™ *in vitro* assays, with information about molecular pathways, cellular networks and clinical phenotypes in target organ systems. Knowledgebase development supports construction of VT models and requires a flexible platform to extract and organize relevant facts from extant scientific literature and curated databases. The knowledge discovery workflow starts with information retrieval (IR) of relevant PubMed abstracts based upon user-defined input of single or multiple keywords, followed by information extraction (IE) and relationship mapping (RM). Currently, we use the text-mining (TM) feature of MySQL with custom perl scripts and the '@Note' tool (http://sysbio.di.uminho.pt/anote/wiki/index.php/Main_Page) to generate a highly customizable, named entity recognition (NER). Existing available ontologies (www.OBOfoundry.org/) were used to build a vocabulary of terms that describe relevant pathology concepts. The results were stored in a relational database and underwent statistical analyses to identify associations that could be further mapped to broader biological concepts, and to allow for further data mining *via* a custom Cytoscape plug-in (cMantic). This TM workflow is being implemented as a modular tool that uses open-source libraries, and that supports efficient extraction of the relevant developmental toxicity facts needed to construct VT models of vascular, eye and limb-bud development. [This work has been reviewed by EPA and cleared for presentation, but does not reflect official Agency policy.]

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KORTE SH[1], NOWAK P[1], BEE W[2], FUCHS A[1], WEINBAUER GF[1]. [1]Covance Laboratories GmbH, Muenster, Germany, [2]Halozyme, San Diego, CA, United States. Feasibility of Continuous and Prolonged Intravenous Infusion in Freely Moving Pregnant Cynomolgus Monkeys

Cynomolgus monkeys constitute the predominant nonhuman primate model in preclinical safety testing and are being used increasingly for DART evaluation. Some (bio)pharmaceuticals require IV infusion to achieve adequate exposure but information on continuous IV infusion in pregnant monkeys is scanty (1). Twenty animals were trained to wear backpacks after mating, e.g. gestational day (GD) 0. On GD 70 ±3, animals (weighing 2.9-5.1 kg) were fitted with a sc port-catheter system (PORT-A-CATH®, P.A.S. PORT®, Deltec). Average duration of gestation is 160 days (2). Aquaeous glucose solution (5%) was administered daily for 8 hours from GD 90 to GD 150 ± 1 at 0.1 mL/kg/h using an ambulatory pump system (CADD-Micro® Infusion Pump, SIMS, Deltec). In six animals, a C-section was done on GD 150±1 and the remaining animals were allowed to deliver. Two of 20 animals died (GD 123, GD 115) with unclear etiology. Among remaining animals, no adverse effects on clinical pathology, body temperature, blood pressure, and organ weights were observed. Episodes of reduced food consumption and clinical signs (swelling of hind limbs and face, and around genital region) occurred in 8 of 20 animals but were considered to be pregnancy-related. Liquid aspired repeatedly from the ports did not show microbial growth. Mean total white blood cell count prior to implantation was 13.5 [10 E9/L] and did not change during the study suggesting a lack of inflammatory reactions. Histopathology revealed local thrombi, fibrosis, foamy histiocytes and inflammatory changes at sites of catheter entry, in the vein and the subcutis around the port region. In conclusion, continuous and prolonged IV infusion during mid-to-late gestational period in cynomolgus monkeys is feasible and well tolerated, thus enhancing the administration regimen options for developmental toxicity studies in this macaque species. 1. Reinheimer TM, Bee WH, Resendez JC, Meyer JK, Haluska GJ,Chellman GJ. 2005. *J Clin Endocrinol Metab*. 90:2275-81; 2. van Esch E, Cline JM, Buse E, Wood CE, de Rijk EPCT, Weinbauer GF. 2008. *Toxicol Pathol* 36:171S-2S.

P36

DEVINE H, MARTIN A, ADAMO M, BARBEAU S, POULIOT L, ROBINSON K. Charles River Laboratories, Preclinical Services Montreal Inc., Senneville, QC, Canada. A Comparison of Development and Behavioral Data for Wistar Han IGS Rats and CD®-IGS Rats

Wistar Han IGS rats are becoming more commonly used in toxicology programs for testing pharmaceuticals and biopharmaceuticals. In consequence, reproductive toxicology testing programs including pre and postnatal (International Conference on Harmonization [ICH] 2) studies and juvenile toxicology studies, to meet U.S. FDA or EMEA guidelines, are being conducted with these rats. A comparison to the CD®-IGS rat, which has been the most commonly used strain for reproductive and juvenile toxicology testing for more than a decade was made. Control data from studies performed with these two strains, treated by standard routes of administration (i.e. gavage or subcutaneous injection) were compared for various parameters of physical, reflexological and sensory development and behavioral function. CD-IGS® (Crl:CD[SD]) and Wistar Han IGS (Crl:WI[Han]) dams were allowed to litter in solid-bottomed cages equipped with an automatic watering valve on corncob bedding. Pre-weaning measurements included physical (i.e. eye opening), reflexological (i.e. righting reflex) and sensory (i.e. auricular startle ontogeny) development, and were conducted before Day 21 post partum. Post weaning behavioral tests, including locomotor activity and startle habituation were conducted over several age ranges from weanling to young adult. Learning and memory tests (i.e. water maze) were primarily conducted in young adults. Comparison of the data, showed no differences in any parameters that could not be explained by differences in body weight. Behavioral tests including auditory startle, motor activity counts and water maze performance showed no differences between CD-IGS® and Wistar Han rats for both the group mean and measures of variance (i.e. coefficient of variation). Crown to rump measurements differed, CD-IGS® rats being larger as adults than Wistar Hans. These data support the use of Wistar Han rats in pre and postnatal and juvenile toxicology studies that include postnatal development and behavioral parameters using group sizes, protocols and test paradigms similar to those used for CD-IGS® rats.

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MARTIN A, BARBEAU S, POULIOT L, PRIMAKOVA I, ROBINSON K. Charles River Laboratories, Preclinical Services Montreal Inc., Senneville, QC, Canada. Postnatal Development and Behavioral Assessments in CD®-1 IGS Mice

The mouse is a rodent species sometimes used for nonclinical reproductive and juvenile toxicology testing of pharmaceuticals and biopharmaceuticals. Postnatal growth, development and neurobehavioral assessments are required for pre and postnatal (ICH-2) studies in the International Conference on Harmonization (ICH). Both FDA and EMEA guidances/guidelines also include these assessments for juvenile toxicology studies. To summarize the results of these parameters, data were compiled from pre and postnatal and juvenile toxicology studies (treated by routine dosage routes). Litters of CD®-1 IGS mice were culled to 4 males and 4 females on Day 4 post partum and weaned on Day 21 post partum. Survival and clinical condition were monitored and the pups evaluated for body weight, physical development (including pinnae detachment and eye opening) and sexual maturation (vaginal opening and preputial separation). For the juvenile toxicology studies, the mouse pups were administered subcutaneously by injection with isotonic vehicles or orally by gavage using modified cannulae from as young as Day 7 post partum, with vehicles (such as aqueous methyl cellulose), at dose volumes of 2 to 10 mL/kg/day. The mice were also evaluated for reflex ontogeny and sensory function preweaning. Visual function at weaning and auditory startle habituation, locomotor activity, passive avoidance and Biel water maze starting on Days 49, 35, 63 and 70 post partum, respectively were evaluated. Results showed that these assessments were successfully conducted in mice. Body weights, sexual maturation, survival and clinical condition provided information on growth and development. Locomotor activity and auditory startle habituation provided information on motor activity and reactivity, respectively; and both tests also provided information on habituation. Data obtained from water maze and passive avoidance demonstrated learning and memory. In conclusion, this battery of tests assessed postnatal growth and development, reflex ontogeny, sensory function, motor activity, reactivity, learning and memory, and therefore can be used to assess whether a pharmaceutical or biopharmaceutical has adversely affected the development of the nervous system in the mouse, as required by regulatory agencies.

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SHOJI S[1], SHOJI I[2], SHOJI T[3], OKAMOTO N[4]. [1]Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Hiroshima, Japan, [2]The Ohio State University, Columbus, OH, United States, [3]Vanderbilt University, Nashville, TN, United States, [4]Hiroshima University, Hiroshima, Hiroshima, Japan. Dysfunction of Embryogenesis in Pharyngeal and Cardiovascular Development Following Atomic Bomb Exposure

Relatively little data has been available on embryonic lethality, pharyngeal arches and cardiovascular anomalies following exposures to environmental stresses such as atomic bomb (A-bomb) radiation exposure. In order to collect basic data for such conditions, we focused on the abnormal development of pharynx and the arterial pole of the heart following parental exposure to A-bomb exposure. In the study, we conducted a thorough review of autopsy results of aborted and stillborn fetuses following parental exposure to A-bomb radiation in Nagasaki. We reported on the relationships between exposure groups and subsequently observed embryonic lethality as well as external and visceral defects, especially in pharyngeal arches and cardiovascular system. We observed high incidences of teratogenesis, particularly cardiovascular and pharyngeal anomalies, in A-bomb exposure groups. These results indicate fetal sensitivity to A-bomb exposures leading to embryonic lethality, dysfunction of primary heart field (PHF), second heart field (SHF) and neural crest cells, and pharynx development, which form pharynx-neurocristopathy and pharyngeal neurocristopathy-induced A-bomb syndromes. The most common cardiovascular defects involved septation and outflow tract of the heart. Specifically, pharyngeal arch and cardiac vascular defects, including dextroposition of the aorta, tetralogy of Fallot, ventricular septal defects, atrioventricular septal defects, coarctation of the aorta, and right aortic arch noted following A-bomb exposure, were similar to those found in our previous studies of environmental stress models and related human syndromes. We have previously studied teratogenesis and cardiovascular anomalies following similar environmental stress exposure and showed that pharynx and cardiovascular system diseases are some of the most common causes of sufferings in A-bomb survivors and in their ultimate mortality. These studies have now put focus on roles of PHF, SHF and neural crest in structural development of the heart. They suggest that affected heart fields, pharyngeal arches, and neural crest cells that migrate to pharynx and cardiovascular system and interfere with developmental processes may be essential for abnormal craniofacial and cardiovascular development, as they disrupt signaling genes and transcription factors. This human model should contribute to investigation of mechanism of such dysfunction in pharyngeal arches and heart fields in human syndromes and diseases, as well as their medical and therapeutic intervention.

P39

Abstract Withdrawn

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ARBOUR-DELAHAYE N, KAPPEN C, SALBAUM JM. Pennington Biomedical Research Center, Baton Rouge, LA, United States. Neural Tube Defects in Non-Obese Diabetic (NOD) Mice

Maternal diabetes during pregnancy is a known teratogen that can cause neural tube defects. These abnormalities result from failure of the neural tube to close during early embryonic development, and affect the brain (anencephaly/exencephaly) and/or spinal cord (spina bifida). The underlying mechanisms in defective neural tube closure are unclear. The NOD mouse is a well-established model of Type 1 diabetes which spontaneously develops diabetes with autoimmune involvement. We first validated the strain for diabetes and neural tube incidence. Approximately 10% of the female NOD mice develop diabetes by 12 weeks, and by 16 weeks, 50% are diabetic. We examined the rate of neural tube defects, and observe exencephaly or spina bifida in 39.3% of the embryos from diabetic pregnancies at embryonic day E10.5. None of the embryos from normal pregnancies have observable neural tube defects. This high incidence of neural tube defects in NOD embryos from diabetic pregnancies will allow us to investigate the relationship of altered gene expression and signaling pathways to specific neural tube defect phenotypes. To determine the profile of expressed genes in NOD embryos exposed to a diabetic intrauterine environment, we will perform transcriptome analysis at E10.5. Earlier stages of embryonic development will also be examined to identify gene expression patterns before and during neural tube closure.

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HERRING BJ[1], LOGSDON AL[1], LOVICH AN[1], LOCKARD JE[1], JANZEN ER[1], RASCO JF[2], DI BONA KR[2], HOOD RD[2,3], SWATLOSKI RP[4,5], ROGERS RD[4,5], BAILEY MM[1]. [1]Department of Biological Sciences, Emporia State University, Emporia, KS, United States, [2]Department of Biological Sciences, The University of Alabama, Tuscaloosa, AL, United States, [3]Ronald D. Hood & Associates, Tuscaloosa, AL, United States, [4]Department of Chemistry, The University of Alabama, Tuscaloosa, AL, United States, [5]Center for Green Manufacturing, The University of Alabama, Tuscaloosa, AL, United States. Anion Influence on the Toxicity of Short-Chain Imidazolium-Based Ionic Liquids in CD-1 Mice

Ionic liquids (ILs), salts composed of ions with wide liquid ranges and with melting points < 100°C, have gained attention in recent years as "green" alternatives to traditional industrial solvents. While ionic liquids are not likely to contaminate the air, there is some potential for human exposure through water or soil contamination from industrial effluents or accidental spills. The influence of the cation on the toxicity of a particular IL has been studied; however no studies to date have investigated the effects of the anion on the toxicity of an IL to a developing fetus. Thus, the current study was performed to assess the influence of the anion on the developmental toxicity potential of two representative imidazolium-based ILs, 1-ethyl-3-methylimidazolium chloride ([emim]Cl) and 1-ethyl-3-methylimidazolium acetate ([emim]Ac). From gestation days (GD) 6-16, mated CD-1 mice were orally dosed with 2500 mg/kg/day [emim]Cl or [emim]Ac, or the vehicle only (DI H_2O). Dams were sacrificed on GD 17, and their litters were examined for adverse effects. A significant increase in maternal morbidity was observed in the [emim]Ac-treated group compared to controls, but no statistically significant decrease in fetal weight or increase in fetal malformations was associated with either IL treatment. The percentage of resorbed or dead fetuses was increased in both treated groups compared to controls, but the differences were not statistically significant. Anion composition influenced the maternal toxicity of a short-chain imidazolium-based ionic liquid; however, there were no anion-associated differences in adverse effects on the developing offspring. This project was made possible by NIH grant number P20 RR016475 from the INBRE Program of the National Center for Research Resources to Emporia State University.

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LOGSDON AL[1], HERRING BJ[1], LOCKARD JE[1], JANZEN ER[1], RASCO JF[2], HOOD RD[2,3], BAILEY MM[1]. [1]Department of Biological Sciences, Emporia State University, Emporia, KS, United States, [2]Department of Biological Sciences, The University of Alabama, Tuscaloosa, AL, United States, [3]Ronald D. Hood & Associates, Tuscaloosa, AL, United States. Evaluation of Effects of Prior Exposure to Green Tea Extract on Cyclophosphamide Teratogenesis

Green tea extract (GTE) has been shown to have antioxidative, anti-mutagenic, and anticarcinogenic properties, due to the high amount of polyphenols, catechins, and catechin gallates present. The most prominent such catechin gallate with antioxidative properties is epigallocatechin gallate (EGCG). Previous studies indicated that EGCG scavenges free radicals and attenuates the effects of reactive oxidative species (ROS). Anticancer drugs, such as cyclophosphamide (CP), produce ROS, which can have adverse effects on development, including limb, digit, and cranial abnormalities. To date, no reports have been published on whether GTE or EGCG can attenuate developmental defects caused by exposure to an ROS-generating agent. Thus, the current study was performed to determine if prior exposure to GTE can decrease teratogenic effects induced by CP. From gestation days (GD) 6-13, mated CD-1 mice were orally dosed with 200 mg/kg/d GTE only, 100 mg/kg/d GTE + CP, 200 mg/kg/d GTE + CP, CP only, or the vehicle only. In all cases CP (20 mg/kg) was administered by IP injection on GD 10. Dams were sacrificed on GD 17, and their litters were examined for adverse effects. Exposure to GTE prior to CP had no effects on fetal weight or maternal weight gain, and appeared to have reduced the incidence of some morphological defects, but the reduction was not statistically significant compared to the incidences in CP exposed fetuses. This project was made possible by NIH grant number P20 RR016475 from the INBRE Program of the National Center for Research Resources to Emporia State University.

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STODGELL CJ[1], ORNOY A[2], O'BARA M[1], GLAZKO G[1], MILLER RK[1]. [1]University of Rochester, Rochester, NY, United States, [2]Hadassah Medical School, Jerusalem, Israel. Embryonic Gene Expression in the Cohen Diabetic Rat Model of Type II Diabetes Mellitus

Introduction: Diabetes Mellitus (DM) is a rapidly growing medical problem. If left uncontrolled in pregnant women, it can lead to neural tube defects, macro- or microsomia, or pregnancy loss. Oxidative stress and alterations in gene expression have been proposed in terms of their etiological mechanism. To understand these mechanisms, gene expression patterns were examined in embryos from a genetic rat model of DM Type II - the Cohen Diabetic rat sensitive to developing DM (CDs) maintained on a high sucrose/low copper (HSD/Cu^{2+}) diet. Gene expression patterns were compared to embryos from the Cohen Diabetic rat resistant to DM (CDr) on the same diet. Methods: Female CDs and CDr rats were fed a HSD/Cu^{2+} diet for 6 weeks to induce DM in the CDs dams, and then bred. The resulting embryos were removed from the dams on d12 of gestation (d0 = morning after mating). Embryos were immediately evaluated for NTDs and stored frozen until total RNA from each CDs and CDr embryo was extracted (n= 10 ea.). RNA was processed according to Affymetrix's recommendations and labeled cDNA was hybridized to the Rat 1.0 ST Expression array. Genes that were significantly differentially expressed (DE) between the two strains were determined by Student's T-test with correction for multiple comparisons. Results: Comparisons of expression levels indicated that 102 genes were DE: 29 overexpressed and 73 downregulated in the CDs embryos. Network and pathway analysis using Ingenuity indicated that the NRF2-Mediated Oxidative Stress Response pathway and the Endoplasmic Reticulum Stress pathway, both of which are involved in response to anoxia and oxidative stress conditions were overrepresented in the CDs strain with NTDs. Also of interest, the PAX4 gene, was upregulated in CDs strain. This gene is involved in several signaling pathways, and has been implicated in the pathophysiology of diabetes. Conclusions: Understanding the genes and their molecular pathways that are affected under conditions that can induce DM, the CDs rat leads us to understand the molecular mechanisms associated with DM induced birth defects. (Supported by the RW & MS Goode Trust, US-Israel BiNational Foundation (0374352) and Israeli Science Foundation (0394193.)

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ORNOY A[1], LIVSHITZ A[1], STODGELL CJ[2], MILLER RK[2]. [1]Hebrew University Hadassah Medical School, Jerusalem, Israel, [2]University of Rochester Medical School, Rochester, NY, United States. The Effects of Hyperglycemia, Hypoxia and a Combination on Embryonic Development and its Redox Status: Results of Molecular Studies

Introduction: Increased embryonic oxidative stress is associated with both diabetic and hypoxia induced embryopathy. We hypothesized that a combination of hypoxia and hyperglycemia will increase embryonic damage produced by either factor individually. We studied the interrelationship between hyperglycemia and hypoxia and their effects on genes involved in the balance of embryonic redox status. Methods: 10.5 day old rat embryos were cultured for 28hr in culture medium with 7 mg/ml of glucose (hyperglycemia) and 20% oxygen, with 10% oxygen (hypoxia) and 2.4 mg/ml of glucose or a combination of both hyperglycemia and hypoxia. The embryos were then examined for growth and anomalies. Antioxidant capacity was determined by activity and gene expression of antioxidant enzymes Cu/Zn SOD, Mn-SOD, CAT and Glutathione peroxidase (GSH-px) using real time PCR. In a genetic model of Type II diabetes, 12 day embryos from both the Cohen Diabetic Sensitive (CDs) rat and the Cohen Diabetic resistant rat (CDr), gene expression patterns were evaluated with Affymetrix microarrays to determine the expression of these genes. Results: Hyperglycemia, hypoxia, a combination, or diabetes decreased embryonic growth and induced a high rate of anomalies. CAT mRNA was decreased in the malformed embryos exposed to hyperglycemia, to hypoxia or their combination, while GSH-px mRNA was decreased only in the embryos exposed to hypoxia and the combination of hypoxia and hyperglycemia. In contrast, Cu/Zn SOD mRNA was increased, while Mn-SOD was drastically decreased. The arrays results are presented in a separate abstract (see Stodgell *et al*). The specific genes tested in the present abstract were not statistically different between the CDs and CDr strains. However, the CAT, SOD and GSH-px genes tested are part of the NRF2-mediated oxidative stress pathway, which had an overrepresentation of genes being differentially affected between the CDs and CDr embryos. Conclusions: Both high glucose levels, hypoxia and diabetes are highly teratogenic; they increase embryonic oxidative stress, up-regulate the expression of Cu/Zn SOD gene/enzyme activity and down regulate the expression of Mn-SOD, CAT and GSH-px genes. (Supported by US-Israel BiNational Foundation (0374352), Israeli Science Foundation (0394193), RW & MS Goode Trust.)

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CHEN J[1], GREENE RM[2], WEBB CL[2], PISANO MM[2], NEAL RE[1,2]. [1]EOHS, SPHIS, University of Louisville, Louisville, KY, United States, [2]Birth Defects Center, University of Louisville, Louisville, KY, United States. Cigarette Smoke Exposure Impacts the Uterine Metabolome

A murine model of gestational cigarette smoke exposure (CSE)-induced low birthweight (LBW), developed in our laboratory, exhibits susceptibility during the peri-implantation period of development. As a first step toward understanding the impact of CSE on normal uterine biochemical homeostasis, which may be linked to delayed implantation and/or the LBW phenotype, the current study examined alterations in uterine metabolome profiles in non-pregnant females in response to CSE. C57BL/6J mice were exposed to cigarette smoke or ambient air (sham-exposed) for 6h/day for 5 days, immediately after which time uterine tissue was collected for analysis. Methanol-extracted metabolites from uterine tissue homogenates were diluted with acidified methanol and subjected to direct inject nano-ESI-MS (Advion Nanomate interfaced to ThermoElectron LTQ-FT-ICR-MS; positive polarity). Duplicate spectra were collected from 4 overlapping spectral windows within the same dataset covering a range of 100-1000 m/z (100,000 resolving power; spectral windows 100-400 m/z, 350-650 m/z, 600-850 m/z and 800-1000 m/z). GeneData Refiner/Expressionist software was utilized to align spectra, remove noise, and perform statistical analysis (ANOVA). Identification of mass features by accurate mass coupled with CID, IRMPD, and ECD induced fragmentation is ongoing. Six mass features of interest ($p<0.05$ and 2-fold difference) were found in the preliminary comparison of differences between the uterine metabolome of cigarette smoke- and sham-exposed groups. Over 20 additional mass features of interest were found if the fold-change distribution was expanded to include a 50% alteration in ion abundance. Preliminary identification of mass features of interest through searching of freely available metabolite databases (METLIN, HMDB) are based on the mass deviation from theoretical prediction, isotopic abundance pattern, and limited to protonated, sodiated, or potassiated adducts. Positive identification of the correct structural isomer of each candidate metabolite molecular formula is on-going. From the metabolite candidates tentatively identified, it is apparent that glycerophospholipid availability in the uterine tissue of non-pregnant mice is compromised by CSE. Research Support: NIH grants DA027466, HD053509 and P20 RR017702.

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SAHAMBI SK, GORDON C, LEBLANC A, LEBEL E. LAB Research Inc., Laval, QC, Canada. Female Rat Fertility: Validation of Procedures and Evaluation Methods in Srague Dawley Rats Using 4-Aminophenol

As a part of the development of the reproductive-embryofetal toxicology capabilities in our laboratory, this study was conducted to assess the fertility and reproduction of female Sprague Dawley rats of the F_0 generation and the early *in-utero* development of the F_1 generation following exposure to 4-aminophenol (4-AP). 4-AP has numerous industrial applications, including dyeing, photography and pharmaceuticals, and has been shown to induce reproductive and developmental toxicity. Adult female Sprague-Dawley rats were orally administered 4-AP (10 mL/kg) at dose levels 0, 50, 100 and 500 mg/kg (doses selected based on literature; n=8) for 14 consecutive days prior to mating, during mating (with untreated male Sprague-Dawley rats) and until gestation day (GD) 7. Body weights, clinical signs and food consumption were monitored throughout the treatment period and until cesarean on GD 13 or 14. Estrous cycle was monitored for two weeks prior to treatment and during treatment until mating. At termination, corpora lutea, dead and live embryos and resorptions were counted. Mating index, fertility index and conception rate were calculated. 4-AP related clinical signs included brown urine in 22-53% of treated animals at all dose levels during the pre-mating period. Reduced body weights and/or food consumption were noted in 100 and 500 mg/kg treated animals along with a markedly higher post-implantation losses at 500 mg/kg. Estrous cycle, mating index, fertility index and conception rate remained comparable in the control and treated animals. These results are comparable to the published literature and demonstrate that the laboratory's procedures and evaluation methods were suitable for assessing the fertility and reproduction of the F_0 females and early *in-utero* development of the F_1 generation.

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WELCH KD, PANTER KE, STEGELMEIER BL, LEE ST, GARDNER DR. USDA/ARS/Poisonous Plant Research Laboratory, Logan, UT, United States. Cyclopamine-Induced Placental Dysplasia in Sheep

Background: Cyclopamine, a steroidal alkaloid, from *Veratrum californicum* is teratogenic causing a range of birth defects. The critical window for cyclopamine-induced synophthalmia formation has been reported to be around gestational day (GD) 14. Lambs with cyclopia are smaller, under developed, and appear premature even though a twin appears fully developed. Initial evaluations suggest this was due to placental dysplasia. The objective of this study was to determine if there are placental dysplasias in ewes with lambs with synophthalmia and other less severe craniofacial malformations. Methods: Nine ewes were dosed orally twice on GD 14 with 0.88 g/kg of *V. californicum*. Pregnancy, pre-partum fetal malformations, and placentome diameter were determined by ultrasound imaging on GD 45, 60, 75, 105, and 135. At GD 135 the ewes were euthanized and the lambs were assessed for gross malformations and several fetal measurements were made as well as several placental measurements. Results: There was no difference in the placentome diameter measurements made *in utero* by ultrasound imaging. The 9 ewes gave birth to 17 lambs. Four of the lambs were cyclopic, 6 had other craniofacial malformations including maxillary dysplasia, mandibular micrognathia and superior deviation of the rostral mandible, while 7 lambs appeared normal. The cyclopic lambs were significantly smaller than the other malformed lambs and the normal lambs. The number of placentomes, placentome area, and placentome weight were all significantly smaller for ewes with cyclopic lambs as well as the total weight of the uterus. There was no difference in the weight of the fetal pituitary glands between the different groups of lambs. However, weights of the fetal adrenal glands were significantly less in the cyclopic lambs. Conclusions: Cyclopic lambs are smaller than lambs with less severe craniofacial malformations, which are similar in size to normal lambs. There appears to be a correlation between the severity of the malformed lambs and placental dysplasia, i.e. ewes with cyclopic lambs have a much smaller uterus and less developed caruncles. Interestingly the size and weight of the pituitary did not differ with malformations, however, histological analysis of the pituitary and hormone profile analyses are still pending.

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BJORNARD K, RIEHLE-COLARUSSO TJ, GILBOA SM, CORREA A. National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, GA, United States. Patterns in the Prevalence of Congenital Heart Defects, Metropolitan Atlanta, 1978-2005

Introduction: With an estimated prevalence of 80 per 10,000 live births, congenital heart defects (CHD) represent a significant healthcare burden in the United States. Monitoring patterns in the prevalence of CHD over time assists in generating etiologic hypotheses. We describe trends in CHD prevalence by phenotype and by race/ethnicity based on nearly three decades of surveillance data. Methods: We included cases with CHD born from 1978-2005 and registered in the Metropolitan Atlanta Congenital Defects Program, a population-based birth defects surveillance system capturing births to mothers residing in the five-county metropolitan area of Atlanta. Cases included live births, stillbirths, and terminations, although cases ascertained in the prenatal period and subsequently terminated prior to 20 weeks gestation were excluded. Denominator data of live births by race/ethnicity (White, Black, Hispanic) were gathered from vital records. Prevalence estimates are reported per 10,000 live births and variations in prevalence by race/ethnicity are assessed with prevalence ratios (PR) and 95% confidence intervals (CI). Results: During the period of 1978-2005, there were 7,301 infants with CHD among 1,079,062 live births, yielding an overall prevalence of 67.7 per 10,000. Between 1978-1983 to 2000-2005, CHD prevalence increased from 50.2 to 86.4 per 10,000, with most of the increase accounted for by increases in prevalence of atrial and ventricular septal defects. During 1978-1983, 1984-1989 and 1990-1994, the prevalence of CHD among Blacks was similar to that among Whites. The prevalence among Blacks was less than among Whites during the time periods of 1995-1999 (PR= 0.86; 95% CI= 0.77-0.95) and 2000-2005 (PR= 0.80; 95% CI= 0.74-0.88). From 2000-2005, the prevalence among Hispanics was no different from the prevalence among Whites. Whites and Hispanics had a higher prevalence of aortic stenosis and ventricular septal defects compared with Blacks. Hispanics had a lower prevalence of atrioventricular septal defects compared with both Whites and Blacks. Conclusions: The overall prevalence of CHD in Atlanta increased from 1978 through 2005, driven by atrial and ventricular septal defects. Selected phenotypes showed differences by race/ethnicity. Further studies are warranted to elucidate whether these findings reflect differences in case ascertainment or classification or differences in susceptibility among population subgroups.

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PACHAJOA H, RODRIGUEZ CA, ISAZA C. Universidad del Valle, Cali, Valle del Cauca, Colombia. Birth Defects and Genetic Diseases in Prehispanic Communities of the Colombian and Ecuadorian Pacific Coast, (300 B.C.-600 A.C.)

Introduction: The Tumaco-Tolita culture inhabited the geo-historical region of the colombo-ecuadorian pacific coast during the years 300 b.C.-600 a.C. This culture was characterized for capturing with impressive realism the different pathologies that suffered their population, as well as evidence of genetic illnesses, birth defects, and the processes of aging and death. Objetive: To describe the phenotypical evidences of birth defects and genetic diseases in the ceramic of the Tumaco-Tolita culture of the main museums of Pre-Columbian ceramics of Colombia. Methods: A medical geneticist, and an archaeologist examined the collection of the Tumaco-Tolita culture of the main museums of Pre-Columbian ceramics of Colombia. The cases that displayed evidences of congenital defects and genetic diseases were documented. Results: Out of the 5000 examined pieces, there were found ceramics with clear or suggestive evidence of birth defects and genetic diseases like Down syndrome, Crouzon syndrome, Achondroplasy, mucopolysaccharidosis (hurler syndrome and Morquio syndrome), sirenomelia and cleft lip. Conclusions: The Tumaco-Tolita culture represented the birth defects and genetic diseases in their ceramics, and it constituted one of the first registries of these conditions in the Pre-Columbian American cultures and the world, in addition it was found clear evidence that some conditions generated status within the society.

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PACHAJOA H, ISAZA C. Universidad del Valle, Cali, Valle del Cauca, Colombia. Concomitant Presence of Cyclopia and Sirenomelia in a Stillbirth Infant before the Epidemic Focus of Sirenomelia in Cali - Colombia (South America)

Introduction: Sirenomelia and cyclopia are congenital malformations due by early blastogenic defects, with similar epidemiologic patterns, and possible common etiopathogenicity. The sirenomelia or mermaid syndrome is a congenital structural anomaly characterized by an abnormal development of the caudal region of the body with different degrees of fusion of the lower extremities and bears resemblance to the mermaid of Greek mythology. Cyclopia is the most severe form of holoprosencephaly, is characterized by the presence of one central eye product of the fusion of the two eyes and the alobar holoprosencephaly. The prevalence of these two pathologies has been estimated close to 1 in 100 000 births, including stillbirths. Case report: We describe the findings in a stillbirth infant with sirenomelia, cyclopia and cephalocele occipital. Born of non consanguineous parents, mother of 16 years old and father of 23 years old by the time of birth; the mother manifested to have used misoprostol at the beginning of pregnancy (first 4 weeks) as a method to abort the fetus. Discussion: Recently, a cluster of sirenomelia in the city of Cali was published. This city is located in the Colombian pacific coast. In a maternity follow up by ECLAMC (Latin-American Collaborative Study of Congenital Malformations), an epidemic focus of sirenomelia was reported during a 55-day period between 12.09.04, and 02.02.05. During that period of time 1,064 children were born and four cases presented this rare disease, which was considered unusual and suggesting of the presence of a cluster. The evidence of an infant with both sirenomelia and cyclopia suggest an epidemiologic pattern, and possible common etiopathogenicity in the city of Cali.

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BAKHIREVA LN[1], SARANGARM P[1], LIU S[1], YOUNG BN[1], DAVIS A[1], COX J[2], PHELAN ST[2], RAYBURN WF[2]. [1]University of New Mexico College of Pharmacy, Albuquerque, NM, United States, [2]University of New Mexico Department of Obstetrics and Gynecology, Albuquerque, NM, United States. Prevalence and Predictors of Complementary and Alternative Medicine Products Use among Pregnant Women in New Mexico

Introduction: The use of complementary and alternative medicine (CAM) products by pregnant women might be prevalent, while safety profile is often unknown. The purpose of this study was to estimate the prevalence and predictors of CAM use among pregnant women in New Mexico. Methods: The data for this cross-sectional analysis are derived a multi-clinic cohort study "Safety of Medications and Perception of Teratogenicity (SMART)". Pregnant women (n=405) recruited from 5 prenatal care clinics in Albuquerque, NM were interviewed about their CAM use in pregnancy. CAM was defined as any product not used by allopathic medicine and did not include vitamins or trace elements. Demographic, social, and medical characteristics were examined as potential predictors of CAM use by Chi-square and logistic regression in univariate and multivariate analyses, respectively. Results: The mean age of study participants was 27.5 ± 6.07 years, 80.9% were Latina, and 32.1% had college degree or higher. The prevalence of CAM product use was 13.6%. The most prevalent products were fish oil (4.2%), Herbalife® (3.2%), and chamomile (1.2%). Women who had a high school diploma or equivalent were more likely to use CAM products (OR=4.4; 95% CI: 1.4; 14.4) compared with women who had lower than high school education independent of ethnicity and other covariates. Women with incomplete college, associate or bachelor's degrees demonstrated a trend towards higher CAM use compared with women who had lower that high school education; however results did not reach statistical significance. Women with a prior history of adverse perinatal outcomes also were more likely to use CAM products (OR=2.2; 95% CI: 0.99-4.7) independent of other risk factors. Discussion: The use of CAM products in New Mexico is prevalent. While some products are benign, the use of Herbalife® is concerning. Women of higher socio-economic status are more likely to use CAM independent of ethnicity and other covariates. An apparent association between CAM use and a history of adverse perinatal outcomes in prior pregnancies requires further investigation.

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WARNER DR, MUKHOPADHYAY P, WEBB CL, GREENE RM, PISANO MM. University of Louisville Birth Defects Center, Department of Molecular, Cellular, and Craniofacial Biology, ULSD, Louisville, KY, United States. PRDM16 Signaling Regulates Murine Secondary Palate Development

PRDM16 is a 170 kDa nuclear protein that contains multiple zinc finger motifs and protein interaction domains. We recently demonstrated that this protein bound both TGFb- and BMP-responsive Smad proteins, and attenuated TGFb signaling in mesenchymal cells derived from the murine embryonic secondary palate. In the current study, we further characterized the role of PRDM16 in development of the secondary palate in mice and defined a cellular mechanism by which PRDM16 functions. Using a reporter assay that consists of 1) the DNA binding domain of Gal4 fused to CREB binding protein (CBP), a known co-activator for TGFb signaling, and 2) a reporter plasmid containing the GAL4 consensus sequence driving luciferase expression, we found that PRDM16 was an inhibitor of CBP/Smad3-dependent signaling. These data, combined with our previous observation that PRDM16 inhibited Smad-dependent TGFb signaling, allow us to conclude that that PRDM16 alters TGFb signaling *via* a protein complex that includes CBP and Smad3. A DNA affinity purification assay confirmed that PRDM16 is part of the transcription factor complex that binds to a consensus Smad-binding DNA sequence, but which is disrupted upon stimulation with TGFb. To begin to understand the function of PRDM16 *in vivo*, we have examined the phenotype associated with Prdm16 gene loss of function and demonstrated that the Prdm16 gene-knockout mouse presents with a complete cleft of the secondary palate. In addition we have conducted a comprehensive screen of gene promoters to which PRDM16 binds in embryonic palatal tissue and have identified several novel gene targets of PRDM16. Taken together, these data demonstrate that proper expression of PRDM16 is essential for normal secondary palate development and that PRDM16 functions to control the response of embryonic palate mesenchymal cells to TGFb signals, and may be a cofactor that controls the specificity of TGFb-induced genes in the developing palate. Supported in part by the Cleft Palate Foundation, the KY Science & Engineering Foundation, and NIH grants DE018215, HD053509, and P20 RR017702 from the COBRE program of the NCRR.

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REZZOUG F[1], HORN KH[2], ESPOSITO ER[1], BIRTLES T[1], GREENE RM[1], PISANO MM[1]. [1]University of Louisville Birth Defects Center, Department of Molecular, Cellular, and Craniofacial Biology, ULSD, Louisville, KY, United States, [2]Bristol-Myers Squibb Co., Department of Toxicology, Drug Safety Evaluation, Mt. Vernon, IN, United States. Maternal Dietary Remediation of Cigarette Smoke Induced Intrauterine Growth Retardation: An Animal Model

While cigarette smoke (CS) is a well known environmental factor associated with infant low birth weight (LBW), mechanism(s) responsible for this adverse developmental outcome remain elusive. Our laboratory has established a murine model of CS-induced intrauterine growth retardation and LBW. Exposure of dams to physiologically relevant levels of CS during gestational days (GD) 1 to 5 results in decreased fetal weight and crown-rump length (CRL) on GD 18. In the current study, the timeline for developmental divergence following *in utero* exposure to CS was examined, and the role of gestational folate levels in developmental delay was assessed. Pregnant mice, maintained on Purina 5021 Diet (vitamin-fortified), were exposed to CS during GD 1-5. Dams were euthanized on GD 8.5, 9.5, 10.5, and 18.5 and reproductive /developmental outcomes evaluated. Unexpectedly, embryos/fetuses from dams maintained on this vitamin-fortified diet did not demonstrate CS-induced growth delay or decreased fetal weight/CRL. However, replacement of this diet with the non vitamin-fortified diet (Purina 5015) originally used to define the LBW model, resulted in reestablishment of CS-induced growth delay and reduced term fetal weight/size. Data from this study also demonstrated that CS-induced developmental delay is evident by GD 9.5. CS exposure has been linked to decreased circulating folate levels. To determine whether differences in folate levels between the two diets underlie the effects of CS on intrauterine growth, pregnant mice were maintained prior to/during gestation on Purina 5015 Diet supplemented with 40 mg/kg folic acid. Dietary supplementation with folic acid failed to rescue the CS-induced developmental delay and reduced fetal weight/CRL, indicating that differences in folate levels between the two diets are not responsible for differential susceptibility to CSE-induced intrauterine growth retardation and LBW. Metabolomic studies assessing interactions between diet and the maternal/embryo unit and the role they play in CSE-induced LBW are currently underway. Collectively, these data demonstrate that *in utero* CS exposure can induce early developmental delay with resultant low birth weight and suggests that maternal nutritional modifications can markedly alter the adverse effects of CSE on pregnancy outcomes. Supported by NIH grants DA027466, HD053509 and P20 RR017702 from the NCRR COBRE Program.

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XU JZ[1], MUKHOPADHYAY P[1], HORN KH[2], WEBB CL[1], BIRTLES T[1], GREENE RM[1], PISANO MM[1]. [1]University of Louisville Birth Defects Center, Department of Molecular, Cellular, and Craniofacial Biology, ULSD, Louisville, KY, United States, [2]Bristol-Myers Squibb Co., Department of Toxicology, Drug Safety Evaluation, Mt. Vernon, IN, United States. Prenatal Exposure to Environmental Tobacco Smoke Alters Gene Expression in the Developing Murine Hippocampus: Neurocognitive Correlates

In the United States about 50% of women smoke or are exposed to environmental tobacco smoke (ETS) during their pregnancy, with the deleterious result that approximately one million infants are exposed prenatally to cigarette smoke each year. Such exposures have been linked to impaired infant/childhood learning and other cognitive/behavioral deficits. Since the hippocampus plays critical roles in learning and cognitive processing, the objective of the present study was to investigate the effects of prenatal ETS exposure on the developing hippocampus. In the present study, pregnant C57BL/6J mice were exposed to either side stream cigarette smoke (a model of environmental tobacco smoke) or ambient air for six hours/day from gestational day (gd) 6 to gd 18.5 utilizing a microprocessor-controlled cigarette-smoke inhalation exposure system. Subsequently, fetal hippocampal tissue was microdissected, cRNA samples were prepared and hybridized to Affymetrix high density murine GeneChips® containing 45,101 gene/EST probes, and changes in gene expression were detected *via* microarray analysis and verified by TaqMan™ QRT-PCR. Sixty-one "expressed" genes in the fetal hippocampus were differentially regulated by maternal exposure to ETS including a variety of genes known to be involved in neurodevelopmental, neurobehavioral and cognitive processes such as NRXN (neurexin), SERT (neurotransmitter transporter, serotonin), SNYE1 (Synaptic nuclear envelope 1), APOD (Apolipoprotein D), MSI2 (Musashi homolog 2), and SEMA5A (Semaphorin 5a). Subregional distribution of candidate gene and protein expression in the CA1, CA3 and dentate gyrus (DG) regions of the hippocampus are currently being examined *via* laser capture microdissection of individual neuronal subtypes and TaqMan™ QRT-PCR, and immunohistochemistry. These results, along with those from ongoing behavioral testing of *in utero* cigarette smoke exposed animals, support the notion that subtle smoke-induced changes in the developing fetal brain can result in long-term behavioral and cognitive deficits. Supported in part by NIH grants DA027466, HD053509, P30 ES014443, and P20 RR017702 from the COBRE program of the NCRR.

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MUKHOPADHYAY P, BROCK G, APPANA S, PISANO MM, GREENE RM. University of Louisville Birth Defects Center, Department of Molecular, Cellular, and Craniofacial Biology, ULSD, Louisville, KY, United States. Developmental MicroRNA Expression Profiling of the Murine Embryonic Neural Tube

Development of the neural tube is a highly orchestrated process relying on precise, spatio-temporal expression of numerous genes and hierarchies of signal transduction and gene regulatory networks. Disrupted expression of genes participating in these networks – in humans and animal models – underlies neural tube defects such as spina bifida, anencephaly, exencephaly and encephalocele. MicroRNAs (miRNAs), an extensive family of small (18–25 bases) noncoding RNAs, generally function as gene silencers and modulators of cell and tissue differentiation. miRNAs regulate expression of genes post-transcriptionally through binding and direct inhibition of translation, and/or destabilization of their target mRNAs. To elucidate potential roles of miRNAs in mammalian neural tube development, miRNA expression profiles from gestational day (GD) 8.5, 9.0 and 9.5 (early, mid and late neural tube closure stages) developing murine neural tubes were compared utilizing miRXplore™ microarrays from Miltenyi Biotech GmbH. Temporal changes in miRNA expression were verified by TaqMan™ Quantitative Real-Time PCR. Cluster analysis of the miRNA expression data was performed using the clValid R package and the UPGMA (hierarchical) clustering method. Expression of approximately 12% of the 609 murine miRNAs evaluated on the microarray was detected in the developing neural tube. Cluster analysis revealed several developmentally regulated clusters among these expressed miRNAs. Target analysis enabled identification of a myriad of protein-coding target genes of the differentially expressed miRNAs within such clusters. Many of these target genes, such as Nucleoporin 50, Ephrin A5, Neural precursor cell expressed, developmentally down-regulated 9 (Nedd-9), Quaking homolog (QkI), and Homeodomain-interacting protein kinase 2 (Hipk2), are associated with vital cellular processes such as cell proliferation, cell adhesion, cell migration, differentiation, and apoptosis, all of which are essential for normal neural tube morphogenesis. Functional relationships between differentially expressed miRNAs and their target genes were identified by Ingenuity Pathway Analysis. In summary, evaluation of miRNA target genes and gene interaction pathways suggested that the expression of numerous protein-encoding genes, indispensable for normal neural tube morphogenesis, may be regulated by differentially expressed miRNAs. Supported in part by the KY Science & Engineering Foundation, and NIH grants HD053509, DA027466 and P20 RR017702 from the NCRR COBRE program.

P56

SEELAN RS, REZZOUG F, BHATTACHERJEE V, GREENE RM, PISANO MM. University of Louisville Birth Defects Center, Department of Molecular, Cellular, and Craniofacial Biology, ULSD, Louisville, KY, United States. Chemokine-Mediated Migration of Mesencephalic Neural Crest Cells

Cleft lip/palate are amongst the most prevalent birth defects, affecting approximately 7000 babies in the United States every year. One of the major causes of clefting is thought to be disruption of developmentally programmed migration of neural crest cells (NCCs) into the orofacial region. Signaling by the chemokine SDF-1 (Stromal Derived Factor-1) through its receptor, CXCR4, is required for the migration of varied stem and progenitor cell populations from their sites of emergence to regions where they differentiate into complex tissues/organs. In the present study, we examined whether SDF-1/CXCR4 signaling mediated mesencephalic (cranial) NCC migration using *in vitro* "transwell" and *in vivo* whole embryo "bead implantation" assays. Migration of chick embryo NCCs in "transwell" culture was determined using SDF-1 and a specific CXCR4 inhibitor, AMD3100. The Migration Index (MI) was determined using HNK-1 immunofluorescence (specific for migrating chick NCCs) and DAPI staining. An approximately two-fold higher MI was observed in the presence of SDF-1 compared to the vehicle control or to SDF-1 treated cells in the presence of the inhibitor AMD3100, suggesting that mesencephalic NCCs migrate in response to SDF-1/CXCR4 signaling. In the *in vivo* studies, Hamilton-Hamburger stage 9-10 chick embryos were cultured *ex ovo* and beads soaked in TN14003 (a peptide that blocks SDF-1 binding to CXCR4), or BSA, were implanted into the dorsal neural tube just posterior to the optic cup axis. Migration of NCCs was assessed by HNK-1 immunofluorescence, which demonstrated that NCC migration from the dorsal-to-ventral axis of the chick embryo was disrupted in the presence of TN14003-treated beads, but not by BSA-soaked beads. TN14003 also caused a significant reduction (~86%) in the number of migrating NCCs. Collectively, results from these studies demonstrate that attenuation of SDF-1 signaling, through the use of specific CXCR4 inhibitors, disrupts the migration of mesencephalic NCCs into the orofacial region, implying a specific role for SDF-1/CXCR4 signaling in mesencephalic NCC migration in the early stage embryo. The data also suggest that aberrant or defective SDF-1/CXCR4 signaling could contribute to orofacial defects. Supported by the Cleft Palate Foundation, NIH grants DE018215, HD053509, and P20 RR017702 from the NCRR COBRE Program.

P57

SEELAN RS, WARNER DR, MUKHOPADHYAY P, GREENE RM, PISANO MM. University of Louisville Birth Defects Center, Department of Molecular, Cellular, and Craniofacial Biology, ULSD, Louisville, KY, United States. Regulation of Sox4 Gene Expression by DNA Methylation during Secondary Palate Development

Orofacial clefts such as cleft palate (CP), and cleft lip with or without cleft palate (CL/P), are amongst the most prevalent birth defects in the United States. Genetic and environmental factors have been implicated in the etiology of CP. Environmentally-induced epigenetic alterations during palate development also may provide a mechanism by which environmental insults trigger abnormal DNA methylation, subsequent alterations in gene expression, and anomalous palate development. Our laboratory has embarked on a comprehensive, multi-faceted strategy to identify genes and epigenetic modifications essential for mammalian secondary palate development utilizing high density microarrays to examine alterations in levels of mRNAs, microRNAs and gene methylation in murine palatal tissue from gestational day (gd) 12 through 14 – the critical period for murine secondary palate development. mRNA profiling during secondary palate development, using Affymetrix GeneChips, coupled with bioinformatic analyses, have identified Sox4 as a candidate genes that is differentially expressed and potentially regulated by DNA methylation. Sox4 mRNA expression in the developing palate is decreased two-fold on gd13 compared to gd12, a finding consistent with CpG methylation changes detected in the 5' flanking region between gd12 and gd13. Specifically, two CpG residues residing in a Differentially Methylated Region (DMR), which are 60%-70% methylated at gd12, become fully methylated by gd13. Increased methylation of these residues correlates with the decrease in Sox 4 mRNA levels during this time period. Our ongoing studies seek to validate the functionality of these CpG residues using methylation-dependent luciferase expression vectors. Since Sox4 knockout mice die early in embryogenesis, the precise role of Sox4 in secondary palate development is unknown. However, Sox 4 is a transcriptional activator that regulates the Wnt and TGFß signaling pathways, both critical signaling mediators of palate development. This affords a likely means for Sox4 regulation of palatal ontogenesis. Combined with other studies suggesting a possible role for Sox4 in CP and CL/P, our findings indicate that Sox4 is transiently expressed and may be epigenetically regulated *via* changes in DNA methylation during secondary palate development. Supported in part by NIH grants DE018215, HD053509, and P20 RR017702 from the NCRR COBRE Program.

P58

SALBAUM JM, KAPPEN C. Pennington Biomedical Research Center, Baton Rouge, LA, United States. Diabetic Embryopathy and Molecular Variation

Intrauterine exposure to adverse conditions, such as diabetes or obesity of the mother, can cause both birth defects and long-term health consequences in the offspring. Maternal diabetes during pregnancy is a well-known teratogen, giving rise to increased frequencies of heart defects and neural tube defects in infants from diabetic pregnancies. Long-term effects include increased susceptibility to metabolic syndrome later in life, and are thought to be due to 'developmental programming'. Exactly how birth defect etiology and long-term health consequences are related to developmental insults on a molecular level remains unclear. We have shown that maternal diabetes has profound effects on gene expression in the developing embryo. Our studies have identified genes with significantly changed expression levels in the embryo under conditions of maternal diabetes. Yet, the functional correlation of altered gene expression to birth defects in diabetic pregnancies is not so straightforward. Neural tube defects, for example, occur at low frequency and also present with different severity, thus characterizing them as phenotypes of incomplete penetrance and variable expressivity. These phenotypic characteristics stand in contrast to observations of consistently altered embryonic gene expression. We therefore conclude that additional mechanisms must be in place to account for the variability of the phenotype. Our transcription profiling experiments show that besides changing expression levels of specific genes, maternal diabetes during pregnancy also increases the overall variation of gene expression levels in the embryo. We propose that this increase in variation may represent the molecular correlate for conveying the differential vulnerability. We suggest that maternal diabetes may affect the overall precision of gene regulation in the embryo, and that a loss of regulatory precision contributes to the susceptibility for birth defects at the molecular level. How regulation of embryonic gene expression is affected by maternal diabetes is not understood, but may include modulation of epigenetic landscapes *via* de-regulated chromatin factors. Unraveling this mechanism will help to understand how teratogenic insults compromise embryonic development, and possibly provide avenues for therapeutic intervention.

TERATOLOGY SOCIETY

JOINT TS/OTIS PREGNANCY REGISTRY WORKSHOP ABSTRACTS

(Presenter designated by underlined author.)

Invited Speakers

W1

HOLMES LB. MassGeneral Hospital for Children, Boston, MA, United States. Classifying Birth Defects in Reproductive Research

Background: Malformations are the outcomes tabulated most often in pregnancy registries. Usually there is no systematic study exam of the exposed and unexposed infants and the findings in routine physical examinations by the infants' pediatricians are the source of information. There is variation in the thoroughness of the examinations and many types of physical findings are recorded. Specific criteria are needed to distinguish between structural abnormalities to be considered a malformation and those outcomes which should be excluded. Methods: A malformation was defined as a structural abnormality with surgical, medical or cosmetic importance. The review of the pediatricians examination findings of infants whose mothers had enrolled in the North American AED (antiepileptic drug) Pregnancy Registry showed that the presence of notable physical features had been recorded in many. A list of features excluded as not being a malformation was developed and a Decision Tree was maintained to insure consistency in the classification process. Results: The physical features excluded were: 1) minor anomalies (transverse palmar crease); 2) birth marks (hemangiomas); 3) positional deformity (torticollis); 4) effects of prematurity (undescended testes); 5) functional deficits (failed newborn hearing test); 6) biochemical findings (hyperbilirubinemia); 7) genetic disorders (albinism); 8) chromosome abnormalities (trisomy 21); renal anomalies detected by prenatal ultrasound, but not the examining pediatrician (unilateral renal agenesis); 10) tiny (<0.4 cm) atrial septal defects and muscular ventricular septal defects (VSDs). There are several types of VSDs, including muscular, perimembranous and atrioventricular septal defects. We include the large muscular VSD which causes symptoms in the infant, but exclude all others muscular VSDs. Echocardiograms in 1,053 newborns showed that 5.3% had a muscular VSD and most (89%) closed spontaneously by 10 months of age (Roguin N *et al*: *JACC* 26:1545-8, 1995). Conclusions: A meaningful comparison can be made between the physical features of the exposed and unexposed comparison group, if the same inclusion/exclusion criteria have been used for each group. Contact with the enrolled woman and her infants' doctors is essential to establishing the findings in each infant.

W2

SAVITZ DA. Mount Sinai School of Medicine, New York, NY, United States. Methodological Challenges in Surveillance of Spontaneous Abortion as a Reproductive Health Endpoint

Monitoring the outcome of pregnancies that have been exposed to selected potential reproductive toxicants is a public health strategy of proven value in the study of structural malformations. However, application of this system to other reproductive health endpoints may not yield the same benefits. There are several features of spontaneous abortion as an endpoint that pose challenges to the value of routine surveillance. 1) Well-defined population that is at risk of manifesting the health endpoint: In order to clearly document the frequency of occurrence, it is essential to know who is at risk, making sure that the occurrence of the outcome itself is not the primary reason for the pregnancy coming to attention. In the case of spontaneous abortion, the roster of women who are early in pregnancy is ill-defined, with no formal clinical documentation and often unclear even to the affected woman herself. 2) Ability to verify the occurrence of the health outcome through case review: Once a suspected event has occurred, it is important to be able to review medical details about that case and have independent experts adjudicate the classification. This requires medical documentation, very limited in the case of spontaneous abortion other than to note that a pregnancy test occurred and a live birth did not result. 3) Reference rates of occurrence for comparing the rates among exposed pregnancies: To be able to make an inference regarding whether the occurrence of spontaneous abortion is excessive or in the normal range, it is necessary to have a comparison population that provides expected values, much as the Metropolitan Atlanta Congenital Defects Program serves that purpose for studying structural malformations. The baseline risk of spontaneous abortion is heavily dependent on how the occurrence of spontaneous abortion is identified, i.e., how carefully and how early they document the occurrence of pregnancy and thus pregnancy loss. While some of these issues can be managed through specific protocols, the prospects for passive registries (as opposed to rigorous research protocols) being informative sources of information on suspected toxicants and spontaneous abortion are not encouraging.

W3

LI DK. Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States. Studying Miscarriage Using Pregnancy Registries

Introduction: Studying risk factors for miscarriage has become increasingly important with the increased number of older pregnant women. Methods: Pregnancy registries. Results: Traditionally, miscarriage is a difficult pregnancy endpoint to study largely due to incomplete ascertainment. With increased automated databases more available in many health care systems, pregnancy registries based on automated databases have become a useful mechanism through which miscarriage can be studied more effectively. Nevertheless, challenges in studying miscarriage remain. Discussion: Methodological issues specifically related to epidemiological studies of risk factors for miscarriage will be discussed.

W4

CONLIN AS, GUMBS GR, SEVICK CJ, SNELL KJ, DESCISCIOLO C, SMITH TC. Naval Health Research Center, San Diego, CA, United States. Organizing Pregnancy Registries during an Emergency Response

Introduction: Emergency responses are one type of special circumstance where pregnancy exposure registries are indicated. The National Smallpox Vaccine in Pregnancy Registry and the Department of Defense's (DoD's) Influenza A (H1N1) Vaccine in Pregnancy Study were both established during emergency responses to public health threats. Although not required by the U.S. Food and Drug Administration like many pregnancy exposure registries, the rapid development of the National Smallpox Vaccine in Pregnancy Registry was necessary due to the potential risk of fetal vaccinia, as well as the anticipated inadvertent vaccination of women during early pregnancy. The current H1N1 vaccination study required a similarly swift study design in order to provide meaningful real-time data about the safety of a newly-marketed vaccine highly recommended for administration to pregnant women. Methods: The National Smallpox Vaccine in Pregnancy Registry (2003-present) is a multidisciplinary collaboration of US DoD and the Centers for Disease Control and Prevention designed to actively enroll and follow women who receive smallpox vaccine during pregnancy or within 42 days of conception. The DoD's Influenza A (H1N1) Vaccine in Pregnancy Study commenced in late 2009 to determine if H1N1 vaccination in pregnancy or periconceptually is independently associated with adverse pregnancy or infant health outcomes in active duty military women. This study prospectively leverages electronic military medical record data for immunization status as well as pregnancy, birth, and infant information. Pregnancy losses can be evaluated in both studies. Results: 471 women (476 pregnancies) are being followed in the National Smallpox Vaccine in Pregnancy Registry, 75% of whom were vaccinated before a standard pregnancy test would have been positive. Rates of pregnancy loss, preterm birth, and birth defects are comparable with those in healthy referent groups. No cases of fetal vaccinia have been identified. Data analyses are ongoing for the DoD Influenza A (H1N1) Vaccine in Pregnancy Study. Discussion: Organizing pregnancy registries during an emergency response requires flexibility, collaboration, appropriate referent populations, and rapid data collection strategies, allowing for the elapsed time before pregnancy and infant health outcomes become available. Ongoing strategic communication of results contributes to the understanding of pharmaceutical effects on fetal health.

W5

CHAMBERS CD[1], SCHATZ M[2], MITCHELL AA[3], LOUIK C[3], JONES KL[1]. [1]University of California San Diego, La Jolla, CA, United States, [2]Kaiser Permanente Medical Center, San Diego, CA, United States, [3]Boston University, Boston, MA, United States. The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS): Launch of a New System for Post-Marketing Surveillance

Many women are reluctant to use any medications or receive vaccines during pregnancy out of fear about possible harms to their unborn child. However, many medical conditions such as asthma and influenza, particularly if left untreated, can harm both the mother and her baby. There is an urgent need for good quality information on the risks or safety of exposures in pregnancy, yet most exposures have not been well-studied in humans. The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), launched in 2009, unites the resources of two leading national epidemiologic research groups with coordination and oversight by a national professional medical organization, the American Academy of Allergy, Asthma and Immunology. VAMPSS combines a cohort study approach under the direction of researchers from the Organization of Teratology Information Specialists (OTIS) with a parallel case-control study approach under the leadership of investigators from the Slone Epidemiology Center (SEC) at Boston University. This coordinated effort relies on comprehensive and integrated methods for data collection from pregnant women or women who have recently delivered, with periodic review of the study results by a standing national and multidisciplinary Advisory Board. Initial federal funding for the VAMPSS system from the Agency for Healthcare Research and Quality (AHRQ) and the U.S. Office of Biomedical Advanced Research and Development Authority (BARDA) supports studies focused on the safety of agents related to maternal respiratory health, including 2009 H1N1 and seasonal influenza vaccines, antiviral medications used to treat or prevent influenza, and asthma medications. In addition to establishing a framework for systematic post-marketing surveillance for the safety of pregnancy exposures, major strengths of the VAMPSS system are that it combines the advantages of both cohort and case-control methods, and is designed to obtain comprehensive information on all maternal exposures including those exposures that are unlikely to be documented in the woman's medical record, such as products purchased over-the-counter, on the internet or borrowed from others, alcohol and tobacco use, and vaccines administered in non-traditional settings. In combination with other sources of data, the VAMPSS system represents an important step forward in the evaluation of drug safety in pregnancy.

W6

MCDONAGH M. CKR Consulting, Mansfield, MA, United States. Universal Call Center for Medicine Use in Pregnancy

Exposure to medications in pregnancy is common; however, prescribing decisions can be challenging. These decisions should be based on the most relevant available drug safety and efficacy data. Still, information on drug safety in pregnancy is often sparse and outside of some existing pregnancy registries, not collected effectively. This purpose of this abstract is to describe a solution to more effectively collect drug exposure data from pregnant women. Over a year ago, a group of healthcare academic and pharmaceutical industry professionals formed a team to discuss possible solutions to meet this need. The solution - The Universal Call Center for Medicine Use in Pregnancy, also known as the "UCC". The UCC will be a call center with a well branded and highly marketed phone number that will serve as a conduit between the public and those groups specifically looking to collect pregnancy exposure data, such as safety offices in pharmaceutical and biotech companies, and pregnancy exposure registries. The UCC will simplify this critical step and will ultimately become a trusted first voice for the public needing more information related to medicine use during pregnancy. The most effective manner to create the UCC will be through the formation of a consortium of pharmaceutical and biotech companies that recognize the critical importance of sound safety and efficacy information for pregnant women. The consortium will be a platform for collaboration and public awareness, and the call center, modeled by the consortium members, will be a conduit to a specific, target public. As the UCC Consortium becomes operational, members would benefit in very specific ways. 1) Potential to obtain more data on pregnant women, thus allowing companies to better assess the safety profile of their drugs and to make better labeling decisions. 2) Potential benefits in pregnancy exposure registries due to increased enrollment. 3) Assist in responsibly serving both patients and prescribing healthcare providers by providing easy access to critical safety information for reproductive age women. 4) Potential for collaboration among companies and key stakeholder groups enabling agility in the study of maternal and fetal safety. Membership into the consortium is available to interested companies.

Platform Presentations

W7

COVINGTON DL, MCKAIN LR, HURST N. Pharmaceutical Product Development Inc., Wilmington, NC, United States. Birth Defect Categorization Systems Employed by Pregnancy Registries

Background: Pregnancy registries monitor pregnancies exposed to specific drugs to determine risk of birth defects. To ensure scientific rigor, interpretation, and reproducibility of results, it is critical to define defects consistently using a standardized system. FDA guidance on establishing pregnancy registries underscores the importance of using a classification scheme and mentions the CDC birth defects code list as an example. Pregnancy registries are one of the only sources of data on the human teratogenic potential of newly marketed drugs. It is critical that birth defects be classified consistently across registries to ensure comparability of results across registries. Objective: To review the methods of ongoing registries and determine what if any birth defect classification systems are employed. Methods: We examined published data from registries identified through internet and literature searches. If published data were not available, we contacted registries to obtain data. We documented the birth defect classification system used by each registry. Results: Of the 36 registries identified, 28 were managed by biopharmaceutical companies or CROs, 3 by teratogen information services, and 5 by academic institutions. 29 were single drug registries and 7 were multi drug. 16 were conducted in multiple countries and 20 only in the US. The CDC birth defect classification system was used by 20 of the 36 registries, all 20 were managed by biopharmaceutical companies or CROs and all were based in the US although 7 of the 20 were also being conducted in other countries. One primarily European registry used the European birth defect classification system. Eight registries used their own internal classification system. Four did not use a system, and 3 remain unknown. Conclusion: It is laudable that 81% of the registries identified reported using a birth defect classification system, and that 58% used a nationally standardized system. Pregnancy registries are hypothesis generating not hypothesis testing studies. If a signal is identified in a pregnancy registry it is critical to evaluate that signal using other data sources. Other pregnancy registries may be a potential source, but only if a birth defect classification system has been used and is adequately described in registry publications.

W8

MCKAIN LF, COVINGTON DL. Pharmaceutical Product Development, Inc, Wilmington, NC, United States. Pregnancy Drug Safety Labeling and Surveillance at the Time of Product Approval

Background: Since FDA published guidance on pregnancy exposure registries in 2002, there is increased interest in these postmarketing studies designed to monitor safety of drug use in pregnancy. Shortly after the guidance was published, FDA began strongly recommending pregnancy registries for new products likely to be used in reproductive age women. This trend continued with the passage of FDAAA in 2007 which granted FDA authority to mandate pregnancy registries. Proposed new pregnancy labeling rules which aim at better describing benefits and risks of drug use for the mother and fetus, further emphasize the importance of human data, including data collected in pregnancy registries. Objectives: To describe pregnancy drug safety labelling information and characterize the establishment of registries for drug approvals post FDAAA. Methods: FDA approvals of new molecular entities and biologic therapies during 2008-2009 were identified and regulatory documents reviewed. Results: Of 51 new molecular entities and biologic therapies approved, 49 are indicated for female use, and most are likely to be used by reproductive age women. None are indicated for use in pregnancy and 3 are specifically contraindicated. Only 4 product labels (8%) reference human pregnancy exposure data, including that of one drug with substantial clinical trial data and 3 others that describe human safety data of related drug classes. Rare pregnancy drug exposures occurring during clinical trials are not detailed. Registries are being conducted for 8 (16%) products, half joining existing registries and half initiating single-drug registries. Among products without registries, at least eight are indicated for different chronic illnesses afflicting reproductive age women. Conclusion: This study confirms that little is known and communicated about pregnancy drug safety at the time of approval; preclinical data dominate labeling and human data are scarce. While nearly 1 in 6 new products collect prospective data through pregnancy registries, passive safety surveillance prevails, even when products are indicated for conditions that occur in pregnancy. Should proposed pregnancy drug labeling go into effect, there may be a significant increase in pregnancy registries.

W9

HERNANDEZ-DIAZ S[1], MITTENDORF R[2], HOLMES LB[3]. [1]Harvard School of Public Health, Boston, MA, United States, [2]Loyola University Chicago, Chicago, IL, United States, [3]MassGeneral Hospital for Children, Boston, MA, United States. Comparative Safety of Topiramate during Pregnancy

Introduction: One recent report has suggested an increased risk of major malformations after *in utero* exposure to topiramate.[1] Objective: To test the hypothesis that prenatal exposure to topiramate increases the risk of adverse pregnancy outcomes. Methods: Since 1997, the North American AED (antiepileptic drug) Pregnancy Registry has enrolled 6,456 pregnant women taking AED, as well as a reference group of 372 friends and family members not taking AED. Data on drug use, dosage, demographic characteristics, vitamin use and the presence of malformations was determined in three telephone interviews and confirmed by medical records. We compared the frequency of adverse pregnancy outcomes in users of topiramate in monotherapy with controls and estimated the relative risk (RR) and 95% confidence interval (CI). Results: The prevalence of major malformations in women exposed to topiramate during the first trimester was 3.8% (11/289). Compared to the prevalence of 1.3% (5/372) in the unexposed reference group; the RR for topiramate was 2.8 (95%CI: 1.0-8.1). The corresponding RRs for lamotrigine and carbamazepine, the most commonly reported AED, were 1.3 (95 CI 0.52 to 3.5) and 2.1 (95 CI 0.82 to 5.4), respectively. Four infants exposed to topiramate had cleft lip, 2 (0.69%) of them were isolated; the expected prevalence of isolated cleft lip is around 0.07%. The prevalence of low birth weight (<2,500 grams) in liveborn singletons without major malformations was 9.8% for topiramate and 3.6% for controls (RR 2.7, 95%CI: 1.4-5.1). Prenatal exposure to topiramate was associated with a mean lesser birth weight of 307 grams (P<0.001) compared to controls. For lamotrigine and carbamazepine, the mean lesser birth weights were 74 and 94 grams, respectively (not significant). Discussion: Topiramate monotherapy was associated with a higher risk of major malformations and low birth weight. Whether these associations are causal or due to unbalanced risk factors among users of specific AED deserves further exploration. 1. Hunt S *et al*. Topiramate in pregnancy: Preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2008;71;272-276. North American AED Pregnancy Registry has six sponsors: Abbott, Eisai, Novartis, Ortho-McNeil, Pfizer and Sepracor.

W10

SCHEUERLE A[1], HARDEN C[2], ALEKAR S[3], LEPPIK I[4], MONTOURIS G[5]. [1]Tesserae Genetics, Dallas, TX, United States, [2]University of Miami School of Medicine, Miami, FL, United States, [3]UCB, Inc., Raleigh, NC, United States, [4]University of Minnesota, Minneapolis, MN, United States, [5]Boston University School of Medicine and Boston Medical Center, Boston, MA, United States. UCB Antiepileptic Drug Pregnancy Registry

Introduction: The UCB Antiepileptic Drug (AED) Pregnancy Registry is a US-based observational exposure registry monitoring safety and pregnancy outcomes in women treated with Keppra® and other UCB AEDs. Exposure to generic levetiracetam is not included. Methods: Enrollment and follow-up are voluntary. Analysis includes prospective cases: those submitted before knowledge of the fetal status or pregnancy outcome. Birth defect (BD) definition is similar to other pregnancy registries. The prevalence comparator is MACDP. Results: As of August 31, 2009, there was enrollment of 409 women taking Keppra®, including seven taking Keppra XR®. Of 360 pregnancies with known outcome, 362 outcomes were reported: 343 live births (two twin pairs), 18 spontaneous losses (including one fetal death), and one induced abortion. First-trimester exposure to Keppra® or Keppra XR® was reported in 326 cases; second- and third-trimester exposure was reported in 30 and 6 cases, respectively. Birth defects were reported in 21 cases. There were 11 BD cases following first trimester Keppra® monotherapy. Major malformations included: ventricular septal defect (VSD), dysplastic pulmonary valve with stenosis, club feet, cleft lip, pyloric stenosis, and polydactyly/hemangioma in one patient each. Three cases met criteria having two minor malformations each. One case each was reported after second trimester (congenital nystagmus/scalp hemangioma) and third trimester (Mongolian spots/skin tag/stork bite) exposure. There were 10 BD cases following first trimester Keppra® in polytherapy. The most common other agent was lamotrigine (4 cases): hydronephrosis/posterior urethral valve; hypospadias; capillary hemangioma, and; membranous VSD/atrial septal defect. There were major malformations in 5 polytherapy cases: congenital adrenal hyperplasia/Chiari I malformation (+phenytoin); facial asymmetry/hypertelorism/natal tooth/wide anterior fontanelle/hemangioma (+phenobarbital); VSD/genu valgum (+oxcarbazepine/clonazepam); cleft palate/left eye ptosis (+carbamazepine), and; ectopic right kidney (+carbamazepine/phenytoin). There was one case of hemangiomata with concomitant valproate. Discussion: The data currently available are limited and, therefore, insufficient to draw conclusions. There does not appear to be a concerning trend in overall prevalence. Three cases of VSD (two in polytherapy) were reported in the study period ending February 28, 2008, with no further cases reported. The results thus far should be reassuring for those managing antiepileptic medications during pregnancy.

W11

LI DK[1], ANDRADE S[2], SCOTT P[3], CHEETHAM C[4], COOPER W[5], DAVIS R[6], DUBLIN S[7], PAWLOSKI P[8], RAEBEL M[9], SMITH D[10], TOH D[11]. [1]Kaiser Permanente Northern California, Oakland, CA, United States, [2]Meyers Primary Care Institute, Worcester, MA, United States, [3]U.S. Food and Drug Administration, Silver Spring, MD, United States, [4]Kaiser Permanente Southern California, Los Angeles, CA, United States, [5]Vanderbilt University School of Medicine, Vanderbilt University School of Medicine, United States, [6]Kaiser Permanente Georgia, Atlanta, GA, United States, [7]Group Health Center for Health Studies,, Seattle, WA, United States, [8]HealthPartners Research Foundation, Bloomington, MN, United States, [9]Kaiser Permanente Colorado, Denver, CO, United States, [10]Kaiser Permanente Northwest, Portland, OR, United States, [11]Harvard Medical School and Harvard Pilgrim Health Care, Boston, MA, United States. Medication Exposure in Pregnancy Risk Evaluation Program

Introduction: Many women use medications during pregnancy, but for most medications, little is known about safety for the woman or fetus. To address this critical gap, the Medication Exposure in Pregnancy Risk Evaluation Program, a collaborative research program between the Food and Drug Administration (FDA) and researchers at the HMO Research Network Center for Education and Research in Therapeutics (CERT), Kaiser Permanente Northern and Southern California, and Vanderbilt University, has been developed. We will describe the organizational structure and data resources of the MEPREP. Methods: Datasets have been created at each site linking healthcare data for women delivering an infant between January 1, 2001 and December 31, 2007 and infants born to these women. Standardized data files include patient characteristics, maternal medication use during pregnancy, and maternal and infant medical care at 11 health plans within 9 states; birth certificate data were obtained from the state departments of public health. Data elements are being validated through medical chart abstraction. Data updates are proposed. Results: The MEPREP currently includes data for 1.1 million children delivered to approximately 825,000 mothers. Overall, 36% of mothers were < 20 years of age and 5% were > 35 years of age on the delivery date; over one-third are Medicaid enrollees. We will describe the program, including characteristics of the study population and the results of validation efforts. Discussion: The MEPREP can support multiple, ongoing studies by providing information on a large, ethnically and geographically diverse population. It is an important resource for evaluation of outcomes (birth defects, perinatal and infant outcomes) associated with medication use during pregnancy.

Poster Presentations

WP1

TERMINI S, COSCIA LA, MCGRORY CH, FRANK A, RAMIREZ CB, MALEY WL, DORIA C, ARMENTI VT. Thomas Jefferson University, Philadelphia, PA, United States. National Transplantation Pregnancy Registry: A 20-Year Perspective

The National Transplantation Pregnancy Registry (NTPR) has continuously collected data from solid-organ transplant recipients on different combinations of immunosuppressive medications since its inception in 1991. The purpose of the NTPR is to study the outcomes of pregnancy in transplant recipients, including pregnancies in female transplant recipients and pregnancies fathered by male transplant recipients. Data are collected *via* questionnaires, phone interviews and medical records. Some of the maternal factors analyzed in the female transplant recipient population include the following: transplant to conception interval, hypertension, diabetes, and rejection during pregnancy and loss of transplant function within 2 years of pregnancy. Newborn birthweight, gestational age, prematurity and birth defects are analyzed. Long-term follow-up of parent and child is also performed. As of December 2009, there are 1,134 female transplant recipients who have reported 1,826 pregnancies with 1,879 pregnancy outcomes including twins and triplets. Female pregnancies have been reported in all types of solid-organ transplant recipients including: kidney (1,356), liver (262), liver-kidney (6), pancreas-kidney [PK] (77), pancreas alone (4), heart (91), lung (24), heart-lung (5) and s mall-bowel (1). The immunosuppressive medications have included: prednisone, azathioprine, cyclosporine, tacrolimus, cyclosporine modified USP, mycophenolate mofetil, enteric-coated mycophenolate sodium, and/or sirolimus. Pregnancies have occurred on varied combinations of immunosuppressive medications. Livebirth percentages depending upon immunosuppression include: kidney 72-80%, liver 71-82%, PK 63-87%, heart 56-71% and lung 58%. Rejection during pregnancy depending upon immunosuppression was reported in: kidney 1-3%, liver 2-8%, PK 0-14%, heart 4-22%, and lung 21%. Conclusions: The NTPR remains an active ongoing database for the collection of pregnancy outcomes in the transplant recipient population. Successful pregnancies have been reported in all types of solid organ transplant recipients. Pregnancy and maternal outcomes vary among the different types of organ recipients. All transplant centers and healthcare professionals involved in the care of these recipients are encouraged to report all pregnancy outcomes to the NTPR. Supported by grants from: Novartis Pharmaceuticals Corp., Astellas Pharma, US, Inc., Roche Laboratories Inc., and Wyeth Pharmaceuticals.

WP2

ROBERTS SS[1,2], MILLER RK[3], JONES JK[4], LINDSAY KL[5], GREENE MF[6], MADDREY WC[7], WILLIAMS IA[8], LIU J[9], SPIEGEL RJ[10],. [1]UNC Wilmington, Wilmington, NC, United States, [2]Kendle International Inc., Wilmington, NC, United States, [3]U of Rochester, Rochester, NY, United States, [4]The Degge Group, Ltd., Arlington, VA, United States, [5]U of Southern California, Los Angeles, CA, United States, [6]Harvard Medical School, Cambridge, MA, United States, [7]UT Southwestern Medical Center, Dallas, TX, United States, [8]CDC, Atlanta, GA, United States, [9]Hoffmann LaRoche, Nutley, NJ, United States, [10]Schering-Plough Corporation, now Merck & Co., Whitehouse Station, NJ, United States. The Ribavirin Pregnancy Registry: Findings After 5 Years of Enrollment

Introduction: Ribavirin, with interferons or pegylated interferons, is used to treat chronic hepatitis C. Ribavirin is an FDA Pregnancy Category X product: contraindicated in pregnancy. The package insert also states that ribavirin is contraindicated in men whose partners may become pregnant. In 2003, the Ribavirin Pregnancy Registry was established to monitor pregnancy exposures to ribavirin and to evaluate the potential human teratogenicity of prenatal ribavirin exposure. Methods: This voluntary registry enrolls pregnant women who have been exposed to ribavirin during pregnancy or during the six months prior to conception either directly, by taking ribavirin, or indirectly through sexual contact with a man taking ribavirin. Women are followed until delivery; live born infants are followed for 1 year. The aim of the Registry is to enroll 131 live births following direct (maternal) exposure to ribavirin and 131 live births following indirect (male) ribavirin exposure, providing 80% power to detect a relative risk of at least 2.6 in the overall number of birth defects reported to the Registry compared with that reported by the Metropolitan Atlanta Congenital Defects Program (3.2%). RESULTS: After more than 5 years of operation, the Registry has enrolled 49 live births with direct exposure and 69 live births following indirect exposure, far short of the goal of 131 live births in each exposure category. Six outcomes with birth defects have been reported: 3 received direct exposures ([6.1% (95% CI: 1.2, 16.86)], and 3 were exposed indirectly [4.3% (95% CI: 0.9, 12.18)]. All were among live born infants: torticollis (2), hypospadias (1), postaxial polydactyl and neonatal tooth (1), glucose-6-phosphate dehydrogenase deficiency (1), and ventricular septal defect and cyst of 4th ventricle of the brain (1). Discussion: Although Registry enrollment has not yet reached the planned sample size, preliminary findings have not detected a signal indicating human teratogenicity for ribavirin. These findings must be interpreted with caution as the ability to draw definitive conclusions concerning direct or indirect exposures at this time is limited. The sponsors anticipate further information as the registry continues. (Supported by ribavirin manufacturers.)

WP3

DESHMUKH US[1], ADAMS J[2], DHILLON R[1], MCCARTHY KD[1], MACKLIN E[1], HOLMES LB[1,3]. [1]Massachusetts General Hospital, Boston, MA, United States, [2]University of Massachusetts Boston, Boston, MA, United States, [3]Harvard Medical School, Boston, MA, United States. Developmental Delay in Children Exposed to Valproate: A Follow-Up Study for the North American Antiepileptic Drug (AED) Pregnancy Registry

Introduction: The North American AED Pregnancy Registry collects data from pregnant women taking anticonvulsant drugs to determine frequencies of major malformations in exposed fetuses. These enrolled women and their infants are a potential resource for additional studies. We present a follow-up study investigating the prevalence of developmental delays among children 36 to 83 months of age whose mothers had enrolled in the Registry and had taken carbamazepine (CBZ), lamotrigine (LTG) or valproate (VPA) monotherapies throughout pregnancy to treat epilepsy. Methods: Recruitment letters were mailed to 1,032 mothers. Interested mothers were screened by telephone and written consent was obtained from 254 women. Data on each enrolled child's development were collected from mothers using the Vineland-II Adaptive Behavior Scales, administered by telephone. Mean adaptive behavior composite (ABC) scores were compared across exposure groups. Results: The overall response rate was 46.0%. Mothers who used LTG had a higher response rate (55.2%) than those who used CBZ (41.1%) or VPA (44.1%) (chi-square; $p < 0.001$). Of those who responded positively, 77.2% completed screening interviews, including 24.9% who were ineligible or lost to follow-up. Participation rates were dependent on marital status, insurance coverage, maternal age, and maternal education. Mothers of children with birth defects were also less likely to participate. Vineland data revealed that VPA-exposed children were more likely to have low or below average adaptive behavior levels and had significantly lower ABC scores (94.3±16.4) relative to children exposed to CBZ (100.6±10.1) or LTG (103.0±11.0) (ANOVA; $p=0.003$). DISCUSSION: These findings suggest that children exposed to VPA during pregnancy are at increased risk for developmental delays. To avoid the sampling bias commonly encountered in pregnancy registries, efforts are underway to increase recruitment of underrepresented families. Despite the challenges of recruitment and selection bias, this hospital-based registry enabled researchers to communicate directly with enrolled mothers, thus facilitating the collection of observational data on the development and adaptive behaviors of their exposed children. This study demonstrates the utility of pregnancy registries in evaluating the long-term effects of prenatal drug exposures. This study was supported by GlaxoSmithKline. Current Registry sponsors include Abbott, Eisai, Ortho-McNeil, Novartis, Pfizer and Sepracor.

WP4

TABACOVA S, SZARFMAN A, LYNDLY JM. U.S. Food and Drug Administration, Silver Spring, MD, United States. Adverse Developmental Events Reported to FDA in Association with Maternal Use of Drugs for Treatment of Hyperthyroidism in Pregnancy

Background: We reviewed reports of adverse developmental events in cases of gestational use of anti-thyroid drugs (propylthiouracil and methimazole) to explore the association of these drugs to embryofetal toxicity and developmental abnormalities. Methods: In this retrospective observational study, all MedWatch reports of adverse developmental events (AE) following prenatal exposures to propylthiouracil (PTU) and methimazole (MMI) submitted to FDA's Adverse Events Reporting System (AERS) from 1970 through 2008 were reviewed to determine and compare the adverse event profile and reporting frequency for the two drugs. Other factors, i.e., concomitant medication, concurrent maternal disease, and genetic background were taken into account where available. Results and conclusions: After excluding duplicate reports, a total of 47 cases of adverse developmental events (32 associated with MMI and 15 with PTU use in pregnancy) were retrieved from FDA's AERS. It is of note that the number of adverse developmental outcomes reported since 1970 was 2-fold higher for MMI than for PTU (comparative use data not taken into account). Birth defects were reported in 90% (29 of 32) and 60% (9 of 15) of AE reports for MMI and PTU, respectively. The malformations reported in association with MMI displayed a distinct and consistent pattern, craniofacial defects (scalp epidermal aplasia, facial dysmorphism, choanal atresia) being the most frequent (about 90% of all malformation cases). In the majority of cases, these malformations were multiple, most often combined with gastrointestinal atresias, hypo- or aplasias. These birth defects were associated with MMI administration in the 1st trimester (but not later in pregnancy) which supports a causal relationship. The malformations reported in association with PTU monotherapy did not display a consistent pattern or a profile similar to MMI, even following 1st trimester exposures (craniofacial malformations were reported only in cases where PTU was given in combination with MMI). AEs reported with PTU exposures after the 1st trimester were fetal/neonatal thyroid insufficiency and goiter, reversible upon PTU discontinuation which supports the causal role of PTU for these defects.

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Thirty-Fourth Annual Meeting of the Neurobehavioral Teratology Society

Held in Conjunction with the 50th Annual Meeting of the Teratology Society and the 22nd Annual Meeting of the Organization of Teratology Information Specialists

Louisville, KY June 26–June 30, 2010

Saturday, June 26, 2010

8:00 a.m.-11:30 a.m.	**Teratology Society Education Course:** ***Marriott Ballroom 6***
8:00 a.m.-5:00 p.m.	**Teratology Society/OTIS Joint Pregnancy Workshop** ***Marriott Ballroom 9***
1:00 p.m.-5:00 p.m.	**NBTS Registration:** ***Marriott Ballroom 7 Foyer***
1:00 p.m.-2:00 p.m.	**NBTS Public Affairs Committee:** ***Filly Meeting Room***
1:30 p.m.-4:45 p.m.	**Teratology Society Education Course:** ***Marriott Ballroom 6***
2:00 p.m.-3:00 p.m.	**NBTS Publications Committee Meeting:** ***Filly Meeting Room***
3:00 p.m.-6:00 p.m.	**NBTS Council Meeting:** ***Filly Meeting Room***

Sunday, June 27, 2010

8:00 a.m.-5:00 p.m.	**NBTS Registration:** ***Marriott Ballroom 7 Foyer***
7:45 a.m.-8:15 a.m.	**Continental Breakfast:** ***Marriott Ballroom 7***
8:15 a.m.-8:30 a.m.	**President's Welcome and Official Opening of 2010 NBTS Meeting:** *Marriott Ballroom 7*
8:30 a.m.-12:00 a.m.	**Session 1, Behavioral Toxicology Symposium:** *Marriott Ballroom 7* **Behavioral Toxicology of Cognition: Extrapolation from Experimental Animal Models to Humans** Chairperson: Merle Paule, National Center for Toxicological Research
8:30 a.m.-8:50 a.m.	Introduction Merle Paule National Center for Toxicological Research, Jefferson, AR
8:50 a.m.-9:25 a.m.	Delay Discounting by Humans and Other Animals: Does the Species Matter? Leonard Green Washington University, St. Louis, MO
9:25 a.m.-10:00 a.m.	The Use of "Animal" Tests of Cognition in Children William H. Overman University of North Carolina, Wilmington, NC
10:00 a.m.-10:15 a.m.	Break
10:15 a.m.-10:50 a.m.	Modeling the Cognitive Deficits of Parkinson's Disease Jay Schneider Thomas Jefferson University, Philadelphia, PA
10:50 a.m.-11:25 a.m.	Delineating Behavioral Domains Underlying Lead-Induced Cognitive Deficits Deborah Cory-Slechta University of Rochester Medical School, Rochester, NY

11:25 a.m.-12:00 p.m. Perinatal PCB Exposure and Deficits In Inhibitory Control: Parallels Between Animals And Humans
Susan Schantz
University of Illinois, Urbana IL

12:00 p.m.-1:20 p.m. Lunch on your own

1:20 p.m.-3:00 p.m. Session 2, NBTS Platform Talks: *Marriott Ballroom 7*

1:20 p.m.-1:40 p.m. The Effect of 2,4-Dichlorophenoxyacetic Acid on Anxiety in the Rat
William Hamlet, Sandra McFadden, Russell Morgan, Amy Vaught
Western Illinois University, Macomb, IL

1:40 p.m.-2:00 p.m. Prenatal Exposure to Phthalates and Newborn Neurobehavior
Kimberly Yolton, Yingying Xu, Jane Khoury
Cincinnati Children's Hospital, Cincinnati, OH

2:00 p.m.-2:20 p.m. Early Developmental Chlorpyrifos Causes Persisting Behavioral and Neurochemical Changes in Zebrafish
Damiyon Sledge, Ann Petro, Jerry Yen, Susan Donerly, Elwood Linney, Edward Levin
Duke University Medical Center, Durham, NC

2:20 p.m.-2:40 p.m. Reversal of Chlorpyrifos Neurobehavioral Teratogenicity in Mice by Adult Allographic Subventricular Zone-derived Neural Stem Cell Transplantation
Joseph Yanai[1,2], Adi Pinkas[1]
[1]The Ross Lab for Studies in Neural Birth Defects, Department of Medical Neurobiology, IMRIC, Hebrew University-Hadassah Medical School, Jerusalem, Israel, [2]Department of Pharmacology and Cancer Biology, Duke Medical School, Durham, NC

2:40 p.m.-3:00 p.m. The Long-term Behavioral Effects of Exposure to Metals and Chronic Stress during Development
Devon Graham[1,2], Robyn Amos-Kroohs[1,2], Amanda Braun[1,2], Curtis Grace[1,2], Tori Schaefer[1,2], Matthew Skelton[1,2], Charles Vorhees[1,2], Michael Williams[1,2]
[1]Cincinnati Children's Research Foundation, Cincinnati, OH, [2]University of Cincinnati, Cincinnati, OH

3:00 p.m.-3:20 p.m. Break: *Marriott Ballroom 7 Foyer*

3:20 p.m.-5:00 p.m. Session 3, NBTS Platform Talks: *Marriott Ballroom 7*

3:20 p.m.-3:40 p.m. Effects of 3,4-Methylenedioxymethamphetamine (MDMA) on Serotonin Transporter and Vesicular Monoamine Transporter 2 Protein and Gene Expression in Rats: Implications for MDMA Neurotoxicity
Dominik Biezonski[1,2], Jerrold Meyer[1]
[1]University of Massachusetts, Amherst, MA, [2]Harvard Medical School, Southborough, MA

3:40 p.m.-4:00 p.m. Effects of Prenatal Cocaine on Conditioned Place Preference in Adolescence: Modification by Post-weaning Housing and Sex
Diana Dow-Edwards[1], Sari Izenwasser[1]
[1]State University of New York, Brooklyn, NY, [2]University of Miami School of Medicine, Miami, FL

4:00 p.m.-4:20 p.m. Evidence for Rapid Sensitization to the Stimulant Effects of MDMA in Adolescent Rats
Jerrold Meyer, Peter Kim, Frederico Fernandes, Dominik Biezonski, Brian Piper
University of Massachusetts, Amherst, MA

4:20 p.m.-4:40 p.m. Methylphenidate-Induced Developmental Neurobehavioral Toxicity in Zebrafish
Edward Levin, Damiyon Sledge, Stephanie Roach, Susan Donerly, Elwood Linney
Duke University, Durham, NC

4:40 p.m.-5:00 p.m. Effects of Overlapping Ages of Exposure to (+)-Methamphetamine (MA) in Rats on Later Allocentric and Egocentric Learning
Charles Vorhees, Matthew Skelton, Devon Graham, Tori Schaefer, Curtis Grace, Amanda Braun, Robyn Amos-Kroohs, Michael Williams
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

6:00 p.m.-8:00 p.m. **Joint NBTS/TS Welcome Reception:** *Marriott Ballroom 1*

Monday, June 28, 2010

8:00 a.m.-5:00 p.m. **NBTS Registration:** *Marriott Ballroom 7 Foyer*

7:45 a.m.-8:15 a.m. **Continental Breakfast:** *Marriott Ballroom 7*

8:15 a.m.-9:00 a.m. **Session 4, Elsevier Distinguished Lectureship:** *Marriott Ballroom 7*
Bisphenol-A Impacts on Sex Differences in Neural Processes
Neil MacLusky, University of Guelph, ON

9:15 a.m.-11:45 a.m. **Session 5, Reproductive Psychiatry Symposium (NBTS/OTIS/TS):** *Marriott Ballroom 6*
Chairpersons: Katherine L. Wisner, University of Pittsburgh Medical Center and Adrienne Einarson, The Motherisk Program

9:15 a.m.–9:20 a.m. Introduction

9:20 a.m.–9:50 a.m. Prenatal SRI Exposure: Where Does Neonatal Behavioral Syndrome End and Neurobehavioral Teratogenicity Begin?
Tim F. Oberlander, University of British Columbia, Vancouver, BC

9:50 a.m.–10:20 a.m. Messages from the Womb: Maternal Antidepressant Use and Fetal Neurobehavior
Amy L. Salisbury, Alpert Medical School of Brown University, Providence, RI

10:20 a.m.–10:50 a.m. An Update on Lithium Treatment during Pregnancy and Lactation
Adele C. Viguera, Neurological Institute, Cleveland Clinic, Cleveland, OH

10:50 a.m.–11:20 a.m. Effects of Developmental Exposure to Methylphenidate on Brain Areas Involved in Cognition, Motivated Behaviors, Appetite and Stress
Teresa Ann Milner, Weill Cornell Medical College, New York City, NY

11:20 a.m.–11:45 a.m. Discussion: How Do We Incorporate These Data into Human Risk Assessment?
Katherine L. Wisner, University of Pittsburgh Medical Center, Pittsburgh, PA

12:00 p.m.-1:15 p.m. **Lunch on your own**

1:15 p.m.-4:45 p.m. **Session 6, Symposium:** *Marriott Ballroom 7*
Complementary Zebrafish Models for Neurobehavioral Teratology Research: Opportunities and Challenges
Chairperson: Edward D. Levin, Duke University Medical Center

1:15 p.m.-1:45 p.m. Embryonic Exposure to Low Levels of Alcohol: Towards the Development of a Realistic Zebrafish Model of Fetal Alcohol Syndrome
Robert Gerlai, University of Toronto, Toronto, ON

1:45 p.m.-2:15 p.m.	Ethanol-induced Effects on Neurobehavioral Function: the Developmental Neurotoxicity of MicroRNAs Tamara Tal, Katerine Saili, Jill Franzosa, Robert Tanguay Oregon State University, Corvallis, OR
2:15 p.m.-2:45 p.m.	Do NMDA Receptor Antagonists Alter Structural and Functional Development in Zebrafish? Frank Scalzo Bard College, Annandale-on-Hudson, NY
2:45 p.m.-3:00 p.m.	Break: *Marriott Ballroom 7 Foyer*
3:00 p.m.-3:30 p.m.	Evaluating the Behavioral Impact of Toxicants in Larval Zebrafish Robert MacPhail US Environmental Protection Agency, Research Triangle Park, NC
3:30 p.m.-4:00 p.m.	Using the Zebrafish (Danio rerio) Model to Investigate Changes in Gene Expression and Behavior following Developmental Exposure to Pyrethroid Pesticides Lori White[1], Keith Cooper[1], Amy DeMicco[1], Jason Richardson[2] [1]Rutgers, The State University of NJ, New Brunswick, NJ, [2]Environmental and Occupational Health Sciences Institute, UMDNJ, Piscataway, NJ
4:00 p.m.-4:30 p.m.	Using Zebrafish to Investigate Persisting Cognitive and Sensorimotor Effects of Early Developmental Chlorpyrifos Exposure Edward D. Levin Duke University Medical Center, Durham, NC
4:30 p.m.-4:45p.m.	Discussion
5:00 p.m.-7:00 p.m.	**Joint Poster Session I (NBTS/TS/OTIS) and Exhibits Open:** *Marriott Ballroom 1* (Posters set up at 11:45 a.m., attended 5:00 – 7:00 p.m.)

1 Neurobehavioral Development following Exposure of Male Mice to Polybrominated Diphenyl Ether 47 on Postnatal Day 10
Virginia Moser[1], Pamela Phillips[1], Katherine McDaniel[1], Jill Gee[1,2]
[1]US Environmental Protection Agency, Research Triangle Park, NC, [2]North Carolina State University, Raleigh, NC

2 Subsequent Effects on Open-field Responses of Exposing Male and Female Hooded Rats Each Day to Alcohol, Caffeine and their Combination during Early and Mid to Late Adolescence, and Early Adulthood
Rob Hughes
University of Canterbury, Christchurch, New Zealand

3 Gene Expression in Developing Brain is Altered by Modest Reductions in Circulating Levels of Thyroid Hormone
Mary Gilbert, Kevin Crofton, Gail Nelson, Geremy Knapp
US Environmental Protection Agency, Research Triangle Park, NC

4 Molecular (Mal)adaptations in Dopamine-modulated Signaling Pathways following Neurodevelopmental Insult
Aliya Frederick, Roger Colbran, Gregg Stanwood
[4]Vanderbilt University, Nashville, TN

5 Effects of Methylphenidate on Motivation in Children with Attention-Deficit/Hyperactivity Disorder
John Chelonis[1,2], Teresa Johnson[2], Sherry Ferguson[1,2], Brian Kubacak[2], Mark Edwards[2], Merle Paule[1,2]
[1]National Center for Toxicological Research, FDA, Jefferson, AR, [2]University of Arkansas for Medical Sciences/Arkansas Children's Hospital, Little Rock, AR

6 Effect of Lifetime Exposure to Acrylamide on Motor Nerve Conduction Velocity in Rats at One Year of Age
Joan Garey[1], Zbigniew Binienda[2], Merle Paule[2]
[1]SRC, Inc, Arlington, VA, [2] National Center for Toxicological Research, FDA, Jefferson, AR

Tuesday, June 29, 2010

8:00 a.m.-5:00 p.m. **NBTS Registration:** *Marriott Ballroom 7 Foyer*

7:45 a.m.-8:15 a.m. **Continental Breakfast:** *Marriott Ballroom 7*

8:30 a.m.-9:15 a.m. **Special Lecture (NBTS/TS/OTIS):** *Marriott Ballroom 6*
Children's Environmental Health: A Good Start Lasts a Lifetime
Linda S. Birnbaum, Director, National Institute of Environmental Health Sciences

9:30 a.m.-12:00 p.m. **Session 7, Symposium (NBTS/TS):** *Marriott Ballroom 6*
Advancing Neurodevelopmental Evaluation in Children: An Interdisciplinary Approach
Chairperson: Susan Makris, US Environmental Protection Agency

9:30 a.m.–9:55 a.m. The Use of Neurodevelopmental Data in Children for Risk Assessment of Environmental Chemicals
Susan Makris, US Environmental Protection Agency, Washington, DC

9:55 a.m.–10:20 a.m. A Multidisciplinary Approach to Advancing the Science of Neurodevelopmental Testing in Cohorts of Infants and Young Children
Judy S. LaKind, LaKind Associates, LLC, Baltimore, MD

10:20 a.m.–10:45 a.m. Getting the Biggest Bang for Your Buck: Choosing Neurodevelopmental Tests That Maximize Power
Lauren Kenworthy, George Washington University Medical School, Washington, DC

10:45 a.m.–11:10 a.m. Threats to Study Validity: The Flynn Effect, Examiner Drift, Confounders, Lost in Translation, and Other Important Considerations
Laura Gutermuth Anthony, George Washington University School of Medicine, Washington, DC

11:10 a.m.–11:35 a.m. Weight-of-the-Evidence Assessment in Neurodevelopmental Epidemiology: A Plea for Consistency
Michael Goodman, Emory University, Atlanta, GA

11:35 a.m.–12:00 p.m. Panel Discussion

12:00 p.m.-2:00 p.m. **NBTS/TS Joint Poster Session II and Exhibits Open:** *Marriott Ballroom 1*
(Posters set up at 8:00 a.m., attended 12:00 – 2:00 p.m.)

7 Effects of Domoic Acid on Early Visual Memory in Infants from the CoASTAL Cohort
Kimberly Grant[1], Tom Burbacher[1], Sparkle Roberts[2], Lynn Grattan[2]
[1]University of Washington, Seattle, WA, [2]University of Maryland, Baltimore, MD

8 Acute Postnatal Exposure to the PentaBDE Commercial Mixture DE-71 at Low Doses (5 or 15 mg/kg/day) Does Not Produce Learning or Attention Deficits in Rats
Lori Driscoll
Colorado College, Colorado Springs, CO

9 Gene-toxicant Interactions: Developmental PBDE Effects on the Behavioral Phenotype of the Mecp2-308 Rett Syndrome Mouse Model
Mari Golub, Roxanne Vallero, Joanne Suarez, Ta Tram Anh, Isaac Pessah, Robert Berman, Janine LaSalle
University of California Davis, Davis, CA

10 Locomotor Responding in Adolescent CD-1 Mice following Acute and Chronic Cocaine Administration is Unaffected by Low Dose Perinatal Bisphenol A Exposure
Jenna Nelms, Abby Meyer, Mellessa Miller, Melissa Ward, Helen Sable
University of Memphis, Memphis, TN

11 Developmental Neurobehavioral Toxicity of Bisphenol A: Defining the Role of Estrogen Related Receptor Gamma
Katerine Saili, Jane LaDu, Michael Simonich, Robert Tanguay
Oregon State University, Corvallis, OR

2:00 p.m.-3:40 p.m. **Session 8, NBTS Platform Talks:** *Marriott Ballroom 7*

2:00 p.m.-2:20 p.m. Genetic Susceptibility to PCB-induced Motor Dysfunction
Chris Curran, Emily Altenhofen, Amber Evans, Rikki Floyd, Cellestine Kamau-Cheggeh, Sarah Kraemer, Breann Hays, Kristi Haik
Northern Kentucky University, Highland Heights, KY

2:20 p.m.-2:40 p.m. Assessment of Prefrontal Cortical Functions in Mice with Genetic and Dietary Alterations of Folate Status
Jessica Ash, Barbara Strupp
Cornell University, Ithaca, NY

2:40 p.m. -3:00 p.m. Behavioral Outcome in Children Exposed Prenatally to Lamotrigine, Valproate, or Carbamazepine: Increased Risks for Valproate
Uma Deshmukh[1], Jane Adams[2], Ruby Dhillon[1], Katherine McCarthy[1], Eric Macklin[1], Lewis Holmes[1,3]
[1]Massachusetts General Hospital, Boston, MA, [2]University of Massachusetts Boston, Boston, MA, [3]Harvard Medical School, Boston, MA

3:00 p.m.-3:20 p.m. Effects of Age of Exposure to 3,4-Methylenedioxymethamphetamine (MDMA) in Rats on Later Learning and Behavior
Charles Vorhees, Matthew Skelton, Devon Graham, Tori Schaefer, Curtis Grace, Amanda Braun, Michael Williams
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

3:20 p.m.-3:40 p.m. Predicting the Acute Behavioral Effects in Rats Inhaling Toluene for Up to 24 hrs: Inhaled vs. Internal Dose Metrics and Tolerance
WM Oshiro, QT Krantz, CJ Gordon, EM Kenyon, and PJ Bushnell
US Environmental Protection Agency, Office of Research and Development, National Health Effects and Environmental Research Laboratory, Research Triangle Park, NC

3:40 p.m.-4:00 p.m. **Break:** *Marriott Ballroom 7 Foyer*

4:00 p.m.-6:00 p.m. **Annual NBTS Business Meeting:** *Marriott Ballroom 7*

8:00 p.m.-10:00 p.m. **NBTS Social Event**

Wednesday, June 30, 2010

7:30 a.m.-9:00 a.m.	**Continental Breakfast:** *Marriott Ballroom 7*
9:00 a.m.-10:45 a.m.	**Session 9, Future Directions in Neurobehavioral Teratology Roundtable:** *Marriott Ballroom 7* Discussants: Philip Landrigan, Lynn Singer, Charles Vorhees, Jerrold Meyer
10:45 a.m.-11:00 a.m.	**Break:** *Marriott Ballroom 7 Foyer*
11:00 a.m.-12:00 p.m.	**Session 10, National Children's Study Panel (NBTS/TS):** *Marriott Ballroom 6*
12:00 p.m.	**NBTS 2010 Formally Adjourned**

23rd International Conference of the Organization of Teratology Information Specialists

Marriott Louisville Downtown

Louisville, Kentucky

June 26th – June 29th, 2010

Friday, June 25, 2010

1:00 PM – 5:00 PM	**OTIS BOARD OF DIRECTORS MEETING**	*Thoroughbred Room*
6:00 PM – 8:00 PM	**OTIS MEETING REGISTRATION**	*Foyer - Marriott Ballroom 9*
5:00 PM – 7:00 PM	**DINNER**	
7:00 PM – 9:00 PM	**OTIS BOARD OF DIRECTORS MEETING (CON'T)**	*Thoroughbred Room*

Saturday, June 26, 2010

7:00 AM – 7:45 AM	**REGISTRATION** **CONTINENTAL BREAKFAST**	*Foyer - Marriott Ballroom 9*
7:45 AM – 8:00 AM	**PRESIDENT'S WELCOME** *Myla Moretti* *Assistant Director, Motherisk Program* *President, OTIS*	*Marriott Ballroom 9*
8:00 AM – 8:50 AM	**THOMAS H. SHEPARD LECTURE** Tribute to Thomas H. Shepard: Scholar, Mentor, Friend *Speaker: Alan Fantel* *Department of Pediatrics, Division of Genetics and Developmental Medicine* *University of Washington* *Seattle, WA*	*Marriott Ballroom 9*
9:00 AM – 10:30 AM	**RAPID FIRE TERATOGENS** *Moderator: Beth Conover* *Nebraska TIS*	*Marriott Ballroom 9*
9:00 AM – 9:15 AM	Ciprofloxacin New York PRN Discussion	
9:15 AM – 9:30 AM	Benzodiazepine Texas TIS Discussion	
9:30 AM – 9:45 AM	Binge alcohol California TIS Discussion	
9:45 AM – 10:00 AM	Pseudoephedrine Arizona TIS Discussion	
10:00 AM – 10:15 AM	Nifedipine Utah Pregnancy Risk Line Discussion	
10:15 AM – 10:30 AM	Abilify Nebraska TIS Discussion	
10:30 AM – 12:30 PM	**RESEARCH COMMITTEE MEETING**	*Thoroughbred Room*
12:30 PM – 5:30 PM	**OTIS/TS PREGNANCY REGISTRY SESSION** *Moderators: Christina Chambers and Lewis Holmes*	*Marriott Ballroom 9*
12:30 PM – 12:40 PM	Introduction	
12:40 PM – 1:10 PM	Classifying Birth Defects in Reproductive Research *Speaker: Lewis Holmes* *Genetics Unit, Mass General Hospital for Children* *Boston, MA*	

1:10 PM – 1:50 PM	Point/Counterpoint
1:10 PM – 1:30 PM	Methodological Challenges in Surveillance of Spontaneous Abortion as a Reproductive Health Endpoint *Speaker: David Savitz* *Department of Community and Preventive Medicine,* *Mt. Sinai School of Medicine* *New York, NY*
1:30 PM – 1:50 PM	Studying Miscarriage Using Pregnancy Registries *Speaker: DeKun Li* *Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente* *Oakland, CA*
1:50 PM - 2:10 PM	Organizing Pregnancy Registries during an Emergency Response *Speaker: Ava Conlin* *Department of Defense Center for Deployment Health Research, Naval Health Research Center* *San Diego, CA*
2:10 PM – 2:30 PM	The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS): Launch of a New System for Post-Marketing Surveillance *Speaker: Christina Chambers* *CTIS, UCSD* *San Diego, CA*
2:30 PM – 3:15 PM	Panel Discussion: FDA Pregnancy Registry Guidance Document Revisions *Speaker: Melissa Tassinari* *US FDA Maternal-Child Health Team* *Silver Spring*
3:15 PM – 3:30 PM	Universal Call Center for Medicine Use in Pregnancy *Speaker: Michael McDonagh* *Amgen*
3:30 PM – 3:45 PM	**BREAK**
3:45 PM – 5:30 PM	**ABSTRACT SESSION** *Marriott Ballroom 9*
3:45 PM – 4:00 PM	Birth Defect Categorization Systems Employed by Pregnancy Registries *Deborah Covington, Laura McKain, Nicole Hurst* *Pharmaceutical Product Development Inc., Wilmington, NC, United States*
4:00 PM – 4:15 PM	Pregnancy Drug Safety Labeling and Surveillance at the Time of Product Approval *Laura F. McKain and Deborah L. Covington* *Pharmaceutical Product Development Inc., Wilmington, NC, United States*
4:15 PM – 4:30 PM	Comparative Safety of Topiramate during Pregnancy *S Hernandez-Diaz, R Mittendorf, LB Holmes* *Harvard School of Public Health, Boston, MA, United States, Loyola University Chicago, Chicago, IL, United States, MassGeneral Hospital for Children, Boston, MA, United States*

4:30 PM – 4:45 PM	UCB Antiepileptic Drug Pregnancy Registry *A Scheuerle, C Harden, S Alekar, I Leppik, G Montouris* *Tesserae Genetics, Dallas, TX, United States, University of Miami School of Medicine, Miami, FL, United States, UCB, Inc., Raleigh, NC, United States, University of Minnesota, Minneapolis, MN, United States, Boston University School of Medicine and Boston Medical Center, Boston, MA, United States*	
4:45 PM – 5:00 PM	Medication Exposure in Pregnancy Risk Evaluation Program *D.K. Li, S. Andrade, P. Scott, C. Cheetham, W. Cooper, R. Davis, S. Dublin, P. Pawloski, M. Raebel, D. Smith, Darren Toh* *Kaiser Foundation Research Institute, Kaiser Permanente, California*	
5:00 PM – 5:30 PM	**POSTER SESSION**	*Marriott Ballroom 9*
6:00 PM – 8:00 PM	**OTIS RECEPTION**	*Bluegrass Room*

Sunday, June 27, 2010

7:30 AM – 8:15 AM	**REGISTRATION**	*Foyer - Marriott Ballroom 9*
8:15 AM – 9:15 AM	**TERATOLOGY SOCIETY WARKANY LECTURE** **50 Years of Progress in Understanding the Causes of Three Common Birth Defects** *Speaker: Diana Juriloff* *University of British Columbia*	*Marriott Ballroom 6*
9:15 AM – 12:00 NOON	**RESEARCH TEAM MEETING**	*Marriott Ballroom 9*
9:15 AM – 9:30 AM	Introduction - Co-Chairs Jerry Briggs and Janine Polifka	
9:30 AM – 10:30 AM	National Birth Defects Prevention Study Focus on Over-the-Counter and Prescription Medications *Speaker: Charlotte A. Hobbs* *UAMS College of Medicine*	
10:30 AM – 11:15 AM	Discussion	
11:15 AM – 11:30 AM	Report from the Scientific Advisory Committee on Joint OTIS/ENTIS Studies	
11:30 AM – 12:00 PM	TBA	
12:00 PM – 1:00 PM	**OTIS/TS ROBERT L. BRENT LECTURE** **Box Lunch Provided** Ionizing Radiation Exposure to the Fetus and Infant from Medical Imaging: A Radiologist's Perspective *Speaker: Donald Frush, Professor of Radiology and Pediatrics, Duke University*	*Marriott Ballroom 6*

1:00 PM – 6:00 PM	**RESEARCH TEAM MEETING (CON'T)**	*Marriott Ballroom 9*
1:00 PM – 2:00 PM	Updates on Research Projects –Autoimmune Diseases in Pregnancy (Johnson) –Post marketing Surveillance for Safety of Adacel, Menactra, and Fluzone in Pregnancy: An OTIS Pregnancy Pilot Project (Johnson) –Antidepressant Discontinuation study (Berard) –West Nile Virus study (Djokanovic) –Update on Motherisk studies (Koren) –SBIR project to develop software and link OTIS sites (Wisner)	
2:00 PM – 3:00 PM	Obesity and Diabetes - Viewpoint of a Maternal-Fetal Medicine Specialist *Speaker: Cecelia Lyons Gaffaney* *Obstetrix Medical Group, CA*	
3:00 PM – 3:15 PM	**BREAK**	
3:15 PM – 4:00 PM	H1N1 Influenza Virus Infection in Pregnancy *Speaker: Sonja Rasmussen* *CDC, NCBDDD* *Atlanta, GA*	
4:00 PM - 5:00 PM	Management of Asthma during Pregnancy *Speaker: Leslie Hendeles* *University of Florida*	
5:00 PM – 5:30 PM	Report from the Lactation Subcommittee	
5:30 PM – 6:00 PM	Report from the Research Committee	

Monday, June 28, 2010

7:30 AM – 8:00 AM	**REGISTRATION**	*Foyer - Marriott Ballroom 9*
8:00 AM – 9:00 AM	**TS/OTIS STATE OF THE ART LECTURE** **Palate Development: Molecular Perspectives & Current Understanding** *Speaker: Robert Greene* *University of Louisville*	*Marriott Ballroom 6*
9:15 AM – 11:45 AM	**OTIS/TS/NBTS SYMPOSIUM** **REPRODUCTIVE PSYCHIATRY** *Moderators: Katherine Wisner, University of Pittsburgh and Adrienne Einarson, Motherisk Program*	*Marriott Ballroom 6*
9:15 AM – 9:20 AM	Introduction	

9:20 AM – 9:50 AM

Prenatal SRI Exposure: Where Does Neonatal Behavioral Syndrome End and Neurobehavioral Teratogenicity Begin?
Speaker: Tim F. Oberlander
Professor of Pediatrics
Department of Pediatrics and Human Early Learning Partnership
Early Human Experience Unit, Centre for Community Child Health Research
University of British Columbia. Vancouver, Canada

9:50 AM – 10:20 AM

Messages from the Womb: Maternal Antidepressant Use and Fetal Neurobehavior
Speaker: Amy L. Salisbury
Assistant Professor of Pediatrics and Psychiatry
Brown Alpert Medical School
Fetal Behavior Studies Director
Brown Center for Children
Women & Infants Hospital
Providence, RI

10:20 AM – 10:50 AM

An Update on Lithium Treatment during Pregnancy and Lactation
Speaker: Adele C. Viguera
Research Staff, Women's Mental Health
Neurological Institute, Cleveland Clinic
Cleveland, Ohio

10:50 AM – 11:20 AM

Effects of Developmental Exposure to Methylphenidate on Brain Areas Involved in Cognition, Motivated Behaviors, Appetite and Stress
Speaker: Teresa A. Milner
Professor of Neuroscience, Department of Neurology and Neuroscience,
Weill Cornell Medical College
Adjunct Professor, Laboratory of Neuroendocrinology, The Rockefeller University

11:20 AM – 11:45 AM

Discussion: How Do We Incorporate These Data into Human Risk Assessment?
Speaker: Katherine Wisner
Professor of Psychiatry, Obstetrics and Gynecology and Reproductive Sciences,
Epidemiology and Women's Studies
Western Psychiatric Institute and Clinic
University of Pittsburgh

12:00 PM – 1:00 PM

LUNCH – on your own

MEETING PLANNING COMMITTEE *Marriott Ballroom 9*

1:15 PM – 2:15 PM

TS/OTIS Special Lecture *Marriott Ballroom 6*
Human Teratogens: Update 2010
Speaker: Lewis Holmes
Chief, Genetics Unit, MassGeneral Hospital for Children, Boston;
Professor of Pediatrics, Harvard Medical School

2:15 PM – 4:00 PM

OTIS ABSTRACT SESSION *Marriott Ballroom 9*
Moderators: Mark Roth, New York PRN

2:15 PM – 2:30 PM

OTIS 1 Enantiomer-Specific Methadone to Infants *Via* The Placenta and Breastmilk
Debra L. Bogen, James M. Perel, Joseph C. Helsel, Barbara H. Hanusa; Matthew Thompson, Katherine L. Wisner
University of Pittsburgh

2:30 PM – 2:45 PM	OTIS 2 Pregnancy Outcome After *In Utero* Exposure to Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers *Diav-Citrin O., S. Shechtman, Y. Halberstadt, V. Finkel-Pekarsky, R. Wajnberg, J. Arnon, E. Di Gianantonio, M. Clementi and A. Ornoy. The Israeli Teratology Information Service, Israel Ministry of Health, the Hebrew University Hadassah Medical school, Jerusalem, Israel, and Servizio di Informazione Teratologica, Padova, Italy.*	
2:45 PM – 3:00 PM	OTIS 3 Motor and Visual Abilities in Children Born by Mother in Treatment with Antidepressants during Pregnancy *Marco De Santi, Carmen De Luca, Ilenia Mappa, Tomasella Quattrocchi, Daniela Ricci, Diego Martinelli, Claudia Brogna, Eugenio Maria Mercuri. Telefono Rosso, Teratology Information Service, Department of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy. Pediatric Neurology Unit, Università Cattolica del Sacro Cuore, Rome, Italy.*	
3:00 PM – 3:15 PM	OTIS 4 Outcome of Pregnancy After Maternal Exposure to Mifepristone *Sally Stephens, Laura Yates, Vaidehi Chincholkar, Simon Thomas* *UKTIS UK Teratology Information Service Wolfson Unit*	
3:15 PM – 3:30 PM	OTIS 5 Understanding the Relationship Between Obesity and Folate Status in the Protection Against Neural Tube Defects; A Systematic Review *Seth J. Stern, Gideon Koren* *Motherisk Program*	
3:30 PM – 3:45 PM	OTIS 6 Pregnancy Outcomes After Alcohol Exposure in Early Pregnancy Experienced in Teratology Information Services *Y Han, JS Choi, HK Ahn, SW Lee, MH Kim, JH Chung, HM Ryu, MY Kim, JH Yang. The Korean Motherisk Program, Department of Obstetrics and Gynecology, Cheil Hospital and Women's Healthcare Center, Kwandong University College of Medicine, Seoul, Korea*	
3:45 PM – 4:00 PM	Question and Answer	
4:00 PM - 5:30 PM	**EDUCATION COMMITTEE MEETING**	*Marriott Ballroom 9*
5:00 PM – 7:00 PM	**TS/OTIS/NBTS POSTER SESSION**	*Marriott Ballroom 1*

Tuesday, June 29, 2010

7:45 AM – 8:15 AM	**REGISTRATION**	*Foyer - Marriott Ballroom 9*
8:30 AM – 9:15 AM	**TS/OTIS STATE OF THE ART LECTURE** **Children's Environmental Health: A Good Start Lasts a Lifetime** *Speaker: Linda Birnbaum* *Director, NIEHS*	*Marriott Ballroom 6*
9:15 AM – 9:30 AM	**BREAK**	

9:30 AM – 11:30 AM	**OTIS OCCUPATIONAL SESSION** **Clinical Approach to Reproductive Occupational Exposures** *Moderator: Sharon Voyer Lavigne*	*Marriott Ballroom 9*
9:30 AM – 10:00 AM	Occupational Risk Assessment during Pregnancy: How to Get It Started *Speaker: Robert Felix* *CTIS, UCSD*	
10:00 AM – 10:30 AM	The Medical Side of Reproductive Counseling: After the Teratology Consult For The Pregnant Worker *Speaker: Diane Ballerino-Regan* *Division of Occupational and Environmental Medicine* *Duke University Medical Center*	
10:30 AM – 11:30 AM	Case Presentations by TIS'	
10:30 AM – 10:45 AM	*Connecticut Pregnancy Exposure Information Service*	
10:45 AM – 11:00 AM	*Utah Pregnancy Riskline*	
11:00 AM – 11:15 AM	*Motherisk Program*	
11:15 AM – 11:30 AM	*Texas Teratogen Information Service*	
11:30 AM – 12:30 PM	**OCCUPATIONAL COMMITTEE MEETING** **Lunch on your own**	*Marriott Ballroom 9*
12:30 PM – 2:00 PM	**OTIS BUSINESS MEETING**	*Marriott Ballroom 9*
2:00 PM – 4:15 PM	**TS/OTIS JOINTABSTRACT SESSION** Common Conditions in Pregnancy: Treatment of Mental Health and Asthma *Moderator: Ludmila Bakhireva, University of New Mexico and Myla Moretti, The Hospital of Sick Childern*	*Marriott Ballroom 9*
2:00 PM - 2:15 PM	Patterns of Psychotropic Drug Use in Pregnancy and Lactation: The MotherSafe Experience 2000-2007 *M Eamus[1], J Oei[1,2], M Hill[3], T Taylor[3], D Kennedy[1,3]. [1]School of Women's and Children's Health, University of NSW, Kensington, NSW, Australia, [2]Dept of Neonatology, Royal Hospital for Women, Randwick, NSW, Australia, [3]MotherSafe, Royal Hospital for Women, Randwick, NSW, Australia.*	
2:15 PM – 2:30 PM	Birth Defects, Preterm Birth and Intrauterine Growth in the Offspring of Women Prescribed Citalopram during Pregnancy *L Colvin[1,2], L Slack-Smith[2], FJ Stanley[1], C Bower[1]. [1]Centre for Child Health Research, Telethon Institute for Child Health Research, The University of Western Australia, West Perth, Australia, [2]School of Dentistry, The University of Western Australia, West Perth, Austria.*	
2:30 PM – 2:45 PM	The Safety of Escitalopram in Pregnancy: A Prospective Cohort Study *C Klieger-Grossmann[1], B Weitzner[1], T Einarson[2], G Koren[1], A Einarson[1]. [1]The Motherisk Program, Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, the Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [2]Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada.*	

2:45 PM – 3:00 PM

Neurodevelopment of Children Exposed *In Utero* to Venlafaxine: Preliminary Results

I Nulman[1,2], M Barrera[1,2], A Pulver, D Streiner[2,3], B Feldman[1,2], G Koren[1,2]. [1]The Hospital for Sick Children, Toronto, ON, Canada, [2]The University of Toronto, Toronto, ON, Canada, [3]Baycrest Centre, Toronto, ON, Canada.

3:00 PM – 3:15 PM **BREAK**

3:15 PM – 3:30 PM

Impact of Changing the Dose of Inhaled Corticosteroids During Pregnancy on the Risk of Maternal Asthma Exacerbations

L Blais[1,2], F Kettani[2], FM Ducharme[3], C Lemière[1,2], M-F Beauchesne[1], A Bérard[1]. [1]Université de Montréal, Montréal, QC, Canada, [2]Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada, [3]CHU Ste-Justine, Montréal, QC, Canada.

3:30 PM – 3:45 PM

Congenital Anomalies in Asthmatic Women using Corticosteroids during Pregnancy: A Meta Analysis from Published Data

JA Namazy[1], VE Murphy[2,3], H Powell[2,4], PG Gibson[2,4], CD Chambers[5], M Schatz[6]. [1]Scripps Clinic, San Diego, CA, United States, [2]University of Newcastle, Newcastle, NSW, Australia, [3]Hunter Medical Research Institute, Newcastle, NSW, Australia, [4]John Hunter Hospital, Newcastle, NSW, Australia, [5]University of California San Diego, La Jolla, CA, United States, [6]Kaiser Permanente Medical Center, San Diego, CA, United States.

3:45 PM – 4:00 PM

Risk of Perinatal Mortality Associated with the Use of Inhaled Corticosteroids for the Treatment of Asthma during Pregnancy

MCB Breton[1], MFB Beauchesne[1,2], CL Lemière[2], ER Rey[3], AF Amélie[2], LB Blais[1,2]. [1]Universite de Montreal, Montreal, QC, Canada, [2]Research Center, Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada, [3]Obstetric and Gynecology Department, CHU Ste-Justine, Montreal, QC, Canada.

4:00 PM – 4:15 PM

Perception of Teratogenicity among Pregnant Women with Asthma or Diabetes Mellitus

P Sarangarm[1], S Liu[1], BN Young[1], ST Phelan[2], J Nawarskas[1], WF Rayburn[2], LN Bakhireva[1]. [1]University of New Mexico, College of Pharmacy, Albuquerque, NM, United States, [2]University of New Mexico, Department of Obstetrics and Gynecology, Albuquerque, NM, United States.

OTIS ABSTRACTS

1. Enantiomer-Specific Methadone to Infants *Via* the Placenta and Breastmilk. Debra L. Bogen, MD, James M. Perel, PhD, Joseph C. Helsel, BS, Barbara H. Hanusa, PhD; Matthew Thompson, MA, Katherine L. Wisner, MD, MS.

Background: Breastfeeding, a public health priority, may improve outcomes for infants exposed prenatally to methadone. Methadone is dispensed as a racemic mixture; R-methadone is the active enantiomer. Pharmacologic data for R-methadone in breastmilk could improve risk-benefit decision making for treatment of lactating women. Objectives: Estimate infant exposure to R-, S- and total methadone *via* breastmilk by milk/plasma ratio (M/P), theoretic infant dose (TID), and relative infant dose (RID). Methods: Women treated with methadone doses of 40-200 mg/day (mean 102 mg/day) provided concomitantly collected plasma and breastmilk samples 1-6 days after delivery. Samples were mostly taken at peak plasma levels thus the infant exposure estimates are for maximum possible infant exposure. R- and S-methadone levels were measured in maternal plasma and breastmilk; M/P, TID, and RID were calculated for each enantiomer and total methadone. Results: The 20 participants were 18-38 years old and publicly insured, nearly half didn't complete high school and only one was not Caucasian. R-methadone concentration was 1.3 to 3.0 times that of S-methadone in all breastmilk samples. Mean (range) R-, S- and total-methadone TID were 20.4 µg/kg/day (3.8-98.9), 12.6 µg/kg/day (1.8-70.7) and 32.9 µg/kg/day (6.0-169.5) respectively. Mean (range) RID of R-, S- and total methadone were 2.7% (0.7-10.1), 1.6% (0.3-7.2) and 2.1% (.52-8.8) respectively. Conclusions: R-methadone is found in higher concentrations than S-methadone in breastmilk. Even at high methadone doses, methadone levels were relatively low and support AAP recommendations that dose shouldn't be a factor in determining whether women on methadone should breastfeed. Background: Conversion to methadone is the standard of care for pregnant, opiate-dependent women. Methadone is dispensed as a racemic mixture; R-methadone is the active enantiomer. Little data have been published about enantiomer specific transfer of methadone across the placenta and infant elimination of methadone. These data could be used to assist in clinical decision making. Objectives: 1) Describe the proportion of R- and S-methadone that transfers to the infant across the placenta. 2) Determine the elimination rate of R- and S-methadone from infant plasma. Methods: Fifteen women treated with methadone during pregnancy provided plasma sample within 1 hour of delivery and concomitant umbilical cord blood samples. R- and S-methadone levels were measured in both samples. Ratios of cord to maternal plasma R-, S- and total-methadone were determined. Eleven infants had cord blood and venous blood samples from 1 to 6 days of age; methadone elimination rate was determined for these infants. Results: Participants were 18-38 years old and publicly insured, 85% had completed high school and only one was not Caucasian. The mean daily methadone dose (range) at delivery was 93 mg (50-138 mg). The mean proportion of R-, S- and total-methadone that crossed the placenta at delivery was 58% (range 24-103%), 55% (range 22-113%) and 57% (range 24 to 106%) respectively. The average elimination rate of R- and S-methadone from cord blood to postpartum samples were 20.5 ng/ml/day (-3.4-62.9) and 18.0 ng/ml/day (-4.8 – 48.6) respectively. Conclusions: Enantiomer specific methadone transfer across the placenta and infant elimination rates are highly variable. Further work is needed to determine the use of these data in clinical decision making.

2. Pregnancy Outcome After *In Utero* Exposure to Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers. Diav-Citrin[1] O., S. Shechtman[1], Y. Halberstadt[1,2], V. Finkel-Pekarsky[1], R. Wajnberg[1], J. Arnon[1], E. Di Gianantonio[3], M. Clementi[3] and A. Ornoy[1,2]. [1]The Israeli Teratology Information Service, Israel Ministry of Health, [2]The Hebrew University Hadassah Medical School, Jerusalem, Israel, and [3]Servizio di Informazione Teratologica, Padova, Italy.

Introduction: Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are a group of compounds used in the management of hypertension and diabetic nephropathy. Their use during late pregnancy has been associated with a characteristic fetopathy. First trimester human pregnancy experience is limited and inconsistent. The primary objective of the study was to prospectively evaluate the rate of major congenital anomalies after pregnancy exposure to ACEI/ARB compared to the rate in a comparison group exposed to other antihypertensives (OAH) and in a comparison group exposed to non-teratogens (NT). Methods: Callers who contacted the Israeli or Padua Teratology Information Services (TISes) in regard to gestational exposure to ACEI/ARB between 1994 and 2007 (Israel), and 1990 and 2008 (Italy) were prospectively collected and followed-up. Results: 252 ACEI/ARB-exposed pregnancies (99.2% first trimester), 256 pregnancies exposed to OAH and 495 pregnancies with NT exposure were followed-up. Treatment indications in the ACEI/ARB group were: hypertension (76.3%), kidney disease (10.3%), cardiac disease (5.4%), systemic lupus erythematosus (4.9%), and diabetes (3.1%). The rate of major congenital anomalies was comparable between the three groups (12/193, 6.2%, ACEI/ARB; 10/213, 4.7%, OAH; 22/471, 4.7% NT; p=0.688). The analysis was repeated among those exposed in the first trimester excluding genetic or cytogenetic anomalies and those related to other known teratogens (8/190, 4.2%, ACEI/ARB; 9/212, 4.2%, OAH; 18/471, 3.8% NT; p=0.954). There were no cases of ACEI fetopathy, even among offspring of 11 women who were exposed during the third trimester of pregnancy (9 throughout). The median gestational age at delivery was two weeks earlier ($p<0.001$), the rate of preterm deliveries more than two-fold higher ($p<0.001$), and the median birth weight was more than 200g lower ($p<0.001$) in the ACEI/ARB and OAH groups compared to the NT group. Conclusions: The present study suggests that ACEI or ARB do not appear to be major human teratogens, when used in the first trimester of pregnancy.

3. Motor and Visual Abilities in Children Born By Mother in Treatment with Antidepressants during Pregnancy. Marco De Santis MD[1], Carmen De Luca MD[1], Ilenia Mappa MD[1], Tomasella Quattrocchi MD[1], Daniela Ricci MD[2], Diego Martinelli MD[2], Claudia Brogna MD[2], Eugenio Maria Mercuri MD[2]. [1]Telefono Rosso, Teratology Information Service, Department of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Rome, Italy. [2]Pediatric Neurology Unit, Università Cattolica del Sacro Cuore, Rome, Italy.

Background: Depression is a common event in pregnancy. Selective serotonin reuptake inhibitor (SSRI) are first line drugs used for the treatment of depression. Tricyclic antidepressants (TCAs) were widely used by women during pregnancy and lactation before the introduction of SSRIs. Recent literature indicates a little increased risk for SSRI exposure both for early and late trimester exposure. Little is known about neurodevelopment of children prenatally exposed to antidepressants. In literature two studies reported adverse effects on both motor development and motor control. The aim of this study was to assess visual function and motor control in 4-6 years old children exposed *in utero* to antidepressants. Methods: We recruited 12 children born by 11 mothers counseled by our TIS (Telefono Rosso, Rome) between 2002 and 2006 in treatment with paroxetine or tricyclic antidepressants +/- benzodiazepines during pregnancy. All children underwent detailed assessment of motor and visual function between 4 and 6 years of age. Movement Assessment Battery for Children was used to identify delay or impairment in motor development. Stereopsis was tested using the TNO test, a test specifically designed for screening for defects of binocular vision. The measurement of motion coherence threshold has been used to test dorsal stream function, while form coherence tasks have been used to test ventral stream function. We also explored cognitive functions using Raven Progressive matrices. Results: All children showed normal cognitive abilities and stereopsis. Two of the 12 children (16.7%) had borderline results on the Movement Assessment Battery for Children Two children (16.6%) had abnormal results for form and/or form and motion threshold and 5 (41.7 %) borderline. Conclusions: Our preliminary data in this cohort suggest that visual and motor impairment cannot be excluded but is relatively rare. Additional studies are needed to verify long term effects of *in utero* exposure to antidepressants.

4. Outcome of Pregnancy after Maternal Exposure to Mifepristone. Sally Stephens, Laura Yates, Vaidehi Chincholkar, Simon Thomas.

Background: Mifepristone is an antiprogestogenic steroid and glucocorticoid antagonist which sensitises the myometrium to prostaglandin induced contractions and softens and dilates the cervix. It is used for medical termination of pregnancy, cervical ripening before mechanical dilatation and induction of labour following intra-uterine fetal death. The published data on mifepristone exposure in pregnancy are limited to case series and case reports. Due to the possibility of multiple reporting, it is difficult to quantify the total number of exposures and congenital malformations. Data on malformations following exposure to mifepristone are limited and not sufficient to conclusively establish it as a teratogen. This on-going prospective case series aims to collect data and assess the potential fetotoxic effects of mifepristone on the outcome of pregnancy. Methods: Using standardised procedures the United Kingdom Teratology Information Service (UKTIS) provided risk assessments and prospectively collected pregnancy outcomes from healthcare professionals for 41 patients who had been exposed to mifepristone during pregnancy. Results: Of the 41 exposures 23 occurred in the 1st trimester, eight in the 2nd trimester, one in the 3rd trimester and nine at unknown timing. Twenty seven infants were liveborn, 11 pregnancies were electively terminated, two miscarried and the remaining two resulted in intrauterine deaths. Of the liveborns infants three were reported to have a congenital malformation. In two cases, the timing of the exposure and known association of the malformations with the coexisting genetic diagnosis made a causal relationship to mifepristone exposure unlikely. The frequency of congenital malformations in live born infants (3/27, 11.1%, 95% CI 2.9 to 30.3) was not significantly higher than the background rate of major congenital anomalies in the general population (2-3%), even if these two cases are included in the analysis. Conclusions: The published data and data collected by UKTIS do not show an increased incidence of congenital malformations or specific pattern of malformation following *in utero* mifepristone exposure, however, the data are too limited to state that there is no increase in risk. Much of the published data has been reported retrospectively and may be biased towards the reporting of adverse outcomes. Data collected prospectively by UKTIS has not demonstrated an increased risk of adverse outcomes although more robust data are required before any definitive conclusions can be drawn.

5. Understanding the Relationship between Obesity and Folate Status in the Protection against Neural Tube Defects; A Systematic Review. Seth J. Stern, Dr. Gideon Koren.

Background: Maternal obesity has previously been identified as a risk factor for neural tube defects (NTD) during pregnancy. As obesity becomes an increasingly prevalent public health concern, its association with teratogenic consequences may become more apparent. While adequate folic acid intake can aid in the reduction of NTD-affected births, it remains unknown if overweight women achieve protective folate levels during the periconceptional period. Objective: The aim of this systematic review was to determine whether obesity and folate status are independent risk factors for NTDs, by examining the association between body weight and folate status. Methods: Embase and Medline were searched for all studies identifying an association between measures of body weight and folate status. Additionally, reference lists of pulled papers were scanned to find any relevant studies. Both serum and erythrocyte folate were considered acceptable indicators of folate status. Results: The search identified a total of 695 articles. Of these articles, 11 identified a negative correlation, 5 identified a positive correlation, and 11 found no correlation between body weight and folate status. Each of the seven papers investigating the association between body weight and serum folate as a primary outcome found a negative correlation. Furthermore, the only three papers that controlled for folate intake found an inverse relationship. No consistent trends were found in regards to erythrocyte folate status. Conclusions: The potential link between increasing measures of body weight and levels of serum and erythrocyte folate remains unresolved. While there appears to be a trend in regards to serum folate, the lack of a congruent association among the investigated studies suggests that further work must be conducted to realize the impact of obesity on folate status. A comprehensive understanding of the prospective relationship will allow for optimal prenatal and periconceptional folic acid supplementation in the prevention of NTDs.

6. Pregnancy Outcomes after Alcohol Exposure in Early Pregnancy Experienced in Teratology Information Services. Y Han, JS Choi, HK Ahn, SW Lee, MH Kim, JH Chung, HM Ryu, MY Kim, JH Yang. The Korean Motherisk Program, Department of Obstetrics and Gynecology, Cheil Hospital and Women's Healthcare Center, Kwandong University College of Medicine, Seoul, Korea.

Background: Alcohol consumption during pregnancy is the cause of Fetal Alcohol Syndrome. Although most pregnant women stop drinking alcohol soon after they are aware of their pregnancy, there is an ongoing debate on the consequences of alcohol exposure in early pregnancy. Therefore, we aimed to study the pregnancy outcome of women exposed to alcohol in the first trimester of pregnancy. M**ethods:** In a prospective cohort study, from January 2000 to March 2009, 1,919 women exposed to alcohol before they know pregnancy and 2,177 women not exposed to alcohol were enrolled at the Korean Motherisk Program. Study outcomes were spontaneous abortion, gestational age at birth, intrauterine fetal death, birth weight, and rate of major malformations. Results: Pregnancy outcomes were evaluated in 1,677 cases and 1,864 controls. Exposure to alcohol was at a gestational age of 4.6 ± 2.3 weeks, with a median cumulative dose prior to being aware of their pregnancy of 1.40 oz. No statistical differences (P>0.05) were observed between cases and controls in any of the pregnancy outcomes studied: a) spontaneous abortions: 7.5% (n= 126/1,677) among exposed women *vs.* 6.9% (n= 129/1,864) among controls; b) preterm births (<37 weeks of gestation): 3.8% (n=57/1,551) *vs.* 4.5% (n=76/1,735), respectively; c) intrauterine fetal deaths: 0.1% (n=2/1,551) *vs.* 0.2% (n=3/1,735), respectively; d) birth weight: 3,287 ± 429 g *vs.* 3,269 ± 463 g, respectively; and e) major congenital malformations: 2.3% (n= 35/1,551) *vs.* 2.6% (n= 45/1,735), respectively. Conclusion: Our data suggest that women exposed to alcohol in early pregnancy, prior to become aware of their pregnancy, is not associated with adverse pregnancy outcome. However, a further study assessing the long-term consequences in the babies born to exposed women, e.g. cognitive impairment, is required.

OTIS POSTERS

1. Update on the Motherisk Alcohol and Substance Use Helpline, 10 Years and Counting. Eunji Kim, Moumita Sarkar, Yvette Navioz, Gideon Koren, Adrienne Einarson.

Introduction: The Motherisk Alcohol and Substance Use Helpline at The Hospital for Sick Children in Toronto, Canada was developed to provide evidence-based information to women and their health care providers about the negative effects associated with alcohol and other recreational drug use in pregnancy and breastfeeding. Objective: To describe the activities of the line in the first 10 years of operation. Methods: A search was conducted on the Motherisk database for a period of November 20, 1998 to November 19, 2008. The information retrieved was analyzed for geographical distribution, demographical characteristics, age group, exposures and other activities. Results: In the first 10 years of service, Motherisk Alcohol and Substance Use Helpline received nearly 18, 000 calls. The majority of the callers who contacted the program inquired for their own needs. Women exposed to alcohol and substances during their pregnancy were more likely to be of Caucasian descent (80%), in stable relationships (70%), employed (65%) with some level of post secondary education (52%). Most of the women inquiring on the helpline were between 18 to 35 years of age. The five most common exposures reported were alcohol, nicotine, marijuana, crack/cocaine and opiates. Inquiries regarding cigarette and marijuana smoking have been stable, whereas reports of cocaine and ecstasy use have been steadily increasing. Demographics of the Motherisk callers are inconsistent with the characteristics of high risk women using alcohol and illicit drugs in pregnancy and breastfeeding as described in the literature. Conclusions: Although the Motherisk Alcohol and Substance Use Helpline is a toll free line easily accessible throughout Canada, a low risk population composed of highly functioning individuals is more likely to use the services provided. Thus, additional research and efforts are needed to engage women in the high risk group, who are likely to continue their alcohol and substance use in pregnancy, and may present with perinatal risk factors due to their substance use.

2. Safety and Effectiveness of Proctofoam-HC® In the Third Trimester of Pregnancy. Ebrahimi N, Vohra S, Koren G.

Background: Hemorrhoids are a very common medical condition in pregnancy with severe impact on women's well-being. Although many products are available for the treatment of hemorrhoids, none have been studied for safety and effectiveness in pregnancy. Proctofoam-HC® is an anti-hemorrhoidal medication prescribed to many pregnant women for the treatment of hemorrhoids. Objective: The objective of this study is to assess the safety and effectiveness of Proctofoam-HC® in the third trimester of pregnancy. Birth weight is the primary outcome used for safety assessment; changes in the severity of each of the hemorrhoidal symptoms (pain, itching, swelling, bleeding, discomfort) as well their Impact on Well-being Score, is used for the assessment of effectiveness of the medication. Methods: 210 pregnant women suffering from hemorrhoids were recruited from six different clinics. All women were prescribed Proctofoam-HC®. Prenatal and postnatal interviews were conducted during which extensive information on medical history, maternal characteristics, delivery complications, neonatal health and birth weight, were collected. 210 pregnant women not suffering from any hemorrhoids, were used as a comparison group. Severity of hemorrhoids and their impact on women's well-being were assessed using a visual analogue scale (HemoRatES), before and after using Proctofoam-HC®. Results: Statistical analysis found no difference in the primary and secondary outcomes between comparison and Proctofoam-HC® treated groups. Significant improvement in severity of hemorrhoidal symptoms and their impact on well-being was found in the treatment group. Conclusions: Proctofoam-HC® is a highly effective medication that can be used in pregnancy to improve, if not eliminate all the symptoms associated with hemorrhoids, without compromising the safety of the developing baby. Proctofoam-HC® significantly improves women's overall well-being with this commonly underrated disease.

3. Effect of High Dose Folic Acid Supplementation on Unmetabolized Folic Acid in Plasma: Implications For Planning and Pregnant Women. Carolyn Tam[1], Jimao Yang[2], Deborah L. O'Connor[2], Gideon Koren[1]. [1]Division of Clinical Pharmacology and Toxicology, [2]Physiology and Experimental Medicine, Hospital for Sick Children.

Background: High dose (4 – 5 mg) folic acid supplementation is often recommended for women who have had a previous pregnancy in which a neural tube defect was detected or who take certain antifolate medications. Although the fetal benefits of folic acid supplementation are well known, little is known about the maternal and fetal safety of folic acid at doses above the tolerable upper limit (1 mg). The liver has limited capacity to convert folic acid to reduced, physiological forms of folate. Folic acid intake that exceeds this capacity results in the appearance of oxidized (unmetabolized) folic acid (FA) in plasma. Circulating FA may contribute to the proposed adverse effects of chronic exposure to high folate intakes and blood folate concentrations, including increased risk for certain cancers and altered epigenetic regulation in the neonate. Objective: To assess the effects of folic acid supplementation (1.1 mg or 5 mg) on plasma FA among healthy women of childbearing age who are also exposed to folic acid fortification of staple foods. Methods: Fasting plasma samples were collected as part of a randomized trial evaluating blood folate concentrations among women consuming 1.1 mg or 5 mg of folic acid daily over a 30 week period. Plasma FA was quantified by reverse-phase HPLC. Results: There was a significant effect of time ($p = 0.01$), but not dose ($p = 0.31$), on plasma FA. Fasting plasma FA concentrations tended to increase after 6 and 12 weeks of folic acid supplementation; however, the changes were not significant ($p = 0.11$, 0.06). Plasma FA concentrations decreased significantly between weeks 12 and 30 ($p = 0.01$); the difference between baseline and week 30 was not significant ($p = 0.12$). **Conclusions:** Although folic acid supplementation increases fasting plasma FA, concentrations remain low with once daily dosing up to 5 mg. Therefore, an otherwise healthy woman for whom the higher dose of folic acid is indicated need not worry about putting her own health at risk for the health of her baby, as there appear to be mechanisms that regulate the absorption and metabolism of folic acid and limit maternal and fetal exposure to FA.

4. Pregnant Women and the H1N1 Vaccine: Perception of Risk and Determinants of Decision-Making. Sakaguchi S, Weitzner B, Carey N, Bozzo P, Koren G, Einarson A. The Motherisk Program, Division of Clinical Pharmacology andToxicology, The Hospital for Sick Children, University of Toronto, Canada.

Background: Following availability of the H1N1 vaccine to the public in October 2009, Motherisk received an increased number of calls from pregnant women inquiring about the safety of the H1N1 vaccine. Objectives: To determine 1) how many received the H1N1 vaccine following their call to Motherisk; 2) reasons for their decision; and 3) the sources of information regarding the vaccine and how this affected their decision-making. Methods: Observational cohort study, using a questionnaire administered *via* telephone. All pregnant women who called Motherisk in October and November of 2009, requesting counseling regarding safety of the H1N1 vaccine, and who had not yet received the H1N1 vaccine, were contacted. A structured questionnaire consisting of 10 questions that included quantitative and semi-qualitative questions was used. Results: To date, we have completed 35 follow-ups. Twenty seven (80%) pregnant woman received the vaccine and 7 (20%) declined. Of those who received vaccine, 61% cited concern about the risk of H1N1 infection for the baby as the reason for their decision, while 71% of those who declined, cited concern about the safety of the vaccine for the baby. Regarding information received, the women stated that the information from Motherisk (63%) and their direct health care providers (54%) was helpful, in contrast to the media of which only 11% found helpful. Conclusions: In studying pregnant women's perceptions and determinants of their decision-making in receiving the H1N1 vaccine, we can gain important information for public education to be applied to future preventative health interventions.

5. Accessing a Caller's Anxiety Level Pre and Post-Teratogen Counseling. Cardenas, Billie; Wolfe, Lori; Debus, Brenda.

Background: Teratogen services always state that we "reduce a patient's anxiety" when we provide information and counselling to our callers. We decided to conduct a survey that would measure the caller's anxiety level before we provided counselling, and then again after we provided the counselling. Methods: A short survey was developed. The idea for this survey was prompted by the cost survey that the Utah Teratogen service conducted a few years ago. We asked our pregnant callers two questions prior to counselling them. Question 1. Right now, based upon your concerns and the reasons you are calling our service, how likely are you to call your doctor or health care provider for more information? Please rate on a scale of 1 to 10, with 1 being "not going to call" and 10 being "definitely will call". Question 2. How likely are you to request pre- or postnatal screening and testing, such as an ultrasound or other tests? Then we also asked them to rate this on a scale of 1 to 10. After providing the counselling, we again asked the same two questions. In addition to these questions, we also recorded the caller's age, week of pregnancy at the first contact to our TIS, and first pregnancy or not. The sample size was 100 callers who were currently pregnant and called the Texas TIS during January and February 2010. The survey was conducted during their first call to our service. Results: We found that our counselling did indeed greatly reduce a caller's anxiety levels! Many of our callers stated that they were also planning to call their health care providers in addition to talking with our TIS. After we provided counselling, the majority no longer felt the need to call anyone else! In many cases, they stated that the information that we provided had calmed their fears and anxieties, and they were no longer worried about the exposures. Conclusions: Teratogen services do provide a vital service to pregnant callers and have a great impact in reducing a patient's anxiety levels. Callers do feel more anxiety if it is their first pregnancy and if it is early in their pregnancy. We did not find an age related effect in anxiety levels.

6. Herpes Infection:Treatment Options during Pregnancy. Angela Chua-Gocheco , Pina Bozzo, Gideon Koren, Adrienne Einarson.

Background: Herpes Simplex viruses, HSV-1 (orolabialis) or HSV-2 (genital herpes) are common viral infections worldwide especially among women of reproductive age. Unfortunately, pregnant women are often asymptomatic, and, if left untreated during pregnancy, these infections may lead to neonatal HSV infection. Identifying and treating HSV-1 and HSV-2 condition during pregnancy is of utmost importance. Objective: To discuss the safety of medications available for treatment of Herpes virus infections during pregnancy. Methods: Literature searches using PubMed and EMBASE were conducted to examine treatment options for herpes simplex infections in pregnancy and to evaluate potential teratogenic risks of topical and oral treatments. Results: Treatment options that are currently available for HSV-1 infections include topical products such as penciclovir, docosanol, acyclovir and zinc oxide. The use of these topically used products during pregnancy would not be of concern due to their limited systemic absorption. Treatment for both HSV-1 and HSV-2 infections, include oral acyclovir, valacyclovir and famciclovir, which may also be used prophylactically to prevent HSV-2 infection near term. Although there are limited controlled studies examining the safety of oral acyclovir and valacyclovir during pregnancy, results from pregnancy registries conducted by the manufacturers are reassuring. Pregnancy outcomes of more than 1000 women did not reveal an increase risk for major malformations. Currently, as there are no studies available for famciclovir, it should not be considered as a first line treatment option for pregnant women. Conclusions: The available treatment options for herpes infection suggest that they are not associated with increase risk for major malformations above the baseline, with the exception of famciclovir, for which there is no available data. Physicians do not need to be concerned with using these medications for the treatment of HSV infections as, in addition to treating the mother, this will decrease the chance of adverse consequences to the neonate.

7. Prenatal Exposure to Mycophenolate Mofetil – Report of Three Cases and Review of the Literature. Klieger-Grossmann C, Garcia–Bournissen F, Vicky Luo, Sermer M, Chitayat D, Koren G.

Background: Mycophenolate Mofetil (MMF) has become a major therapeutic option for the management of patients undergoing transplantation, as well as for the treatment of autoimmune conditions including systemic lupus erythematosus (SLE) and inflammatory diseases. Limited human studies and post marketing surveillance have suggested that MMF use during pregnancy increases the risk for congenital malformations. This is of utmost importance given that many patients receiving the drug are women of child-bearing age. As many pregnancies are unplanned, it is imperative to assess the teratogenic risk of MMF. We prospectively identified and followed pregnant women exposed to MMF during pregnancy and report the pregnancy outcomes. Methods: We searched all records of women who contacted Motherisk Program, at the Hospital for Sick Children, and the Special Pregnancy Program- Maternal Unit, Mount Sinai Hospital in Toronto between 2000 and 2008 Results: Three pregnancies exposed to MMF during the first trimester of pregnancy were identified. Two women gave birth to healthy babies and one had an early miscarriage. The two babies did not exhibit any malformations, as evaluated by obstetricians and pediatricians involved in their follow up. Postnatal follow-up showed normal growth and development. Discussion: We did not observe malformations in our prospectively followed patients, which is in agreement with another small prospective series that also failed to find any malformations, and in contrast with the information obtained from retrospective case series. We believe that it is possible that the rate of malformations associated to MMF use in pregnancy has been exaggerated by selection bias, and may be smaller than previously believed.

8. Fetal Safety of Cetirizine Use in Pregnancy – A Prospective Controlled Cohort Study. Djokanovic N, Moretti M, Boskovic R, Martinovic J, Koren G. The Motherisk Program, Division of Clinical Pharmacology & Toxicology, The Hospital for Sick Children, Toronto, Canada.

Background: Cetirizine, a non-sedating second–generation H1-receptor antagonist, is widely used to treat allergic rhinitis and urticaria, but the data on pregnancy outcome are limited. Objective: To determine whether exposure to cetirizine during pregnancy increases the risk of major malformations or other adverse pregnancy outcomes. Methods: Pregnant women who were counseled by the Motherisk Program in regard to cetirizine exposure (n=134) were enrolled in a controlled, cohort study and compared to an equal number of pregnant women counseled for non-teratogenic exposures. The primary outcome was the rate of major malformations and secondary endpoints were the rates of miscarriage, stillbirth, preterm delivery, gestational age at birth, and birth weight. Results: There were no significant differences found between the cetirizine exposed and comparison group in the pregnancy outcome: rate of live births, miscarriages, stillbirths, and elective termination (p=0.345). There was also no difference in the rates of major malformations (2/130=1.5% *versus* 2/128=1.6%; p=0.625), gestational age at birth (38.96±2.3 *versus* 39.59±1.4 weeks; p=0.103), prematurity (p=0.047) and mean birth weight (3389±657 *versus* 3547±523 grams; p=0.081). Conclusions: The use of cetirizine during pregnancy does not appear to be associated with an increased risk of major malformations or other adverse fetal outcomes.

9. Therapeutic Use of Opiods: A Prospective, Comparative Study of Pregnancy Outcomes. Osadchy A[1], Weitzner B[1], Lam J[1], Einarson A[1]. [1]The Motherisk Program, Hospital for Sick Children, Toronto, ON, Canada.

Background: Data on pregnancy outcomes of women taking medically prescribed opioid analgesics throughout pregnancy are incomplete. Although this class of medications does not appear to be teratogenic, a possible association between opioid analgesic use in early pregnancy and elevated risk of cardiac malformations has been reported recently. Adverse pregnancy outcomes other than malformations associated with maternal exposure to opioids are rarely reported. Neonatal opioid withdrawal syndrome has been described frequently in the context of maternal opioid addiction. Little information exists on neonatal withdrawal due to opioids used for medical reasons. Objectives: (1)To determine whether exposure to medically prescribed opioids is associated with increased risk of major malformations (2)To examine rates of spontaneous abortions, therapeutic abortions, stillbirths, birth weight and gestational age at delivery (3)To estimate the rate of neonatal withdrawal symptoms in infants exposed to prescribed opioids late in pregnancy. Methods: This is an observational cohort study with two comparison groups. From the Motherisk Program prospectively collected database, cohort of women who took opioid-containing medications for medical reasons at any stage of pregnancy will be identified and followed up. Pregnancy outcomes will be compared to those of two matched control groups: women with similar medical conditions who used non-opiod medications for pain relief (1) and women exposed to non-teratogens (2). Results: To date, 35 follow ups on pregnant women exposed to opioid-contaiting medications have been completed. Among exposed women, 3/35 delivered prematurely. Among infants of exposed women, 1 died due to severe prematurity (to be confirmed by physician) and there were 4 malformations (2 hernias, 1 cleft lip and palate, 1 unspecified). Conclusion: The study is ongoing and more data will be collected from the Motherisk database and in collaboration with the OTIS.

10. The Fetal Safety of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers. Moretti ME, MSc, Caprara D, MD, MSc, Drehuta I, BSc, Yeung E, BSc, Cheung S, BSc, Federico L, MSc, Koren G, MD. The Motherisk Program, The Hospital for Sick Children, Toronto, CANADA

Background: Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are known to cause fetal renal damage in pregnancy. Their safety after first trimester exposure has been debated, with both positive and negative studies. Objectives: Our aim was to determine whether the use of ACE inhibitors or ARBs in the first trimester of pregnancy is associated with an increased risk for major malformations or other adverse pregnancy outcomes. Methods: All subjects were prospectively enrolled from among women contacting the Motherisk Program in Toronto. At initial contact, details of maternal medical history and exposures were collected. Pregnancy outcome was recorded on follow up interview after the completion of pregnancy. To control for the potential effects of hypertension, a control group of hypertension treated with other antihypertensives, as well as healthy controls were also recruited. Results: Maternal characteristics (age, pregnancy history, alcohol consumption and smoking habits) were not different among the three groups. There were no differences in rates of major malformations. Both the ACE-ARBs and disease matched groups exhibited significantly lower birth weight and gestational ages than the healthy controls ($p<0.001$ for both variables). There was a significantly higher rate of miscarriage noted in the ACE/ARB group ($p<0.001$). Conclusions: These results suggest that ACE inhibitors/ARBs do not appear to be major human teratogens following first trimester exposure, however, they may increase the rate of miscarriage.

11. Evaluation of the Impact of a Smoking Cessation Intervention during Pregnancy. Morin Caroline, B.Pharm, M.Sc.; Mareschal Véronique, M.D.; Therrien Roxane, B.Pharm., M.Sc.; Duperron Louise, M.D.; Ferreira E, Pharm D.

Background: Twenty-five percent of pregnant women smoke cigarettes, despite the fact that this is a major cause of perinatal morbidity and mortality. Therefore, we develop a program in our institution to help them to stop smoking. Objective: To compare the rate of smoking cessation and neonatal birth weight between pregnant women randomised to a smoking cessation program («intervention group») or to usual care («control group»). Methods: Monocentric comparative randomised prospective study. The intervention consisted of a 20-30 minute session with a pharmacist for smoking cessation counselling (risks and benefits, non pharmacological and pharmacological methods to quit smoking, etc.), and several telephone follow-ups. A treatment with nicotine patches was proposed to women when non pharmacological approaches were insufficient. Pregnant women were included if they were followed at obstetric outpatient clinic of Ste-Justine Hospital or at the Clinique René-Laennec between January 1st 2002 and December 31st 2004, in Montreal. They had to be pregnant between 8 and 17 weeks, to smoke at least 5 cigarettes per day, to be at least 18 years old and consent to participate. Results: Fourteen women were included in each group. Three women stopped smoking in the intervention group and no one stopped in the control group. The mean neonatal birth weight was 3 425 g (2 635 g - 4 505 g) in the intervention group and 3 169 g (2 065 g – 3 840 g). The mean weight percentile was 43 (5-97) in the intervention group and 32 (<3-70) in the usual group. Conclusion: A structured program including the possibility of using nicotine replacement therapy and combining an intensive follow-up can result in a higher chance to stop smoking for pregnant women and possibly a higher neonatal birth weight.

Teratology Society

Code of Ethics

Preamble

The objective of the Teratology Society is to stimulate scientific interest in and to promote the exchange of ideas and information on problems of abnormal biological development at the fundamental or clinical level. The Mission of this Society is to promote research and the exchange of ideas and research results that reveal the causes, improve the diagnosis and treatment, and prevent the occurrence of abnormal development and birth defects; to communicate that information to physicians, public health officials, concerned health advocacy and lay groups and other interested parties that promote the elimination of birth defects when possible and amelioration of them when they occur; and to provide education and training on the causes, mechanisms, treatment and prevention of birth defects.

Code of Ethics

As a member of the Teratology Society, I shall:

1. Strive to assure credibility by conducting my work and myself with objectivity and integrity.

2. Communicate information with potential or real health implications expeditiously and responsibly, with due regard for the significance and credibility of the available data.

3. Present my scientific or professional judgments with full disclosure of the extent of factual support.

4. Not allow conflict of interest to influence my judgment.

5. Observe the spirit and letter of the laws, regulations, and ethical standards relating to the welfare of humans and animals involved in experimental or clinical procedures.

6. Maintain high health and safety standards for the protection of my experimental subjects, co-workers, and others.

7. Adhere to the Guidelines for Ethical Publication and Presentation of Scientific Information and Data as published in the journal.

Adherence to the Code of Ethics is a condition of membership in the Teratology Society.

Teratology Society Guidelines for Ethical Publication and Presentation of Scientific Information and Data

Members of the Teratology Society subscribe to the Code of Ethics adopted by the Society membership on June 8, 1990. These guidelines for publication and presentation are complementary to the Code of Ethics and are an extension of the philosophy embodied in the Code as it applies specifically to publication and presentation of information by members of the Teratology Society as they function as authors, reviewers, editors, consultants and experts to government, universities, industry and the courts.

Responsibilities for Authors

1. Avoid the following unethical practices, which are unacceptable in publications or presentations:
    a. Plagiarism-presenting the work of others, in whole or in part, as one's own.
    b. Fraud-fabrication of results or reports, in whole or in part.
    c. Suppression or distortion of data.
    d. Submission of the same data simultaneously to more than one journal unless it has been justified openly to both editors or upon request of an editor as in a review article.

2. Co-authors should have full knowledge of and agreement with the contents and conclusions of the paper and have made a substantial contribution to the work.

3. Manuscripts should reference published preliminary accounts or abstracts from the same work to permit association of preliminary and full reports of studies.

4. "Personal communication" citations or references (oral presentations) should have the approval of the cited individual.

5. The author must cite fairly the work of others. Appropriate citations are an important component of scholarship.

6. For all studies involving human subjects or tissues, the following conditions should be met:
    a. The principles in the Declaration of Helsinki must be followed.
    b. These studies must have received formal approval from the appropriate institutional review board, ethical review committee or equivalent, and such approval should be indicated in the manuscript.
    c. If there is significant risk or discomfort to subjects, the manuscript must indicate that informed consent was obtained.
    d. Photographs of patients' faces should be included only if there is scientific relevance, and written consent should have been obtained for the publication of such photographs.

7. For all studies involving the use of animals, the following conditions should be met:
    a. All research animals must have been obtained and used in compliance with federal, state, and local laws and institutional regulations.
    b. The Society recommends that animals be maintained in accordance with the guidelines of the NIH (Guide for the Care and Use of Laboratory Animals, 1996). Any veterinary accreditation should be noted in the manuscript.
    c. The author must have received permission from their institutional Animal Care and Use Committee, and the manuscript must indicate that such approval was received.

8. Authors must specify all sources of funding for the submitted work and must also indicate any potential financial or other interests that might be perceived to bias the research. Some examples include, but are not limited to:
    a. The author acknowledges that he/she (or spouse or dependent) is employed by a company which owns the patent on the compound that appears in the manuscript.
    b. The author acknowledges that he/she (or spouse or dependent) do(es) consulting work for an organization that competes with the organization that holds the patent on the compound that appears in the manuscript.
    c. The author acknowledges that he/she has a grant from a company to do this research; the funding organization does not have control over the resulting publication.
    d. The author acknowledges his/her professional affiliation, whether it be academia, government, industry or special interest group. If the paper is the result of work-for-hire, the sponsor of the research is acknowledged.

9. For reports of original data, at least one author (e.g., the corresponding or principal investigator) is expected to have full access to all of the data in the study and to take responsibility for its accuracy.

Responsibilities of Reviewers

1. Reviewers are obligated to make expert, critical, and unbiased scientific and literary appraisals of reports of research, or other publications as requested, in the fields of the reviewers' knowledge.

2. Reviews should be done in a timely manner to not impede release of information. If a colleague of the reviewer is asked to review the paper, the person must be qualified in the opinion of the editorial staff of the journal, and the colleague's name must be identified for the Editor as the actual reviewer prior to the review.

3. A reviewer should not review a paper if:
    a. The reviewer does not feel it his or her area of expertise.
    b. The reviewer feels there may be a conflict of interest, or,
    c. The reviewer feels that a close personal, professional or competitive relationship with the author or one of the co-authors might bias the review.

4. Reviewer's criticisms must be sufficiently detailed to justify the conclusion and should be referenced if necessary to help the author.

5. The reviewer should assess whether the work of others is properly cited.

6. If the paper substantially resembles a published paper or another paper under review, this should be reported to the editor.

7. Unpublished contents of a paper under review must be considered privileged information and must not be disclosed to anyone outside of the review process.

Responsibilities of Editors

1. The editor manages and implements the policies of the journal and is responsible for the scientific and literary quality.

2. The editor, to the best of his/her ability must assure that all authors receive confidential, expert, critical and unbiased reviews of their work in a timely fashion.

3. An editor may not take part in the editorial management of the review of the editor's own papers. The editor also should avoid conflict of interest in the review of papers closely related to the editor's own work or organizational affiliation.

4. If an editor becomes aware that the main substance or conclusion of a paper published in the editor's journal may be erroneous, the editor should communicate such to the original author, if possible, and facilitate publication of a correction.

5. If an editor becomes aware of scientific misconduct related to a manuscript published or about to be published in the editor's journal, the editor should consult with Chair of the Publications Committee concerning the appropriate course of action.

Responsibilities of the Publications Committee

The Teratology Society Publications Committee will investigate any breach of these policies and make recommendations to Teratology Society Council.

References

In preparing these guidelines, liberal use was made of the following sources:

1. Endocrinology instructions to authors. http://endo.endojournals.org/
2. National Research Council. 1996. Guide for the care and use of laboratory animals. Washington DC: National Academy Press.
3. Toxicological Sciences instructions to authors. http://toxsci.oxfordjournals.org/
4. Teratology Society website. http://www.teratology.org/

TERATOLOGY SOCIETY
MEMBERSHIP APPLICATION

TERATOLOGY SOCIETY
1821 Michael Faraday Drive
Suite 300
Reston, VA 20190-5348
Tel: (703) 438-3104 Fax: (703) 438-3113
E-mail: tshq@teratology.org

CRITERIA FOR MEMBERSHIP

REGULAR MEMBERS—Regular Membership shall be considered for individuals who have publications in the field of teratology and substantive interest in the purposes of the Teratology Society. Applicants must obtain one signature of support, submit documentation of interest in teratology and provide their current *curriculum vitae*, including positions held and publications. Publications listed shall be in teratology, as broadly defined. The list shall include only those published in refereed journals; one or more publications (not abstracts) are required, with the applicant as the first author, or two or more publications are required, with the applicant as other than the first author. Manuscripts "in press" shall be considered only if a copy is submitted together with verification of acceptance for publication. In lieu of appropriate publications, other documentation of active participation in teratology (e.g. administrative or industrial experience with likelihood of continued interest) shall be considered. Regular Members may attend the Annual Business Meeting, vote, hold an elected office, and submit and sponsor abstracts.

COMBINED REGULAR MEMBERSHIP—Where husband and wife both qualify for Regular Membership, they may elect to have a Combined Membership entitling each of them to be listed as a member and to vote, but only one shall pay the cost of and receive a subscription to *Birth Defects Research*. Both must apply for Regular Membership individually.

ASSOCIATE MEMBERS—Associate Membership shall be considered for individuals who do not have publications in the field of teratology or direct scientific involvement in teratology. Such individuals may belong to other disciplines or professions, but demonstrate active participation in issues related to teratology, in line with the objectives of the Society. Active professional interest in teratology is to be documented by one signature from Regular Members. Applicants must also submit documentation of interest in teratology, and their current *curriculum vitae*. Associate Members may attend the Annual Business Meeting but may not vote, hold an elected office, or sponsor abstracts. Associate Members may present abstracts.

STUDENT MEMBERS—Requirements for Student Members consist of sponsorship by a member of the Teratology Society and the signature of the applicant's Major Professor, whose signature verifies that the applicant is a student in good standing and is pursuing degree work in the field of teratology. The Major Professor also will provide the expected date of graduation. Applicants must also submit documentation of interest in teratology, and their current *curriculum vitae*. Student Members are expected to apply for Regular/Associate Membership status at the first Annual Meeting of the Society after they graduate or after fulfillment of their postdoctoral fellowship. Those who do not achieve Regular/Associate Membership status by the time of the succeeding Annual Meeting will no longer be members of the Society. Student Members may attend the Annual Business Meeting but may not vote or sponsor abstracts.

DOCUMENTATION OF INTEREST IN TERATOLOGY—A brief statement giving your reasons for applying and list your most significant qualifications for membership.

PROFESSIONAL BACKGROUND—A current *curriculum vitae*, including positions held and publications.

APPLICATION PROCESS—Student Membership applications are reviewed as they are received. Regular and Associate Membership applications are reviewed three times a year. The application deadlines are March 1, July 1, and November 1. Approved applicants will be notified and mailed an annual dues form approximately 3 months after the application deadline. The official journal of the Teratology Society is *Birth Defects Research*. The journal is published in three parts, *Part A: Clinical and Molecular Teratology*, *Part B: Development and Reproductive Toxicology* and *Part C: Embryo Today Reviews*. A subscription to Part C, and either Part A or Part B is included as part of the annual membership dues for Regular and Associate members with the option to subscribe to all three publications for an additional fee. Student members have the option of paying for a subscription.

Please mail your completed original application, *curriculum vitae*, and documentation to:

TERATOLOGY SOCIETY
1821 Michael Faraday Drive
Suite 300
Reston, VA 20190-5348
Tel: (703) 438-3104 Fax: (703) 438-3113
E-mail: tshq@teratology.org

APPLICATION FOR MEMBERSHIP

MEMBERSHIP CLASS:

❑ **Regular** ❑ **Associate** ❑ **Student** ❑ **Combined**

If student, expected graduation date _____

Major Professor _____
Signature Name (printed or typed)

Name of Applicant: _____

CURRENT POSITION AND ADDRESS:

Institution _____

Position _____ Department _____

Office Address _____

Office Phone _____ Fax _____

City _____ State _____ Zip _____

E-mail Address _____ Home Phone _____

ACADEMIC TRAINING:
Field of Specialization _____

Institution	Dates of Attendance	Majors	Degrees

NAME AND SIGNATURE OF SPONSOR:
(Your sponsor must be a regular Member of the Teratology Society. If you do not have a member sponsor, please contact the Teratology Society.)

_____
Sponsor's Name (printed or typed) Signature Date

DOCUMENTATION OF INTEREST IN TERATOLOGY:
Attach a brief statement giving your reasons for applying and list your most significant qualifications for membership.

PROFESSIONAL BACKGROUND:
Attach a current curriculum vitae, including positions held and publications.

APPLICANT SIGNATURE:

_____
Signature Date

HOW DID YOU LEARN ABOUT THE TERATOLOGY SOCIETY?

❑ Member ❑ Web site ❑ Annual Meeting ❑ Other _____

CONSTITUTION: ARTICLE II—MEMBERSHIP

Section 1
There shall be the following types of memberships:

1. Regular	3. Associate	5. Honorary	7. Student
2. Combined	4. Sustaining	6. Emeritus	

Section 2
Dues. Members shall pay the Society annual dues as specified in the Bylaws.

Section 3
Regular Membership. Regular membership in the Society shall be open to persons who have demonstrated substantive interest in its purposes. Substantive interest is defined in the Bylaws, and a description is included on the application forms. Applications for membership must be endorsed by one member of the Society. Nominations are submitted to the Secretary and reviewed by the Membership Committee. A list of applicants meeting the requirements for membership will be transmitted by the Secretary during the first week in February, June, and October. The lists are communicated to the membership, who will have thirty (30) days to respond. Responses shall be reviewed by the Membership Committee. Its recommendations will be submitted to the Council for approval.

Section 4
Combined Membership. A Combined Membership is offered to those individuals where members are married/partnered and both qualify for Regular Membership. They may elect to have a Combined Membership entitling each of them to be listed as a member and to vote, but only one shall pay the cost of and receive a subscription to *Birth Defects Research.*

Section 5
Associate Membership. Associate Membership in the Society shall be open to persons who do not have publications in the field of teratology or direct scientific involvement in teratology. Such individuals may belong to other disciplines or professions but demonstrate active participation in issues related to teratology in line with the objectives of the Society. Active professional interest in teratology is to be documented by one signature of support from a Regular member on the membership application or in a separate correspondence referencing the Associate Membership application. Associate Members may attend the Annual Business Meeting but may not vote, hold an elected office or sponsor abstracts. Associate Members may present abstracts. As part of their annual dues, Associate Members shall receive a subscription to *Birth Defects Research.* Nominations are submitted to the Secretary and reviewed by the Membership Committee. A list of applicants meeting the requirements for membership will be transmitted by the Secretary during the first week in February, June, and October. The lists are communicated to the membership, who will have thirty (30) days to respond. Responses shall be reviewed by the Membership Committee. Its recommendations will be submitted to the Council for approval.

Section 6
Sustaining Membership. All organizations interested in any aspect of Teratology shall be eligible for Sustaining Membership. Each Sustaining Member shall have the privilege of being represented without a vote at meetings of the Society by one delegate appointed by the Sustaining Member. Sustaining Members also shall receive one subscription to *Birth Defects Research* as part of their annual dues. A list of Sustaining Members shall be printed once a year in *Birth Defects Research.*

Section 7
Honorary Membership. Honorary Members may be elected by the Membership at the Annual Business Meeting, upon unanimous recommendation by the Council, from among the Regular members by a simple majority of those voting at the meeting. Honorary Members shall have all the voting rights and privileges of active members, are exempt from payment of annual dues, and shall receive *Birth Defects Research* gratis.

Section 8
Emeritus Membership. Members who have retired from their professional posts shall become Emeritus Members upon written request to the Secretary. Emeritus Members shall have all the voting rights and privileges of active members and are exempt from payment of annual dues, but they shall not receive *Birth Defects Research* gratis.

Section 9
Student Membership. Student Membership in the Society shall be open to persons pursuing degree work or postdoctoral studies in the field of teratology. Applications for membership must be endorsed by one member of the Society. Student Members shall not have voting rights but shall receive the journal *Birth Defects Research*. The Journal subscription(s) are available at the Publisher's basic price.

Section 10
Termination of Membership. Membership in the Society shall cease through any of the following:

1. By resignation.
2. If a member has defaulted in the payment of annual dues for two consecutive years. However, members whose dues are not paid by January of each year shall not continue to receive *Birth Defects Research*.
3. If, after consideration of a report from Council, the majority of the members of the Society present at the Annual Business Meeting decide that a member shall be expelled from membership on the grounds that his/her conduct is detrimental to the honor or interests of the Society and its objectives or is calculated to bring the work of the Society or its members into disrepute. Guidance for appropriate conduct of members is given in the Code of Ethics.

Section 11
Reinstatement. Members who have resigned or who become inactivated for nonpayment of dues may apply to be reinstated (see Bylaws). Applications are submitted to the Secretary and are reviewed by the Membership Committee. A list of applicants meeting the requirements for reinstatement will be transmitted by the Secretary during the first week in February, June and October. The lists are communicated to the membership, who will have thirty (30) days to respond. Responses shall be review by the Membership Committee. Its recommendations will be submitted to Council for approval.

Section 12
Rights. The rights and privileges of any member in the Society shall cease on termination of his/her membership.