THE TERATOLOGY SOCIETY

This event has been accredited by the McGill Center for Continuing Health Professional Education.

29th Annual Meeting for Organization of the Teratology Information Specialists (OTIS)

June 25–28, 2016

40th Annual Meeting of the Developmental Neurotoxicology Society (DNTS)

June 26–29, 2016

THE TERATOLOGY SOCIETY

Program & Abstracts

New Horizons in Birth Defects Research

56th Annual Meeting

San Antonio

JUNE 25-29, 2016

GRAND HYATT SAN ANTONIO

Program Overview

FRIDAY, JUNE 24, 2016

3:00 PM–6:00 PM
Council 1A Meeting

3:00 PM–6:00 PM
Registration Open

3:00 PM–6:00 PM
Speaker Ready Room Open

SATURDAY, JUNE 25, 2016

7:00 AM–6:00 PM
Registration Open

7:00 AM–6:00 PM
Speaker Ready Room Open

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

8:30 AM–12:00 Noon
Education Course Session 1
Embryology in Modern Times

12:00 Noon–1:30 PM
Finance Committee Meeting

12:00 Noon–1:30 PM
Student Affairs Committee Meeting

1:30 PM–5:00 PM
Education Course Session 2
Development and Teratology of the Heart

5:30 PM–7:30 PM
Student and Postdoctoral Fellow Mixer

6:30 PM–9:30 PM
Council 1B Meeting, Committee Reports, and Leadership Training

SUNDAY, JUNE 26, 2016

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

7:00 AM–8:00 AM
Dine with a Teratology Ambassador
(Advance Signup is Required)

7:00 AM–6:00 PM
Registration Open

7:00 AM–6:00 PM
Speaker Ready Room Open

8:00 AM–8:15 AM
President's Welcome

8:15 AM–9:00 AM
Josef Warkany Lecture
(Joint with DNTS and OTIS)
Framing Our Birth Defects Questions with Systems Biology: Learning from Our Mentors

9:00 AM–12:00 Noon
Student and Postdoctoral Fellow Platform Session 1

10:00 AM–10:30 AM
Spouse and Guest Meet-and-Greet

12:00 Noon–1:30 PM
Awards Committee Meeting

12:00 Noon–1:30 PM
Publications Committee Meeting

12:00 Noon–1:30 PM
Science Committee Meeting

12:00 Noon–1:30 PM
Student and Postdoctoral Fellow Lunch Workshop
Advancing Your Career in Birth Defects Research and Prevention
(Advance Registration Required)

1:30 PM–2:00 PM
F. Clarke Fraser New Investigator Award
Of Mice, Math, and Modeling

2:00 PM–2:30 PM
James G. Wilson Publication Award
A Comparison of ToxCast Test Results with In Vivo and Other In Vitro Endpoints for Neuro, Endocrine, and Developmental Toxicities: A Case Study Using Endosulfan and Methidathion

2:30 PM–5:30 PM
The State of the Art of Testing Drugs: Present and Future Symposium

2:30 PM–5:30 PM
Pregnancy Registry Updates Symposium (Joint with OTIS)

5:30 PM–6:00 PM
Patricia Rodier Mid-Career Award for Research and Mentoring
(Joint with DNTS)
Research on Long Term Outcomes following Prenatal Exposures: Rarely Studied But Sorely Needed

6:00 PM–7:30 PM
Welcome Reception, Student and Postdoctoral Fellow Research Showcase, and Exhibits Attended
(Joint with DNTS)

7:30 PM–9:00 PM
Communications Working Group Meeting

MONDAY, JUNE 27, 2016

7:00 AM–6:00 PM
Registration Open

7:00 AM–6:00 PM
Speaker Ready Room Open

7:00 AM–8:00 AM
2017 Program Committee Meeting

8:00 AM–9:00 AM
Keynote Speaker
Translating Rapid Whole Genome Sequences into Precision Medicine for Babies in Intensive Care Nurseries

9:00 AM–12:00 Noon
Wiley-Blackwell Symposium
(Joint with DNTS)
Neurodevelopmental Deficits from Fetal Exposure to Methamphetamine, Cocaine, and Alcohol: Emerging Mechanisms and Human Consequences

9:00 AM–12:00 Noon
Platform Session 2: Developmental Teratology and Toxicology

12:00 Noon–1:30 PM
***BDRA* Editorial Board Meeting**

12:00 Noon–1:30 PM
Past Presidents' and Honorees' Luncheon *(By Invitation Only)*

1:30 PM–5:30 PM
March of Dimes Symposium
New Approaches to the Treatment of Birth Defects

1:30 PM–5:30 PM
Integrative *In Vitro* Models for Neurovascular Development Function Symposium (Joint with DNTS)

5:30 PM–7:30 PM
Poster Session 1 and Exhibits Attended
(Joint with DNTS and OTIS)

7:30 PM–10:00 PM
Teratology Society and MARTA Student Career Event

TUESDAY, JUNE 28, 2016

6:30 AM–6:00 PM
Registration Open

6:30 AM–7:00 AM
Sunrise Mini Course Coffee and Continental Breakfast

7:00 AM–8:30 AM
Sunrise Mini Course
"Big Data"

7:00 AM–6:00 PM
Speaker Ready Room Open

8:00 AM–8:30 AM
Morning Coffee and Pastries

8:30 AM–9:00 AM
Robert L. Brent Lecture: Teratogen Update (Joint with OTIS)
Preventing the Preventable: Where Do We Stand on Fetal Alcohol Spectrum Disorders in 2016?

9:00 AM–12:30 PM
Public Affairs Symposium
(Joint with DNTS and OTIS)
Depression and Its Treatment in Pregnancy

9:00 AM–12:30 PM
Every Assay Needs an Anchor: The Search for Reference Developmental Toxicants Workshop

12:30 PM–1:30 PM
Nominations and Elections Committee Meeting

12:30 PM–1:30 PM
Public Affairs Committee Meeting

12:30 PM–1:30 PM
Web Site Committee Meeting

1:30 PM–3:30 PM
Increasing Prevalence of Gastroschisis Symposium

1:30 PM–5:30 PM
Advances in Placental Research Symposium (Joint with OTIS)

3:45 PM–5:30 PM
Platform Session 3: Clinical Teratology

5:30 PM–7:30 PM
Poster Session 2 and Exhibits Attended

WEDNESDAY, JUNE 29, 2016

6:30 AM–7:30 AM
Teratology Society 35th Annual Volleyball Game

7:00 AM–2:30 PM
Registration Open

7:00 AM–2:30 PM
Speaker Ready Room Open

7:30 AM–8:00 AM
Morning Coffee and Pastries

8:00 AM–8:30 AM
Narsingh Agnish Fellow Lecture
Educational Convergence of Sciences: Basic-Clinical-Discovery-Regulatory

8:30 AM–9:30 AM
Teratology Society and European Teratology Society Exchange Lecture
GMOs and Glyphosate

9:30 AM–10:30 AM
Special Report
Exploring the Link between Zika Virus and Microcephaly

9:30 AM–12:30 PM
Platform Session 4: Epidemiology

10:30 AM–11:00 AM
Warkany Tea

11:00 AM–12:30 PM
Strategies for Postapproval Assessment Workshop

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

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

12:30 PM–1:30 PM
Science and Public Policy Workshop
How It Affects You and How You Can Shape It

1:30 PM–4:30 PM
Assessing the Developmental Toxicity of Nanomaterials Symposium

1:30 PM–4:30 PM
ILSI HESI Symposium
Ontogeny of the FcRn in Gestation across Species: Implications for Monoclonal Antibody Developmental Toxicity Testing and Human Risk Assessment

4:00 PM–5:00 PM
CME Certificates Pick Up

4:45 PM–6:15 PM
Business Meeting

6:30 PM–7:30 PM
Banquet Reception

7:30 PM–11:00 PM
Banquet

THURSDAY, JUNE 30, 2016

7:00 AM–10:00 AM
Council 2 Meeting

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J.G. WILSON 1961–1962	E.M. JOHNSON 1974–1975	M.S. CHRISTIAN 1988–1989	W. SLIKKER JR. 2002–2003
F.C. FRASER 1962–1963	L.S. HURLEY 1975–1976	E.F. ZIMMERMAN 1989–1990	R.W. TYL 2003–2004
M.M. NELSON 1963–1964	J.L. SEVER 1976–1977	C.A. KIMMEL 1990–1991	K.L. JONES 2004–2005
D.A. KARNOFSKY 1964–1965	E.V. PERRIN 1977–1978	R.K. MILLER 1991–1992	M.S. TASSINARI 2005–2006
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R.L. BRENT 1967–1968	W.J. SCOTT JR. 1981–1982	K.K. SULIK 1995–1996	B.F. HALES 2009–2010
T.H. SHEPARD 1968–1969	D.M. KOCHHAR 1982–1983	J.F. CORDERO 1996–1997	J.M. ROGERS 2010–2011
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Members interested in serving on a committee should contact the leadership or staff at tshq@teratology.org.

2016 Sustaining Members

(as of March 25, 2016)

The Teratology Society thanks the following Sustaining Members:

PLATINUM

Charles River

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Pfizer Inc.

Reproductive Toxicology Center

SILVER

Eli Lilly and Company

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2016 Annual Meeting Sponsors

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The Teratology Society thanks the following Sponsors:

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Society of Toxicology

CONTRIBUTOR

Stephen B. Harris Group

General Information

The Teratology Society is pleased to be able to hold our Annual Meeting concurrently with the Annual Meetings of the Developmental Neurotoxicology Society (DNTS) and Organization of Teratology Information Specialists (OTIS), allowing for joint sessions and the opportunity for networking between attendees.

Registration

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

Hours:

Friday, June 24	3:00 PM–6:00 PM
Saturday, June 25	7:00 AM–6:00 PM
Sunday, June 26	7:00 AM–6:00 PM
Monday, June 27	7:00 AM–6:00 PM
Tuesday, June 28	6:30 AM–6:00 PM
Wednesday, June 29	7:00 AM–2:30 PM

What Does the Meeting Registration Fee Cover?

The Teratology Society Annual Meeting registration fee covers a number of food and beverage functions as well as the administrative costs for the meeting. The functions include:

- Welcome Reception on Sunday
- Daily morning coffee and pastries
- Three mid-morning beverage breaks
- Daily afternoon beverage breaks with cookies
- Two light receptions during poster sessions
- One Student and Postdoctoral Fellow Lunch Workshops (Trainees only)
- Student and Postdoctoral Fellow Career Event (Trainees only)
- Warkany Tea on Wednesday during the mid-morning break
- Banquet on Wednesday

For meals on your own, there are dining options within the hotel. There are also several restaurants within walking distance or a short taxi ride. More information about area restaurants can be obtained from the hotel concierge.

Hotel Map

To assist you in locating the registration desk, meeting rooms, and Exhibit Hall, a map of the Grand Hyatt San Antonio is on page 326.

Sister Society Sampler Program

This year, each Teratology Society meeting registrant will receive two tickets that may be used to "sample" scientific sessions offered by one or both of our sister societies (DNTS and OTIS). This sampler program is being offered to foster more interaction and networking between the Societies at the Annual Meeting. The program is reciprocal—DNTS and OTIS registrants will also receive tickets to sample scientific sessions being offered by the Teratology Society. More details will be available at the registration desk.

Teratology Society Booth

Come test your knowledge of our field at the Teratology Society booth. There will be different games each night including prizes and many laughs to be shared as you put your teratology trivia to the test. While you are there, find out more information about the Society and membership, or if you are already a member, find out about ways to become more involved.

Spouse and Guest Meet-and-Greet

The Spouse and Guest Meet-and-Greet event is a great opportunity to meet fellow travelers, touch base with past friends, and coordinate your plans for exploring everything that San Antonio has to offer. Please join us at 10:00 am on Sunday, June 26 in the Republic A room at the Grand Hyatt San Antonio. The event will provide an opportunity for you to ask city experts suggestions for must-see attractions in San Antonio or have them answer any questions you may have about the city and its history. This event is free and open to guests of all registered attendees of the Teratology Society, DNTS, and OTIS meetings.

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 onsite.

First Aid and Security

The Grand Hyatt San Antonio has house phones located throughout the hotel for use in case of an emergency. If you need medical or security assistance pick up the house phone and dial 55. The hotel operator will connect you to the correct department.

AWARDS/LECTURES

Josef Warkany Lecturer

This lecture 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 **Elaine M. Faustman,** University of Washington on Sunday, June 26 at 8:15 am.

F. Clarke Fraser New Investigator 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. The award recipient must be an active member of the Teratology Society with evidence of a successful independent research career in birth defects research. This year's award recipient is **Nicole Churchill Kleinstreuer,** NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, NIEHS who will present on Sunday, June 26 at 1:30 pm.

James G. Wilson Publication Award

This 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 *A Comparison of ToxCast Test Results with* In Vivo *and Other* In Vitro *Endpoints for Neuro, Endocrine, and Developmental Toxicities: A Case Study Using Endosulfan and Methidathion*. **Marilyn H. Silva,** California Environmental Protection Agency, will present the data on Sunday, June 26 at 2:00 pm.

Patricia Rodier Mid-Career Award in Research and Mentoring

This award honors the legacy of Dr. Patricia Rodier, a past President of the Developmental Neurotoxicology Society and a Council member of the Teratology Society. The purpose of the award is to recognize a mid-career individual who has demonstrated successful independent research in neurobehavioral teratology, birth defects, or other related fields involving the central nervous system; and has demonstrated a commitment to mentorship of students, postdoctoral fellows, young investigators, and/or trainees. This year's award recipient is **Christina D. Chambers,** University of California, San Diego, who will present on Sunday, June 26 at 5:30 pm.

Narsingh Agnish Fellowship

This award recognizes Narsingh Agnish's contributions to the Teratology Society, particularly the implementation of the Education Course. The Narsingh Agnish Fellowship is awarded to a long-standing member of the Teratology Society who has made a major contribution to education in the field of teratology or a related discipline. The 2016 recipient is **Richard K. Miller,** University of Rochester Medical Center, who will present on Wednesday, June 29 at 8:00 am.

Birth Defects Research Distinguished Scholar Awards

Muriel J. Harris

These awards recognize distinguished authors for the importance, impact, and relevance of their published works in the field of birth defects research. The dual purpose of these awards is to provide recognition to the authors of high impact papers and to encourage authors trained in various disciplines to submit high-quality papers to *Birth Defects Research*. Award recipients will be recognized during the Annual Meeting Banquet on Wednesday, June 29.

Birth Defects Research Part A

Diana M. Juriloff

The 2016 recipients of this award are **Muriel J. Harris** and **Diana M. Juriloff,** University of British Columbia, for their research associated with neural tube defects, (reference papers: *Mouse Mutants with Neural Tube Closure Defects and Their Role in Understanding Human Neural Tube Defects*; *BDRA* 79, 3: 187–210, 2007 and *An Update to the List of Mouse Mutants with Neural Tube Closure Defects and Advances toward a Complete Genetic Perspective of Neural Tube Closure*; *BDRA* 88, 8: 653–669, 2010).

Birth Defects Research Part B

The 2016 recipient of this award is **Timothy F. Oberlander,** University of British Columbia, for his research on neonatal effects associated with prenatal exposures (reference paper: *Major Congenital Malformations Following Prenatal Exposure to Serotonin Reuptake Inhibitors and Benzodiazepines Using Population-Based Health Data*; *BDRB* 83, 1: 68–76, 2008).

Robert L. Brent Lecture

This lecture 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 2016 Robert L. Brent Lecture will be presented by **Christina D. Chambers,** University of California, San Diego, on Tuesday, June 28 at 8:30 am.

Edward W. Carney Distinguished Service Award

This award honors Edward W. Carney, Past President of the Teratology Society, for his exemplary dedication and service to the Society and the field of teratology. The 2016 Edward W. Carney Distinguished Service Award recipient is **Anthony R. Scialli,** Scialli Consulting LLC. Dr. Scialli has had a wide reaching impact on the Teratology Society stemming from his nearly 30 years of membership and service to our Society, his active role in seven committees/focus areas, and his service as the Society's President. The personal impact he has had on our field is clear as he is known to many as a consummate scientist, a trusted advisor, and an outstanding teacher and mentor to numerous students, fellows, and current members. Beyond being well respected internationally and with an exemplary publication record, his advisory roles to TERIS, US FDA, CDC, and other state, national, and international agencies stand out as examples of his strong leadership within our field. Through these and other numerous contributions he has left an indelible mark on the Teratology Society and the field of birth defects research at large.

Student and Postdoctoral Fellow Awards

In addition to the awards listed above, several student and postdoctoral fellow awards will be presented during the Banquet on Wednesday, June 29. These awards include the Edward W. Carney Trainee Award, Marie W. Taubeneck Award, Wilson Presentation Awards, and Bradford Poster awards. Please join us to celebrate these students and postdoctoral fellows who are the future of teratology.

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 56th Annual Meeting. The CME Program is available on the Teratology Society website at **www.teratology.org**.

The Society offers 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 in the agenda.

Teratology Society CME Program

This event is approved for up to 25.25 credits by the Office for Continuing Professional Development. The Office for CPD, Faculty of Medicine, McGill University is fully accredited by the Committee on Accreditation of Canadian Medical Education (CACME).

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 an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association, physicians may convert Royal College MOC credits to AMA PRA Category 1 Credits™. Information on the process to convert Royal College MOC credit to AMA credit can be found at **www.ama-assn.org/go/internationalcme**.

Each physician should claim only credit commensurate with the extent of their participation in the activity.

Daily Breakdown of CME Credits

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

Saturday, June 25: 4.5 credits
Sunday, June 26: 2 credits
Monday, June 27: 7.25 credits
Tuesday, June 28: 7.5 credits
Wednesday, June 29: 4 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 online on the Society's website and at the registration desk.

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.

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 during registration hours and from 4:00 pm–5:00 pm on Wednesday, June 29. Certification of Continuing Medical Education credits is the responsibility of the attendee.

HIGHLIGHTS

Welcome Reception

The Welcome Reception will be held in Texas Ballroom B on Sunday, June 26 at 6:00 pm. The reception is open to registered attendees of the Teratology Society and DNTS Annual Meetings. Please wear your badge to gain entrance to the reception.

Student and Postdoctoral Fellow Research Showcase

The Student and Postdoctoral Fellow Research Showcase is a new and exciting opportunity for students and postdoctoral fellows to showcase their research. The showcase will take place during the Welcome Reception and is open to all students and postdoctoral fellows assigned to a Poster or Platform Session.

Exhibits

Exhibits will be open in Texas Ballroom B to attendees Sunday through Tuesday in the evenings and will feature companies and organizations offering teratology-related products, information, and services. Scientific posters will be displayed in the Exhibit Hall on Sunday, Monday, and Tuesday. Although the Exhibit Hall will be open and posters on display Sunday afternoon through Tuesday evening, the exhibits will be attended only during the times listed below.

Exhibits Attended

Sunday, June 26 ..... 6:00 PM–7:30 PM
Monday, June 27 ..... 5:30 PM–7:30 PM
Tuesday, June 28 ..... 5:30 PM–7:30 PM

Poster Sessions

The Poster Sessions will be held in Texas Ballroom B on Monday, June 27 and Tuesday, June 28. The Teratology Society, DNTS, and OTIS Joint Poster Session 1 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 5:30 pm–7:30 pm. Poster Session 2 will take place on Tuesday. The posters for this session will be on display starting at 12:30 pm. The authors will be present for discussion from 5:30 pm–7:30 pm.

Banquet and Award Presentations

The Banquet will be held on Wednesday, June 29. The reception (with a cash bar) will be held in the Texas Ballroom Foyer beginning at 6:30 pm. Dinner will be served at 7:30 pm in Texas Ballroom B. Banquet tickets are required for this event. The tickets are included in your registration materials and are not transferable. Guest tickets may be purchased at the registration desk until 12:00 noon on Monday, June 27. Teratology Society Awards recognized during the banquet are as follows:

Travel Awards
James C. Bradford Memorial Student Poster Award
Wilson Presentation Awards
Marie W. Taubeneck Award
Edward W. Carney Trainee Award
Birth Defects Research Distinguished Scholar Awards
Edward W. Carney Distinguished Service Award
Recognition of Other Awards Presented Throughout the Week

35 Years of Volleyball

Come one, come all, and join the fun! The 35th Annual Volleyball Game is scheduled for Wednesday, June 29 from 6:30 am–7:30 am at the Factory of Champions located at 8227 Broadway, San Antonio, TX, 78209. Those interested should meet in the Grand Hyatt San Antonio lobby at 6:00 am on Wednesday morning, in order to taxi over to the court. 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 and Postdoctoral Fellow Activities

Special events for student and postdoctoral fellow 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 the field. The following special events are scheduled.

Student and Postdoctoral Fellow 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 Bar Rojo at 5:30 pm on Saturday, June 25.

Future Annual Meetings

57th Annual Meeting
Grand Hyatt Denver
Denver, Colorado
June 24–28, 2017

58th Annual Meeting
Hilton Clearwater
Clearwater, Florida
June 23–27, 2018

59th Annual Meeting
Sheraton San Diego Hotel & Marina
San Diego, California
June 22–26, 2019

Student/Postdoc Treasure Hunt—At this year's Annual Meeting, the students and postdocs are encouraged to participate in the annual Teratology Society Treasure Hunt. This activity is intended to facilitate networking between the students/postdocs and the established Society members at the Annual Meeting. A list of tasks will be available at the registration desk. All students/postdocs who complete the list will receive a prize, and there will be a random drawing for all participants who complete at least half of the list (two chances for those who complete all tasks) for a grand prize of $100. The drawing will take place at the Teratology Society Banquet. All who participate are winners, but you must be present to collect a prize. Tasks will include interacting with various members and participating in activities over the course of the meeting. Consider the experience a human treasure hunt. It is a great opportunity to discuss your research, connect with members and attendees, learn about different career paths, and forge relationships that you will "treasure" throughout your career!

Dine with a Teratology Ambassador—The Dine with a Teratology Ambassador program is a special opportunity for students and postdoctoral fellows to meet with Associate and Regular members of the Society while enjoying a light breakfast. This event will take place on Sunday, June 26 from 7:00 am until 8:00 am. Advance signup is required. Please stop by the registration desk for more information.

Student and Postdoctoral Fellow Platform Session: Wilson Presentation Award Competition—This year's Student and Postdoctoral Platform Session showcases the work of ten 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 recipients will be announced during the Teratology Society Banquet on Wednesday, June 29. Make plans to support the Society's student and postdoctoral members by attending this session on Sunday, June 26 at 9:00 am.

Teratology Society and MARTA Student Career Event—Take advantage of this great networking opportunity! Join the Middle Atlantic Reproduction and Teratology Association (MARTA) and the Teratology Society for dinner and conversation at a Student Career Event in Texas Ballroom A on Monday, June 27 from 7:30 pm–10:00 pm. This popular event is for students and postdoctoral fellows attending the joint meetings of the Teratology Society, DNTS, and OTIS. As you prepare for the next phase in your professional career, we offer you this opportunity to meet with other 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.

Edward W. Carney Trainee Award—This award supports graduate student or postdoctoral scholar travel to meetings that offer significant educational opportunities in the field of reproductive and developmental toxicology, such as the annual meetings of the Teratology Society and the Society of Toxicology. It is supported by the Edward W. Carney Trainee Award Fund which was established in memory of Dr. Carney to encourage education and training in reproductive and developmental toxicology. The award will be presented during the Teratology Society Banquet.

Marie W. Taubeneck Award—This award is presented to a student or postdoctoral fellow in recognition of scholarship in teratology and service to the Teratology Society. An important aspect of the Award is recognition by fellow trainees. The Marie W. Taubeneck Fund established in memory of Dr. Taubeneck supports this award. The award will be announced during the Teratology Society Banquet.

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 DNTS. It is jointly sponsored by MARTA and Sanofi U.S. Inc. The award will be announced during the Teratology Society Banquet.

GRAND HYATT SAN ANTONIO

Conference Site

Discover the distinctly diverse personality of San Antonio in grand style. Set along the spectacular River Walk, the Grand Hyatt San Antonio places you near The Alamo, trendy downtown bars, hot clubs, renowned restaurants, and all the attractions that make this one of the most culturally rich cities in the country.

Whether you prefer a quick sandwich or a sizzling steak and seafood combination prepared to perfection, Grand Hyatt San Antonio has you covered. Using the freshest ingredients, their popular restaurants and dining spots exceed all expectations. When it is time for cocktails and conversation, you will find the Bar Rojo to be one of the best in city. Ruth's Chris Steak House River Walk offers specialty menu items like Happy Jack's Crawfish Sausage and Eggs as part of its breakfast buffet, burgers for lunch, and sizzling hot steaks for dinner. Only have time for a quick bite? Conveniently open 24 hours a day, visit Perk's Coffee and More for coffee, a sandwich, or a snack.

Business Center

The Grant Hyatt San Antonio's Business Center, on the hotel's third level, offers a complete mobile office with on demand printer, copier, and fax, plus computers with high-speed Internet access.

Printing Your Boarding Pass

The Grand Hyatt San Antonio offers Hyatt Fast Board™. Check in for your flight and print your boarding pass in the lobby of the hotel. The secure connection ensures your information remains private, while you enjoy fast and convenient access to flight information, weather, and traffic conditions.

Internet Access

The Grand Hyatt San Antonio offers complimentary wireless Internet access in sleeping rooms and in public areas. Please note that this service is not available in the meeting rooms or the meeting room foyers.

GROUND TRANSPORTATION

(All prices are subject to change.)

San Antonio Airport Shuttle

Shuttle transportation to and from San Antonio International Airport and downtown is provided for a fee by SATRANS, the city's official airport shuttle, daily between 7:00 am and 1:00 am. Reservations are required. For more information visit **www.saairportshuttle.com** or call 210.281.9900.

(Please make your reservations at your earliest convenience; advance reservations are required.)

Taxis

Taxis can be pre-arranged to provide you with the quickest and most efficient mode of transportation. You can pre-arrange your taxi at **sataxis.com** or by calling 210.444.2222.

Hotel Parking

Both Self- and Valet-Parking are available in the Grand Hyatt San Antonio's underground garage. Rates include in/out privileges. Please note, due to the limited height, oversized vehicles, toppers, or trailers are not permitted.

Daily Self-Parking:
Hotel Guest: $29
Overnight Parking: $29

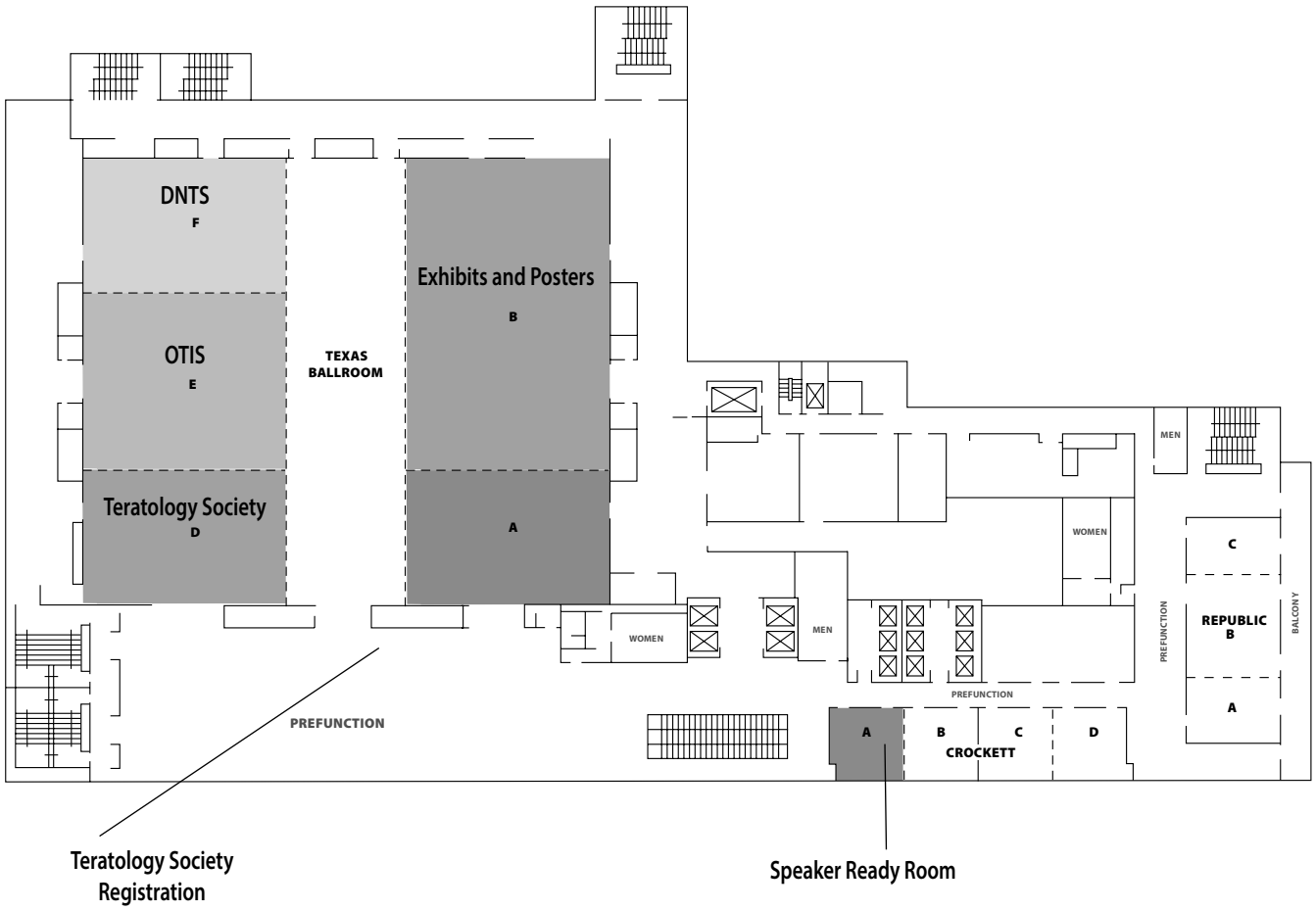
Hourly Self-Parking:
First Hour: $10
Each additional hour is $5 with a maximum of $29.

Valet Parking:
Overnight Hotel Guest: $39
Oversize Truck: $45

Hourly Valet Parking:
First Hour: $20
Each additional hour is $5 with a maximum of $39.

Grand Hyatt San Antonio Hotel Map

Fourth Floor



Program Agenda

FRIDAY, JUNE 24, 2016

3:00 PM–6:00 PM **COUNCIL 1A MEETING—Republic B**

3:00 PM–6:00 PM **REGISTRATION OPEN—Texas Ballroom Foyer**

3:00 PM–6:00 PM **SPEAKER READY ROOM OPEN—Crockett A**

SATURDAY, JUNE 25, 2016

7:00 AM–6:00 PM **REGISTRATION OPEN—Texas Ballroom Foyer**

7:00 AM–6:00 PM **SPEAKER READY ROOM OPEN—Crockett A**

8:00 AM–8:30 AM **EDUCATION COURSE COFFEE AND CONTINENTAL BREAKFAST—Texas Ballroom D**

(Education Course Session 1 Registrants Only)

8:30 AM–12:00 Noon **EDUCATION COURSE SESSION 1—Texas Ballroom D**

(Separate Registration Required)

Embryology in Modern Times

Organized by the Education Committee, Chairperson, Chris J. Stodgell, University of Rochester

8:30 AM–8:40 AM	**Welcome** *Teratology Society President, Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.*
8:40 AM–8:45 AM	**Course Overview** *Education Committee Chairperson, Chris J. Stodgell, University of Rochester*
8:45 AM–9:30 AM	**Embryology in Modern Times: Periconceptional Period** CME *Gary C. Schoenwolf, University of Utah*
9:30 AM–10:15 AM	**Embryonic Period: The Tale of the Somites and the Three Tubes** *John M. DeSesso, Exponent, Inc.*
10:15 AM–10:30 AM	**Break**
10:30 AM–11:15 AM	**The Fetal Period: Functional Consequences** CME *Charles V. Vorhees, Cincinnati Children's Hospital Medical Center*
11:15 AM–12:00 Noon	**Embryology and Physiology of the Perinatal Period** CME *Sarah G. Obican, University of South Florida*

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

12:00 Noon–1:30 PM **FINANCE COMMITTEE MEETING—Crockett B**

SATURDAY/SUNDAY

12:00 Noon–1:30 PM **STUDENT AFFAIRS COMMITTEE MEETING—Republic A**

1:30 PM–5:00 PM **EDUCATION COURSE SESSION 2—Texas Ballroom D**

(Separate Registration Required)

Development and Teratology of the Heart

Organized by the Education Committee, Chairperson, Chris J. Stodgell, University of Rochester

1:30 PM–1:35 PM	**Course Overview** *Education Committee, Chairperson, Chris J. Stodgell, University of Rochester*
1:35 PM–2:20 PM	**Cardiac Development: A Delicate Interplay of Form and Function** CME *H. Scott Baldwin, Vanderbilt Children's Hospital*
2:20 PM–3:05 PM	**Abnormal Heart Development** CME *Mary R. Hutson, Duke University School of Medicine*
3:05 PM–3:20 PM	**Break**
3:20 PM–4:05 PM	**Genesis of Cardiovascular Malformations** *John M. DeSesso, Exponent, Inc.*
4:05 PM–4:50 PM	**Clinical Management of Congenital Heart Defects** CME *George A. Porter Jr., University of Rochester*
4:50 PM–5:00 PM	**Discussion**

5:30 PM–7:30 PM **STUDENT AND POSTDOCTORAL FELLOW MIXER—Bar Rojo**

6:30 PM–9:30 PM **COUNCIL 1B MEETING, COMMITTEE REPORTS, AND LEADERSHIP TRAINING—Crockett C**

SUNDAY, JUNE 26, 2016

7:00 AM–8:00 AM ***BDRB* EDITORIAL BOARD MEETING—Republic A**

7:00 AM–8:00 AM **DINE WITH A TERATOLOGY AMBASSADOR—Republic B**

(Advance Signup is Required)

7:00 AM–6:00 PM **REGISTRATION OPEN—Texas Ballroom Foyer**

7:00 AM–6:00 PM **SPEAKER READY ROOM OPEN—Crockett A**

7:30 AM–8:00 AM **MORNING COFFEE AND PASTRIES—Texas Ballroom A**

8:00 AM–8:15 AM **PRESIDENT'S WELCOME—Texas Ballroom D**

Teratology Society President, Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.

8:15 AM–9:00 AM **JOSEF WARKANY LECTURE—Texas Ballroom D**

(Joint with DNTS and OTIS)

Framing Our Birth Defects Questions with Systems Biology: Learning from Our Mentors (L1) CME

Chairperson: Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.

Lecturer: Elaine M. Faustman, University of Washington

9:00 AM–12:00 Noon **STUDENT AND POSTDOCTORAL FELLOW PLATFORM SESSION 1—Texas Ballroom D**

Organized by the Student Affairs Committee

Chairperson: Dana L. Shuey, Incyte

Presenting author is underlined.

9:00 AM–9:15 AM **Introduction**
Dana L. Shuey, Incyte

9:15 AM–9:30 AM **1** **Physiological and Ethanol-Enhanced Embryonic and Fetal DNA Oxidation in Brca1 Knockout Progeny**
Drake D[1], Wells PG[1,2]. [1]Department of Pharmaceutical Sciences, University of Toronto, Toronto, ON, Canada, [2]Department of Pharmacology & Toxicology, University of Toronto, Toronto, ON, Canada.

9:30 AM–9:45 AM **2** **Altered Expression of Placental Proteins Related to Angiogenesis in Pregnancies Exposed to Alcohol**
Holbrook BD[1], Bishop S[2], Williams S[2], Cano S[2], Davies S[3], Bakhireva LN[2], Savage DD[3]. [1]Department of Obstetrics and Gynecology, School of Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, United States, [2]Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy, University of New Mexico Health Sciences Center, Albuquerque, NM, United States, [3]Department of Neurosciences, School of Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, United States.

9:45 AM–10:00 AM **3** **Teratogenicity of the Herbal Supplement Vinpocetine in Harlan-Sprague Dawley Rats**
Catlin NR[1], Foster P[1], Mylchreest E[2], Miller L[2], Cunny HC[1], McIntyre BS[1]. [1]Division National Toxicology Program, NIEHS, Durham, NC, United States, [2]Southern Research Institute, Birmingham, AL, United States.

10:00 AM–10:15 AM **Break—Texas Ballroom A**

10:15 AM–10:30 AM **4** **Reduced Expression of the Long Noncoding RNA GALNR Mediates High Glucose-Induced Apoptosis by Up-Regulating Gadd45α in Diabetic Embryopathy**
Dong D, Yang P. University of Maryland, Baltimore, Baltimore, MD, United States.

10:30 AM–10:45 AM **5** **Therapeutic Potential of RNAi Silencing CRMP-4 Combined with MSCs in Animal Models with Spina Bifida Aperta**
Cao SY, Yuan ZW. China Medical University, Shenyang, China.

10:45 AM–11:00 AM **6** **Determining Developmental Neurotoxicity of Pesticides Utilizing Metabolomic Profile from Neural Progenitor Cells**
McKenzie M[1,2], Amosu M[1,2], Wu X[1,2], Wallace S[3], Henderson M[4], Bian X[2], Lu K[1,2], Stice S[2,3], Smith M A[1,2]. [1]Environmental Health Science University of Georgia, Athens, GA, United States, [2]Regenerative Bioscience Center University of Georgia, Athens, GA, United States, [3]ArunA Biomedical Inc., Athens, GA, United States, [4]Environmental Protection Agency, Athens, GA, United States.

11:00 AM–11:15 AM **7** **Use of Antibiotics during Pregnancy and the Risk of Spontaneous Abortion**
Muanda FTM[1,2], Sheehy OS[2], Berard AB[1,2]. [1]Faculty of Pharmacy, University of Montréal, Montréal, QC, Canada, [2]Research Center, CHU Sainte-Justine, Montréal, QC, Canada.

SUNDAY

11:15 AM–11:30 AM	**8**	**Harm-Reduction Tobacco Products Interfere with the Differentiation of Craniofacial Bone** *Sparks NRL[1], Bondesson M[3], zur Nieden NI[2]. [1]Environmental Toxicology Graduate Program, University of California, Riverside, Riverside, CA, United States, [2]Cell Biology and Neuroscience and Stem Cell Center, University of California, Riverside, Riverside, CA, United States, [3]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, TX, United States.*
11:30 AM–11:45 AM	**9**	**Exposure of Organogenesis-Stage Embryos to Hydroxyurea Alters the Expression of P53-Family Related Genes that Are Involved in Limb Development** *El Husseini N, Hales B. McGill University, Montréal, QC, Canada.*
11:45 AM–12:00 Noon	**10**	**An Evaluation of ToxCast Angiogenic Disruptors for Effects on Mitochondrial Bioactivity Profiles** *Leung MCK[1,2], Kapraun DF[1], Williams AJ[1], Knudsen TB[1]. [1]United States Environmental Protection Agency, Research Triangle Park, NC, United States, [2]Oak Ridge Institute for Science and Education, Oak Ridge, TN, United States.*

10:00 AM–10:30 AM **SPOUSE AND GUEST MEET-AND-GREET—Republic A**

(Open to Teratology Society, DNTS, and OTIS Spouses and Guests)

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

12:00 Noon–1:30 PM **AWARDS COMMITTEE MEETING—Crockett B**

12:00 Noon–1:30 PM **PUBLICATIONS COMMITTEE MEETING—Crockett C**

12:00 Noon–1:30 PM **SCIENCE COMMITTEE MEETING—Crockett D**

12:00 Noon–1:30 PM **STUDENT AND POSTDOCTORAL FELLOW LUNCH WORKSHOP—Texas Ballroom D**

Advancing Your Career in Birth Defects Research and Prevention (W1)
Chairpersons: Christine Perdan Curran, Northern Kentucky University and Dana L. Shuey, Incyte

(Advance Registration Required)

12:00 Noon–12:05 PM	**Introduction**
12:05 PM–12:25 PM	**Publishing in the Sciences** *Michel Vekemans, Hopital Necker-Enfants Malades*
12:25 PM–12:45 PM	**The Most Common Mistakes in Statistical Analysis: How to Recognize and Avoid Them** *Charles V. Vorhees, Cincinnati Children's Hospital Medical Center*
12:45 PM–1:05 PM	**Finding Your Place in a Transdisciplinary World** *Melissa S. Tassinari, US Food and Drug Administration*
1:05 PM–1:25 PM	**Growing Pains: Moving from Mentee to an Independent Career** *Sarah G. Obican, University of South Florida*
1:25 PM–1:30 PM	**Discussion**

1:30 PM–2:00 PM **F. CLARKE FRASER NEW INVESTIGATOR AWARD—Texas Ballroom D**

Of Mice, Math, and Modeling (L2)
Chairperson: Bruce K. Beyer, Sanofi U.S. Inc.

Presented by Marilyn Preus

Lecturer: Nicole Churchill Kleinstreuer, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, NIEHS

2:00 PM–2:30 PM **JAMES G. WILSON PUBLICATION AWARD—Texas Ballroom D**

A Comparison of ToxCast Test Results with In Vivo and Other In Vitro Endpoints for Neuro, Endocrine, and Developmental Toxicities: A Case Study Using Endosulfan and Methidathion

Chairperson: Norbert Makori, WIL Research Laboratories

Lecturer: Marilyn H. Silva, California Environmental Protection Agency

2:30 PM–5:30 PM **THE STATE OF THE ART OF TESTING DRUGS: PRESENT AND FUTURE SYMPOSIUM—Texas Ballroom D**

Chairpersons: Kenjie Amemiya, Genentech and Elise Madison Lewis, Charles River Laboratories

2:30 PM–3:00 PM	**S1**	**Revisions to the ICH S5 Guidelines: Thinking Outside the Box** *Anthony M. DeLise, Novartis Pharmaceuticals Corporation*
3:00 PM–3:30 PM	**S2**	**Hitting the Target with DARTS(tudies): Using Biology to Assess Reproductive Risk** *Kenjie Amemiya, Genentech*
3:30 PM–4:00 PM	**S3**	**Alternatives in Developmental Toxicology: How Far We Have Come (and Have Left to Go)** *Kimberly C. Brannen, Merck*
4:00 PM–4:15 PM		**Break —Texas Ballroom A**
4:15 PM–4:45 PM	**S4**	**Integrating Alternative Developmental Toxicity Assays for Pharmaceutical Risk Assessment** *Maia L. Green, Merck*
4:45 PM–5:15 PM	**S5**	**Harmonization of the Pediatric Nonclinical Testing Guidelines: The Who, What, When, and Why of ICH S11** *Susan Bielmeier Laffan, GlaxoSmithKline*
5:15 PM–5:30 PM		**Discussion**

2:30 PM–5:30 PM **PREGNANCY REGISTRY UPDATES SYMPOSIUM—Texas Ballroom E**

(Joint with OTIS)

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

2:30 PM–2:35 PM		**Introduction**
2:35 PM–2:55 PM	**S6**	**Gestational Age at Enrollment** CME *Sonia Hernandez-Diaz, Harvard School of Public Health*
2:55 PM–3:15 PM	**S7**	**Prevalence Reference Rates for Pregnancy Registries and for Labeling** CME *Leyla Sahin, US Food and Drug Administration*
3:15 PM–3:35 PM	**S8**	**Modern Methods of Pregnancy Registry Recruitment: Successes and Challenges** CME *Jennifer Zellner, University of California, San Diego*
3:35 PM–3:55 PM	**S9**	**Minor Anomalies: An Unreliable Outcome for Pregnancy Registries** CME *Lewis B. Holmes, MassGeneral Hospital for Children*
3:55 PM–4:10 PM		**Break —Texas Ballroom A**

SUNDAY/MONDAY

4:10 PM–4:25 PM **S11** **Improving Safe Use of Medications during Pregnancy: The Roles of Patients, Physicians, and Pharmacists**
Lynch MM[1], Amoozegar J[1], McClure EM[1], Squiers LB[1], Broussard CS[2], Lind JN[2], Polen KN[2], Frey MT[2], Gilboa SM[2], Biermann, J[3]. [1]RTI International, Research Triangle Park, NC, United States, [2]Centers for Disease Control and Prevention, Atlanta, GA, United States, [3]March of Dimes Foundation, White Plains, NY, United States.

4:25 PM–4:40 PM **S12** **Integration of a Teratologist's Clinical Review of Birth Defects Reported through Pharmacovigilance**
Golembesky A[1], Scheuerle A[2]. [1]UCB Pharma, Raleigh, NC, United States, [2]University of Texas Southwestern Medical Center, Dallas, TX, United States.

4:40 PM–4:55 PM **S13** **Time Trends of Microcephaly in Texas: What's Up?**
Langlois PH[1], Scheuerle AE[2], Marengo LK[1], Hoyt AT[1], Ethen MK[1], Canfield MA[1]. [1]Texas Department of State Health Services, Austin, TX, United States, [2]University of Texas Southwestern Medical Center, Dallas, TX, United States.

4:55 PM–5:30 PM **Discussion**

5:30 PM–6:00 PM **PATRICIA RODIER MID-CAREER AWARD FOR RESEARCH AND MENTORING—Texas Ballroom D**

(Joint with DNTS)

Research on Long Term Outcomes following Prenatal Exposures: Rarely Studied But Sorely Needed (L3)
Chairpersons: Bruce K. Beyer, Sanofi U.S. Inc. and Patricia Janulewicz, Boston University

Lecturer: Christina D. Chambers, University of California, San Diego

6:00 PM–7:30 PM **WELCOME RECEPTION, STUDENT AND POSTDOCTORAL FELLOW RESEARCH SHOWCASE, AND EXHIBITS ATTENDED—Texas Ballroom B**

(Joint with DNTS)

7:30 PM–9:00 PM **COMMUNICATIONS WORKING GROUP MEETING—Republic B**

MONDAY, JUNE 27, 2016

7:00 AM–6:00 PM **REGISTRATION OPEN—Texas Ballroom Foyer**

7:00 AM–6:00 PM **SPEAKER READY ROOM OPEN—Crockett A**

7:00 AM–8:00 AM **2017 PROGRAM COMMITTEE MEETING—Republic B**

7:30 AM–8:00 AM **MORNING COFFEE AND PASTRIES—Texas Ballroom B**

8:00 AM–9:00 AM **KEYNOTE SPEAKER—Texas Ballroom D**

Translating Rapid Whole Genome Sequences into Precision Medicine for Babies in Intensive Care Nurseries (L4) CME
Chairperson: Sonja A. Rasmussen, Centers for Disease Control and Prevention

Speaker: Stephen F. Kingsmore, Rady Pediatric Genomics and Systems Medicine Institute

9:00 AM–12:00 Noon **WILEY-BLACKWELL SYMPOSIUM—Texas Ballroom D**

(Joint with DNTS)

Neurodevelopmental Deficits from Fetal Exposure to Methamphetamine, Cocaine, and Alcohol: Emerging Mechanisms and Human Consequences
Chairpersons: Charles V. Vorhees, Cincinnati Children's Hospital Medical Center and Peter G. Wells, University of Toronto

9:00 AM–9:05 AM		**Introduction**
9:05 AM–9:45 AM	**S14**	**Oxidative Stress Mechanisms of Neurodevelopmental Deficits Initiated by Methamphetamine and Ethanol** CME *Peter G. Wells, University of Toronto*
9:45 AM–10:25 AM	**S15**	**Effects of Methamphetamine on Brain and Behavioral Development** CME *Charles V. Vorhees, Cincinnati Children's Hospital Medical Center*
10:25 AM–10:40 AM		**Break—Texas Ballroom B**
10:40 AM–11:20 AM	**S16**	**Dopaminergic Mechanisms of Cocaine-Initiated Neurodevelopmental Deficits** CME *Gregg D. Stanwood, Florida State University*
11:20 AM–12:00 Noon	**S17**	**Human Neurodevelopmental, Behavioral, and Growth Consequences of Exposure to Prenatal Methamphetamine and Alcohol** CME *Lynne M. Smith, Harbor-UCLA Medical Center*

9:00 AM–12:00 Noon **PLATFORM SESSION 2—Texas Ballroom F**

Developmental Teratology and Toxicology
Chairpersons: Barbara F. Hales, McGill University and Alan M. Hoberman, Charles River Laboratories

Presenting author is underlined.

9:00 AM–9:15 AM		**Introduction**
9:15 AM–9:30 AM	**11**	**Untreated and Ethanol-Exposed DNA Repair-Deficient Oxoguanine Glycosylase 1 (*Ogg1*) Knockout Progeny May Be Susceptible to Postnatal Neurodevelopmental Abnormalities Mediated by Epigenetic Mechanisms** *Bhatia S[1], Wells PG[1,2]. [1]Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [2]Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada.*
9:30 AM–9:45 AM	**12**	**MARCKS Acetylation Regulated by TIP60 and SIRT2 Prerequisite for Phosphorylation Dismantles Its Cellular Organelle Protection and Neural Tube Closure in Diabetes** *Yang P, Xu C, Reece EA, Yang P. University of Maryland, Baltimore, Baltimore, MD, United States.*
9:45 AM–10:00 AM	**13**	**Ocular Features and Limb Anomalies in Patients with Microcephaly and Presumed Zika Virus Congenital Infection in Pernambuco, Brazil** *Ventura CV[1,3], Ventura LO[1,2], Maia M[3], Belfort Jr R[3]. [1]Altino Ventura Foundation (FAV), Recife, PE, Brazil, [2]HOPE Eye Hospital, Recife, PE, Brazil, [3]Federal University of São Paulo (Unifesp), São Paulo-SP, Brazil.*
10:00 AM–10:15 AM	**14**	**Genetic Susceptibility to Thyroid Hormone Disruption and Immunotoxicity in PCB-Treated Mice** *Curran CP, Colter BH, Villalona Y, Caudill S. Northern Kentucky University, Highland Heights, KY, United States.*

MONDAY

10:15 AM–10:30 AM **15** **Differences in Ambient and Oral Exposure to Quaternary Ammonium Compounds in Mice**
Razvi RM[1], Patel HR[1], Repine CM[1], Chapman TW[1], Melin VE[1,2], Shea CS[1,2], Hrubec TC[1,2]. [1]E. Via College of Osteopathic Medicine, VA Campus, Blacksburg, VA, United States, [2]VA-MD College of Veterinary Medicine, Virginia Tech, Blacksburg, VA, United States.

10:30 AM–10:45 AM **Break—Texas Ballroom B**

10:45 AM–11:00 AM **16** **The Germ Cell-Specific Loss of the Copper Transporter, *Ctr1*, during Embryogenesis Results in Severe Disruption of Spermatogenesis in Mice**
Di Bona KR[1], Ghaffari R[2], Richburg JH[1,2]. [1]Center for Molecular and Cellular Toxicology, College of Pharmacy, The University of Texas at Austin, Austin, TX, United States, [2]Institute of Cellular and Molecular Biology, College of Natural Sciences, The University of Texas at Austin, Austin, TX, United States.

11:00 AM–11:15 AM **17** **Adverse Effect of Valproic Acid on an *In Vitro* Gastrulation Model Entails Activation of Retinoic Acid Signaling: A Potential Mechanism for Its Teratogenic Action**
Marikawa Y, Li A. University of Hawaii, Honolulu, HI, United States.

11:15 AM–11:30 AM **18** **QAC-Induced Neural Tube Defects by Dosing and Environmental Exposure**
Hrubec TC[1,2], Melin VE[1,2], Shea CS[1], Potineni H[2], Razvi RM[1], Patel HR[1], Repine CM[1], Chapman TW[1]. [1]E. Via College of Osteopathic Medicine, VA Campus, Blacksburg, VA, United States, [2]VA-MD College of Veterinary Medicine, Virginia Tech, Blacksburg, VA, United States.

11:30 AM–11:45 AM **19** **Lack of Active Placental Transfer of Certolizumab Pegol: Preclinical and Clinical Data**
Mahadevan U[1], Porter C[2], Armstrong-Fisher S[3,4], Baker T[5], Kevorkian L[5], Nesbitt A[5]. [1]UCSF Medical Center, San Francisco, CA, United States, [2]Department of Immunopathology, NHS Grampian, Aberdeen, United Kingdom, [3]Academic Transfusion Medicine Unit, University of Aberdeen, Aberdeen, United Kingdom, [4]Scottish National Blood Transfusion Service, Aberdeen, United Kingdom, [5]UCB Pharma, Slough, United Kingdom.

11:45 AM–12:00 Noon **20** **Are Quaternary Ammonium Compounds Immunotoxic?**
McDonald VA[1], Hrubec TC[2,3]. [1]Department of Biology, Virginia Tech, Blacksburg, VA, United States, [2]E. Via College of Osteopathic Medicine, Virginia Campus, Blacksburg, VA, United States, [3]VA-MD College of Veterinary Medicine, Virginia Tech, Blacksburg, VA, United States.

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

12:00 Noon–1:30 PM **PAST PRESIDENTS' AND HONOREES' LUNCHEON—Texas Ballroom A**
(By Invitation Only)

12:00 Noon–1:30 PM ***BDRA* EDITORIAL BOARD MEETING—Republic A**

1:30 PM–5:30 PM **MARCH OF DIMES SYMPOSIUM—Texas Ballroom D**

New Approaches to the Treatment of Birth Defects
Chairpersons: Jan M. Friedman, University of British Columbia and Joe Leigh Simpson, March of Dimes Foundation

1:30 PM–2:15 PM **S18** **Tuberous Sclerosis Complex: From Bedside to Bench and Back Again** CME
Hope Northrup, University of Texas Medical School at Houston

2:15 PM–3:00 PM **S19** **Treatment of Lysosomal Storage Diseases: Lessons for Other Genetic Disorders** CME
Lorne Clarke, University of British Columbia, Vancouver

3:00 PM–3:15 PM		**Break—Texas Ballroom B**
3:15 PM–4:00 PM	**S20**	**Bone Marrow Transplantation and Umbilical Cord Blood Transplantation for Inborn Errors of Metabolism** CME *Vinod K. Prasad, Duke University*
4:00 PM–4:45 PM	**S21**	***In Utero* Treatment of Meningomyelocele: Open and Minimally Invasive Fetal Surgery** CME *Michael A. Belfort, Baylor College of Medicine, Houston*
4:45 PM–5:30 PM	**S22**	***In Utero* Treatment of Cardiac Malformations** CME *Wayne Tworetzky, Boston Children's Hospital*

1:30 PM–5:30 PM **INTEGRATIVE *IN VITRO* MODELS FOR NEUROVASCULAR DEVELOPMENT FUNCTION SYMPOSIUM—Texas Ballroom F**

(Joint with DNTS)

Chairpersons: Thomas B. Knudsen, US Environmental Protection Agency and William Slikker Jr., National Center for Toxicological Research, US FDA

1:30 PM–1:35 PM		**Introduction** *Thomas B. Knudsen, US Environmental Protection Agency*
1:35 PM–2:20 PM	**S23**	**Assembly of Stem Cell-Derived Human Tissues for Screening Applications** CME *William Murphy, University of Wisconsin*
2:20 PM–3:05 PM	**S24**	**Blood-Brain-Barrier Development and Function** CME *Sherry Ferguson, National Center for Toxicological Research, US FDA*
3:05 PM–3:20 PM		**Break—Texas Ballroom B**
3:20 PM–4:05 PM	**S25**	**High-Throughput Screening of Zebrafish to Identify Modifiers of Nervous System Development and Function** CME *Randall T. Peterson, Harvard Medical School*
4:05 PM–4:50 PM	**S26**	**Human Neurovascular Unit On-A-Chip: Microscale Systems for Tissue-Level Response** CME *John Wikswo, Vanderbilt University*
4:50 PM–5:30 PM		**Discussion**

5:30 PM–7:30 PM **POSTER SESSION 1 AND EXHIBITS ATTENDED—Texas Ballroom B**

(Joint with DNTS and OTIS)

Teratology Society Posters P1–P18
DNTS Posters P01–P12
OTIS Posters 1–13

7:30 PM–10:00 PM **TERATOLOGY SOCIETY AND MARTA STUDENT CAREER EVENT—Texas Ballroom A**

(Open to Teratology Society, DNTS, and OTIS Student and Postdoctoral Fellows)

TUESDAY, JUNE 28, 2016

6:30 AM–6:00 PM **REGISTRATION OPEN—Texas Ballroom Foyer**

6:30 AM–7:00 AM **SUNRISE MINI COURSE COFFEE AND CONTINENTAL BREAKFAST—Texas Ballroom D**

(Sunrise Mini Course Registrants Only)

7:00 AM–8:30 AM **SUNRISE MINI COURSE—Texas Ballroom D**

(Separate Registration Required)

"Big Data"

Organized by the Education Committee, Chairperson, Chris J. Stodgell, University of Rochester

7:00 AM–7:45 AM **Diagnosis and Management of Big Data: Practical Considerations for Prospective Biomedical Studies** CME
Jeanne Holden-Wiltse, University of Rochester School of Medicine and Dentistry

7:45 AM–8:30 AM **Novel Approaches for the Assessment of Environmentally-Induced Birth Defects** CME
Rebecca C. Fry, UNC Gillings School of Global Public Health

7:00 AM–6:00 PM **SPEAKER READY ROOM OPEN—Crockett A**

8:00 AM–8:30 AM **MORNING COFFEE AND PASTRIES—Texas Ballroom B**

8:30 AM–9:00 AM **ROBERT L. BRENT LECTURE: TERATOGEN UPDATE—Texas Ballroom D**

(Joint with OTIS)

Preventing the Preventable: Where Do We Stand on Fetal Alcohol Spectrum Disorders in 2016? CME

Chairperson: Sonja A. Rasmussen, Centers for Disease Control and Prevention

Speaker: Christina D. Chambers, University of California, San Diego

9:00 AM–12:30 PM **PUBLIC AFFAIRS SYMPOSIUM—Texas Ballroom D**

(Joint with DNTS and OTIS)

Depression and Its Treatment in Pregnancy

Chairpersons: Kembra L Howdeshell, National Institute of Environmental Health Sciences and Asher Ornoy, Hebrew University Hadassah Medical School

9:00 AM–9:05 AM **Introduction**
Kembra L. Howdeshell, National Institute of Environmental Health Sciences

9:05 AM–9:45 AM **S27** **Depression Treatment in Pregnancy: Are We Asking the Right Questions?** CME
Katherine L. Wisner, Northwestern University

9:45 AM–10:25 AM **S28** **What Can Prenatal Exposure to SSRI Antidepressants Teach Us About Child Development?** CME
Timothy F. Oberlander, University of British Columbia

10:25 AM–10:40 AM **Break—Texas Ballroom B**

10:40 AM–11:20 AM **S29** **The Safety of Tricyclic Antidepressants and Mood Stabilizers in Pregnancy: What Should We Use for the Treatment of Bipolar Disorders?** CME
Asher Ornoy, Hebrew University Hadassah Medical School

11:20 PM–12:00 Noon **S30** **New Insights into How SSRIs Shape the Developing Brain: From Mice to Public Health Implications** CME
Jay Gingrich, Columbia University, Sackler Institute of Developmental Psychobiology

12:00 Noon–12:30 PM **Panel Discussion: Mild Psychiatric Diseases in Pregnancy—To Treat or Not Treat**

9:00 AM–12:30 PM **EVERY ASSAY NEEDS AN ANCHOR: THE SEARCH FOR REFERENCE DEVELOPMENTAL TOXICANTS WORKSHOP—Texas Ballroom E**

Chairpersons: Patience Browne, US Environmental Protection Agency and Nicole Churchill Kleinstreuer, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, NIEHS

9:00 AM–9:30 AM	**W2**	**An Exposure-Based Validation List for Developmental Toxicity Screening Assays** *George P. Daston, Procter & Gamble Company*
9:30 AM–10:00 AM	**W3**	**An Expert-Driven Approach to Identifying Reference Developmental Toxicants** CME *Elizabeth A. Maull, National Toxicology Program, NIEHS*
10:00 AM–10:30 AM	**W4**	**Testing in Alternative Assays with a Range of Reference Developmental Toxicants** CME *Nicole Churchill Kleinstreuer, National Institute of Environmental Health Sciences, NTP, NICEATM*
10:30 AM–10:45 AM		**Break—Texas Ballroom B**
10:45 AM–11:15 AM	**W5**	**A Performance-Based Approach for Validating Computational Tools for Developmental and Reproductive Toxicity** CME *Patience Browne, US Environmental Protection Agency*
11:15 AM–11:45 AM	**W6**	**A High-Throughput Screening Assay to Detect Thyroperoxidase Inhibitors and Discover Structural Alerts** CME *Steven O. Simmons, National Center for Computational Toxicology, US EPA*
11:45 AM–12:15 PM	**W7**	**High-Content Screening of Developmental Neurotoxicity in Zebrafish Embryos** CME *David C. Volz, University of California, Riverside*
12:15 PM–12:30 PM		**Discussion**

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

12:30 PM–1:30 PM **NOMINATIONS AND ELECTIONS COMMITTEE MEETING—Republic A**

12:30 PM–1:30 PM **PUBLIC AFFAIRS COMMITTEE MEETING—Crockett C**

12:30 PM–1:30 PM **WEB SITE COMMITTEE MEETING—Crockett B**

1:30 PM–3:30 PM **INCREASING PREVALENCE OF GASTROSCHISIS SYMPOSIUM—Texas Ballroom E**

Chairperson: Margaret A. Honein, Centers for Disease Control and Prevention

1:30 PM–1:50 PM	**S31**	**Increasing Prevalence of Gastroschisis Worldwide** CME *Kathryn E. Arnold, Centers for Disease Control and Prevention*
1:50 PM–2:10 PM	**S32**	**Embryology of Gastroschisis** CME *Thomas W. Sadler, Consultant*
2:10 PM–2:30 PM	**S33**	**Genetic and Nongenetic Risk Factors for Gastroschisis** CME *Sonja A. Rasmussen, Centers for Disease Control and Prevention*
2:30 PM–2:50 PM	**S34**	**The Potential Role of Common Exposures in Young Women for Gastroschisis: Sexual Activity, Contraception, Medications, and Drugs** CME *Christina D. Chambers, University of California, San Diego*

TUESDAY

2:50 PM–3:10 PM **S35** **Investigating the Association between Gastroschisis and Biomarkers of Chlamydia Infection and Inflammation** CME
Marcia Lynn Feldkamp, University of Utah

3:10 PM–3:30 PM **Discussion**

1:30 PM–5:30 PM **ADVANCES IN PLACENTAL RESEARCH SYMPOSIUM—Texas Ballroom D**

(Joint with OTIS)

Chairpersons: Richard K. Miller, University of Rochester Medical Center and Sarah G. Obican, University of South Florida

1:30 PM–1:40 PM **Introduction**
Sarah G. Obican, University of South Florida

1:40 PM–2:10 PM **S36** **Predicting Fetal and Newborn Health: The Role of the Placenta and Its Imaging** CME
Richard K. Miller, University of Rochester Medical Center

2:10 PM–2:50 PM **S37** ***In Utero* Imaging of the Human Placenta: Approaches for Diagnosis of Fetal Health** CME
Alfred Z. Abuhamad, Eastern Virginia School of Medicine

2:50 PM–3:30 PM **S38** **Human Placental Pathology—Diagnosis in the 21st Century: New Approaches and Techniques** CME
Carolyn Margaret Salafia, Placenta Analytics, Inc.

3:30 PM–3:45 PM **Break—Texas Ballroom B**

3:45 PM–4:25 PM **S39** **Unexpected Beginnings: Role of Pregnancy and Parturition in Establishing Our Microbiome** CME
Maxim D. Seferovic, Baylor College of Medicine, Houston

4:25 PM–5:05 PM **S40** **Placenta-Specific microRNAs and Pregnancy Health** CME
Yoel Sadovsky, Magee Womens Research Institute, University of Pittsburgh

5:05 PM–5:30 PM **Discussion**

3:30 PM–3:45 PM **BREAK—Texas Ballroom B**

3:45 PM–5:30 PM **PLATFORM SESSION 3—Texas Ballroom E**

Clinical Teratology

Chairpersons: James L. Mills, Eunice Kennedy Shriver *National Institute of Child Health and Human Development, NIH and Cynthia A. Moore, Centers for Disease Control and Prevention*

Presenting author is underlined.

3:45 PM–4:00 PM **Introduction**

4:00 PM–4:15 PM **21** **Exposure to Valproate during Pregnancy: Facial Features and Signs of Autism**
*Stadelmaier R[1], Nasri H[2], Deutsch C[3], Bauman M[4], Adams J[5], Stodgell C[6], Holmes LB[2]. [1]Albert Einstein College of Medicine, New York, NY, United States, [2]MassGeneral Hospital for Children, Boston, MA, United States, [3]*Eunice Kennedy Shriver Center, *Waltham, MA, United States, [4]Boston University School of Medicine, Boston, MA, United States, [5]University of Massachusetts, Boston, Boston, MA, United States, [6]University of Rochester School of Medicine, Rochester, NY, United States.*

4:15 PM–4:30 PM **22** **Maternal Use of Selective Serotonin-Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn: An Update of the Current Evidence and Clinical Implications**
Alwan S[1], Bandoli G[2], Chambers CD[2]. [1]University of British Columbia, Vancouver, BC, Canada, [2]University of California, San Diego, La Jolla, CA, United States.

4:30 PM–4:45 PM **23** **Effects of Opioid Maintenance Therapy on Infant Brain Development**
Stephen JM[1,2], Flynn L[1], Van Meter J[1,2], Lowe J[2], Bakhireva LN[2]. [1]The Mind Research Network, Albuquerque, NM, United States, [2]University of New Mexico, Albuquerque, NM, United States.

4:45 PM–5:00 PM **24** **The Need of Orthopedic Care and Physical Activity Level in a Group of Middle-Aged Individuals with Thalidomide Embryopathy**
Ghassemi Jahani S-A, Danilesson A, Karlsson J, Brisby H. Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Department of Orthopaedic, Gothenburg, Sweden.

5:00 PM–5:15 PM **25** **Health Related Quality of Life and Socio-Demographics in Middle-Aged Individuals with Thalidomide Embryopathy**
Danilesson AJ, Ghassemi Jahani S-A. Institute of Clinical Sciences Sahlgrenska Academy, University of Gothenburg, Department of Orthopaedic, Gothenburg, Sweden.

5:15 PM–5:30 PM **26** **Betaine Supplementation Reduces Congenital Defects Induced by Prenatal Alcohol Exposure**
Karunamuni G[1], Gu S[1], Doughman YQ[1], Sheehan MM[1], Ma P[1], Peterson LM[1], Linask KK[2], Jenkins MW[1], Rollins AM[1], Watanabe M[1]. [1]Case Western Reserve University, Cleveland, OH, United States, [2]University of South Florida, St. Petersburg, FL, United States.

5:30 PM–7:30 PM **POSTER SESSION 2 AND EXHIBITS ATTENDED—Texas Ballroom B**

Teratology Society Posters P19–P46

WEDNESDAY, JUNE 29, 2016

6:30 AM–7:30 AM **TERATOLOGY SOCIETY 35TH ANNUAL VOLLEYBALL GAME—Factory of Champions**

7:00 AM–2:30 PM **REGISTRATION OPEN—Texas Ballroom Foyer**

7:00 AM–2:30 PM **SPEAKER READY ROOM OPEN—Crockett A**

7:30 AM–8:00 AM **MORNING COFFEE AND PASTRIES—Texas Ballroom D**

8:00 AM–8:30 AM **NARSINGH AGNISH FELLOW LECTURE—Texas Ballroom D**

Educational Convergence of Sciences: Basic-Clinical-Discovery-Regulatory CME
Organized by the Education Committee, Chairperson, Chris J. Stodgell, University of Rochester

Speaker: Richard K. Miller, University of Rochester Medical Center

8:30 AM–9:30 AM **TERATOLOGY SOCIETY AND EUROPEAN TERATOLOGY SOCIETY EXCHANGE LECTURE—Texas Ballroom D**

GMOs and Glyphosate
Chairpersons: Susan L. Makris, US Environmental Protection Agency and Shay Giles, University College Dublin

Teratology Society
John M. DeSesso, Exponent, Inc.

European Teratology Society
Jochen Buschmann, Fraunhofer Institute for Toxicology and Experimental Medicine

WEDNESDAY

9:30 AM–10:30 AM **SPECIAL REPORT—Texas Ballroom D**

Exploring the Link between Zika Virus and Microcephaly

Chairpersons: Sonja A. Rasmussen, Centers for Disease Control and Prevention and Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.

9:30 AM–9:35 AM		**Introduction**
9:35 AM–9:55 AM	**SR1**	**Exploring the Link between Zika Virus and Microcephaly** *Lavinia Schuler-Faccini, Brazilian Society of Medical Genetics*
9:55 AM–10:15 AM	**SR2**	**Exploring the Link between Zika Virus and Adverse Pregnancy and Birth Outcomes** *Margaret A. Honein, Centers for Disease Control and Prevention*
10:15 AM–10:30 AM		**Discussion**

9:30 AM–12:30 PM **PLATFORM SESSION 4—Texas Ballroom E**

Epidemiology

Chairpersons: José F. Cordero, University of Georgia and Peter Langlois, Texas Department of State Health Services

Presenting author is underlined.

9:30 AM–9:45 AM		**Introduction**
9:45 AM–10:00 AM	**27**	**Hair Dye Use and the Risk of Congenital Malformations: Results from a New Zealand Birth Defects Case-Control Study** *'t Mannetje AM[1], Borman B[1], Eng AJ[1], Ellison-Loschmann L[1], Douwes JE[1], Pearce N[2]. [1]Centre for Public Health Research, Massey University, Wellington, New Zealand, [2]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
10:00 AM–10:15 AM	**28**	**Maternal and Infant Genetic Variants in Folate, Homocysteine and Trans-Sulfuration Pathways Modify the Association between Prenatal Selective Serotonin Reuptake Inhibitors Use and Risk of Congenital Heart Defects** *Nembhard WN[1,2], Tang X[3,2], Hu Z[3,2], MacLeod S[1,2], Stowe Z[4], Webber D[1], The National Birth Defects Prevention Study[1]. [1]Division of Birth Defects Research, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, United States, [2]Arkansas Children's Hospital Research Institute, Little Rock, AR, United States, [3]Division of Biostatistics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, United States, [4]Department of Psychiatry, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, United States.*
10:15 AM–10:30 AM	**29**	**Contribution of Total Prevention of Folic Acid Preventable Spina Bifida and Anencephaly towards Achieving Health-Related Sustainable Development Goals in India** *Kancherla V, Oakley GP. Emory University Rollins School of Public Health, Atlanta, GA, United States.*
10:30 AM–11:00 AM		**Warkany Tea—Texas Ballroom A**
11:00 AM–11:15 AM	**30**	**Descriptive Epidemiology of Microcephaly in Texas** *Canfield MA[1], Langlois PH[1], Marengo LK[1], Hoyt AT[1], Ethen MK[1], Scheuerle AE[2]. [1]Texas Department of State Health Services, Austin, TX, United States, [2]UT Southwestern Medical Center, Dallas, TX, United States.*

11:15 AM–11:30 AM	**31**	**Antidepressant Use in Pregnancy and the Risk of Attention Deficit with or without Hyperactivity Disorder in Children** Boukhris T[1,2], Sheehy O[2], Berard A[1,2]. [1]Faculty of Pharmacy, University of Montréal, Montréal, QC, Canada, [2]Research Center, CHU Sainte-Justine, Montréal, QC, Canada.
11:30 AM–11:45 AM	**32**	**Multicentric Study of Genetic and Environmental Risk Factors Associated to Myelomeningocele in a Sample of 500 Trios of the Mexican Mestizo Population** Mutchinick OM[1], Aguayo A[1], Ortiz G[1], Muñoz LA[1], Luna L[1], Sánchez ME[1], Berumen E[2]. [1]Genetics Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, Mexico, [2]Fundación Teletón, Estado de México, Mexico.
11:45 AM–12:00 Noon	**33**	**Risk of Preterm Birth following Late-Pregnancy Exposure to Medications Used in the Treatment of Autoimmune Diseases** Berard A[1,2], Sheehy O[1], Girard S[1,2], Zhao J[1]. [1]Research Center CHU Sainte-Justine, Montréal, QC, Canada, [2]University of Montréal, Montréal, QC, Canada.
12:00 Noon–12:15 PM	**34**	**Folate, Iron, and Choline Intake in Pregnant Women with Substance Use Disorders** Shrestha S[1], Jimenez EY[2], Cano S[1], Williams S[1], Stephen JM[1], Bakhireva LN[1]. [1]University of New Mexico Health Sciences Center and the Mind Research Network, Albuquerque, NM, United States, [2]Center for Education Policy Research, University of New Mexico, Albuquerque, NM, United States.
12:15 PM–12:30 PM	**35**	**Indoor Air Pollution and Orofacial Clefts in a Rural Population of Northern China** Liu Y, Li Z, Wang B, Ren A. Institute of Reproductive and Child Health, Ministry of Health Key Laboratory of Reproductive Health, Peking University, Beijing, China.

10:30 AM–11:00 AM **WARKANY TEA—Texas Ballroom A**

11:00 AM–12:30 PM **STRATEGIES FOR POSTAPPROVAL ASSESSMENT WORKSHOP—Texas Ballroom D**

Chairpersons: Cheryl S. Broussard, Centers for Disease Control and Prevention and Melissa S. Tassinari, US Food and Drug Administration

11:00 AM–11:05 AM		**Introduction**
11:05 AM–11:25 AM	**W8**	**What Do You Need to Consider When Designing an Approach to Data Collection to Maximize Success in Collection of Exposures and Outcomes** *Sara Ephross, Consultant*
11:25 AM–11:45 AM	**W9**	**BD-STEPS: The Next Generation of Birth Defects Research** CME *Cheryl S. Broussard, Centers for Disease Control and Prevention*
11:45 AM–12:05 PM	**W10**	**What Is US Food and Drug Administration Looking for to Assess and Label Risk?** CME *Lockwood Taylor, US Food and Drug Administration*
12:05 PM–12:25 PM	**W11**	**New Approaches to the Design and Analysis of Studies Evaluating Drug Safety during Pregnancy** CME *Krista Huybrechts, Harvard Medical School*
12:25 PM–12:30 PM		**Discussion**

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

WEDNESDAY

12:30 PM–1:30 PM **EDUCATION COMMITTEE MEETING—Republic A**

12:30 PM–1:30 PM **MEMBERSHIP COMMITTEE MEETING—Crockett B**

12:30 PM–1:30 PM **SCIENCE AND PUBLIC POLICY WORKSHOP—Texas Ballroom D**

How It Affects You and How You Can Shape It
Chairpersons: Wafa A. Harrouk, US Food and Drug Administration and Belen Tornesi, AbbVie Inc.

12:30 PM–12:35 PM	**W12**	**Introduction**
12:35 PM–12:50 PM		**How FASEB Amplifies the Voice of Working Scientists** *Howard H. Garrison, Federation of American Societies for Experimental Biology*
12:50 PM–1:05 PM		**How FASEB Speaks to the Nation's Leaders** *Parker Antin, Federation of American Societies for Experimental Biology*
1:05 PM–1:20 PM		**Teratology Society Engagement in FASEB** *Belen Tornesi, AbbVie Inc.*
1:20 PM–1:30 PM		**Discussion**

1:30 PM–4:30 PM **ASSESSING THE DEVELOPMENTAL TOXICITY OF NANOMATERIALS SYMPOSIUM—Texas Ballroom D**

Chairpersons: Julia M. Gohlke, Virginia Tech and Susan L. Makris, US Environmental Protection Agency

1:30 PM–1:35 PM		**Introduction**
1:35 PM–2:15 PM	**S41**	**An Overview of Developmental Toxicity Testing for Nanomaterials** CME *Karin Hougaard, National Research Center for the Working Environment*
2:15 PM–2:55 PM	**S42**	**Inhaled Cadmium Oxide Nanoparticles during Pregnancy Alters Fetal Development and Neonatal Growth in a Mouse Model** CME *Jason L. Blum, New York University School of Medicine*
2:55 PM–3:10 PM		**Break —Texas Ballroom A**
3:10 PM–3:50 PM	**S43**	**Maternal Gestational Nanomaterial Exposures: Uterine and Fetal Microvascular Consequences** CME *Timothy R. Nurkiewicz, West Virginia University School of Medicine*
3:50 PM–4:30 PM	**S44**	**Overview of Nanomaterial Regulation: Data Gaps and Research Needs for Risk Assessment** CME *Maureen Gwinn, Office of Research and Development, US EPA*

1:30 PM–4:30 PM **ILSI HESI SYMPOSIUM—Texas Ballroom E**

Ontogeny of the FcRn in Gestation across Species: Implications for Monoclonal Antibody Developmental Toxicity Testing and Human Risk Assessment
Chairpersons: William J. Breslin, Eli Lilly and Company and Graeme J. Moffat, Amgen, Inc.

1:30 PM–1:35 PM	**S45**	**Introduction** *Graeme J. Moffat, Amgen, Inc.*
1:35 PM–2:25 PM	**S46**	**Cross-Species Ontogeny of Placental Fc Receptors: What We Think We Know and What We Know We Don't** *John M. DeSesso, Exponent, Inc.*
2:25 PM–3:00 PM	**S47**	**Ontogeny of FcRn in Gestation across Nonclinical Species** *Susan Bielmeier Laffan, GlaxoSmithKline*

3:00 PM–3:15 PM		**Break —Texas Ballroom A**
3:15 PM–3:45 PM	**S48**	**FcRn Expression in Human Placenta during Fetal Development** *Susan Westmoreland, AbbVie Inc.*
3:45 PM–4:15 PM	**S49**	**Nonclinical to Clinical Translation: Placental Transfer of Fc Containing Biotherapeutics and Ontogeny of FcRn Expression in the Placenta and Yolk Sac** *Lakshmi Sivaraman, Bristol-Myers Squibb Company*
4:15 PM–4:30 PM		**Discussion**

4:45 PM–6:15 PM **BUSINESS MEETING—Texas Ballroom D**

6:30 PM–7:30 PM **BANQUET RECEPTION—Texas Ballroom A**

7:30 PM–11:00 PM **BANQUET—Texas Ballroom B**

Travel Awards
James C. Bradford Memorial Student Poster Awards
Wilson Presentation Awards
Marie W. Taubeneck Award
Edward W. Carney Trainee Award
***Birth Defects Research* Distinguished Scholar Awards**
Edward W. Carney Distinguished Service Award
Recognition of Other Awards Presented throughout the Week

THURSDAY, JUNE 30, 2016

7:00 AM–10:00 AM **COUNCIL 2 MEETING—Crockett B**

Exhibitor Information

(as of March 25, 2016)

Exhibits and Posters are located in Texas Ballroom B. Although the Exhibit Hall will be open Sunday afternoon through Tuesday evening, the exhibits will be attended only during the times listed below.

Exhibits Attended

Welcome Reception	Poster Session 1	Poster Session 2
Sunday, June 26	*Monday, June 27*	*Tuesday, June 28*
6:00 PM–7:30 PM	5:30 PM–7:30 PM	5:30 PM–7:30 PM

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

CHARLES RIVER

251 Ballardvale Street
Wilmington, MA 01887

Tel: 877.CRIVER.1
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Chicago, IL 60609

Tel: 773.254.2700
Website: www.experimur.com

Experimur
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Experimur is a full-service toxicology testing and research laboratory with extensive experience in the conduct of developmental (Seg I, II, & III) and reproductive (single and multi-generation) toxicity assessments, including sperm morphology and vaginal cytology, as well as general toxicity (acute, subchronic, chronic, and carcinogenicity), neurotoxicity, and pharmacokinetic/ADME studies in species ranging from rodents to primates. With an experienced and well-trained team that has worked together for over 28 years and successfully completed thousands of GLP-compliant preclinical studies, we are committed to providing our customers with top quality and unmatched service. We invite you to visit our spectacular custom-built, AAALAC-accredited, USDA-registered, 54,000 square foot state-of-the art facility and vivarium, which includes extensive in-house support services for histology diagnostic pathology, clinical pathology, and analytical chemistry.

EXPONENT, INC.

1800 Diagonal Road, Suite 500
Alexandria, VA 22314

Tel: 571.227.7261
Website: www.exponent.com

Exponent's veteran toxicologists and epidemiologists are drawn from the chemical and pharmaceutical industries, academia, and government. They have international regulatory experience in designing and interpreting developmental and reproductive toxicity (DART) and developmental neurotoxicology studies; assessing potential endocrine disruption; performing quantitative risk assessments and cancer risk assessments related to children. Our experts are also ready to assist you in complying with the new FDA Pregnancy and Lactation Labeling Rule.

FACEB MARC PROGRAM

9650 Rockville Pike, Suite L-6209
Bethesda, MD 20814

Tel: 301.634.7020
Website: www.faseb.org/marc

The FASEB MARC (Maximizing Access to Research Careers) Program provides a variety of activities to support the training of students, doctorates, faculty, and researches from underrepresented groups who are engaged in the biomedical and behavioral sciences research and training. We offer poster/platform presenter travel awards for scientific meetings (national and regional) and FASEB Science Research Conferences. We also sponsor career/leadership development and grantsmanship training seminars and workshops.

NATIONAL BIRTH DEFECTS PREVENTION NETWORK

1321 Upland Drive, Suite 1561
Houston, TX 77043

Website: www.nbdpn.org

The National Birth Defects Prevention Network (NBDPN) is a volunteer-based organization that addresses the issues of birth defects surveillance, research, and prevention under one umbrella by maintaining a national network of state and population-based birth defects programs.

SAN DIEGO INSTRUMENTS

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San Diego, CA 92121

Tel: 858.530.2600
Website: www.sandiegoinstruments.com

San Diego Instruments (SDI) has served the scientific community for over 30 years with its manufacture and distribution of scientific testing systems. SDI behavioral testing systems afford you the utmost in quality and performance, giving you the edge in an industry where power, flexibility, and ease of use are everything.

SMITHERS AVANZA

11 Firstfield Road
Gaithersburg, MD 20878

Tel: 240.364.6360
Website: www.smithersavanza.com

Smithers Avanza Toxicology Services, a division of Smithers Avanza, is a GLP-compliant, AAALAC-accredited, USDA-registered, OLAW-assured, and DEA-licensed facility located in Gaithersburg, Maryland. Our team conducts safety assessment studies for pharmaceuticals and vaccines, in multiple species. Our services include general toxicology, DART, clinical chemistry, kinetics, safety pharmacology, infusion technology, and pathology.

THE TERATOLOGY SOCIETY

1821 Michael Faraday Drive, Suite 300
Reston, VA 20190

Tel: 703.438.3104
Website: www.teratology.org

The Teratology Society is composed of a multidisciplinary group of scientists from a variety of disciplines including researchers, clinicians, epidemiologists, and public health professionals from academia, government, and industry who study birth defects, reproduction, and disorders of developmental origin. Our Mission is to prevent birth defects and disorders of developmental origin by: promoting research and exchange of ideas, communicating information to health professionals and other interested parties, and providing education and training. Visit the booth to learn more about the Society and membership.

UNITED STATES DRUG TESTING LABORATORIES

1700 South Mount Prospect Road
Des Plaines, IL 60018

Tel: 847.375.0770
Website: www.usdtl.com

USDTL is a boutique toxicology laboratory that specializes in the detection of drugs of abuse and long term alcohol biomarkers in biological tissues and fluids.

US FOOD AND DRUG ADMINISTRATION OFFICE OF WOMEN'S HEALTH

10903 New Hampshire Avenue
Building 32, Room 2333
Silver Spring, MD 20993

Tel: 301.769.9440
Website: www.fda.gov/womens

The US Food and Drug Administration Office of Women's Health addresses the health issues of the nation's women by funding scientific research and collaborating with national organizations and government agencies to sponsor outreach and education efforts.

Birth Defects Research (Part A) 106:348–351 (2016)

TERATOLOGY SOCIETY

LECTURE ABSTRACTS

(Presenter designated by underlined author.)

Josef Warkany Lecture

(Joint with DNTS and OTIS)

Chairperson: Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.

L1

FAUSTMAN EM. University of Washington, Seattle, WA, United States. Framing Our Birth Defects Questions with Systems Biology: Learning from Our Mentors

A special aspect of the Teratology Society has been the role that mentors play in nurturing the next generation of scientists. What better time to remember this, than during our Warkany Lecture. From his summer visits to Seattle some 25 years ago that helped to shape the nascent field of teratology to today, Dr. Warkany's inspiration in setting the stage for multidisciplinary research on birth defects has not been lost. Three themes will be highlighted in this talk that represent hallmarks of Dr. Warkany's legacy. First, is the recognition of the environment in the etiology of birth defects. How have our early ideas of environment evolved to influence current experiences with Zika virus? Second, is the role of genetics and environment in child health and development. Third, but not least, is the role of timing and the dynamics of response across the lifecourse. Using examples from Dr. Warkany's visits to the Pacific Northwest, this lecture will focus on early origins of adult disease, genes x environment x time, and mechanisms of both normal and abnormal development. In developmental toxicology, we embrace both reductionist, as well as organism-based high content models and Dr. Warkany was instrumental in stimulating clinical and pathological frameworks for interpreting these models of developmental health outcomes. These early Seattle-based think tanks provided a wealth of inspiration—influencing Dr. Warkany as well as Drs. Shepard, Streissguth, Juchau, and Emmanual. Dr. Junchau created the pharmacological context for our discussions by providing concepts of dose response and tested our beliefs in metabolism that still are challenging our approaches today in prenatal and pediatric care. Dr. Emmanual, who hosted Dr. Warkany's visits at our Center for Child Health and Human Development, provided the epidemiological stimulus for our themes on epigenetic and multigenerational challenges. Current interpretations for complex endpoints, such as behavior, only serve to reinforce our need for multidisciplinary mentors and systems based approaches for tracing environmental impacts on healthy child development. Dr. Warkany exemplified the melding of art and science to define these challenges and opportunities that we continue to build upon today.

F. Clarke Fraser New Investigator Award

Chairperson: Bruce K. Beyer, Sanofi U.S. Inc.

L2

KLEINSTREUER NC. NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, NIEHS, Research Triangle Park, NC, United States. Of Mice, Math, and Modeling

This year's recipient of the F. Clarke Fraser award is Dr. Nicole C. Kleinstreuer, deputy director of the National Toxicology Program Interagency Center for Alternative Toxicological Methods (NICEATM). Dr. Kleinstreuer will discuss her career in birth defects research, how she has applied her background in mathematics and modeling to understanding developmental toxicity mechanisms and predicting chemical effects on pathways that govern critical embryonic processes, from vascular development to nuclear hormone receptor signaling. She will discuss how Dr. Fraser's life and work have influenced her own path, and the many valuable lessons she has gained from her experiences with the Teratology Society. Dr. Kleinstreuer trained in the Virtual Embryo group at the US EPA, and led NICEATM's computational toxicology work before accepting her current position, where she continues to lead international efforts to develop and validate computational models and *in vitro* alternative systems for developmental toxicity testing.

Patricia Rodier Mid-Career Award for Research and Mentoring

(Joint with DNTS)

Chairpersons: Bruce K. Beyer, Sanofi U.S. Inc. and Patricia Janulewicz, Boston University

L3

CHAMBERS CD. University of California, San Diego, La Jolla, CA, United States. Research on Long Term Outcomes following Prenatal Exposures: Rarely Studied But Sorely Needed

Although many known human teratogens are associated with effects on central nervous system functioning, few human epidemiological studies of exposures in pregnancy routinely incorporate neurodevelopmental follow-up of prenatally exposed children. In cases where it is already known that the primary effect of a human teratogen is on brain, the task is to delineate what are the characteristic deficits, and how frequently these occur with or without associated structural defects. Our work on Fetal Alcohol Spectrum Disorders has been focused on defining this pattern and prevalence of deficits, as well as on developing methods for earlier recognition of alcohol-related impairment that can lead to more effective early interventions. In the case of prenatal exposure to agents that have not yet been evaluated for teratogenicity, we are invested in the concept that neurobehavioral outcomes should be encompassed in the range of outcomes that are evaluated for all agents. To this end, many MotherToBaby pregnancy cohort studies, in addition to evaluation of children for structure and growth, incorporate staged neurobehavioral assessments. The approach involves screening questionnaires for all children and diagnostic testing for a subset. While studies with this scope are costly in time and resources, arguably this should be standard practice for postmarketing pregnancy safety studies.

Keynote Speaker

Chairperson: Sonja A. Rasmussen, Centers for Disease Control and Prevention

L4

KINGSMORE SF. Rady Children's Institute for Genomic Medicine, Rady Children's Hospital, San Diego, CA, United States. Translating Rapid Whole Genome Sequences into Precision Medicine for Babies in Intensive Care Units

Genetic disorders and congenital anomalies are the leading causes of infant mortality. Diagnosis of most genetic diseases in neonatal and pediatric intensive care units (NICUs and PICUs) is not sufficiently timely to guide acute clinical management. We are using rapid whole-genome sequencing (STATseq) in two regional NICUs and PICUs to assess the rate and types of molecular diagnoses and the prevalence, types, and effect of diagnoses that are likely to change medical management in critically ill infants. We did a retrospective comparison of STATseq and standard genetic testing in a case series from the NICU and PICU of a large children's hospital between November 2011 and October 2014. The participants were families with an infant younger than four months with an acute illness of suspected genetic cause. The intervention was STATseq of trios (both parents and their affected infant). The main measures were the diagnostic rate, time to diagnosis, and rate of change in management after standard genetic testing and STATseq. 20 (57%) of 35 infants were diagnosed with a genetic disease by use of STATseq and three (9%) of 32 by use of standard genetic testing (p=0•0002). Median time to genome analysis was five days (range 3–153) and median time to STATseq report was 23 days (5–912). 13 (65%) of 20 STATseq diagnoses were associated with *de novo* mutations. Acute clinical usefulness was noted in 13 (65%) of 20 infants with a STATseq diagnosis, four (20%) had diagnoses with strongly favorable effects on management, and six (30%) were started on palliative care. 120-day mortality was 57% (12 of 21) in infants with a genetic diagnosis. In selected acutely ill infants, STATseq had a high rate of diagnosis of genetic disorders. Most diagnoses altered the management of infants in the NICU or PICU. The high mortality rate indicates that there is a substantial opportunity to improve outcomes and for precision palliative care for NICU and PICU infants after timely diagnosis with genetic diseases.

Robert L. Brent Lecture: Teratogen Update

(Joint with OTIS)

Chairperson: Sonja A. Rasmussen, Centers for Disease Control and Prevention

L5

CHAMBERS CD. University of California, San Diego, La Jolla, CA, United States. Preventing the Preventable: Where Do We Stand on Fetal Alcohol Spectrum Disorders in 2016?

Due to challenges in recognizing prenatal alcohol-affected children, the prevalence of Fetal Alcohol Spectrum Disorders is thought to be underestimated in the US using traditional methods of surveillance. However, a multi-site cross-sectional active case ascertainment study that has been completed in four communities in the US in 2016 suggests that 2–4% of first grade children may be affected by alcohol. These striking figures reflect on the general failure of efforts in the US to prevent this disorder. Methods that allow for early identification of alcohol-exposed or affected pregnancies provide some opportunities for targeted intervention. Various biomarkers of alcohol exposure have been developed and may have an increasingly important role in identifying women in pregnancy who do not admit to risky alcohol consumption. However, truly eliminating this disorder requires successful interventions prior to pregnancy when it is possible to prevent alcohol exposure from occurring during the early weeks of embryonic development/prior to pregnancy recognition. Despite decades of educational efforts, the data on risky drinking in young US women have trended in the wrong direction; in a national sample surveyed 2011–2013, 18.2% of nonpregnant women 18–44 reported binge drinking, with an average consumption of six drinks per occasion on an average of 3.1 occasions in the last 30 days. Some success in reducing this risk has resulted from targeted interventions in nonpregnant women using variations on Screening and Brief Intervention approaches and the Project Choices model. Yet general health advisories that suggest that women avoid alcohol if planning pregnancy are met by some with disdain. As we move forward, prevention of Fetal Alcohol Spectrum Disorders should be a major focus of research.

Narsingh Agnish Fellow Lecture

Organized by the Education Committee, Chairperson, Chris J. Stodgell, University of Rochester

L6

MILLER RK. University of Rochester, Rochester, NY, United States. Educational Convergence of Sciences: Basic-Clinical-Discovery-Regulatory

The discipline of teratology and membership of the Teratology Society have been served well by educational courses since 1974. In 1984, the first Education Course associated with the Annual Meeting was initiated in Boca Raton, Florida. These annual courses have been supplemented by the Sunrise Mini Course over the years, as well as separate multiday educational programs. These instructional efforts were complemented by courses developed at the US FDA, ACOG Symposia, and the Society's own *Teratology Primers* for student education that were published in 2005 and 2010. Yet, the core elements of teratology have lagged behind other disciplines even with these courses in place. These underlying elements—education at the collegiate, pharmacy, medical, nursing, and doctoral levels; all have been reduced in favor of other disciplines. Four examples of graduate and medical (through all four years), postgraduate, and continuing medical and pharmacy education in teratology will be presented as possible models for increasing the knowledge base for teratology and applications within all sciences. As time permits, additional novel approaches for teratology education will be based upon audience participation.

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TERATOLOGY SOCIETY

SYMPOSIUM ABSTRACTS

(Presenter designated by underlined author.)

The State of the Art of Testing Drugs: Present and Future Symposium

Chairpersons: Kenjie Amemiya, Genentech and Elise Madison Lewis, Charles River Laboratories

S1

DELISE AM. Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States. Revisions to the ICH S5 Guideline: Thinking Outside the Box

The current ICH Guideline on Reproductive Toxicity [ICH S5(R2)] was written over 20 years ago. Since its implementation, significant experience has been gained in testing pharmaceuticals using the testing paradigms described within this guideline. However, there have been considerable advances in novel testing strategies, technologies, and regulatory knowledge. With the revision of the ICH S5(R2) guideline, there is now an opportunity to modernize testing paradigms, update and expand existing sections, as well as align with other more recently issued guidelines, e.g., ICH M3(R2), ICH S6(R1), and ICH S9. This presentation will provide an overview of the topics to be addressed in the revision of the ICH S5(R2) guideline.

S2

AMEMIY AK, LI R, SCHUTTEN M. Genentech, South San Francisco, CA, United States. Hitting the Target with DARTS(tudies): Using Biology to Assess Reproductive Risk

During the research phase of drug development, the potential for both efficacy and toxicity are assessed via a broad understanding of target biology. This assessment often includes an evaluation of potential reproductive toxicity based on knowledge of the target's role in embryonic/fetal development, known drug class effects, and the use of knockout models. As drugs progress through clinical trials, the requirement for *in vivo* developmental and reproductive toxicology (DART) studies is considered. At this stage, general toxicity studies will have defined on- and off-target-mediated effects indicative of reproductive toxicity or potential effects on offspring. In some cases, by utilizing this comprehensive knowledge and data derived from research and preclinical studies it may be possible to predict the outcome in fertility, embryo-fetal development, and/or pre- and postnatal development studies. Therefore, sponsors may reason that reproductive hazard/risk assessment can be adequately made without the use of designated DART studies and in an effort to reduce animal use; they may present such approaches to regulatory health authorities. Herein, we present a case study for which the biology, pharmacology, and general toxicology data for a Hedgehog Pathway Inhibitor, Vismodegib (Erivedge), predicted the outcome in an embryo-fetal development study, thus providing rationale for such an approach.

S3

BRANNEN KC. Merck, West Point, PA, United States. Alternatives in Developmental Toxicology: How Far We Have Come (and Have Left to Go)

As the developmental toxicology community has increasingly leveraged advances in developmental and molecular biology, genomics, and bioinformatics, progress has been made towards the goals of early, agile testing and use of the 3Rs. The state of the art in alternative methods in developmental toxicity testing will be reviewed, including the achievements made to date, the areas that still require further investigation, and progress. Zebrafish, embryonic stem cells, whole embryo culture, and the DASTON list project will be discussed.

S4

GREEN M, ZHU L, REDFERN B, CHEN F, WANG E, TANIS K, YU Y, WYSOCZANSKI E, KACZOR A, SISTARE F, MATTSON B, DEGEORGE J, LEBRON J. Merck and Co., Inc., West Point, PA, United States. Integrating Alternative Developmental Toxicity Assays for Pharmaceutical Risk Assessment

Alternative models in developmental and reproductive toxicology enhance our capabilities in drug development and design by providing a pharmaceutical risk assessment during early phases of discovery. Since no one model is perfect for every context, we used a battery of assays to predict *in vivo* reprotoxicity. We adopted the mouse embryonic stem cell test (mEST) and rat whole embryo culture assay (WEC) to demonstrate how these *in vitro* assays not only identify most probable rat teratogens, but how an integrated assessment is used to screen for potential embryo-fetal developmental (EFD) toxicity based on an exposure model. Also, in order to capture relevant molecular endpoints that may not exist in preclinical species, efforts are underway to refine and optimize the human embryonic stem cell test (hEST). The mEST and hEST utilize transcriptomics to assess molecular endpoints which get expressed during differentiation or growth inhibition of embryonic stem cells (ESC). The WEC assay determines the potential for developmental toxicity through the treatment of embryos during organogenesis GD 9–11. The rodent assays were evaluated for their ability to predict the teratogenic potential of 84 compounds with known rodent *in vivo* EFD outcome. We used an exposure-based model to investigate the relationship between mEST and WEC endpoints and Cmax exposures reached at teratogenic, subteratogenic, and maximally tolerated nonteratogenic doses in rat EFD studies. When one or both assays are positive, 20/22 rat teratogens are identified (91% sensitivity) with a negative predictivity of 93%. When data for one assay is available and is negative or both assays are negative, 28/62 rat nonteratogens are correctly predicted; and therefore, a specificity of 45% indicates a significant false positive rate. In a preliminary assessment, human ESCs were treated for 14 days with compound at multiple concentrations below and above the human plasma exposure (Cmax) associated with teratogenic or nonteratogenic outcomes. A significant number of potential RNA biomarkers were identified. As the utility of *in vitro* assays evolve, they continue to prove vital in efforts to reduce animal use, in search for mechanisms, and/or in efforts to distinguish teratogenic potential of drugs at relative human therapeutic exposures.

S5

LAFFAN S. GlaxoSmithKline, King of Prussia, PA, United States. Harmonization of the Pediatric Nonclinical Testing Guidelines: The Who, What, When, and Why of ICH S11

In our current testing environment, the EU, US, and Japan each have their own nonclinical pediatric testing rules, recommendations and/or guidelines. With the growing similarity between the US and EU regulations and an acknowledgement that medicines of today are developed globally, a streamlined, more standard approach is under discussion to drive the future of nonclinical juvenile animal testing to effectively and efficiently support pediatric drug development. This is the aim of the new safety guidance ICH S11 "Nonclinical Safety Testing in Support of Development of Pediatric Medicines." This presentation will introduce the ICH organization, overview the process to draft a new ICH guidance, and then will outline the topics to be addressed in the guidance. Lastly, this presentation will describe the newly proposed points to consider for a harmonized approach to nonclinical pediatric drug testing through inception of the ICH S11 pediatric guidance, for both small and large molecules.

Pregnancy Registry Updates Symposium

(Joint with OTIS)

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

S6

HERNANDEZ-DIAZ S. Harvard University, Boston, MA, United States. Gestational Age at Enrollment

Left truncation occurs when follow-up starts after eligibility criteria are met, (e.g., if we delete the first months of follow-up for some individuals in a clinical trial). The bias can be worse if inclusion criteria are applied at that shifted time at enrollment (e.g., subjects with adverse effects diagnosed in the first months are excluded) or if this time is different for exposed versus reference groups. Yet, pregnancy cohorts are often restricted to those women who remained pregnant time after conception (i.e., at enrollment), having a prenatal diagnosis is often an exclusion criteria, and gestational age at enrollment may differ among comparison groups. The risk of malformations can be underestimated if women with a prenatal diagnosis are excluded; or overestimated if they were preferentially enrolled. We explored the influence of gestational age at enrollment, and enrollment before or after prenatal screening, on the estimation of drug effects in pregnancy exposure registries. We assessed the associations between first trimester antiepileptic drug (AED) exposure and risk of major congenital malformations in the North American AED Registry (1996–2015). We performed logistic regression analyses, conditional or unconditional on gestational age at enrollment, to estimate relative risk (RR) for first trimester AED users compared to nonusers. We also compared first trimester users of valproic acid and lamotrigine. Analyses were repeated in women who enrolled before prenatal screening. Enrollment occurred earlier among 7,029 AED users than among 581 nonusers; it was similar between AEDs. Comparing AED users with nonusers, RR (95% confidence interval) of congenital malformations (n=216) changed from 3.1 (1.4–8.5) to 3.2 (1.4–9.0) after conditioning on gestational week at enrollment, and to 2.0 (0.7–10.1) upon further restriction to before-screening enrollees. When comparing valproic acid users and lamotrigine users, the RR of congenital malformations was not substantially changed by conditioning or restricting. Estimates of congenital malformation risks for AED users relative to nonusers are sensitive to before/after-screening enrollment. This difference was not apparent in between active drugs comparisons due to similar gestational age at enrollment.

S7

SAHIN L. US Food and Drug Administration, Harvard, MA, United States. Prevalence Reference Rates for Pregnancy Registries and for Labeling

To assess the safety of drugs or biologic products during pregnancy, the US FDA often issues a postmarketing requirement to the manufacturer for a pregnancy registry to collect data on exposures to medical products during pregnancy and evaluate pregnancy outcomes. However, variation in methodology used to assess major malformation prevalence rates in the study population and the reference population make it challenging to derive conclusions and compare results across studies. Factors, such as application of inclusion and exclusion criteria, and the duration of postnatal follow-up, impact prevalence rates of major malformations. Greater standardization in the process for defining and classifying major malformations that could be caused by teratogenic exposures to drugs or biologics is needed in order to provide meaningful assessment of outcomes. This presentation will highlight some of the processes that are needed to assess prevalence rates of major malformations in the reference and the exposed population. On June 30, 2015, the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include removal of the pregnancy categories (A, B, C, D, and X) from all prescription drug and biological product labeling and inclusion of information about the risks of using these products during pregnancy, described in the context of background risk in the general population and the disease population, if this information is available. This presentation will provide an update on challenges of implementing the rule and identifying prevalence reference rates for labeling.

S8

ZELLNER JA, MILLER D, JOHNSON DL, CHAMBERS CD. University of California, San Diego, La Jolla, CA, United States. Modern Methods of Pregnancy Registry Recruitment: Successes and Challenges

The digital and social media age has resulted in new avenues of recruitment for pregnancy registries, including but not limited to paid advertising via Facebook, Google AdWords, and more recently LinkedIn and Instagram. Often at a fraction of the cost, these modern methods offer direct-to-consumer marketing that can reach significantly larger audiences than more traditional methods of recruitment (e.g., healthcare provider and patient self-referrals from drug labeling, print advertising in scientific journals, and tradeshow exhibition at medical conferences). For example, a Facebook advertisement that has been optimized to target women 18–40 in North America who are interested in pregnancy-related topics and content has an estimated daily reach of 3,000–7,900 active users, out of a possible 20 million users who meet these criteria. Targeted advertising is particularly critical for pregnancy exposure registries in order to identify and recruit cases with rare exposures. In its 18 years of existence, OTIS/MotherToBaby Pregnancy Studies has used a combination of methods to recruit pregnant participants into multisite observational cohort studies. In May 2015 the digital components of the Google and Facebook advertising program were retooled and optimized to better target eligible pregnancies and to enhance recruitment. OTIS/MotherToBaby Pregnancy Studies' experience of implementing and evaluating the effectiveness of this digital marketing program will be presented, including an analysis of ad performance statistics (e.g., impressions, click-through rates, cost per click) and referrals by recruitment method and by study cohort; the extent to which this optimized program yielded a) referrals that met eligibility criteria and b) increased enrollments; and the cost per enrollment. Successes and challenges along with future directions in marketing and recruitment for pregnancy registries will also be discussed.

S9

HOLMES LB. MassGeneral Hospital for Children, Boston, MA, United States. Minor Anomalies: An Unreliable Outcome for Pregnancy Registries

Minor anomalies have been defined, arbitrarily, as a physical feature with no medical or surgical significance, which occur in less than 4% of newborn infants (Marden PM et al. *J Pediatr* 64:357–371, 1964). Examples of teratogen-induced minor anomalies are the short nose with anteverted nostrils in phenytoin or phenobarbital-exposed newborns and the thin vermilion of the upper lip in alcohol-exposed infants. Systematic examinations with a study protocol have shown that 16 to 40% of newborns had one or more minor anomalies (Leppig KA et al. *J Pediatr* 110:531–537, 1987). Unfortunately, many pediatricians do not record in their examinations the minor anomalies they identify. In addition, the findings in three systematic studies showed the limitations of tabulating minor anomalies. Study #1: 444 newborns, examined separately by two examiners (Holmes LB et al.: *Teratology* 36:291–297, 1987), showed poor overall agreement (Kappa=0.08). Reproducibility was poorest for more subjectively defined minor anomalies, such as anteverted nostrils (Kappa=0.28). Study #2: (Holmes LB et al.: *NEJM* 344:1132–1138, 2001), the findings in the systematic surface examination assessed the effect of the examiner knowing that no unexposed control infants were included. In that situation, the frequency of the features of "the anticonvulsant face" were identified more often. This increased recognition decreased when, subsequently, the examiner knew that unexposed controls were included (Harvey EA et al.: *Birth Def Res (A)* 67:452–456, 2003). Study #3: In the Diabetes in Early Pregnancy Study (Mills JL et al. *NEJM* 319:1617–1623, 1988) there were masked examiners in five collaborating centers. Definitions had been reviewed at a planning meeting and were agreed upon, but the findings in study exams showed quite varied frequencies. For example, the frequencies of anteverted nares at the five centers were 3.1%, 6.3%, 18.3%, 28.1%, and 57.8%. These findings demonstrate several limitations in considering minor anomalies an outcome to be tabulated: 1) poor recording on presence of minor anomalies by examining pediatricians; 2) poor reproducibility of the findings; 3) both observer and context biases. Based on these findings, we recommend that minor anomalies not be included as outcomes to be tabulated in a pregnancy registry.

S10

Withdrawn by Author.

S11

LYNCH MM[1], AMOOZEGAR J[1], MCCLURE EM[1], SQUIERS LB[1], BROUSSARD CS[2] , LIND JN[2], POLEN KN[2], FREY MT[2], GILBOA SM[2], BIERMANN, J[3]. [1]RTI International, Research Triangle Park, NC, United States, [2]Centers for Disease Control and Prevention, Atlanta, GA, United States, [3]March of Dimes Foundation, White Plains, NY, United States. Improving Safe Use of Medications during Pregnancy: The Roles of Patients, Physicians, and Pharmacists

Purpose: Given that data for more than 90% of medications are insufficient to determine fetal risks, women are often faced with making decisions about medication use during pregnancy without adequate safety information. This study explored the roles that women, physicians, and pharmacists play in making decisions about medication use during pregnancy, to identify shared challenges and opportunities. Methods: Trained moderators conducted six online focus groups (n=48) and in-depth, follow-up interviews (n=12) with women who used commonly prescribed medications to treat chronic or acute conditions either while pregnant or while planning a pregnancy. Interviewers also conducted in-depth interviews with nine physicians and five pharmacists. All focus groups and interviews assessed participants' knowledge, attitudes, practices, and access to information about medication use during pregnancy. Two researchers independently coded the focus group and interview transcripts with NVivo 10.0 software to identify themes and explore patterns across the three groups. Results: Because of concerns about risks to the developing baby, the women, physicians, and pharmacists interviewed strive to "play it safe" with medication use during pregnancy. All three groups described the need for an engaged patient who can make informed decisions. The groups also described challenges related to communication between physicians and patients, between pharmacists and patients, and between physicians and pharmacists about patients' pregnancy status, as well as a lack of patient-centric resources. Conclusions: Women, physicians, and pharmacists are highly motivated to protect developing babies from the potential harms of medication use during pregnancy. Strategic message development to help 1) physicians discuss the benefits and risks of medication use during pregnancy with their patients, and 2) pharmacists screen for pregnancy and counsel on medication safety are needed. Improved informational resources for both groups could help maximize the effectiveness of these interactions.

S12

GOLEMBESKY A[1], SCHEUERLE A[2]. [1]UCB Pharma, Raleigh, NC, United States, [2]University of Texas Southwestern Medical Center, Dallas, TX, United States. Integration of a Teratologist's Clinical Review of Birth Defects Reported through Pharmacovigilance

Review of birth defects by a clinical geneticist is common practice for postmarketing pregnancy exposure registries. This clinical review assesses the presence of malformations and the possible temporal association between malformation, embryogenesis, and medication exposure. Teratology review is not routinely integrated in birth defect cases reported through pharmacovigilance mechanisms; this is the first known report to initiate such a review. The UCB Pharma drug safety database was searched for possible birth defect cases in pregnancies exposed to certolizumab pegol (CZP, a PEGylated Fc-free anti-TNF approved in the US for the treatment of rheumatoid arthritis, Crohn's disease, psoriatic arthritis, and axial spondyloarthritis) as of February 1, 2015. The database includes pregnancies reported from clinical studies and spontaneous reports from patients or healthcare professionals. Prospective and retrospective reports were included. Data on timing of CZP exposure, pregnancy outcomes, comorbidities, and infant events were extracted by two independent reviewers. Birth defects reported as part of participation in pregnancy registries (e.g., OTIS) and paternal exposures were excluded. All other birth defect cases were reviewed by a clinical geneticist. A total of 384 maternal CZP-exposed pregnancies with known outcome were reported. 16 birth defect cases were identified; five cases already reported in pregnancy registries were excluded from review. In the remaining 11 cases, clinical geneticist review identified 13 malformations. These malformations were classified into organ systems to identify potential patterns. Clarification was requested in eight cases resulting in 12 queries. Specific queries for further information included requests for more specific exposure dates, better pregnancy dating, patient racial background, and the extent of birth defect including the need for surgical intervention. Because this first expert review took place long after the cases were reported, these data could not be obtained. 10 malformations could not be adequately assessed for possible temporal association. Pharmacovigilance reports have well-known limitations, including incomplete documentation. These limitations are particularly problematic when trying to evaluate safety in pregnancy. Timely expert clinical review of birth defect reports, combined with regular follow-up information, would significantly improve the quality of the safety database for signal detection and safety evaluations of birth defects.

S13

LANGLOIS PH[1], SCHEUERLE AE[2], MARENGO LK[1], HOYT AT[1], ETHEN MK[1], CANFIELD MA[1]. [1]Texas Department of State Health Services, Austin, TX, United States, [2]University of Texas Southwestern Medical Center, Dallas, TX, United States. Time Trends of Microcephaly in Texas: What's Up?

Anticipating the possible arrival of Zika virus, we examined the birth prevalence of microcephaly in Texas. We found a 3-fold increase, from 6.62 cases per 10,000 live births in 1999 to 19.79 in 2012. This was equivalent to an 8.5% average increase per year, and was highly statistically significant ($p < 0.0001$). The purpose of the current study was to find clues explaining that increase. Case data were taken from the Texas Birth Defects Registry. We used Poisson regression with year as a continuous independent variable and adjusted for births; that was stratified for each clinical and sociodemographic group, and tested for interaction (time trend difference between groups). It was not possible to analyze proportionate vs. disproportionate microcephaly. For clinical variables, the magnitude of the time trend differed significantly ($p < 0.003$) between the following groups. Possible/probable microcephaly cases increased on average 14.4% per year compared to definite (8.3%). Microcephaly as an isolated defect grew at 12.1% vs. multiple malformation cases (6.8%). Cases with no documented cause grew at 10.1%, cases with other malformations grew at 6.7%, and those with other documented causes at 2.6%. Full term cases who did not meet head circumference criteria for microcephaly increased at 11.8%, while cases with heads smaller than three standard deviations below average grew at 4.7%. Among other variables examined, microcephaly in Hispanics increased on average 12.2% per year compared with 7.1% for non-Hispanic (NH) White, 7.3% for NH Black, and 8.2% for NH Other. Microcephaly birth prevalence for normal weight mothers grew at 16.4% vs. 6.3–7.5% in other body mass index groups. Among self-paid deliveries, microcephaly increased at 31.3% per year, compared with private insurance (4.6%), Medicaid (9.1%), and other (12.7%). Different regions in Texas varied significantly. Several observations suggest that the apparent increase in microcephaly occurrence from 1999–2012 in Texas was driven at least partly by changes in clinical practice or health care. These include higher increases in cases that were possible/probable or isolated, and in cases that had no documented cause or that had less severe microcephaly. It was also supported by differences in delivery payment source.

Wiley-Blackwell Symposium
Neurodevelopmental Deficits from Fetal Exposure to Methamphetamine, Cocaine, and Alcohol: Emerging Mechanisms and Human Consequences

(Joint with DNTS)

Chairpersons: Charles V. Vorhees, Cincinnati Children's Hospital Medical Center and Peter G. Wells, University of Toronto

S14

WELLS PG[1,2], BHATIA S[1], DRAKE D[1]. [1]Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [2]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada. Oxidative Stress Mechanisms of Neurodevelopmental Deficits Initiated by Methamphetamine and Ethanol

In utero exposure of mouse progeny to alcohol (ethanol) and methamphetamine causes substantial postnatal neurodevelopmental deficits. One emerging pathogenic mechanism underlying these deficits involves fetal brain production of reactive oxygen species (ROS) that oxidatively damage DNA leading to altered gene expression, likely via epigenetic mechanisms. Mechanisms of fetal ROS production include induction of ROS-producing NADPH oxidases and drug bioactivation to free radical intermediates by prostaglandin H synthases. Antioxidative enzymes like catalase in the fetal brain, while low, provide critical protection. In addition to altering signal transduction, ROS can oxidatively damage cellular macromolecules including lipids, proteins, and DNA, the latter of which may be repaired by various enzymes. Fetal deficiencies in several DNA repair proteins, including oxoguanine glycosylase 1 (OGG1) and breast cancer protein 1 (BRCA1), enhance the risk of both drug-initiated postnatal deficits and deficits in untreated progeny, the latter of which may be relevant to conditions like autism spectrum disorders. Risk is further regulated by fetal nuclear factor erythroid 2-related factor 2 (Nrf2), a ROS-sensing protein that upregulates an array of proteins including antioxidative enzymes and at least some DNA repair proteins. (Support: Canadian Institutes of Health Research.)

S15

VORHEES CV. Cincinnati Children's Research Foundation and University of Cincinnati, Cincinnati, OH, United States. Effects of Methamphetamine on Brain and Behavioral Development

Rats treated with (+)-methamphetamine (MA) during neonatal development (equivalent to third trimester brain development in humans) results in allocentric learning and memory (L&M) deficits in the Morris water maze, egocentric learning deficits in the Cincinnati water maze, and working and reference memory deficits in the radial water maze. Neonatal MA causes sharp increases in plasma ACTH and corticosterone. To test whether these changes contribute to the L&M deficits, we severed and autotransplanted the adrenals at P10 and then treated pups with MA or saline from P11–20. This reduced MA-induced corticosterone increases by approximately 50% but did not attenuate the adult L&M deficits. In adult offspring treated with MA from P11–20, we found reduced neostriatal dopamine levels, D_2 receptor density, and PKA activity. To test the functional consequences of these changes, we treated rats neonatally with MA as before and tested them as adults for locomotor activity. MA-exposed rats exhibited exaggerated hyperactivity in response to the D_1 agonist SKF-82958, reduced hyperactivity to the NMDA antagonist MK-801, and mild under-response to D_2 autoreceptor agonist, quinpirole, but no changes in response to serotonergic agonists. MA increases reactive oxygen species (ROS) prenatally in mice and in adult rats. We tested the involvement of ROS in neonatal MA's effects two ways: by measuring F_2 isoprostanes (F_2-IsoPs; markers of ROS) and by pretreatment with the spin trapping agent alpha-phenyl-N-tert-butyl nitrone (PBN) prior to each dose of MA. There was no change in F_2-IsoPs in striatum or hippocampus after the first day, nor after the completion of neonatal MA treatment. PBN did not attenuate MA-induced L&M deficits. In order to investigate striatal D_1 effects after P6-15 MA exposure, we used microPET/CT imaging using the D_1 ligand TISCH during adulthood. We found no effects of MA treatment; we also examined brain oxygen activity using 2-fluoro-2-deoxyglucose and found no changes in activity in response to SKF-82958. In sum, third trimester-equivalent MA (P11–20 or P6–15) in rats leads to long lasting L&M impairments on multiple tests and changes in dopaminergic and glutamatergic receptor function assessed pharmacologically. However, the exact mechanism of MA-induced brain changes remains to be elucidated.

S16

STANWOOD G. Florida State University, Tallahassee, FL, United States. Dopaminergic Mechanisms of Cocaine-Initiated Neurodevelopmental Deficits

In a low-dose intravenous animal model, *in utero* cocaine exposure produces a permanent reduction in dopamine D_1 receptor signaling, elongations of dendritic morphology of cortical pyramidal cells, and changes in structure and protein expression in subtypes of cortical interneurons. Specific cognitive and motor behaviors are altered in adolescent and adult offspring as a result, and these deficits have strong parallels in the clinical literature. The abnormalities are elicited during a specific period of embryonic development and occur only in brain regions receiving dense dopaminergic input. Very similar changes are present in the medial frontal cortex of dopamine D_1 receptor null mice, and D_1 receptors potently modulate both dendritic outgrowth and interneuron migration. These results suggest that loss of D_1 receptor-mediated signaling during development in both the genetic knockout and following prenatal cocaine produces analogous alterations in cellular organization. Studies in specific biogenic amine transporter mutants suggest complex roles for dopamine and norepinephrine transporters in mediating the effects of gestational cocaine on the developing cerebral cortex. Conditional approaches are allowing us to now examine cell-type heterogeneity in dopamine D_1 and D_2 receptor modulation of brain development. Moreover, emerging data from several labs now point to transgenerational effects mediated at least in part through epigenetic mechanisms. Taken together, these studies demonstrate the mechanisms by which alterations in dopaminergic activity during critical epochs of development alters circuits mediating cognitive and emotional behaviors, and may lead to subsequent psychiatric disease later in life.

S17

SMITH L[1,2], LAGASSE L[2], DERAUF C[2], NEWMAN E[2], ARRIA A[2], HUESTIS M[2], DELLA GROTTA S[2], DANSEREAU L[2], NEAL C[2], LESTER B[2]. [1]Harbor-UCLA, Torrance, CA, United States, [2]IDEAL Community Research Network, Torrance, CA, United States. Human Neurodevelopmental, Behavioral, and Growth Consequences of Exposure to Prenatal Methamphetamine and Alcohol

Numerous adverse effects on childhood neurodevelopment and behavior have been attributed to prenatal methamphetamine exposure. However, these data have been limited by a small sample size, lack of a control group, and reliance on maternal self-report instead of objective measures of drug exposure. We report findings from the Infant Development and Lifestyle (IDEAL) Study, to our knowledge the first longitudinal, prospective study of prenatal methamphetamine exposure in children up to age 7.5 years. We enrolled 412 mother-infant pairs (204 methamphetamine-exposed and 208 unexposed matched comparisons) with exposure determined by maternal self-report and/or positive meconium toxicology. Serial assessments of growth, development and behavioral assessments were conducted from birth through age 7.5 years. In the newborn period, no withdrawal syndrome was observed though there was a heightened risk for being born growth restricted. Newborns demonstrated more signs of stress, which normalized to the level of comparison neonates by one month of age. From ages 12 months to 7.5 years, subtle fine motor, attention, and behavioral deficits were observed with some findings associated with heavier drug exposure. The data suggest children exposed to methamphetamine have increased risks for targeted, subtle neurodevelopmental and behavioral issues in a dose-dependent manner. Possible mechanisms will be explored including a discussion of existing neuroimaging data in methamphetamine-exposed children. Findings will also be discussed in the context of the prenatal drug coexposures of nicotine, marijuana, and alcohol, with a particular emphasis on fetal alcohol effects.

March of Dimes Symposium
New Approaches to the Treatment of Birth Defects

Chairpersons: Jan M. Friedman, University of British Columbia and Joe Leigh Simpson, March of Dimes Foundation

S18

NORTHRUP H. UTHealth McGovern Medical School, Department of Pediatrics, Division of Medical Genetics, Houston, TX, United States. Tuberous Sclerosis Complex: From Bedside to Bench and Back Again

Tuberous Sclerosis Complex (TSC) is a single gene disorder resulting in formation of benign tumors (hamartomas and hamartias) in multiple organ systems. TSC affects ~1/6,000 births with wide variability in phenotype. Mutations in either of two genes, *TSC1* and *TSC2*, can cause TSC. The protein products of *TSC1* and *TSC2*, hamartin and tuberin respectively, form a multimer in the cells of the body that control an ancestrally conserved insulin signaling pathway important in regulating cell growth. Discovery of the genes and their molecular mechanisms has led to US FDA-approved therapies for many of the medical problems facing affected patients. From clinical description to genes to molecular mechanism to therapy, the story of TSC highlights the power of genetic discovery to improve the lives of affected patients.

S19

CLARKE L. University of British Columbia, Vancouver, BC, Canada. Treatment of Lysosomal Storage Diseases: Lessons for Other Genetic Disorders

The lysosomal storage diseases are the group of genetic disorders that have advanced the most rapidly from gene identification to approved therapeutics. Critical to this rapid progression have been insights provided by comprehensive studies of disease pathogenesis as well as disease natural history data gained from registries. The therapeutic advances that have occurred for these disorders highlight the importance of genotype phenotype correlation studies, precise natural history data as well as fundamental studies of the cell biology of disease utilizing either cell lines or animal models. These studies have led to the establishment of direct gene product replacement strategies in addition to alternative therapeutics directed to the misfolded protein response, stop codon read through as well as methods to alter substrate and distal pathways that are linked to disease pathogenesis. These approaches and data obtained from these studies will be reviewed. The approaches that have been successful in the lysosomal storage diseases provide an excellent framework for the establishment of therapeutic advances for birth defects and other genetic disorders.

S20

PRASAD VK. Duke University Medical Center, Durham, NC, United States. Bone Marrow Transplantation and Umbilical Cord Blood Transplantation for Inborn Errors of Metabolism

The mucopolysaccharidoses (MPSs) and other inborn errors of metabolism (IEMs) are caused by single-gene defects. They lead to progressive cellular accumulation of chemical substrates and dysmorphism and damage to multiple organs including the central nervous, musculoskeletal, cardiorespiratory, and other systems. Children also develop multiple deformities. Enzyme replacement therapy (ERT) is available for MPS I, II, and VI and a few other IEM and may be beneficial in some patients. However, ERT does not improve neurocognitive function because of its inability to cross the blood-brain barrier. In contrast, allogeneic hematopoietic stem cell transplantation (HSCT) allows donor-derived, enzyme-producing cells to migrate to the brain and other organs to provide permanent enzyme therapy and thus help somatic organs, improve neurocognitive function and quality of life, and prolong survival, particularly when performed early in the course of the disease. In the past, bone marrow has been the graft source but in the last ten years increasing numbers of patients have been treated with unrelated donor (URD) umbilical cord blood transplant (UCBT), allowing rapid and increased access to transplantation with favorable outcomes. This presentation will describe published and our institutional clinical experiences and will attempt to provide therapy guidelines for patients with IEM.

S21

BELFORT MA[1,2]. [1]Baylor College of Medicine, Houston, TX, United States, [2]Texas Children's Fetal Center, Houston, TX, United States.
In Utero Treatment of Meningomyelocele: Open and Minimally Invasive Fetal Surgery

Introduction: This invited talk will present background information on meningomyelocele (MMC) and its prenatal treatment. In addition I will present data from Texas Children's Fetal Center, one of the only Centers in the world performing fetoscopic MMC repair, showing that minimally invasive fetal surgery for MMC in an exteriorized CO_2 filled uterus (ENDO) is associated with a lower rate of maternal and fetal complications than via hysterotomy (OPEN). Study Design: Retrospective study of singleton pregnancies. Selection was based on MOMS trial inclusion criteria, and all had the same pre/intra/postoperative care protocols. The rates of obstetric, maternal, fetal, and early neonatal complications were compared. Membrane and placental pathology was also compared between the groups. Results: Maternal demographic parameters and gestational age at fetal surgery and at delivery were similar for ENDO vs. OPEN respectively. ENDO took significantly longer than OPEN ($p<0.001$) but blood loss (ml) was less for ENDO ($p=0.04$). There was no difference in the rate of abruption or chorioamnionitis respectively and pathology showed no significant differential effect of CO_2 on the membranes. PPROM rate was similar but PPROM occurred significantly later in ENDO. 33% ENDO and 0% OPEN had vaginal delivery ($p < 0.001$). Conclusion: Fetoscopic MMC repair does not increase maternal/fetal complications, allows vaginal delivery, and reduces long-term maternal risks by avoiding a scarred uterus. Fetoscopic surgery in CO_2 offers possibilities for development of *in utero* surgeries heretofore not considered realistic or feasible.

S22

TWORETZKY W. Boston Children's Hospital, Boston, MA, United States.
In Utero Treatment of Cardiac Malformations

Fetal cardiac interventions are performed for two major indications. First, to balloon dilate a stenotic or atretic aortic or pulmonary valve in order to preserve and promote left or right ventricular size and function. This in turn would prevent progression to the left or right ventricular hypoplasia that would necessitate a univentricular or Fontan palliative circulation with all its long-term complications. The other major indication is to improve survival in cardiac defects that might otherwise have an extremely high chance of perinatal mortality. These defects include hypoplastic left heart syndrome with intact or highly restrictive atrial septum and the constellation of aortic stenosis with severe mitral regurgitation and intact atrial septum. Twin pregnancies or major associated noncardiac anomalies are fetal contraindications for fetal cardiac intervention. Significant maternal medical problems or obesity are maternal contraindications. The procedures are performed with the mother awake with epidural anesthesia. The fetus is given intramuscular analgesia and paralysis. The procedures are performed percutaneously under ultrasound guidance using a 19 or 18 gauge cannula. Aortic valve dilations are performed in fetuses with still normal sized left heart structures with features that predict evolution to HLHS if left alone. For aortic valve balloon dilation, the cannula is inserted into the dilated left ventricle and a wire and balloon catheter advanced across the stenotic aortic valve after which the balloon is inflated several times and then removed. For pulmonary valve atresia, the cannula is inserted into the smaller and hypertrophied right ventricle after which the atretic valve has to be perforated with a sharp needle prior to balloon dilation. For HLHS with intact atrial septum, the septum accessed via the left or right atria, punctured with the stylet or a sharp needle and then either a balloon or stent is inflated across the septum to decompress the left atrium. The goal is to have these patient more stable in the immediate neonatal period and relieve the high pressure left atrium with its adverse effects on the lung and pulmonary vasculature. The most common procedural complications are fetal loss (5–10%), bradycardia and dysfunction, and hemopericardium. The challenges ahead include optimizing patient selection, improving procedural success and minimizing complications.

Integrative *In Vitro* Models for Neurovascular Development Function Symposium

(Joint with DNTS)

Chairpersons: Thomas B. Knudsen, US Environmental Protection Agency and William Slikker Jr., National Center for Toxicological Research, US FDA

S23

MURPHY WL. University of Wisconsin, Madison, WI, United States. Assembly of Stem Cell-Derived Human Tissues for Screening Applications

The need for human, organotypic culture models coupled with the requirements of contemporary drug discovery and toxin screening (i.e., reproducibility, high throughput, transferability of data, clear mechanisms of action) frame an opportunity for a paradigm shift. The next generation of high-throughput cell-based assay formats will require a broadly applicable set of tools for human tissue assembly and analysis. Toward that end, we have recently focused on: 1) generating iPS-derived cells that properly represent the diverse phenotypic characteristics of developing or mature human somatic cells; 2) assembling organotypic cell culture systems that are robust and reproducible; 3) translating organotypic cell culture models to microscale systems for high-throughput screening; and 4) combining genomic analyses with bioinformatics to gain insights into organotypic model assembly and the pathways influenced by drugs and toxins. This talk will emphasize recent studies in which we have explored biologically driven assembly of organotypic vascular and neural tissues. These tissues mimic critical aspects of human tissues, can be used for predictive neurodevelopmental toxicity, and for identification of vascular disrupting compounds. We have also begun to use assembled human tissues to develop models of developmental disorders, degenerative diseases, and infectious disease effects.

S24

FERGUSON SA, PANOS JJ. National Center for Toxicological Research, US FDA, Jefferson, AR, United States. Blood-Brain-Barrier Development and Function

The study of blood-brain-barrier (BBB) development and function is critical. Certain diseases/toxicants can alter permeability (e.g., prenatal dioxin exposure alters BBB permeability *in vitro* (Miyazaki et al., 2015)). However, there is little research describing appropriate *in vivo* rodent models, suggesting that the rat is not an adequate model. Characterizing BBB development, maintenance, and disease states *in vivo* is time consuming and daunting, potentially leading to a preference for *in vitro* models (Lippmann et al., 2013). Further, BBB permeability differs across species (Sinha, 2003), brain development rates are not consistent across species, birth is not a consistent marker across species for BBB development (Engelhardt, 2006), and human and rodent brain glucose usage is dissimilar at birth (Nehlig, 1997). Results of studies using PET radioligands have indicated profound differences in glycoprotein transport in rats and guinea pigs compared with minipigs, nonhuman primates, and humans (Syvanen et al., 2009). Such differences have contributed to the development of human stem cell-based BBB models (Aday et al., 2016). However, recent advances in mouse models have aided in the study of BBB development, maintenance, and aging (Sohett & Daneman, 2013). Such models have produced convincing information indicating a functioning BBB during rodent embryogenesis (Daneman et al., 2010). Several of those models affect the BBB by acting on endothelial cell (EC) function to enact changes in angiogenesis and BBB maintenance. ECs of the BBB are unique compared to those of other tissues in that they incorporate intracellular tight junctions (TJs), absence of fenestrations, and reduced transcytosis (Obermeier et al., 2013). Novel models to aid in the cost-effective and high-throughput study of BBB permeability, including zebrafish and grasshopper, are being developed (Geldenhuys et al., 2012). Stem cell modeling of angiogenesis and BBB maintenance using rat cortical neural progenitor cells can provide high-throughput screening of BBB function *in vitro* (Lippman et al., 2013). The combination of *in vivo* and *in vitro* models will likely be powerful tools for assessing CNS access to drugs and toxicants whether this is a desired or unwanted effect.

S25

PETERSON RT[1,2]. [1]Massachusetts General Hospital, Boston, MA, United States, [2]Harvard Medical School, Boston, MA, United States. High-Throughput Screening of Zebrafish to Identify Modifiers of Nervous System Development and Function

Assessing the effects of chemical compounds on the nervous system is a complex and laborious task, making it difficult to apply the tools of modern high-throughput science. As a result, drug discovery and toxicology for the nervous system lag behind other organ systems. In an effort to address this problem, we have developed a panel of automated high-throughput behavioral and developmental assays that can be performed with live zebrafish in a 96-well plate format. These assays, which incorporate robotics, optics, and high-throughput video analysis, can be used to screen >1,000 small molecules per day and detect behavioral or developmental changes caused by compounds with diverse mechanisms of action. We have validated the assays with a training set of 700 existing neuroactive compounds affecting several distinct neurotransmitter systems. Compounds from each functional class produce distinctive behavioral profiles that resemble each other but are distinct from those of other functional classes, suggesting a strong correlation between zebrafish behavioral profiles and compound mechanisms of action. We have also screened 25,000 diverse small molecules and discovered more than 800 compounds that alter zebrafish behavior or development in diverse ways. Some of these novel compounds function via well-characterized pathways, while others appear to function via novel pathways. We anticipate that this *in vivo* approach to compound assessment will enlarge significantly the toolset of neuroactive compounds for neuroscience research, will facilitate screening of compounds for cerebrovascular or nervous system toxicity, and will also provide novel therapeutic avenues for treating various CNS disorders.

S26

WIKSWO JP, BOWMAN AB, BROWN JB, CODREANU SG, MARKOV DA, MAY JA, MCCAWLEY LJ, MCLEAN JA, NEELY MD, PENSABENE V, SHERROD SD, SHI M, WEBB DJ. Vanderbilt University, Nashville, TN, United States. Human Neurovascular Unit On-A-Chip: Microscale Systems for Tissue-Level Response

To truly understand the contribution of genetics, environment, drugs, and maternal health to fetal development and resulting birth defects, we need new tools to model and investigate these complex interactions. Animal studies have been invaluable, but in many cases they fail to recreate human physiology, and traditional cell culture models lack the complexity to capture the full disorder. To help bridge this gap and give investigators a new tool in their experimentation arsenal, we are developing organs-on-chips that provide highly accessible—but still complex—cell culture models of a target organ. With these engineered tissues and their accompanying perfusion systems, it is possible to model blood-brain-barriers (BBBs), fetal membranes, mammary glands, or other organs. These microfluidic platforms and associated pumps and valves let us create tissue-specific microenvironments and test the effects of drug exposure over time, including immune response (which is often an evolving response), tissue recovery and repair. In our human Neurovascular Unit (NVU), for example, we have seen BBB disruption soon after toxin exposure but partial recovery after 24 hours, and we have identified compounds capable of preventing BBB disruption. Through ion mobility-mass spectrometry analysis we have also demonstrated that disruptions to the BBB lead to metabolic changes within the NVU. An important challenge will be to address the urgent need to screen the effects of common environmental hazards on fetal development and overall health by adapting our NVU to adequately recapitulate specific stages in the development of the fetal BBB, either as a static system or as one whose temporal development tracks that of the fetus. This should be a feasible goal, given our success with the adult NVU. Research reported herein was supported by Assistance Agreement No. 83573601 awarded by the US Environmental Protection Agency to Vanderbilt University, and by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UH3TR000491. The views expressed in this abstract are solely those of the authors and do not necessarily reflect those of either agency. The US EPA does not endorse any products or commercial services mentioned in this publication.

Public Affairs Symposium
Depression and Its Treatment in Pregnancy

(Joint with DNTS and OTIS)

Chairpersons: Kembra L Howdeshell, National Institute of Environmental Health Sciences and Asher Ornoy, Hebrew University Hadassah Medical School

S27

WISNER KL. Northwestern University, Chicago, IL, United States. Depression Treatment in Pregnancy: Are We Asking the Right Questions?

Major Depressive Disorder (MDD) is a common complication of pregnancy, with 7.5% of women having a new episode during pregnancy and 6.5% with an incident episode postpartum. Suicide accounts for 20% of deaths in postpartum women and it is the second leading cause of mortality. Screening for perinatal depression was recommended by the USPSTF; however, for many pregnant women, accessible and acceptable mental health intervention is limited. MDD is associated with poor nutrition, obesity, smoking, alcohol and drug use, interpersonal violence, and poverty. Severe maternal antenatal stress is associated with offspring mental disorders and multiple birth defects. Children exposed to maternal MDD *in utero* have higher cortisol levels than infants of nondepressed mothers, a biochemical change that continues through adolescence which places the offspring at higher risk for mental illness. Notably, maternal treatment of MDD during pregnancy normalizes infant cortisol levels. Investigations of SSRI antidepressant use in pregnancy have largely yielded studies on adverse outcomes, including preterm birth, cardiac defects, poor neonatal adaptation, persistent pulmonary hypertension of the newborn, and psychomotor developmental effects. The challenge is to separate the impact of these two exposures (SSRI and MDD) on the reproductive outcome. A major methodological challenge in interpreting observational studies is the problem of confounding. Few studies have evaluated the benefit of antidepressant treatment that justifies the risk. The prescriber is left with the responsibility of deciphering whether the "benefits outweigh the risks" with limited information on benefits and a large literature on risks. However, evaluating the efficacy of any drug requires establishment of the dosing regimen. Data to inform SSRI dose requirements across pregnancy are meager. Pregnancy induces alterations in cytochrome (CYP) 450 isoenzymes. CYP3A4, 2D6 and 2C9 are increased, and doses of drugs metabolized by these CYPs must be increased. CYP2C19 activity decreases and dose reductions are needed. We must provide the optimal drug doses across the changing milieu of pregnancy to maximally reduce disease burden while minimizing adverse effects. A strategy for optimal pharmacologic treatment for pregnant women will facilitate exploring potential benefits to balance the extensive literature on risks to the maternal-fetal pair.

S28

OBERLANDER TF. University of British Columbia, Vancouver, BC, Canada. What Can Prenatal Exposure to SSRI Antidepressants Teach Us About Child Development?

Selective serotonin reuptake inhibitor (SSRI) antidepressants are commonly used during pregnancy and the postpartum period. SSRIs inhibit the reuptake of a key neurodevelopmental signal, serotonin (5HT), thereby increasing central 5HT levels during developmentally sensitive periods. Given serotonin's key role in early brain growth, SSRI use in pregnancy raises critical and unanswered questions about the long term developmental effects associated with early changes in brain 5HT levels. Recent attention has focused on increased risks for disordered or delayed development associated with prenatal exposure to SSRIs, particularly related to risks for attentional and mood disorders, as well as autism spectrum disorder (ASD). However, recent preclinical data are now showing that under particular developmental circumstances, SSRIs may protect against the effects of early exposure to maternal stress. Similar human findings remain very limited. This presentation will explore the question of whether there is similar clinical evidence in early childhood illustrating that prenatal SSRI exposure could—either directly or indirectly—confer a potential developmental benefit against the effects of perinatal maternal mood disturbances. With this in mind, this keynote will focus on a review of recent clinical findings that illustrate a variety of developmental outcomes in children with *in utero* SSRI exposure. This presentation will seek to offer a broader perspective that illustrates risks and possible benefits that may be associated with the use of SSRIs during pregnancy, thus also potentially offering key lessons about child development in general.

S29

ORNOY A. Hebrew University Hadassah Medical School, Jerusalem, Israel. The Safety of Tricyclic Antidepressants and Mood Stabilizers in Pregnancy: What Should We Use for the Treatment of Bipolar Disorders?

Although the most widely used antidepressant drugs are the SSRIs and SNRIs, a significant proportion of patients with depression or bipolar disorder are still treated with "elder" antidepressants or with mood stabilizers. The mood stabilizers (lithium, valproic acid (VPA), carbamazepine, oxcarbazepine, and lamotrigine) are generally more effective in the manic phase, while the tricyclic and tetracyclic drugs are generally used during depression. Imipramine, desipramine, and other tricyclic drugs are not teratogenic in humans or pregnant animals, but the exposed infants may have withdrawal symptoms. The tetracyclic drugs like mirtazapine and maprotiline are also not considered to be teratogenic, but the human data in pregnancy is limited. Among the mood stabilizers, lithium was more commonly used for the treatment of pregnant patients. However, lithium exposure during pregnancy was shown to increase the rate of rather severe cardiac anomalies including Ebstein's anomaly, hence pregnant women are advised to perform fetal echocardiography but not to stop treatment. No neurodevelopmental damage has been demonstrated in infants exposed *in utero* to tricyclics or lithium. Carbamazepine and oxcarbazepine are similar structurally and have similar pharmacologic effects. Carbamazepine is a known human teratogen that increases the rate of neural tube defects (NTD) to 0.5–1% as well as the rate of other congenital anomalies, especially cardiovascular. Although there is relatively little data on the safety of oxcarbazepine in pregnancy, judging from animal studies, it seems to have a similar teratogenic effect. Carbamazepine may also cause neurodevelopmental delay. VPA seems to be the most teratogenic antiepileptic drug causing 1–2% of NTD and a significant increase in the rate of major congenital anomalies: ie, cardiac and limb anomalies, facial clefts, hypospadias. Treatment with VPA may be associated with a specific "valproate syndrome" with facial dysmorphic features and neurodevelopmental delay, especially in language. It may also significantly increase the rate of Autism Spectrum Disorder. Lamotrigine seems to be without significant teratogenic or neurotoxic effects. Indeed, the use of lamotrigine in pregnant women with bipolar disorder is steadily increasing. It is the physician's role to choose the most appropriate drug for treatment of depression in pregnancy rather than withholding treatment.

S30

GINGRICH JA[1,3], MALM H[5], ANSORGE MA[1,3], BROWN A[1,3], CAGLIOSTRO M[1,2], ARANGO V[1,2], WEISSMAN MM[1,3], SOURANDER A[4,1]. [1]Columbia University, New York, NY, United States, [2]New York State Psychiatric Institute, New York, NY, United States, [3]Sackler Institute, New York, NY, United States, [4]Turku University, Turku, Finland, [5]Helsinki University, Helsinki, Finland. New Insights into How SSRIs Shape the Developing Brain: From Mice to Public Health Implications

Serotonin exerts profound effects on neurodevelopment before assuming its mature role as a neurotransmitter. SSRI augmentation of serotonin signaling during sensitive periods of development produces changes in rodent anxiety- and depressive-like phenotypes that are long lasting and delayed in their onset. The rodent SSRI-sensitive period overlaps with human second and third trimester but the long-term effects of human gestational SSRI exposure remain unknown. One of the curious features of the serotonin transporter is that it is transiently expressed in nonserotonergic neurons of the limbic forebrain. SSRI blockade of these transiently expressed, "ectopic" transporters might underlie the enduring effects of early SSRI exposure on limbic circuitry. In this presentation, we review the biologic basis for how SSRIs interact with the developing brain to produce late onset changes in anxiety and depression-like behaviors in rodents. He reviews his recent finding that like rodents, the fetal rhesus macaque also expresses transient, "ectopic" serotonin transporters in the forebrain. He also discusses recent findings showing that human fetal exposure to SSRIs during pregnancy is associated with higher rates of depression in adolescents than expected based on familial loading alone. This association with mood disorders is specific as there are no effects of gestational SSRI exposure on subsequent rates of autism or ADHD. These human findings have potential public health relevance as antidepressant treatment is currently recommended for the management of mood and anxiety symptoms during pregnancy. Consequently, the use of SSRIs in pregnant women has increased steadily over the past 20 years. Alarmingly, our findings indicate that the use of SSRIs during pregnancy to mitigate maternal symptoms may paradoxically alter brain development of the growing fetus in ways that lead to an iatrogenic increase in mood disorders. More research is needed to effectively guide the clinical management of peripartum mental illness to optimize outcomes for both the mother and her fetus.

Increasing Prevalence of Gastroschisis Symposium

Chairperson: Margaret A. Honein, Centers for Disease Control and Prevention

S31

ARNOLD KE. Division of Congenital and Developmental Disorders, Centers for Disease Control and Prevention, Atlanta, GA, United States. Increasing Prevalence of Gastroschisis Worldwide

The overall prevalence of birth defects has been relatively stable in the United States; one of the most noteworthy exceptions has been the documented increasing prevalence of gastroschisis. Gastroschisis is a congenital defect in which the intestines protrude without a membranous covering through an opening in the abdominal wall, typically located to the right of the umbilicus, requiring urgent surgery after birth. Despite the fact that gastroschisis is readily apparent at birth, the defect was not well documented before the 1950s. Gastroschisis was first delineated in a 1953 series of seven cases, ten years later only 32 gastroschisis cases had been reported in the medical literature. When systematic monitoring of birth defects began in the mid-1960s in parts of Europe, North America, and South America, gastroschisis was very rare, estimated at 1 in 50,000 live births. Over the next three decades, however, the prevalence of gastroschisis was observed to be increasing globally, with few exceptions. A 10- to 20-fold increase in prevalence during the 1980s through early 2000s led experts at that time to characterize gastroschisis as a worldwide epidemic. In the United States, birth defects surveillance programs expanded from three states in the early 1970s to 43 states by 2015. While multiple individual states have observed increasing trends in gastroschisis, collaborative multistate studies of gastroschisis prevalence in the United States showed a prevalence increase from 2.3 to 4.2 per 10,000 live births during 1995–2005, and a continued increase from 1995–2005 (3.6 per 10,000 live births) to 2006–2012 (4.9 per 10,000 live births) in the most recent study. It appears that neither advances in technology, changing case definitions, nor the potential misclassification of other birth defects with a similar presentation, can explain the dramatic increase in the prevalence of gastroschisis over time. As the first of five presentations in this symposium, we will review the available data on the prevalence of gastroschisis worldwide.

S32

SADLER TW. University of Utah, Salt Lake City, UT, United States. Embryology of Gastroschisis

Gastroschisis is a ventral body wall defect that occurs lateral to the umbilicus, predominantly on the right side. As a result of the defect, intestines and occasionally the stomach and other abdominal organs protrude into the amniotic cavity. Causes of gastroschisis are unknown. There appears to be a genetic contribution in some cases and women of a younger age (<20) are more likely to have a child with the defect, suggesting an environmental factor may be contributing in this cohort. The embryological origins of gastroschisis are also largely unknown, although many theories have been proposed. Most of these have focused on disruptions caused by vascular accidents or failure of the yolk sac to be incorporated into the umbilical stalk. Despite the popularity of these hypotheses, most of the evidence indicates that gastroschisis is a primary malformation involving abnormalities in classical cell phenomena, such as signaling, proliferation, migration, etc. Thus, there are two time points when gastroschisis may be induced: 1) during establishment of the left and right sides (laterality) of the embryo at the end of the second and beginning of the third weeks postconception; 2) during formation and closure of the ventral body wall by the lateral body wall folds in the third and forth weeks of development. Laterality is specified at the end of the second week with appearance of the primitive streak and node and continues during the process of gastrulation. A signaling cascade established at this time, involving *NODAL* and *PITX2*, specifies the left side of the embryo. As a consequence, cells contributing to the lateral body wall folds, heart, and other structures are also specified and are highly susceptible to disruptions that result in defects that probably include gastroschisis. Slightly later, during the third and forth weeks, body wall folds form, move ventrally, and fuse in the midline. Formation of the folds is dependent upon cell proliferation, while fusion requires adherence, cell death, and reorganization of cell layers. These processes have been shown to be susceptible to teratogenic insult and if disrupted can result in cleft lip, cleft palate, neural tube defects, and presumably gastroschisis.

S33

RASMUSSEN SA. Centers for Disease Control and Prevention, Norcross, GA, United States. Genetic and Nongenetic Risk Factors for Gastroschisis

Gastroschisis is an abdominal wall defect typically located to the right of the umbilical cord in which intestines and sometimes other abdominal contents protrude through the abdominal wall opening. Surgical repair is required shortly after birth. The etiology of this defect is unknown. Based on the elevated recurrence risks seen in families with a child with gastroschisis, genetic factors are believed to play a role in its etiology. However, several pieces of evidence also support the role of nongenetic factors, including the increased occurrence of gastroschisis among younger mothers, the increasing birth prevalence of gastroschisis observed in recent years by several birth defects monitoring systems, and the frequent occurrence of gastroschisis in a cluster pattern. An improved understanding of nongenetic risk factors for gastroschisis is needed for development of prevention strategies. This presentation will summarize the latest information on genetic and nongenetic risk factors for gastroschisis. Challenges faced by investigators working to better understand gastroschisis etiology will also be discussed.

S34

CHAMBERS CD. University of California, San Diego, La Jolla, CA, United States. The Potential Role of Common Exposures in Young Women for Gastroschisis: Sexual Activity, Contraception, Medications, and Drugs

Although the causes of gastroschisis are not well understood, the defect is associated with a unique epidemiology, strongly suggesting that environmental factors play a key role in the etiology. The markedly higher risk in young mothers and the possible vascular etiology have pointed to a number of age-related and vasoactive risk factors. Among these are lower prepregnancy body mass index, sexually transmitted diseases, other infections, vasoactive over-the-counter medications, some pain relievers, immune-related factors such as suggested intolerance to paternal antigen, alcohol, tobacco, cocaine, and methamphetamine. However, the number of studies that have had sufficient sample sizes and adequate exposure data to evaluate these associations is limited and results have been conflicting. Evaluating trends in types of exposures occurring over time that mirror trends in rates of gastroschisis may be one approach to addressing this issue. However, other than maternal age, no single type of exposure seems to account for a large proportion of the risk; given the frequency with which some of these exposures take place, clearly there are susceptibility factors or combinations of exposures that must play a role.

S35

FELDKAMP ML[1], ENIOUTINA EY[2], GEISLER WM[3], KRIKOV S[1], BYRNE JLB[1,4], BOTTO LD[1]. [1]Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, UT, United States, [2]Division of Clinical Pharmacology, Department of Pediatrics, University of Utah, Salt Lake City, UT, United States, [3]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States, [4]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT, United States. Investigating the Association between Gastroschisis and Biomarkers of Chlamydia Infection and Inflammation

Gastroschisis is an abdominal wall defect that has been associated with self-reported pregnancy history of a periconceptional sexually transmitted infection (STI), the majority of which were due to Chlamydia trachomatis (CT). CT infections are the most prevalent bacterial STI among young women, the group at highest risk for gastroschisis-affected pregnancies. These infections are often subclinical, making self-reported information a suboptimal marker of exposure. To overcome this challenge, we developed a case-control study, collecting blood, environmental exposures, and sexual history at the time of prenatal diagnosis. The goal is to investigate the association between gastroschisis and the presence in pregnancy of serological markers indicative of CT infection and CT-specific inflammatory responses. The case group includes women prenatally diagnosed with gastroschisis. Controls are women with a normal diagnostic ultrasound, matched to cases on weeks of gestation. Both groups came from the same cohort of women referred to the University of Utah's Maternal Fetal Medicine's Diagnostic Center for their diagnostic ultrasound. Blood samples are collected and interviews conducted by an on-site study coordinator. We will analyze both humoral- and cellular-mediated immune response to CT among cases and controls with assays that use CT organisms (elementary bodies) from different serovars known to be associated with CT genital infections in the US. Enrollment is ongoing, with 122 participants enrolled to date (43 cases; 82 controls). In an interim analysis, cases were significantly more likely to have begun sexual activity at a younger age, have more sexual partners, and change partners between pregnancies compared with controls. Cases also more often had humoral evidence of a recent CT infection (39.4% of cases compared vs. 18% among controls), which was associated with a four-fold increase in gastroschisis. Further, peripheral blood mononuclear cells from cases proliferated more vigorously than controls when stimulated *in vitro* with CT organisms. In summary, data to date suggest case women engage in behaviors that increase their risk for acquiring STIs during the periconception period and more often have humoral evidence of recent CT infection. We will further investigate this association and determine the most appropriate set of biomarkers for use in the future.

Advances in Placental Research Symposium

(Joint with OTIS)

Chairpersons: Richard K. Miller, University of Rochester Medical Center and Sarah G. Obican, University of South Florida

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MILLER RK[1], MCALEAVEY S[2], WOOD RW[1], CARROLL-NELLENBACK J[3], ORMACHEA J[2], HYRIEN O[1], KATZMAN P[1], STODGELL CJ[1], PRESSMAN E[1], THORNBURG L[1], SZLACHETKA K[1], PARKER K[2]. [1]University of Rochester School of Medicine and Dentistry, Rochester, NY, United States, [2]University of Rochester Hajim School of Engineering and Applied Sciences, Rochester, NY, United States, [3]University of Rochester School of Arts and Science, Rochester, NY, United States. Predicting Fetal and Newborn Health: The Role of the Placenta and Its Imaging

Human placenta is the interface between mother and baby. It is anchor, conduit, and controller of the complex vascular networks that develop concurrently with the fetal circulatory system and organs. Placental invasion into endometrium and subsequent growth from implantation concurrent with development of fetal circulation results in the complex placental architecture readily available for study at term. Placental structure and function are subject to challenges from environmental and infectious agents. In light of urgent concerns arising from the Zika epidemic, we will discuss how human *ex vivo* placental models become infected and transmit other viruses, (HIV, Echo 11, CMV, and Coxsackie), and how disease progression is influenced by inflammatory cytokines. There is also a pressing need to associate *in utero* evaluation of placental anatomy and function with neonatal outcome and detailed placental characterization possible at term. Ultrasound technologies have progressed dramatically in the past few years, and provide striking opportunities for detailed characterization of *in utero* placental perfusion. Elastography has moved from the research laboratory to clinical instrumentation, and provides us with a means to evaluate tissue stiffness *in utero*. The Parker Hypothesis (Parker '14) proposes that the elastographic measures of soft tissues such as placenta are deeply linked to the fractal branching distribution of the vasculature. We have demonstrated using *ex vivo* placental perfusions a relationship between the frequency dependence of placenta stiffness and pharmacologically-induced alterations in fetal vasculature. In comparison, infarcts are stiff, and provide dramatic examples of elastographic sensitivity to placental pathology. Term placentae have been perfused with radiopaque gels suitable for computed tomography using large bore clinical instruments and small animal microCT systems to provide high resolution imaging of individual lobules. The resultant large data sets are amenable to automated identification and characterization of branching morphology, as well as to fractal analysis. We anticipate that postdelivery studies in conjunction with ultrasound and MR imaging throughout pregnancy will provide enhanced understanding to the development process, and offer insights that will have prognostic utility. Thus, these emerging technologies are expected to provide enhanced tools for predicting risk to fetus/newborn and managing pregnancies. (Support: RW&MS Goode Foundation.)

S37

ABUHAMAD AZ. Eastern Virginia School of Medicine, Norfolk, VA, United States. *In Utero* Imaging of the Human Placenta: Approaches for Diagnosis of Fetal Health

The human placenta plays a critical role in pregnancy development through several functions, deemed essential for the wellbeing of the mother and child. The placenta is also actively involved in vascular remodeling in early gestation to ensure adequate utero-placental perfusion throughout pregnancy. Mounting evidence suggests that abnormal placental development in early gestation is associated with many maternal and fetal pathologic conditions, which can manifest later in pregnancy such as fetal growth restriction, spontaneous preterm birth, and preeclampsia. Obstetrical ultrasound is the most optimal imaging modality for pregnancy evaluation. Ultrasound is noninvasive, widely available, and is fully integrated into prenatal care. The ability to evaluate the placental microvasculature by current ultrasound technology is limited by the resolution of color Doppler, compounded by motion artifact of surrounding placental tissue. The development of novel ultrasound tools that further expand our ability to evaluate in real time human placental structure and function, will allow for the identification of early markers of placental dysfunction. The wide availability and acceptance of ultrasound in obstetric practice will facilitate the rapid dissemination and integration of novel ultrasound markers into prenatal care. In my presentation, I will review the literature with regards to placental tissue and vascular structure in pregnancy complications and will present novel ultrasound tools that may have a significant impact on our ability to assess the placenta in real time and in early gestations.

S38

SALAFIA CM[1,2], THOMAS DM[3], ROBERTS DJ[4], STRAUGHEN JK[5]. [1]Institute for Basic Research, Staten Island, NY, United States, [2]Placental Analytics, New Rochelle, NY, United States, [3]Center for Quantitative Obesity Research, Montclair State University, Montclair, NJ, United States, [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [5]Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, United States. Human Placental Pathology-Diagnosis in the 21st Century: New Approaches and Techniques

It is generally agreed that placental pathology accounts for the majority of perinatal morbidity and mortality. Despite decades of scientific and technical advances, reductions in maternal and fetal morbidity and mortality remain elusive. In fact, typically, once a pathological pregnancy is diagnosed the plan is for prompt delivery. On the other hand, if the mother or fetus do not show adverse symptoms, physicians and health care providers rarely evaluate the placenta. If a placental prodrome could be diagnosed *in vivo*, risk for maternal or fetal complications could be estimated and acted upon before clinical symptoms are apparent. This is especially relevant in early diagnoses of gestational diabetes mellitus, which can be controlled through carefully monitored diet and activity changes. Unfortunately, a financially feasible, scalable, minimal risk method for accurately diagnosing preclinical placental pathology does not currently exist. To address this gap, there have been increased efforts to identify early gestation biomarkers of placental dysfunction using innovative imaging technology. We propose that novel contexts of readily available placental measures and routine collection of *in vivo* placental images in all pregnancies may be sufficient for early risk determination of complicated pregnancies. The determination of a level of positive predictive value that would allow intervention may be a different question.

S39

AAGAARD K. Baylor College of Medicine, Houston, TX, United States. Unexpected Beginnings: Role of Pregnancy and Parturition in Establishing Our Microbiome

Hominids and *hominins* serve as remarkable hosts to microbes, and we have coevolved over the past 4.5 million years as highly plethoric communities. Precisely when and how these microbes take up residence during development and over the span of an individual's lifetime remains unclear. Moreover, the role of the microbiome in parturition is relatively unexplored. The burden of perinatal (pregnancy and newborn) morbidity and mortality related to infection and/or inflammation is astounding. The WHO estimates that 9.6% or 12.9 million births worldwide are born preterm at <37 weeks of gestation. Significant data suggesting that intrauterine infection is an important modifier for the risk of preterm birth have emerged over the past four decades. However, causative microbial culprits have yet to be identified and interventional trials with antimicrobials have uniformly failed to demonstrate a significant benefit. To the contrary, treatment for clinically asymptomatic commonly associated polymicrobial communities (i.e., bacterial vaginosis or trichomonas vaginalis) has resulted in an increase in the rate of preterm birth. With respect to the potential source of microbiota related to preterm birth, it has generally assumed that the majority of intrauterine infections originate in the lower genital tract, with microbiota ascending into the otherwise sterile intrauterine environment to infect the placenta (preterm birth), fetal membranes (chorioamnionitis), umbilical cord (funisitis), and the fetus (sepsis). However, we and others have recently demonstrated that 1) the vaginal and gut microbiome communities are distinctly structured in pregnancy; 2) the placenta is in fact not sterile, but rather harbors a low-abundance microbiome; and 3) the placental microbiome varies by virtue of preterm gestation. Through ongoing longitudinal metagenomic studies characterizing the human and primate antenatal and perinatal microbiome, we are piecing together new understandings as to when, how, and where it varies in the course of human gestation. With mindful design of clinical translational studies accompanied by robust molecular and clinical data, we continue to assemble the capacity to significantly discern causal inference of the role of the maternal and placental microbiome in the timing of parturition and establishment of the early microbiome.

S40

SADOVSKY YS[1,2]. [1]Magee-Womens Research Institute, Pittsburgh, PA, United States, [2]University of Pittsburgh Department of OBGYN and Reproductive Sciences, Pittsburgh, PA, United States. Placenta-Specific microRNAs and Pregnancy Health

Intact placental function is essential to fetal development and growth. In addition to controlling gas and nutrient exchange and providing immune and endocrine support to the developing embryo, the placenta functions as a barrier against microbial invasion into the fetal compartment. The trophoblast, which is directly bathed in maternal blood, constitutes the frontline placental defense, and restricts the spread of pathogens into the fetal microenvironment. We recently found that cultured primary human trophoblasts from term, healthy placentas are resistant to infection by diverse types of DNA and RNA viruses. Moreover, this resistance can be conferred to nonplacental cells by transferring trophoblastic conditioned medium to recipient cells. Placental specific microRNAs, expressed from the chromosome 19 microRNA cluster (C19MC), partly mediate this antiviral effect. In addition, we recently found that medium preconditioned by human villous trophoblasts upregulates interferon-stimulated genes (ISG) in an interferon-receptor dependent manner. While it is known that human trophoblasts produce hormones and control the transport of signaling molecules across the maternal-fetal interface, we and others recently found that trophoblastic microRNAs can be released to the plasma. Circulating plasma microRNAs can be bound by proteins, or packaged within several types of extracellular vesicles, including apoptotic bodies, microvesicles, and exosomes. Within this context, we found that while all trophoblastic extracellular vesicles contain C19MC microRNAs, exosomes execute the most robust antiviral effect, which is independent of ISG induction. Investigating the patterns of microRNA transport *in vivo* among the maternal, placental, and fetal compartments in humans and mouse models, we assessed several approaches to optimize microRNA expression in the mouse placenta *in vivo*. Using these tools, we detected the trafficking of placental microRNAs to the maternal and fetal compartments, and from the maternal circulation to the feto-placental unit. Together, our findings establish previously unrecognized mechanisms of feto-placental protection against viral pathogens, and suggest that placental miRNAs circulate to the maternal and fetal compartments, where they may orchestrate an antiviral response.

Assessing the Developmental Toxicity of Nanomaterials Symposium

Chairpersons: Julia M. Gohlke, Virginia Tech and Susan L. Makris, US Environmental Protection Agency

S41

HOUGAARD KS[1], HANSEN JS[1], JACKSON P[1], KYJOVSKA Z[1], BOISEN AMZ[1], YAUK C[2], HALAPPANAVAR S[2], JENSEN KA[1], WALLIN H[1], VOGEL U[1]. [1]National Research Centre for the Working Environment, Copenhagen, Denmark, [2]Environmental Health Science and Research Bureau, Health Canada, Ottawa, ON, Canada. An Overview of Developmental Toxicity Testing for Nanomaterials

Nanomaterials (NMs) are usually defined as particles with at least one axis between 1 and 100 nm in length. Engineering of particles by control of size/shape, doping or addition of coatings etc. may provide new or enhanced physico-chemical properties compared to that of bulk materials. Development of NMs proceeds at a high pace and many new nanotechnology-enabled products are expected to be introduced in commerce in the near future. Concern is emerging exposure to nanoparticles may increase—of particular concern is exposure of pregnant women. Developmental toxicity testing is integrated into (e.g., the US EPA's NM research strategy and investigation hereof is recommended by the Reproductive Health Research Team under the NIOSH National Occupational Research Agenda). Mechanistically, it is plausible that exposure to NMs may interfere with fetal development; however, very few studies have attempted to test this hypothesis. The few reports that are currently available in the literature[(1)] show that NMs interfere somewhat with intrauterine development, irrespective of their size, chemical composition and route of exposure. Research in this area is still in the hypothesis-generating stages, and the diversity in study designs hampers the establishment of harmonized guidelines as to toxicity testing as well as general conclusions regarding developmental toxicity of NMs. Furthermore, the applied methodology does not always reflect state-of-the-art, and most mammalian studies do not provide data on gestational and lactational endpoints (e.g., maternal weight gain, gestation length, litter size, etc.) even if such data are easy to obtain. This presentation provides a brief introduction to NMs, their source, composition, uses, and exposure potential, and summarizes research that has been conducted to evaluate the effects of NMs on the developing fetus, the difficulties in conducting and interpreting these studies, and possible mechanistic considerations. Testing strategies and knowledge/data gaps will also be discussed. [(1)]Hougaard KS, Campagnolo L et al., (2015). A perspective on the developmental toxicity of inhaled nanoparticles. *ReprodToxicol* 56, 118–140.

S42

BLUM JL, ZELIKOFF JT. New York University School of Medicine, Tuxedo, NY, United States. Inhaled Cadmium Oxide Nanoparticles during Pregnancy Alters Fetal Development and Neonatal Growth in a Mouse Model

One industrially-important metal oxide nanoparticle (NP) is cadmium oxide (CdO). A study was performed using timed-pregnant CD-1 mice to determine if Cd associated with inhaled CdO NP could reach the placenta and adversely affect the developing fetus and/or neonate. Pregnant mice were exposed by inhalation either every other day to 100 μg of freshly generated CdO/m^3 (Exposure 1) or daily to 230 μg CdO/m^3 (Exposure 2). In each exposure, mice were exposed to CdO NP or carrier gas (control) for 2.5 hours from 4.5 *days post coitus* (*dpc*) through 16.5 *dpc*. At 17.5 *dpc*, fetuses and placentas from both exposures 1 and 2 were collected, measured, and weighed. A subgroup from the second exposure was allowed to give birth and neonates were weighed daily until weaning. Cadmium in the uterus and placenta, as well as in other maternal organs, was elevated in NP-treated mice, but was undetectable in fetuses at 17.5 *dpc*. Daily inhalation of 230 μg CdO NP/m^3 decreased the incidence of pregnancy (i.e., no evidence of implantation) by 23%, delayed maternal weight gain, increased placental weight, and decreased fetal length, as well as delayed neonatal growth. This presentation will also demonstrate that changes in maternal endocrine signaling could, at least in part, begin to explain some of the Cd-induced alterations in fetal development and neonatal growth. This study demonstrates that inhalation of CdO NP during pregnancy adversely affects reproductive fecundity and alters fetal and postnatal growth of the developing offspring. This presentation will demonstrate the public health implications, particularly to already vulnerable subpopulations of a common workplace nanomaterial, cadmium oxide.

S43

NURKIEWICZ TR. West Virginia University, Morgantown, WV, United States. Maternal Gestational Nanomaterial Exposures: Uterine and Fetal Microvascular Consequences

Engineered nanomaterial (ENM) exposures have increased in frequency and intensity in diverse environments. However, the influence of such exposures on maternal and/or fetal health during critical periods of gestation are poorly understood. The microcirculation is perhaps the most important tissue involved in maternal-fetal nutrient and waste exchanges, as well as the maintenance of a host of physiological gradients necessary for proper fetal development. We have recently identified that maternal ENM inhalation not only impairs uterine microvascular function, but also impedes fetal development and vascular function. Moreover, creation of this hostile gestational environment may serve as the basis for the development of adult disease. This presentation will describe 1) well-characterized ENM inhalation exposures in pregnant rats, this includes real-time aerosol measurements, deposition and dose-responses; 2) the functional microvascular consequences in dams and pups, this includes endothelial and vascular smooth muscle dysfunction, mechanotransduction and flow disruptions; and 3) specific underlying mechanisms, this includes circulating inflammatory mediators, cell signaling in the vascular wall, and mitochondrial dysfunction. At the end of this session, attendees will be able to 1) understand the critical concepts of pulmonary ENM exposure; 2) identify the maternal-uterine microvascular mechanisms of dysfunction that follow ENM exposure; 3) identify the fetal ramifications of maternal ENM exposure during gestation; and 4) describe the potential influence of these fetal exposures on adult disease.

S44

GWINN MR. US Environmental Protection Agency, Washington, DC, United States. Overview of Nanomaterial Regulation: Data Gaps and Research Needs for Risk Assessment

Regulation of nanomaterials is very much in the early stages, with decisions complicated by the remaining unanswered questions related to the risks of exposure to nanomaterials. Nanomaterials are produced for a variety of uses, and the main characteristics that make them so appealing in some applications may also make them more potentially more hazardous to human health and the environment. Human health effects associated with exposure to nanomaterials during manufacturing or use in consumer products are not well investigated or known. There is a lack of information on the effects of the nanomaterials as compared to many of the macro-scale materials. Although research examining the toxicology of nanomaterials has been ongoing for many years, early studies largely focus on respiratory effects, and are limited by lack of understanding of appropriate dose metrics. More recently, efforts have been made to better understand other toxicities following exposure to nanomaterials, but large data gaps still remain, particularly related to the fetal impacts of maternal exposures. These data limitations impact the ability to adequately assess the risks associated with nanomaterials, making it difficult to evaluate nanomaterials beyond a case-by-case basis. As the use of nanomaterials increases rapidly, there is an even greater need to understand the complexities of the issues surrounding the potential effects of exposure to nanomaterials. Many of the existing standards for regulation described here are based on materials in their macro-scale forms but these may not be sufficient to protect against the nano-scale counterparts. This presentation will describe the current issues related to the risk assessment of nanomaterials and the potential regulations under which nanomaterials could be regulated.

ILSI HESI Symposium Ontogeny of the FcRn in Gestation across Species: Implications for Monoclonal Antibody Developmental Toxicity Testing and Human Risk Assessment

Chairpersons: William J. Breslin, Eli Lilly and Company and Graeme J. Moffat, Amgen, Inc.

S45

BRESLIN WJ[1], MOFFAT GJ[2]. [1]Lilly Research Laboratories, Indianapolis, IN, United States, [2]Amgen Inc., Thousand Oaks, CA, United States. Ontogeny of the FcRn in Gestation across Species: Implications for Monoclonal Antibody Developmental Toxicity Testing and Human Risk Assessment

With the increasing development and use of Fc-containing biopharmaceuticals, primarily immunoglobulins (IgGs), increased understanding of potential placental transfer of these molecules would improve our ability to assess embryonic and fetal risk in humans. Available data indicates that exposure of Fc-containing biopharmaceuticals to the embryo during the period of major organogenesis is markedly lower than during late stage fetal development. The primary mechanism for placental transfer of Fc-containing molecules across mammalian species is via neonatal Fc-receptor (FcRn) mediated placenta/yolk sac transcytosis but little is known about the temporal pattern of expression of this transport mechanism throughout pregnancy. This symposium will present an overview of the current state of science on FcRn-mediated placental transfer, results of recent research to determine the ontogeny of FcRn in placenta/yolk sac throughout gestation across several animal species including humans, and discuss the implications of the findings for human risk assessment.

S46

DESESSO JM[1,2]. [1]Exponent, Inc., Alexandria, VA, United States, [2]Georgetown University School of Medicine, Washington, DC, United States. Cross-Species Ontogeny of Placental Fc Receptors: What We Think We Know and What We Know We Don't

Species differences in the biodistribution of immunoglobulins (IgG) are governed, at least in part, by anatomical and developmental differences at the parental-offspring interface (placenta) among experimental animals and humans. To understand the geography and efficiency of the sites of IgG transfer to the embryo, it is important to compare the function of the extraembryonic membranes, the development of the uteroplacental circulation, modes of implantation, and extent of embryonic invasion into maternal tissue as well as placental physiology and function in each species of interest. To that end, this presentation will describe the extent, timing, and mechanism of placental transfer of IgG and Fc-containing biopharmaceuticals in the human, nonhuman primate (NHP), rodent, and rabbit with a focus on how these factors may influence developmental toxicity risk assessment. Most regulatory bodies consider the NHP to be the best, if not the only, pharmacologically relevant model, despite the inadequate statistical power associated with the low numbers of subjects employed in current experimental designs. The growing body of data concerning placental transfer of biopharmaceuticals and new research into the ontogeny of the FcRn in various species may provide the basis for developing a tiered safety testing approach that will be useful in the developmental toxicity safety assessment of this important novel class of therapeutic agents.

S47

LAFFAN SB. GlaxoSmithKline, King of Prussia, PA, United States. Ontogeny of FcRn in Gestation Across Nonclinical Species

This talk will present the nonclinical results, to date, of the ILSI HESI DART neonatal Fc receptor (FcRn) ontogeny consortium effort. Placental and/or visceral yolk sac FcRn tissue concentration in cynomolgus monkey, rabbit, rat, mouse, and guinea pig will be discussed and compared. The FcRN concentration was quantified via protein mass spectrophometric techniques throughout different stages of gestation, with a focus on early gestation to the extent feasible in each species. This information could improve the characterization of nonclinical animal models that are used for developmental toxicity testing of monoclonal antibody-based medicines.

S48

WESTMORELAND S[1], TORNESI B[2]. [1]AbbVie Inc., Worcester, MA, United States, [2]AbbVie Inc., North Chicago, IL, United States. FcRn Expression in Human Placenta during Fetal Development

With the increase in Fc-containing biopharmaceuticals (including mAbs) being developed for disease indications in individuals that include females of child-bearing age, there is a need to better understand placental transfer of these molecules to the fetus for the purposes of human risk assessment. The neonatal Fc receptor (FcRn) is essential for transfer of protective maternal IgG antibodies across the placenta to the fetus in all species. The development of therapeutic human biologics has presented a concern regarding transfer of biologics during pregnancy across the placenta to the fetus. Empirically, exposure to the embryo during the period of major organogenesis (first trimester) is considered to be markedly lower. Understanding FcRn expression during pregnancy is necessary to fully evaluate the potential risk of transfer of biologics to the fetus during different stages of development. In this study, we examined human placental samples from the three trimesters by immunohistochemistry to characterize the temporal and regional expression of FcRn. We examined FcRn in the syncytiotrophoblasts, cytotrophoblasts, and endothelium of the fetal vessels. Other cells within the placenta, including the decidual and chorion villous stromal macrophages (the Hofbauer cell) were also examined. This report will summarize what is known to date about human placental expression of FcRn.

S49

SIVARAMAN L. Bristol-Myers Squibb Company, New Brunswick, NJ, United States. Nonclinical to Clinical Translation: Placental Transfer of Fc Containing Biotherapeutics and Ontogeny of FcRn Expression in the Placenta and Yolk Sac

Members of the Health and Environmental Sciences Developmental and Reproductive Toxicology (HESI DART) group, working through BioSafe, had previously published the available data on placental transfer of a wide range of Fc-containing biotherapeutics across multiple species including humans. The initial analyses identified a significant data gap on the early gestational (organogenesis) placental transfer of Fc-containing biotherapeutics. Our recent efforts have focused on understanding the ontogeny of FcRn expression in the placenta and yolk sac across species in order to assess the potential for early gestational transfer of Fc-containing drugs (reduce the data gap) and compare the FcRn-mediated transfer potential across species. In this talk, the new cross species FcRn expression data will be integrated with what is known about the placental transfer of Fc-containing biotherapeutic drugs to improve our understanding of species differences in placental transfer and the suitability of current animal models in assessing human embryonic and fetal risk from Fc-containing biotherapeutic drug exposures.

Birth Defects Research (Part A) 106:375–376 (2016)

TERATOLOGY SOCIETY

SPECIAL REPORT ABSTRACTS

(Presenter designated by underlined author.)

Special Report
Exploring the Link between Zika Virus and Microcephaly

Chairpersons: Sonja A. Rasmussen, Centers for Disease Control and Prevention and Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.

SR1

SCHULER-FACCINI L[1,2,3]. [1]Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil, [2]Brazilian Teratogen Information Service, Porto Alegre, Rio Grande do Sul, Brazil, [3]Brazilian Medical Genetics Society, Porto Alegre, Rio Grande do Sul, Brazil. Exploring the Link between Zika Virus and Microcephaly

In early 2015, an outbreak of Zika virus (ZIKV), a flavivirus transmitted by *Aedes* mosquitoes, was identified in northeast Brazil, an area where Dengue virus was also circulating; by September, reports of an increase in the number of infants born with microcephaly in ZIKV affected areas began to emerge. In October, the Ministry of Health (MoH) confirmed an approximate 20-fold increase in birth prevalence of microcephaly in northeast Brazil, compared with earlier data (based on birth certificates data). ZIKV RNA was identified in the amniotic fluid and in brain tissues of some severe affected babies (including fetal losses). These events prompted alerts around the world, including WHO concerning the possible association of microcephaly with prenatal ZIKV infection. A comprehensive protocol for notification and investigation of all infants with microcephaly and women with ZIKV infection during pregnancy was implemented in Brazil. Until the end of January 2016, 404 cases of microcephaly (head circumference under the third centile) with a specific pattern of brain anomalies detected by brain image and/or clinic maternal history of zika infection were reported by the MoH in Brazil. Brain images showed a consistent pattern of widespread brain calcifications frequently associated with symmetric cell migration abnormalities (e.g., lissencephaly, pachygyria). The size of the brain matter was markedly decreased with ventricular enlargement due to cortical/subcortical atrophy. Excessive and redundant scalp skin, also suggests acute intrauterine injury, indicating halted cerebral growth. Neurological exam showed hypertonia and tremors in the majority of children. Optical abnormalities included macular degeneration and choriorretinitis. However, as ZIKV infection is widely spread in Brazil, and only recently RT-PCR are largely available to test pregnant women, we still do not know the absolute teratogenic risk following the prenatal infection. It is still unknown if third trimester infections can lead to functional abnormalities which would be detected only later in development. Finally the specific pathogenic mechanisms should be investigated through animal models, which would help to understand the spectrum of anomalies presently observed in human babies. Data from other countries will help to establish the definitive causal relationship.

SR2

HONEIN M, JAMIESON DJ. Division of Congenital and Developmental Disorders, Centers for Disease Control and Prevention, Atlanta, GA, United States. Exploring the Link between Zika Virus and Adverse Pregnancy and Birth Outcomes

Zika virus (ZIKV) is a flavivirus spread to people primarily through the bite of an infected *Aedes* species mosquito. In May 2015, Brazil reported a lab confirmed case of ZIKV infection, but patients with rash illness suspected to be caused by ZIKV were reported in northeastern Brazil beginning in February 2015. In the fall of 2015, Brazil reported higher than expected rates of congenital microcephaly in states where ZIKV outbreaks had occurred. Laboratory tests confirmed ZIKV infection in several infants born with microcephaly, and a preliminary case series reported ZIKV symptoms during early pregnancy among several mothers of infants with microcephaly. In response to this public health threat, CDC activated its Emergency Operations Center (EOC) on January 22, 2016. On February 1, 2016, the World Health Organization declared ZIKV a public health emergency of international concern, as evidence suggesting a link between ZIKV infection and increased risk for microcephaly and other brain and eye abnormalities mounted. Several public health investigations are underway to better understand the link between ZIKV infection and microcephaly and other adverse pregnancy outcomes. The talk will include highlights of a few of these public health investigations: 1) in Puerto Rico, prospective active surveillance of pregnant women with ZIKV infection to follow them through delivery and their children through age three years to identify birth defects and other adverse developmental outcomes; 2) in Colombia, enhanced surveillance of pregnant women with ZIKV infection to identify adverse pregnancy and infant outcomes and the gestational timing of highest risk; and 3) in the United States, establishment of the US Pregnancy Registry for ZIKV infection to monitor outcomes among pregnant women, primarily returning travelers, with ZIKV infection and their infants. Efforts to enhance state-based birth defects surveillance systems to rapidly ascertain ZIKV-associated birth defects and link families to appropriate services are also underway. Our knowledge about ZIKV and adverse pregnancy and birth outcomes is evolving rapidly. This presentation will share the most up-to-date information and preliminary results from ongoing investigations.

Birth Defects Research (Part A) 106:377–383 (2016)

TERATOLOGY SOCIETY

WORKSHOP ABSTRACTS

(Presenter designated by underlined author.)

Student and Postdoctoral Fellow Lunch Workshop Advancing Your Career in Birth Defects Research and Prevention

Chairpersons: Christine Perdan Curran, Northern Kentucky University and Dana L. Shuey, Incyte

W1

VEKEMANS M[1], VORHEES CV[2], TASSINARI MS[3], OBICAN SG[4]. [1]Hopital Necker-Enfants Malades, Paris, France, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States, [3]US Food and Drug Administration, Washington, DC, United States, [4]University of South Florida, New Tampa, FL, United States. Student and Postdoctoral Lunch Workshop: Advancing Your Career in Birth Defects Research and Prevention

This workshop provides an opportunity for trainees to hear from early and established researchers in industry, government, and academe about issues critical to their careers. Short presentations will be followed by an informal question and answer period. The speakers and topics for the 2016 workshop are as follows. Dr. Vekemans serves as editor-in-chief for *Birth Defects Research, Part A*, his presentation, *Publishing in the Sciences*, will offer tips on how to prepare manuscripts for top journals in birth defects research. Dr. Vorhees will present *The Most Common Mistakes in Statistical Analysis: How to Recognize and Avoid Them*. The typical graduate student takes a single course in data analysis, but receives minimal training on the types of analyses needed for many developmental biology and teratology studies. This presentation will provide background on how to design studies and data analyses with strong validity. The Teratology Society was one of the earliest pioneers in understanding the power of working across disciplines on an important problem in biomedical science. Dr. Tassinari will present *Finding Your Place in a Transdisciplinary World*. This presentation will provide an overview on the importance of team-building and career transitions. No matter what your career path, you need to establish your own record of accomplishments distinct from those of your research and career mentors. Dr. Obican will present *Growing Pains: Moving from Mentee to an Independent Career*, which will provide advice on how to navigate this important early career transition.

Every Assay Needs an Anchor: The Search for Reference Developmental Toxicants Workshop

Chairpersons: Patience Browne, US Environmental Protection Agency and Nicole Churchill Kleinstreuer, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, NIEHS

W2

DASTON GP. Procter & Gamble, Cincinnati, OH, United States. An Exposure-Based Validation List for Developmental Toxicity Screening Assays

Validation lists that dichotomize outcomes into categories of developmentally toxic or not, fail to take into account key factors like potency, dose-response, and maternal comorbidity that are critical in evaluating *in vivo* studies and using them for regulatory decisions. A better approach is to validate against a list of exposures—concentrations of chemicals known to be developmentally toxic *in vivo*—where ideally, each chemical can be its own control at a lower dosage that does not elicit developmental toxicity. We have developed a short list of exposures using pharmacokinetic data and developmental toxicity data from rat experiments (with human data also used when available). The list is being evaluated in a variety of *in vitro* assay systems. *In vitro* systems can vary greatly in factors such as protein binding, presence of extra-embryonic membranes, etc., that can influence target site concentration; therefore, it is expected that the concentration-response curves will be shifted to the left or right vs. the *in vivo* data. Such a shift would not mean that the assay is invalid as long as the shift is consistent in direction and magnitude.

W3

MAULL E. National Institute of Environmental Health Sciences, NICEATM, Research Triangle Park, NC, United States. An Expert-Driven Approach to Identifying Reference Developmental Toxicants

The National Toxicology Program (NTP) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) convened a panel of developmental toxicology experts from government, industry, and academia with the charge of developing a robust list of chemicals and/or drugs that can be used to help validate alternative testing methods for developmental toxicity. The primary focus for this expert panel was to build off previous efforts and identify agents/exposures that produce a range of developmental effects. The panel was also asked to identify a few potent/multistage teratogens as well as several negative agents to ensure that the final list covers a range of potencies and mechanisms. A comprehensive preliminary list of chemicals, agrochemicals, and pharmaceuticals were chosen to represent a variety of physicochemical properties and chemical classes with wide mechanistic coverage. A literature search for *in vivo* developmental toxicity data on these chemicals is underway, and data are being extracted using a standardized ontology and curated into a database to facilitate comparison with results from *in vitro* and alternative assays.

W4

KLEINSTREUER NC. National Institute of Environmental Health Sciences, NTP, NICEATM, Research Triangle Park, NC, United States. Testing in Alternative Assays with a Range of Reference Developmental Toxicants

A panel of developmental toxicology experts, convened by the National Toxicology Program, provided advice on a preliminary list of reference developmental toxicants with a range of potencies and effects. Chemicals from this list are being tested in a number of alternative medium- or high-throughput platforms, including *in silico* structure-based models, *in vitro* test methods (e.g., primary cells, stem cells, cell lines), and lower order *in vivo* small model organisms (e.g., zebrafish, *c. elegans*) for comparison to available *in vivo* mammalian (rodent, rabbit, and/or human) developmental toxicity data curated from the literature. Preliminary results from multiple alternative assays will be presented and compared to mammalian effect data. This expert-driven list facilitates evaluation of *in vitro* and *in silico* models with chemicals that produce a range of developmental defects, ranging from overt malformations to functional deficits and more subtle effects.

W5

BROWNE P. US Environmental Protection Agency, Washington, DC, United States. A Performance-Based Approach for Validating Computational Tools for Developmental and Reproductive Toxicity

The US Environmental Protection Agency's Endocrine Disruptor Screening Program is now using computational tools including *in vitro* high-throughput screening (HTS) assays and predictive models to evaluate potential endocrine bioactivity of environmental chemicals that may alter development and reproduction. Before novel approaches can be used in a regulatory context, new methods must be appropriately validated for their intended purpose. Rather than using the traditional interlaboratory approach which may require years to complete, computational methods are amenable to a performance-based approach using more chemicals rather than more labs. The first step is defining a relatively large set of reference chemicals, spanning a range structures and potencies. Robust reference chemicals may be established from previous validations and curation of high quality literature studies and the endocrine bioactivity (or lack thereof) is independently confirmed. Once established, reference chemicals can be used to interrogate the performance of computational approaches, and if the performance is as good or better than existing methods used for chemical regulation, computational tools can be used as alternatives to traditional methods. The performance-based evaluation of a ToxCast/Tox21 model of estrogen receptor (ER) bioactivity demonstrated excellent accuracy, sensitivity, and specificity relative to low throughput ER binding, ER transactivation (ERTA), and uterotrophic studies used to evaluate ER bioactivity. A similar performance-based approach evaluating ToxCast/Tox21 model of androgen receptor (AR) bioactivity prediction also demonstrated excellent performance of HTS alternatives to existing of low throughput AR binding and Hershberger bioassay results used to screen AR bioactivity. To interpret these and other mechanistic events in a biological framework that includes both bioactivity and potential adverse *in vivo* outcomes, efforts are underway to establish reference chemicals for additional endpoints and map these to endocrine toxicity pathways. The US EPA's transition to include computational tools in endocrine screening and testing reduces cost and animal use, and increases the rate of identifying endocrine-active environmental chemicals that may alter development and reproduction. *This abstract does not necessarily represent US EPA policy.*

W6

SIMMONS S. US Environmental Protection Agency, ORD, NCCT, Research Triangle Park, NC, United States. A High-Throughput Screening Assay to Detect Thyroperoxidase Inhibitors and Discover Structural Alerts

In support of the Endocrine Disruption Screening Program (EDSP21), the US EPA ToxCast program is developing assays to enable screening for chemicals that may disrupt thyroid hormone synthesis. Thyroperoxidase (TPO) is critical for TH synthesis and is a known target of thyroid-disrupting chemicals that adversely impact neurodevelopment. The AUR-TPO assay was recently developed to screen >1,900 ToxCast chemicals for potential TPO inhibition activity. Parallel assays were used to determine which AUR-TPO actives were more selective for TPO inhibition. Additionally, the TPO inhibition activities of 150 chemicals were compared between the AUR-TPO assay and an orthogonal peroxidase oxidation assay using guaiacol as substrate to confirm putative TPO inhibition profiles. Bioactivity results from the AUR-TPO assay were used to identify chemical substructures associated with *in vitro* TPO inhibition. Substructure profiles were generated for each chemical in the ToxCast test set using the publicly-available ToxPrint 2.0 chemotypes. Chemotypes enriched among the putative TPO inhibitors were identified using a cumulative hypergeometric probability ($p < 0.01$). Of the total 729 chemotypes evaluated, 44 were overrepresented among TPO inhibitors. Another 24 chemotypes were found to be significantly underrepresented among AUR-TPO actives. Examination of these chemotypes revealed four basic pharmacophores that accounted for 70% of the ToxCast chemicals active in the AUR-TPO assay: aromatic alcohols, aromatic amines, thiocarbonyls, and phosphothioates. Chemico-structural analysis of AUR-TPO screening results enabled the identification of chemical features that likely drive TPO inhibition in the AUR-TPO assay, highlighting the potential to identify thyroid-disrupting chemicals *in silico* using structural alerts identified by chemotype analysis and confirmed by *in vitro* testing. The pharmacophores identified using this approach also offer key insights into mechanisms of TPO inhibition, which should strengthen the development of predictive tools. *This abstract does not necessarily reflect the policy of the US EPA.*

W7

VOLZ DC[1], VLIET SM[1], RAFTERY TD[2]. [1]University of California, Riverside, CA, United States, [2]Duke University, Durham, NC, United States. High-Content Screening of Developmental Neurotoxicity in Zebrafish Embryos

The developing nervous system is a sensitive target for chemical exposure in both humans and animal models, and early life-stage exposures can lead to long-term effects on motor activity, sensory function, and cognition. Developed and issued by the Organization for Economic Co-operation and Development (OECD), the developmental neurotoxicity (DNT) test guideline (OECD TG 426) is used to assess the potential effects of pre- and postnatal chemical (mainly pesticide) exposure on the morphology and function of the developing nervous system within preweaning, adolescent, and young adult rodents. While DNT data are lacking for thousands of chemicals used in commerce, it is impractical to screen these chemicals using the existing DNT test guideline, as this test relies on a large number of animals and is expensive, low-throughput, and labor-intensive. Therefore, there is a recognized need to rely on cell-based assays and alternative nonmammalian models to support screening and prioritization of chemicals for DNT testing in rodents. To this end, we recently developed a high-content screening assay that quantifies spontaneous activity—the first sign of locomotion that results from innervation of primary motoneuron axons to target axial muscles—within single zebrafish embryos after exposure to chemicals in concentration-response format. Within this assay, 192 viable embryos are arrayed into a 384-well plate over a 20-minute time period, resulting in one embryo per well and 16 initial embryos per treatment. Following static exposure from 5 to 25 hours postfertilization (hpf), automated image acquisition procedures and custom analysis protocols are then used to quantify spontaneous activity within live, nonmalformed embryos. This platform will focus on the development and optimization of this assay, as well as follow-up hypothesis-driven studies based on a small pilot screen of the US EPA's ToxCast Phase I chemicals. In addition, this platform will discuss our current efforts to develop a second-generation assay that, if successful, will increase sample sizes from 192 to 384 embryos per plate, decrease image acquisition durations from 80 to 40 minutes per plate, and increase assay throughput from 384 (one plate) to 3,072 wells (eight plates) per week.

Strategies for Postapproval Assessment Workshop

Chairpersons: Cheryl S. Broussard, Centers for Disease Control and Prevention and Melissa S. Tassinari, US Food and Drug Administration

W8

EPHROSS SA. Consultant, GlaxoSmithKline, Chapel Hill, NC, United States. What Do You Need to Consider When Designing an Approach to Data Collection to Maximize Success in Collection of Exposures and Outcomes?

Little is known about human pregnancy for the vast majority of medications at the time of approval. While well-designed and executed pregnancy exposure registries, specifically designed per product, can be an efficient initial approach to assess medication safety, they are not appropriate for every medication and the majority of medications do not have one. Postmarketing approaches to assess medical product safety in pregnancy depends on successful collection of pregnancy exposure and pregnancy outcomes often using a variety of complementary study designs, each with its own strengths and limitations, to maximize collection of pregnancy exposures and outcomes. Considerations for maximizing exposure collection success include multiproduct and multicompany studies for similar medications and disease states. This shared infrastructure will result in "economies of scale" for study awareness among pregnant women and health care professionals, enhancing enrollment opportunities for multiple medications and the ability to evaluate polytherapy. Accurately projecting the target population of exposed pregnant women, understanding the disease natural history during pregnancy and need for continued treatment, and considering how the medication likely will be prescribed and used, including chronic versus episodic use, are important elements to consider. Considerations for outcome collection success include linkage of maternal exposure with pregnancy and infant outcome across multiple health care providers, minimizing loss to follow-up, ensuring accurate timing in pregnancy, adequate length of follow-up for the outcome(s) to be evaluated, systematic collection, and comparing pregnancy exposure registries and other primary surveillance studies to existing population-based pregnancy exposure and outcomes systems to evaluate generalizability. Accumulating data from multiple, complementary sources (including disease-specific and multiproduct pregnancy registries, case-control surveillance, administrative claims, and electronic health record databases) over long periods of time will maximize success in collecting pregnancy exposures and outcomes. This approach is advantageous to monitoring the effects of medication exposures in pregnancy, maximizing the value of the information, and better enabling hypothesis-testing follow-up studies as appropriate.

W9

BROUSSARD CS, TINKER SC, REEFHUIS J. Centers for Disease Control and Prevention, Atlanta, GA, United States. BD-STEPS: The Next Generation of Birth Defects Research

This presentation will highlight characteristics of a new US data source for birth defects research, the Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS). BD-STEPS is the next major endeavor for the Centers for Birth Defects Research and Prevention, building upon the foundation of the National Birth Defects Prevention Study (NBDPS), which collected data on births from 1997 to 2011. BD-STEPS, which began data collection with 2014 births, is a population-based case-control study of 17 selected birth defects, conducted in seven centers across the United States. Case infants are identified through state or regional birth defects surveillance systems, and control infants are selected from birth or hospital records from the same source populations. Mothers of case and control infants are interviewed about various topics surrounding their health and their pregnancies. BD-STEPS extends the NBDPS by continuing data collection on many maternal exposures (e.g., maternal health conditions, and prescription and nonprescription medications). Furthermore, it expands upon the initial effort by collecting information on additional exposures (e.g., certain health conditions and medical/surgical procedures) and by obtaining more detailed information on other exposures (e.g., reasons for use and dosage for specific medications). Data from studies like BD-STEPS can be used for postapproval assessment of medication safety in pregnancy, particularly for investigating birth defect outcomes; this presentation will also address strengths and limitations of this approach. BD-STEPS represents a key strategy of CDC's Treating for Two: Safer Medication Use in Pregnancy initiative, to expand and accelerate research into medication safety to provide healthcare providers and consumers with better information to make treatment decisions.

W10

TAYLOR LG. US Food and Drug Administration, Silver Spring, MD, United States. What Is US Food and Drug Administration Looking for to Assess and Label Risk?

The US Food and Drug Administration (FDA) must carefully select 1) the most useful safety evidence to evaluate a medication's potential adverse effects, and then 2) the best way to communicate this information in a medication label. Postmarketing pregnancy-related medication safety evidence is derived from case reports, pregnancy exposure registries, and population-based studies. Each data source has distinct advantages and challenges when assessing risk, though each can also complement the others. Studies with notable methodologic limitations complicate risk interpretation. These limitations include small sample sizes, confounding, studies with no or inappropriate comparator groups, failure to assess individual medications and/or outcomes, as well as issues related to multiple testing. Confounding by treatment indication is a common threat to study validity; assessing risk from these studies is particularly challenging because the risk of birth defects from maternal disease may be poorly understood. Studies that do not have these potential limitations, or that adequately address them, are most helpful in developing labeling language regarding risk. Furthermore, investigators should cautiously interpret their results in the presence of study limitations. The FDA's newly implemented pregnancy labeling standards require a risk summary statement followed by a description of the data that provide the scientific basis for the risk summary statement. Since health care providers (HCPs) use this labeling information to make prescribing decisions, regulators must carefully consider the methodologic limitations of the safety evidence and appropriately communicate this evidence in light of medication benefits. The FDA aims to translate postmarketing safety evidence into clear and meaningful labeling language. The label then becomes a valuable tool, empowering HCPs to make informed prescribing decisions leading to optimal care of the pregnant patient.

W11

HUYBRECHTS KF. Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States. New Approaches to the Design and Analysis of Studies Evaluating Drug Safety during Pregnancy

Prescription medication use during pregnancy is common and increasing. It has been reported that 83% of publicly-insured pregnant women have a dispensing for one or more prescription medications, and 42% have a dispensing for a prescription medication classified in the former US Food and Drug Administration categories D or X. Yet, pregnant women are systematically excluded from preapproval randomized trials that help US FDA assess the safety of medications. Drug safety studies in pregnancy typically require very large study populations because the outcomes tend to be rare. Administrative healthcare databases are used increasingly for this purpose, but the strengths, weaknesses, and pitfalls of this approach are not well understood. One particularly relevant data source is the Medicaid Analytic eXtract (MAX) since Medicaid covers the medical expenses for 40–50% of births in the United States. The key design and analytic issues to consider when using these data sources to evaluate drug safety in pregnancy will be discussed and illustrated using two recent studies on the risk of congenital malformations associated with psychotropic medication use during pregnancy (antidepressants and antipsychotics) using the MAX data. These studies demonstrate the importance of distinguishing the effects of the medication from the effects of the (severity of the) underlying indication and the feasibility of doing so in the context of large healthcare databases. The opportunities that some of the newer epidemiologic methods offer to pregnancy research will also be presented. Whereas a broad variety of methods will be mentioned, the emphasis will be on sensitivity and robustness analyses. In particular, we will illustrate how sensitivity analyses and quantitative bias analyses can be used to test the strength of the findings under various assumptions in terms of exposure, outcome, and confounder misclassification; the use of positive and negative controls to evaluate the validity of the data source; and the use of external data to adjust for unmeasured confounders. We will end by presenting new initiatives on the value of pooling across multiple data sources to enable the evaluation of very rare exposures (e.g., polytherapy, dose) and to follow-up on safety signals generated in a single data source.

Science and Public Policy Workshop How It Affects You and How You Can Shape It

Chairpersons: Wafa A. Harrouk, US Food and Drug Administration and Belen Tornesi, AbbVie Inc.

W12

ANTIN P, TORNESI B, HARROUK W, GARRISON H. Federation of American Societies for Experimental Biology, Bethesda, MD, United States. How FASEB Amplifies the Voice of Working Scientists

In the 21st century, public policy has a huge impact on the way that science is done. Decisions about funding and a host of regulatory issues involving animals, fetal tissue, grant applications, reporting, and publications affect the daily activities of working scientists. The competition for limited resources available to scientists, especially those working in the academic setting, has become difficult. As a result, scientists need to leverage their efforts to ensure that research progress is not hampered. One of the ways that scientists can increase their chances of maximizing their resources is by working with organizations such as the Federation of American Societies for Experimental Biology (FASEB). FASEB is one of the nation's largest coalitions of biomedical researchers, representing 30 scientific societies and over 125,000 researchers from around the world. The Teratology Society has been supporting advocacy efforts to its members through its participation as a member organization of the FASEB since 1998. This session will introduce Teratology Society members and other meeting attendees to the work FASEB does in the science policy arena, as well as the breadth of resources FASEB is able to provide to Teratology Society members, including fact sheets, articles, and reports. Speakers will include Teratology Society representative to FASEB (Belen Tornesi) as well as FASEB representatives Howard Garrison (FASEB Director of Public Affairs) and Parker Antin (FASEB President). Parker Antin will give an overview of FASEB's major accomplishments over the past year and describe how FASEB advocates for the research community. Belen Tornesi and Wafa Harrouk will discuss their experiences working with FASEB as members of the FASEB Board and serving on FASEB committees. Howard Garrison will provide an overview of current issues and will suggest ways that members of the Teratology Society can contribute.

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TERATOLOGY SOCIETY

PLATFORM ABSTRACTS

(Presenter designated by underlined author.)

Student and Postdoctoral Fellow Platform Session 1

Organized by the Student Affairs Committee

Chairperson: Dana L. Shuey, Incyte

1

DRAKE D[1], WELLS PG[1,2]. [1]Department of Pharmaceutical Sciences, University of Toronto, Toronto, ON, Canada, [2]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada. Physiological and Ethanol-Enhanced Embryonic and Fetal DNA Oxodation in *Brca1* Knockout Progeny

DNA repair-deficient knockout (KO) mouse progeny with a homozygous (-/-) deletion of the breast cancer 1 (*Brca1*) gene die *in utero*, while heterozygous (+/-) *Brca1* KO embryos develop normally. We previously reported that +/- *Brca1* conditional KO (cKO) embryos exhibit enhanced DNA oxidation and embryopathies when exposed in culture to ethanol (EtOH), which enhances embryonic formation of reactive oxygen species (ROS). *In vivo*, +/- *Brca1* cKO fetuses exposed *in utero* to EtOH similarly exhibit enhanced fetal DNA oxidation and postnatal neurodevelopmental deficits. Herein, +/- KO mice were mated and embryos were extracted on gestational day (GD) 10, genotyped and assessed by western blot for Brca1 protein levels. Brca1 was decreased by 40% in +/- *Brca1* KO embryos compared to wild type (+/+) littermates. Pregnant +/- *Brca1* KO dams were treated intraperitoneally on GD 12 or 17 with a single dose of EtOH (4 g/kg) or saline vehicle. Embryos and fetal brains were extracted 6 hr post treatment, genotyped and assessed by western blot for γH2AX formation, indicating DNA double strand breaks (DSBs), as well as by ELISA for the embryopathic oxidative DNA lesion 8-OH-2'-deoxyguanosine (8-OHdG). *Brca1* genotype effects were observed in both embryos and fetal brains with and without EtOH exposure. Among progeny exposed only to saline, γH2AX was increased in +/- *Brca1* embryos and fetal brains compared to +/+ littermates ($p<0.05$), suggesting that a DNA repair deficiency can increase vulnerability to the pathogenic effects of physiological ROS levels, which may be relevant to adverse developmental outcomes like autism spectrum disorders. Similarly, EtOH-exposed +/- *Brca1* KOs exhibited enhanced DNA oxidation and DSBs compared to EtOH-exposed +/+ littermates, as well as to saline-exposed +/- progeny ($p<0.05$). Among EtOH-exposed progeny, the increased γH2AX and 8-OHdG levels in +/- *Brca1* embryos and fetal brains suggest that oxidatively damaged DNA plays a pathogenic role in the mechanism of Fetal Alcohol Spectrum Disorders (FASD), and that Brca1 protects against EtOH-initiated oxidatively damaged DNA, and possibly FASD. These results indicate a broader biological role for Brca1 (beyond breast cancer) in protecting the developing embryo and fetus from both physiological ROS levels and EtOH-initiated oxidative stress. (Support: CIHR)

2

HOLBROOK BD[1], BISHOP S[2], WILLIAMS S[2], CANO S[2], DAVIES S[3], BAKHIREVA LN[2], SAVAGE DD[3]. [1]Department of Obstetrics and Gynecology, School of Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, United States, [2]Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy, University of New Mexico Health Sciences Center, Albuquerque, NM, United States, [3]Department of Neurosciences, School of Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, United States. Altered Expression of Placental Proteins Related to Angiogenesis in Pregnancies Exposed to Alcohol

Despite a large body of research on Fetal Alcohol Spectrum Disorder (FASD), the mechanisms by which *in utero* alcohol exposure causes neurodevelopmental deficits is still poorly understood. Prior research using our rat model of moderate drinking during pregnancy has demonstrated altered expression of proteins associated with angiogenesis, both in the placenta and the fetal cerebral cortex. Specifically, *in utero* ethanol exposure significantly altered Cerebral Cavernous Malformation Protein 3 (CCM-3) and Annexin-A4 (ANX-4) in placenta and fetal cortex at term. The aim of the present study was to evaluate whether placental expression of these angiogenesis-related proteins would also be altered in the human placentae of subjects exposed to alcohol. Patients for this study were recruited from our ENRICH prospective birth cohort and included alcohol using and abstaining subjects. Prospective and repeated Timeline Follow-Back (TLFB) interviews were administered to ascertain the level of maternal alcohol use. Following delivery, placental core samples were collected. Phosphatidylethanol (PEth) levels were obtained from a neonatal dried blood spot. Alcohol-exposed subjects were defined as one or more of the following: 1) An AUDIT-C score >8, 2) >84 drinks during pregnancy per TLFB, and/or 3) a PEth level >25 ng/mL. Placental samples were analyzed for CCM-3 and ANX-4 via western blot testing, using Actin as a reference protein. To date, a total of 18 placental specimens (eight alcohol-exposed and ten alcohol abstainers) have been analyzed. ANX-4 expression in alcohol-exposed placental tissue was significantly reduced by 33% compared to its expression in the control group ($p = 0.040$). Placental CCM-3 expression in the alcohol group was elevated by 12%, an effect that was not statistically significant. Our preliminary results indicate that alcohol exposure during pregnancy may affect proteins involved in angiogenesis in the human placenta. As these proteins are altered in placenta and fetal cortex in a rodent model of prenatal ethanol exposure, altered expression of these proteins may potentially serve as markers of altered neurovascular development in brain. Supported by R01 AA02177, P50 AA022534 and UL1 TR000041.

3

CATLIN NR[1], FOSTER P[1], MYLCHREEST E[2], MILLER L[2], CUNNY HC[1], MCINTYRE BS[1]. [1]Division National Toxicology Program, NIEHS, Durham, NC, United States, [2]Southern Research Institute, Birmingham, AL, United States. Teratogenicity of the Herbal Supplement Vinpocetine in Harlan-Sprague Dawley Rats

Vinpocetine, a semi-synthetic derivative of the *Vinca minor* extract vincamine, inhibits phosphodiesterase type 1 and voltage-sensitive Na^{2+} channels, and displays vasodilatory activity in cerebral tissue. Human exposure occurs through its use as dietary supplement for its purported nootropic and neuroprotective effects. Increasing use of vinpocetine among college students for memory enhancement is of particular concern because they are of reproductive age. A rat prenatal toxicity study was conducted to characterize potential maternal and embryo-fetal toxicity. Vinpocetine was administered via oral-gavage to time-mated Harlan-Sprague Dawley rats (n = 25/group) at dose levels of 0, 5, 20, or 60 mg/kg/day from gestation day (GD) 6-20. Dose levels were based upon a dose-range finding study that demonstrated a dose-dependent increase in early resorptions at ≥ 20 mg/kg/day vinpocetine, and total resorptions at ≥ 80 mg/kg/day. At necropsy on GD 21, dams exhibited a dose-dependent increase in postimplantation loss (3.3%, 10.7%, 11.1%, and 83.1% at 0, 5, 20, and 60 mg/kg, respectively) that was associated with a higher frequency of early resorptions and fewer live fetuses at term. There were no effects on fetal weight nor were there any external fetal findings. However, fetuses from dams exposed to 0, 5, 20, and 60 mg/kg exhibited a dose-dependent increase in ventricular septum defects and full thoracolumbar supernumerary ribs, with incidences of 0/293 (0/21), 3/239 (3/19), 8/261 (7/21), and 2/51 (2/8) of the fetuses (litters), and 1/293 (1/21), 5/239 (3/19), 12/261 (4/21), and 12/47 (3/7) of the fetuses (litters), respectively. These data demonstrate that vinpocetine administration to pregnant rats is associated with embryo-fetal toxicity and teratogenicity, suggesting a potential hazard for pregnant women who may be taking vinpocetine.

4

DONG D, YANG P. University of Maryland, Baltimore, Baltimore, MD, United States. Reduced Expression of the Long Noncoding RNA GALNR Mediates High Glucose-Induced Apoptosis by Up-Regulating Gadd45α in Diabetic Embryopathy

High glucose of pregestational diabetes induces neural stem cell apoptosis in the developing neuroepithelium leading to neural tube defects (NTDs). The mechanism underlying the proapoptotic effect of high glucose is still unclear. Our recent studies demonstrated that noncoding RNAs including miRNAs and long noncoding RNAs (lncRNAs) mediate the proapoptotic effect of high glucose in diabetic embryopathy. In a lncRNA profiling study using neurulation stage embryos, we found that maternal diabetes significantly down-regulated the expression of Gadd45α-associated long noncoding RNA, named GALNR. Gadd45α (growth arrest and DNA damage-inducible 45 alpha) is a stress sensor in mediating cell response to stress and regulates cell apoptosis. Here, we investigated the roles of Gadd45α and GALNR, and their relationship, in high glucose-induced cell cycle arrest and apoptosis in neural stem cell. Both maternal diabetes *in vivo* and high glucose *in vitro* significantly up-regulated Gadd45α and down-regulated GALNR expression. Silencing Gadd45α or overexpressing GALNR blocked high glucose-induced neural stem cell cycle arrest and apoptosis. Knocking down GALNR mimicked high glucose-induced neural stem cell cycle arrest and apoptosis, and this effect was abolished by Gadd45α silencing. Further study showed that GALNR overexpression repressed Gadd45α expression, whereas GALNR silencing up-regulated Gadd45α. An RNA pulldown assay demonstrated that GALNR directly interacted with Gadd45α mRNA leading to Gadd45α mRNA degradation in an Ago-2-dependent manner. Thus, our study reveals that Gadd45α is a target gene of GALNR, and reduced GALNR expression-increased Gadd45α leads to apoptosis under high glucose conditions. The GALNR-Gadd45α circuit may formulate a novel epigenetic mechanism underlying the cause of diabetic embryopathy.

5

CAO SY, YUAN ZW. China Medical University, Shenyang, China. Therapeutic Potential of RNAi Silencing CRMP-4 Combined with MSCs in Animal Models with Spina Bifida Aperta

Neural tube defects (NTDs) are severe congenital anomalies of the central nervous system that result from incomplete neurulation, spina bifida aperta is one of the main types of neural tube defects. However, the lack of effective treatments during pregnancy remains problematic. Our previous study found that the transplanted mesenchymal stem cells (MSCs) survived and differentiated into neural lineage cells and we first found that CRMP-4 expressions in spinal cord of spina bifida aperta were increased significantly. Many studies have shown that the increased CRMP-4 expression associated with neuronal apoptosis. Therefore, we transplanted the CRMP-4 RNAi virus vector together with MSCs into the defect region of fetal spinal cord at E16 with the combined techniques of fetal surgery, microinjection, and microsurgery for the treatment of spina bifida aperta. The results showed that the expression of CRMP-4 and the apoptosis of neurons was decreased, the expression of sensory neuron and motor neuron markers was increased, and the synaptic regeneration was promoted. At the same time, improve the spinal cord niche, and the survival rate and differentiation rate of transplanted MSCs were improved. We measured the area of the spinal cord defect and motor evoked potential in spina bifida aperta. The results showed that the motor function of the treatment group was improved. Our treatment has a certain effect. Our study provides a new method for the treatment of spina bifida aperta.

6

MCKENZIE M[1,2], AMOSU M[1,2], WU X[1,2], WALLACE S[3], HENDERSON M[4], BIAN X[2], LU K[1,2], STICE S[2,3], SMITH M A[1,2]. [1]Environmental Health Science University of Georgia, Athens, GA, United States, [2]Regenerative Bioscience Center University of Georgia, Athens, GA, United States, [3]ArunA Biomedical Inc., Athens, GA, United States, [4]Environmental Protection Agency, Athens, GA, United States. Determining Developmental Neurotoxicity of Pesticides Utilizing Metabolomic Profile from Neural Progenitor Cells

Many pesticides utilize neurotoxicity to be effective, but a secondary consequence may be toxicity to the developing human brain. To address this concern, our objectives were to use neural progenitor cells to 1) determine the effects of three pesticides: lindane, aldicarb, and chlorpyrifos on developing neurons, and 2) further develop our system by adding a metabolism component using C3A liver cells or astrocytes. Viability assays were conducted in neural progenitor cells (hNP™) to determine the dose range, and test doses were selected based on viability. After exposing both hNP™ and hN2™ cells (differentiated neurons) to a pesticide for 48 hours, media were collected and derivatized for metabolomic analysis. In addition, C3A cells were treated with pesticides, and the conditioned medium was applied to hNP™ or hN2™ cell cultures for an additional 48 hours after which medium was removed, and metabolites derivatized for GC/MS. For astrocyte cocultures with neural progenitor cells, the same procedure was followed as described above. There was no significant decrease in viability of developing neurons after treatment with aldicarb or lindane at 30 μM or less and for chlorpyrifos at 100 μM or less. Principal component analysis of the metabolomic profile was a more sensitive indicator of pesticide-induced changes than viability. Cells showed biomolecular alterations in response to chlorpyrifos exposure at 0.3, 3 and 30 μM concentration whereas lindane and aldicarb were different from control at 3 and 30 μM but not at 0.3 μM. When neuronal cells were cocultured with astrocytes and treated with chlorpyrifos, their neurite outgrowth was restored, suggesting that astrocytes may play a role in detoxifying compounds. Our team demonstrated astrocytes provide a neuroprotective effect to the hNP™ and hN2™ cells when grown in coculture. We hypothesize that astrocytes metabolize chlorpyrifos utilizing P450 enzymes following the same pathway as liver cells. A comparison of chlorpyrifos metabolites from astrocytes and C3A liver cell line supports this conclusion. We demonstrated that dual cell cultures provide a more robust model for cell culture assays creating a stronger link to systems biology and minimizing whole animal testing, and that metabolomics is a more sensitive assay than viability.

7

MUANDA FTM[1,2], SHEEHY OS[2], BERARD AB[1,2]. [1]Faculty of Pharmacy, University of Montréal, Montréal, QC, Canada, [2]Research Center, CHU Sainte-Justine, Montréal, QC, Canada. Use of Antibiotics during Pregnancy and the Risk of Spontaneous Abortion

Although antibiotics are widely used during pregnancy, evidence regarding their fetal safety remains limited. We aimed to assess the association between the use of antibiotics classes and types and the risk of spontaneous abortion (SA) taking into account indication of use. We conducted a nested case-control study within the Quebec Pregnancy Cohort (1998–2009). Planned abortions and pregnancies exposed to fetotoxic drugs were excluded. SA was defined as having a diagnosis or procedure related to SA before the 20th week of pregnancy. Index date was defined as the gestational age of the SA. 10 controls per case were randomly selected and matched on index date and calendar year of pregnancy. Use of antibiotics was defined by filled prescriptions between the first day of gestation until index date and was compared to 1) nonexposure, and to 2) exposure to penicillin/cephalosporins. We also studied each specific type of antibiotics separately using the same comparator groups. Conditional generalized estimation equation (GEE) regressions were used to estimate crude and adjusted odds ratios (OR), and 95% confidence intervals (95%CI), taking into account the indications and other potential confounders. A total of 1,428 (16.4%) of the 8,702 pregnancies ending with a SA had at least one filled prescription for an antibiotic during early pregnancy as compared to 11,018 (12.6%) of the matched controls. Adjusting for potential confounders, use of azithromycin (aOR 1.65, 95%CI 1.34-2.02, 110 exposed cases) and clarithromycin (aOR 2.35, 95%CI 1.90-2.91, 111 exposed cases) were associated with an increased risk of SA. Use of tetracyclines and quinolones had similar impact on the risk of SA suggesting a class effect (aOR 2.59, 95%CI 1.97-3.41, 67 tetracycline-exposed cases; aOR 2.72, 95%CI 2.27-3.27, 160 quinolone-exposed cases). Sulphonamide (aOR 2.01, 95%CI 1.36-2.97; 30 exposed cases), and metronidazole (aOR 1.70, 95%CI 1.27-2.26; 53 exposed cases) were also increasing the risk of SA. Similar results were found when using penicillin/cephalosporins as comparator group. Macrolides excluding erythromycin as well as quinolones, tetracyclines, sulfonamides, and metronidazole use during early pregnancy were associated with an increased risk of SA even after taking into account maternal infections.

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SPARKS NRL[1], BONDESSON M[3], ZUR NIEDEN NI[2]. [1]Environmental Toxicology Graduate Program, University of California, Riverside, Riverside, CA, United States, [2]Cell Biology and Neuroscience and Stem Cell Center, University of California, Riverside, Riverside, CA, United States, [3]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, TX, United States. Harm-Reduction Tobacco Products Interfere with the Differentiation of Craniofacial Bone

In utero tobacco exposure is linked to fetal abnormalities including improper development of craniofacial bone. Pregnant women, who cannot refrain from smoking, are often lured to using harm reduction tobacco products (HRTPs), which are marketed as safer alternatives. These products include ultra-filtered cigarettes with reduced carcinogen content, and chewing tobacco, the use of which omits exposure to harmful combustion products. While these HRTPs might decrease cancer risk in the mother, it is unclear whether they act as teratogens, affecting the development and differentiation of bone tissue. Using *in vitro* pluripotent stem cell models and zebrafish embryos, we provide here the first evidence that HRTPs are teratogenic to the developing craniofacial skeleton. *In vitro*, subtoxic HRTP doses decreased osteoblast differentiation in differentiating human embryonic stem cells, which derive osteoblasts primarily from the neural crest (NC) lineage. In exposed zebrafish, the precursors to the NC-derived basibranchial, ceratobranchial, and hypobranchial bones were completely absent. Mechanistically, HRTPs increased NADPH oxidase activity and reactive oxygen species levels, concomitant with diminished superoxide dismutase and catalase activity, while coadministration of antioxidants reversed inhibition of osteoblast differentiation. HRTPs also decreased the expression of FOXO1/3a, transcription factors regulating free scavenging enzymes, both at the mRNA and nuclear protein activation level. A similar regulation was found for TWIST1, a transcription factor crucial for bone specification and potential target of FOXO1/3a. Together, these data suggest that HRTPs initiate oxidative stress-induced disruption of embryonic skeletal development by modulation of transcription factors, which are otherwise necessary for osteoblast specification, production, and protection.

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EL HUSSEINI N, HALES B. McGill University, Montréal, QC, Canada. Exposure of Organogenesis-Stage Embryos to Hydroxyurea Alters the Expression of P53-Family Related Genes That Are Involved in Limb Development

Hydroxyurea (HU), an anticancer agent, is a model teratogen used to study the embryonic stress response during organogenesis. Embryos exposed to HU on gestational day (GD) 9 have severe hind-limb and tail malformations, including syndactyly, polydactyly, and kinky tails. Previously, we showed that HU treatment on GD9 significantly activated the P53 signalling pathway. P53 and related family proteins, P63 and P73, are implicated in limb development; absence of *Trp53* sensitizes limbs to teratogenic insult while loss of *Trp63* or *Trp73* results in severe skeletal deformities. Here we investigated the impact of HU exposure on the expression of P53-family related genes that are involved in limb development. Saline or HU (low-dose—LD: 400 mg/kg; high-dose—HD: 600 mg/kg) was administered intraperitoneally to CD-1 mice on GD9; dams were euthanized 3 h later, embryos extracted, and gene expression was analyzed. Ingenuity Pathway Analysis™ of the gene expression profiles of these embryos revealed that among the transcripts with altered expression 42 genes were causally associated with morphogenesis of bones and limbs. There were 135 genes associated with the P53 family proteins, P53, P63, and P73. Ninety transcripts were unique to P53, four unique to P63, and five unique to P73. Sixteen of the P53 family related genes are involved in skeletal and limb morphogenesis. We examined the expression of three candidate genes that are associated with both the P53 family and limb development: *Ptch1*, a cell surface receptor that is essential for proper digit formation and associated with preaxial polydactyly; *Pax9*, purportedly involved in distal limb development; and *Jag2*, associated with syndactyly and phalanx development. qRT-PCR analysis showed that *Ptch1* [LD: 0.79 ±0.05 HD: 0.66 ±0.03; n=5] and *Pax9*, [LD: 0.65 ±0.1, HD: 0.53 ±0.04; n=5] were both significantly downregulated, while *Jag2* [LD: 1.5 ±0.05, HD: 1.66 ±0.06; n=5] was significantly upregulated. Together, these data suggest that P53 family proteins may play a role in mediating the effects of HU on the expression of several key genes that are important in limb development. Funded by CIHR MOP-57867. NELH is the recipient of an award from CIHR-REDIH.

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LEUNG MCK[1,2], KAPRAUN DF[1], WILLIAMS AJ[1], KNUDSEN TB[1]. [1]US Environmental Protection Agency, Research Triangle Park, NC, United States, [2]Oak Ridge Institute for Science and Education, Oak Ridge, TN, United States. An Evaluation of ToxCast Angiogenic Disruptors for Effects on Mitochondrial Bioactivity Profiles

Angiogenesis is a critical developmental process and a potential target for chemical teratogenesis. Over one-tenth of the Tox21 library of 10,000 compounds have been shown to disrupt mitochondrial function (Attene-Ramos et al., 2015). Previous studies utilizing ToxCast chemicals have shown a correlation between vascular disruption in *Tg(kdrl:EGFP)*^{mitfab692} zebrafish embryos and mitochondrial disruption reported in literature (McCollum et al., submitted). To more closely examine this correlation, we culled ToxCast data for mitochondrial translocator protein (TSPO; NovaScreen) and mitochondrial membrane potential (MMP) and biomass (Tox21 and Apredica) for a total of 192 chemicals tested for adverse effects on vascular development in transgenic zebrafish embryos (McCollum et al., submitted; Tal et al., submitted). This set included 40 compounds that disrupted vascular development in zebrafish embryos (zVDC) and 152 compounds that did not. The zVDC set displayed consistent *in vitro* bioactivity on mitochondrial membrane potential (with a Pearson Chi-Square value of 16.92, $p < 0.0001$), but did not have consistent effects on mitochondrial biomass (0.4; $p = 0.527$) or translocator protein ligand binding (0.05; $p = 0.823$). The effect on MMP is consistent with the hypothesis that disruption of the mitochondrial respiratory complexes is a potential mode of action of angiogenic disruptors (complex I for pyridaben, fenpyroxymate, tebufenpyrad, and rotenone; complex III for pyraclostrobin and trifloxystrobin; and complex V for triclocarban). After cytotoxicity correction, the ToxCast bioactivity profiles of 37 of the zVDC could be condensed into 136 gene annotations in a chemical-assay target bipartite network, which revealed clusters associated with Cyp450s, GPCRs, and nuclear receptor signaling, in addition to vascular disruption. These results in the zebrafish model suggest that angiogenic disruptors in the ToxCast library have a positive correlation with mitochondrial respiratory disruption but neither biomass nor TSPO binding. Further analysis is underway to determine if a structural signature or physical property can be identified for these chemical structures. *This abstract does not necessarily reflect US EPA policy.*

Platform Session 2
Developmental Teratology and Toxicology

Chairpersons: Barbara F. Hales, McGill University and
Alan M. Hoberman, Charles River Laboratories

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BHATIA S[1], WELLS PG[1,2]. [1]Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [2]Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada. Untreated and Ethanol-Exposed DNA Repair-Deficient Oxoguanine Glycosylase 1 (*Ogg1*) Knockout Progeny May Be Susceptible to Postnatal Neurodevelopmental Abnormalities Mediated by Epigenetic Mechanisms

Oxidative DNA damage and altered DNA methylation occurs in the brains of autistic mouse models, and in the fetal brains of mice exposed *in utero* to ethanol (EtOH). We previously reported that reactive oxygen species (ROS)-initiated DNA damage in fetal brains, and postnatal neurodevelopmental deficits, were enhanced in EtOH-exposed oxoguanine glycosylase 1 (*Ogg1*) knockout (KO) progeny, which cannot repair the pathogenic DNA lesion 8-oxo-2'-deoxyguanosine lesion (8-oxodG). Using *Ogg1* KO mice, we are investigating the role of 8-oxodG-dependent epigenetic changes, particularly 5-methylcytosine (5-mC) formation, in the mechanism of postnatal neurodevelopmental abnormalities initiated by physiological and EtOH-enhanced levels of ROS, potentially relevant to autism and fetal alcohol spectrum disorders (ASD, FASD) respectively. 5-mC in the brains of untreated young and adult *Ogg1* wild type (WT) and KO progeny and in EtOH-treated *Ogg1* WT and KO fetal brains exposed *in utero* was measured by ELISA, and repetitive behaviour for young mice by a marble burying test. Brain 5-mC was not different in young *Ogg1* KO vs. WT mice, but was increased in adult *Ogg1* KO mice vs. young *Ogg1* KO mice ($p<0.05$), showing an increase with age. Postnatal repetitive behaviour was increased in *Ogg1* KO mice vs. *Ogg1* WT mice ($p<0.001$) in male but not female progeny. The effect of ROS-mediated 8-oxodG levels on 5-mC was measured in fetal brains extracted 1 and 6 h post maternal treatment with EtOH (2 g/kg i.p.) on gestational day 17. Fetal brain 5-mC was increased at 6 h in EtOH-treated *Ogg1* WT progeny ($p<0.01$) but not in EtOH-treated *Ogg1* KO littermates, compared to saline-treated *Ogg1* WT and KO progeny respectively. The results suggest that inability to repair 8-oxodG can result in an increase in 5-mC with age, which may contribute to the neurodevelopmental abnormalities seen in untreated *Ogg1* KO mice. A similar increase in 8-oxodG and 5-mC levels, with a decrease in *Ogg1* expression, has been reported in autistic mouse models. Neurodevelopmental abnormalities in DNA repair-deficient progeny caused by physiological and EtOH-enhanced ROS formation may be mediated in part by DNA methylation, and OGG1 may be a biomarker of risk for ASD and FASD. (Support: CIHR)

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YANG P, XU C, REECE EA, YANG P. University of Maryland, Baltimore, Baltimore, MD, United States. MARCKS Acetylation Regulated by TIP60 and SIRT2 Prerequisite for Phosphorylation Dismantles Its Cellular Organelle Protection and Neural Tube Closure in Diabetes

Neurulation at early embryonic development is a process of folding the developing neuroepithelium into a neural tube, the primitive form of the central nervous system. Failed neural tube closure leads to neural tube defects (NTDs), severe structural birth defects affecting offspring mortality and morbidity. High glucose of maternal diabetes induces NTD formation both in human and animal models. We have demonstrated that mitochondrial dysfunction and endoplasmic reticulum (ER) stress in the developing neuroepithelium are critically involved in NTD formation in diabetic pregnancies; however, the mechanism underlying cellular organelle stress in diabetic embryopathy is unclear. The myristoylated alanine-rich C-kinase substrate protein (MARCKS) is required for neural tube closure but its regulation and function are scarcely illustrated. Here, the regulatory mechanism of acetylation and phosphorylation of MARCKS was addressed by coimmunoprecipitation (CoIP) of MARCKS with Tip60, an acetylatransferase, and Sirtuin 2 (SIRT2), a NAD-dependent protein deacetylase, respectively. The phosphorylation dead MARCKS (pd-MARCKS) transgenic male mice and SIRT2 transgenic male mice were crossed with nondiabetic and diabetic female mice to generate embryos for analysis. Embryonic day 8.5 (E8.5) and E10.5 embryos were used for analyzing MARCKS protein modifications. The localization of MARCKS on mitochondria and endoplasm reticulum (ER) were determined by confocal microscopy. ER stress, apoptosis and oxidative stress were analyzed in the developing neuroepithelium. High glucose of maternal diabetes-induced MARCKS acetylation at lysine 165, a prerequisite for MARCKS phosphorylation. WhileTip60 acetylated MARCKS, SIRT2 deacetylated MARCKS and inhibited MARCKS phosphorylation. Phosphorylated MARCKS dislocated from and diminished its protection to cellular organelles leading to mitochondrial dysfunction and endoplasmic reticulum stress. Phosphorylation dead MARCKS (pd-MARCKS) reversed maternal diabetes-induced cellular organelle stress, apoptosis, and delayed neurogenesis in the developing neuroepithelium and ameliorated NTDs. Restoring the MARCKS upstream regulator, SIRT2, in the developing neuroepithelium exerted identical effects as those of pd-MARCKS. Our studies revealed a new regulatory mechanism in MARCKS acetylation and phosphorylation, which disrupt neurulation under diabetic conditions by diminishing MARCKS' cellular organelle protective effects.

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VENTURA CV[1,3], VENTURA LO[1,2], MAIA M[3], BELFORT JR R[3]. [1]Altino Ventura Foundation (FAV), Recife, PE, Brazil, [2]HOPE Eye Hospital, Recife, PE, Brazil, [3]Federal University of São Paulo (Unifesp), São Paulo-SP, Brazil. Ocular Features and Limb Anomalies in Patients with Microcephaly and Presumed Zika Virus Congenital Infection in Pernambuco, Brazil

Background: In 2015, the Ministry of Health reported a 20-fold increase in the prevalence of microcephaly in Brazil, which was associated to Zika virus (ZIKV) transmission. Purpose: To report the ocular features and limb anomalies in newborns with microcephaly and presumed diagnosis of ZIKV congenital infection. Methods: We assessed the ophthalmological findings and limb anomalies in 40 newborns with microcephaly born in Pernambuco, Brazil between May and December 2015, the period of highest peak of microcephaly reports in the country. Results: The patients' mean age at examination was 2.2 ± 1.2 months (range, 0.1-7.27 months); 21 (52.5%) infants were male. 27 (67.5%) mothers reported dengue-like symptoms during pregnancy. Fundoscopic alterations were seen in 37 (46.3%) eyes of 22 (55.0%) infants. The main fundoscopic findings included macular pigmentation in 22 eyes (27.5%), optic disc hypoplasia in 16 (20.0%) eyes, and chorioretinal atrophy in six (7.5%) eyes. Seven infants (17.5%) presented limb anomalies and six (15.0%) presented spasms of superior and inferior limbs. Conclusion: Ocular involvement and limb anomalies were identified in 55.0% and 17.5% of the infants with presumed ZIKV congenital infection, respectively. These findings raise the hypothesis that ZIKV has a neurological tropism, and acts like an important environmental teratogen.

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CURRAN CP, COLTER BH, VILLALONA Y, CAUDILL S. Northern Kentucky University, Highland Heights, KY, United States. Genetic Susceptibility to Thyroid Hormone Disruption and Immunotoxicity in PCB-Treated Mice

Polychlorinated biphenyls (PCBs) are persistent organic pollutants known to affect the developing brain and to disrupt thyroid hormone levels. We have developed a mouse model that allows us to look at genetic susceptibility to developmental PCB exposure in order to identify humans at highest risk. Previously, we reported that both high-affinity *Ahr^{b}Cyp1a2(-/-)* and poor-affinity *Ahr^{d}Cyp1a2(-/-)* mice are more susceptible to learning, memory, and motor deficits compared with wild type *Ahr^{b}Cyp1a2(+/+)* mice. We treated pregnant dams using corn oil-soaked food or food dosed with an environmentally relevant mixture of coplanar and noncoplanar PCBs. Treatments began on gestational day 0 and continued until weaning at postnatal day 25 (P25). We used enzyme-linked immunoassays to measure thyroid hormone levels in plasma of mice at P14, based on previous studies showing that is a critical time for thyroid hormone disruption in early brain development. We found a significant main effect of treatment ($P < 0.05$) with PCB-treated mice having lower T4 levels than controls as well as reduced spleen ($P < 0.01$) and thymus ($P < 0.001$) wet weights. There was also a significant gene x treatment interaction with the most susceptible *Ahr^{b}Cyp1a2(-/-)* having significantly reduced spleen ($P < 0.001$) and thymus ($P < 0.001$) wet weights. Together, these results confirm our previous results that both the AHR and CYP1A2 affect susceptibility to developmental PCB exposure and that thyroid hormone disruption is highest in mice with the *Ahr^b* genotype. Supported by ES020053 and GM103436.

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RAZVI RM[1], PATEL HR[1], REPINE CM[1], CHAPMAN TW[1], MELIN VE[1,2], SHEA CS[1,2], HRUBEC TC[1,2]. [1]E. Via College of Osteopathic Medicine, VA Campus, Blacksburg, VA, United States, [2]VA-MD College of Veterinary Medicine, Virginia Tech, Blacksburg, VA, United States. Differences in Ambient and Oral Exposure to Quaternary Ammonium Compounds in Mice

Neural tube defects (NTDs) occur when there is incomplete closure of the neural tube during development, resulting in severe central nervous system defects. Exposure to the quaternary ammonium compounds (QACs) Alkyldimethylbenzyl Ammonium Chloride (ADBAC) plus Didecyldimethyl Ammonium Chloride (DDAC) increases the incidence of NTDs in mice. Exposure to these and structurally similar QACs is common during pregnancy as they are present in many household products including: shampoos, soaps, laundry detergent, fabric softeners, contact lens solutions, mouthwash, makeup, and cleaners. The aim of the current study was to determine the contribution of maternal, paternal, and ambient exposures to development of NTDs in the offspring. We hypothesized that acute exposure of either parent would result in NTD formation. Three groups were housed in Facility-A which previously used ADBAC+DDAC: 1) dosed males x dosed females, 2) dosed males x undosed females, and 3) undosed males x dosed females. Two groups were held in Facility-B with active use of ADBAC+DDAC: 1) dosed males x dosed females, and 2) ambiently-exposed males x ambiently-exposed females. Controls were held in Facility-C, a non-QAC use facility. All mice were born and raised in Facility-C with no prior exposure to ADBAC+DDAC. At six weeks of age, mice in the exposure groups were transferred to their respective facilities. Males received 30 mg/kg ADBAC+DDAC in Facility-A, and 7.5 mg/kg in Facility-B, by oral gavage once daily for ten days. Pregnant females received a single dose of 30 mg/kg in facility-A and 7.5 mg/kg in Facility-B on gestational day 8. Embryos were evaluated on gestational day 9.5 for NTDs. NTDs were highest in Facility B which had active ADBAC+DDAC use. There was no significant difference between ambient-exposed and dosed groups. NTDs were also significantly higher when both males and females were exposed; but, independent male and female exposure also resulted in NTDs (N= 8–13 per treatment group with significance set at $p<0.05$ by ANOVA). These results indicate that male or female exposure alone can cause NTDs and that ambient exposure from use of the disinfectant in the room can cause NTDs. Supported by: E. Via College of Osteopathic Medicine–Virginia Campus.

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DI BONA KR[1], GHAFFARI R[2], RICHBURG JH[1,2]. [1]Center for Molecular and Cellular Toxicology, College of Pharmacy, The University of Texas at Austin, Austin, TX, United States, [2]Institute of Cellular and Molecular Biology, College of Natural Sciences, The University of Texas at Austin, Austin, TX, United States. The Germ Cell-Specific Loss of the Copper Transporter, *Ctr1*, during Embryogenesis Results in Severe Disruption of Spermatogenesis in Mice

Copper (Cu) is an essential trace metal for mammalian growth and development due to its role as a catalytic or structural cofactor for a variety of cellular enzymes, where it serves a fundamental role in a variety of biological processes, including energy synthesis, iron acquisition, and cellular metabolism. Elevated protein and mRNA levels of the high affinity Cu influx transporter, CTR1, are found in the liver, kidney, and testis of adult mice indicating a critical need of Cu for their function. Immunohistochemistry of wild type mice indicate an abundant expression of CTR1 specific to pachytene spermatocytes and Sertoli cells. In order to investigate the functional role of CTR1 and Cu homeostasis in the developing testis, mice were generated using Cre-lox technology with a germ or Sertoli cell-specific homozygous deletion of *Ctr1 (SLC31A1)* occurring during embryogenesis (onset of Cre: embryonic day 15–18 or 14.5, respectively). The *in utero* loss of *Ctr1* in germ cells resulted in a reduction of testis mass (over 80%) by early adulthood (postnatal day, PND, 41) due to the progressive loss of germ cells from the seminiferous tubules. Sertoli cell vacuolization and multinucleate giant cells were observed beginning in the pubertal period (PND 28), remaining present through adulthood. Additionally, older germ cell-specific *Ctr1* knockout mice (PND 70) displayed Sertoli cell-only syndrome (germ cell aplasia) with no signs of spermatogenic recovery. Alternatively, Sertoli cell-specific *Ctr1* knockout mice were found to be fertile at adulthood with testis, which appeared histologically identical to wild type mice. These results reveal a germ cell-specific need for CTR1 and the importance of Cu homeostasis in the establishment and maintenance of spermatogenesis. Further research is underway to reveal the complex interactions in the testis required to maintain Cu homeostasis and to investigate the possibility of a potential alternative mechanism of Sertoli cell Cu acquisition.

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MARIKAWA Y, LI A. University of Hawaii, Honolulu, HI, United States. Adverse Effect of Valproic Acid on an *In Vitro* Gastrulation Model Entails Activation of Retinoic Acid Signaling: A Potential Mechanism for Its Teratogenic Action

Valproic acid (VPA), an antiepileptic drug, is a notorious teratogen that causes neural tube defects (NTDs) and axial skeletal defects (ASDs), although the mechanisms by which VPA induces these malformations are not fully understood. The misregulation of gastrulation impairs elongation and patterning of the embryo along the anterior-posterior body axis, and has been implicated as an etiology of NTDs and ASDs. Previously, we established an *in vitro* morphogenesis model using mouse P19C5 stem cell embryoid bodies (EBs), which exhibits axial elongation and gene expression profiles characteristic of gastrulation. Here, using this *in vitro* gastrulation model, we investigated the morphogenetic and molecular effects of VPA to gain mechanistic insights into its teratogenic actions. VPA diminished the elongation of EBs at therapeutic concentrations, whereas the nonteratogenic analog valpromide did not. The morphogenetic effect of VPA was likely due to the inhibition of histone deacetylase, as trichostatin A exhibited similar effects. VPA altered temporal and spatial expression patterns of various developmental regulator genes, including the up-regulation of *Cdx1* and *Hoxa1*, known transcriptional targets of retinoic acid (RA) signaling. Although VPA by itself did not activate RA signaling, VPA-induced up-regulation of *Cdx1* and *Hoxa1* was repressed by BMS493, an RA receptor inhibitor, suggesting that VPA enhances the transcriptional responses of RA signaling target genes. Notably, the cotreatment of EBs with VPA and BMS493 rescued axial elongation as well as temporal and spatial gene expression profiles, indicating that VPA requires active RA signaling to exert its morphogenetic effects. With the effective use of the *in vitro* gastrulation model, the present study provides a mechanistic link between VPA and enhanced RA signaling as a potential cause of NTDs and ASDs.

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HRUBEC TC[1,2], MELIN VE[1,2], SHEA CS[1], POTINENI H[2], RAZVI RM[1], PATEL HR[1], REPINE CM[1], CHAPMAN TW[1]. [1]E. Via College of Osteopathic Medicine, VA Campus, Blacksburg, VA, United States, [2]VA-MD College of Veterinary Medicine, Virginia Tech, Blacksburg, VA, United States. QAC-Induced Neural Tube Defects by Dosing and Environmental Exposure

In 2010, we observed neural tube defects (NTDs) in control mouse embryos. The NTDs were caused by the disinfectant used in the mouse room, a quaternary ammonium cleaner (QAC) containing alkyldimethylbenzylammonium chloride (ADBAC) and didecyldimethylammonium chloride (DDAC). This presentation synthesizes our research since then. Since NTDs were first observed in environmentally-exposed mice, our working hypothesis was that both intentional dose and environmental exposure contribute to the NTDs. We spent the first two years reestablishing clean control mice. We first attempted to house mice in an "ADBAC+DDAC free room" in the QAC-facility, but the room and mice quickly became contaminated. We finally achieved "clean" mice when we moved the breeding colony to a facility that did not utilize QAC disinfectants; although, the effects of exposure persisted for two generations. We then focused on characterizing the teratogenicity of ADBAC+DDAC. Both the disinfectant product and the active ingredients caused NTDs. Chronic exposure with dosed feed, or a single oral dose to gestational day 8 females, caused NTDs. Chronic exposure to males with dosed feed, or daily doses for ten days prior to breeding, caused NTDs. More NTDs were seen when both males and females were exposed than when only one sex was exposed. With environmental exposure, mice bred and raised in the QAC-facility had the most NTDs. Discontinued use of QAC disinfectant decreased NTDs in dosed mice by about half. "Clean mice" transferred to a QAC use facility and exposed ambiently, had NTD rates similar to those of dosed mice. Lastly, mice housed the QAC-free-facility but held in caging material that came from the QAC use facility, had NTDs. NTDs ranged from 3–15% in the different experiments (N=8-17/exposure group, significance in all studies was set at $p<0.05$ by ANOVA). While administered ADBAC+DDAC dose did influence the amount of NTDs, ambient environmental exposure appeared to have the most influence on NTD rate. These results highlight how the mouse room environment can impact research and raise questions about the safety of QAC disinfectants. Supported by: NIH-NIEHS R21E5016886, Passport Foundation, VA-MD College of Veterinary Medicine, E. Via College of Osteopathic Medicine.

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MAHADEVAN U[1], PORTER C[2], ARMSTRONG-FISHER S[3,4], BAKER T[5], KEVORKIAN L[5], NESBITT A[5]. [1]UCSF Medical Center, San Francisco, CA, United States, [2]Department of Immunopathology, NHS Grampian, Aberdeen, United Kingdom, [3]Academic Transfusion Medicine Unit, University of Aberdeen, Aberdeen, United Kingdom, [4]Scottish National Blood Transfusion Service, Aberdeen, United Kingdom, [5]UCB Pharma, Slough, United Kingdom. Lack of Active Placental Transfer of Certolizumab Pegol: Preclinical and Clinical Data

Materno-fetal transfer of antibodies across the placenta is mediated by Fc-region binding to the neonatal Fc receptor (FcRn). Anti-TNFs are used to treat a range of inflammatory diseases which can affect women of childbearing age. Anti-TNFs adalimumab, etanercept, infliximab have a G1 antibody Fc-region; certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF. Based on the structural difference, we hypothesized that CZP does not bind to FcRn and is not transferred across the placenta. Binding affinity of adalimumab, CZP, etanercept and infliximab to FcRn was measured *in vitro* (Surface Plasmon Resonance technology). Transcytosis across a cell layer was measured in a human FcRn-transfected cell line. In rodent studies, placental transfer to the fetus of a rodent CZP-surrogate, PEGylated Fab' and a complete IgG were compared. Materno-fetal transfer of CZP was studied in an *ex vivo* human placental perfusion model. Neonatal levels of adalimumab, CZP and infliximab were measured by ELISA and compared with maternal levels in women receiving these anti-TNFs during pregnancy. Binding affinity to FcRn was: 132nM (infliximab), 225nM (adalimumab), 1500nM (etanercept); no measurable affinity of CZP binding detected. FcRn-mediated transcytosis across a cell layer (mean±SD; n=3) was: 249.6±25.0 (infliximab), 159.0±20.2 (adalimumab), 81.3±13.1 (etanercept), 3.2±3.4 (CZP), 5.9±4.6 ng/mL (negative-control). Level of CZP-surrogate PEGylated Fab' was >100-fold lower than complete IgG anti-TNF in fetuses of pregnant rats. *Ex vivo* placental perfusion model showed no measurable transfer of CZP. In clinic, neonatal infliximab and adalimumab levels were always higher than maternal levels, whereas neonatal CZP level was always much lower, often below the quantification limit. The inability of CZP to bind FcRn resulted in negligible FcRn-mediated transcytosis *in vitro*. Other anti-TNFs demonstrated FcRn binding and were actively transported across a cell layer by FcRn. Given FcRn plays a key role in the transfer of IgG antibodies from mother to fetus via the Fc-region, placental transfer of a PEGylated Fab' like CZP should be low. Animal and *ex vivo* human placental models and clinical data support this conclusion. In summary, the lower placental transfer seen with CZP is explained by its different molecular structure that lacks an Fc region. (Resubmission from Rheumapreg 2014.)

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MCDONALD VA[1], HRUBEC TC[2,3]. [1]Department of Biology, Virginia Tech, Blacksburg, VA, United States, [2]E. Via College of Osteopathic Medicine, Virginia Campus, Blacksburg, VA, United States, [3]VA-MD College of Veterinary Medicine, Virginia Tech, Blacksburg, VA, United States. Are Quaternary Ammonium Compounds Immunotoxic?

Quaternary ammonium compounds (QACs or Quats) are commonly used in disinfectants and other household products including shampoos and laundry detergents. Exposure to QACs result in developmental and reproductive toxicity in mice, while in humans, increased immune sensitivity and asthma are documented. Immune system development occurs during pre- and early-postnatal periods. Exposures during this period can have lifelong effects that result in immune suppression or chronic inflammation. The possibility that QACs are toxic to the developing immune system has not been studied. Macrophages are a key mediator between the innate and adaptive immunity and altered macrophage function can indicate immunotoxicity. We hypothesized that low levels of QAC exposure would be immunotoxic and result in reduced phagocytic activity. We developed a phagocytosis assay using mouse J774 cells and bovine macrophages. Cells were seeded at 1X105 and exposed to Labsan 256-cpq [(ADBAC 6.76%) (DDAC 10.1%)] for 24 hours at a concentration range from 0.00005% to 0.01%. Viability curves were established to demonstrate a dose-dependent response to QAC concentrations and to identify a concentration that could show a functional change in phagocytosis independent of QAC-induced mortality. Cells exposed to QAC concentrations that did not result in significant mortality, were then incubated for 24 hours with 1 uM fluorescent beads. Image Stream flow cytometry was used to determine phagocytic efficiency. Labsan concentrations greater than 0.005% were lethal to 100% of cells while those at or below 0.00005% were comparable to the negative control. Phagocytosis efficiency (# of phagocytosing cells/ # of total cells) was tested at 0%, 0.00001%, 0.00005% and 0.0001 Labsan. Phagocytosis activity was high in the control, and test concentration of 0.00001% and 0.00005%. However, at the concentration of 0.0001% efficiency decreased to 9%. This decrease indicates an altered functional effect independent of cell mortality, as viability decrease was only 10% at this concentration. Our data show that QACs affect cellular functions before viability, indicating a possible immunotoxic effect. If developmental exposure to QACs result in altered immune function in adults, then contribution to human disease could be significant. Supported by E. Via College of Osteopathic Medicine-Virginia Campus.

Platform Session 3
Clinical Teratology

Chairpersons: James L. Mills, Eunice Kennedy Shriver *National Institute of Child Health and Human Development, NIH and Cynthia A. Moore, Centers for Disease Control and Prevention*

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STADELMAIER R[1], NASRI H[2], DEUTSCH C[3], BAUMAN M[4], ADAMS J[5], STODGELL C[6], HOLMES LB[2]. [1]Albert Einstein College of Medicine, New York, NY, United States, [2]MassGeneral Hospital for Children, Boston, MA, United States, [3]*Eunice Kennedy Shriver* Center, Waltham, MA, United States, [4]Boston University School of Medicine, Boston, MA, United States, [5]University of Massachusetts, Boston, Boston, MA, United States, [6]University of Rochester School of Medicine, Rochester, NY, United States. Exposure to Valproate during Pregnancy: Facial Features and Signs of Autism

Valproic acid (VPA) is the most teratogenic anticonvulsant drug in clinical use today. VPA-exposed children have been shown to have an increased frequency of dysmorphic craniofacial features defined subjectively, but not objectively. VPA exposure has also been associated with an increased frequency of Autism Spectrum Disorder (ASD). ASD has been associated with both an increased head size and an increased cephalic index (brachycephaly and increased skull width), as well as minor malformations (Rodier et al: *Teratology* 55:319-325, 1997). The purpose of this study was to determine whether there is an increased frequency of dysmorphic facial features associated with prenatal VPA exposure, and whether there are any distinctive features in VPA-exposed children with ASD compared to VPA-exposed children without ASD. 52 children exposed to VPA during the first trimester of pregnancy and 126 unexposed children were examined for the presence of craniofacial features defined both subjectively and objectively. VPA-exposed children were also evaluated by experienced clinicians for ASD using the SCQ, ADI-R, and ADOS. Standardized z-scores, for specific features, were calculated using population means conditioned on age and gender. One-way ANOVAs were used to compare the z-scores of VPA-exposed children to unexposed children and VPA-exposed children with ASD to those without ASD. When population means were not available for specific measurements, facial proportions of children with the presence or absence of features were contrasted with a two-tailed Z-test. The Bonferroni correction was used to adjust for multiple comparisons. The surface examinations identified an increased frequency ($p<0.05$) of telecanthus and hypoplastic fingernails in the VPA-exposed children. Several measured features of the VPA-exposed children were significantly ($p<0.01$) smaller: anterior-posterior head length, nose length, interpupillary distance, third finger length, and head circumference/height index. Two features were larger ($p<0.01$) in the VPA-exposed children: cephalic index, bitemporal width and mouth width. No significant differences were identified between the VPA-exposed groups, with and without ASD. The "face" of VPA-exposed children show some overlap with the facial features in phenytoin and phenobarbital-exposed children. Our findings raise the question of the basis for the effect of prenatal exposure to VPA on head shape.

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ALWAN S[1], BANDOLI G[2], CHAMBERS CD[2]. [1]University of British Columbia, Vancouver, BC, Canada, [2]University of California, San Diego, San Diego, La Jolla, CA, United States. Maternal Use of Selective Serotonin-Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn: An Update of the Current Evidence and Clinical Implications

Maternal use of selective serotonin reuptake inhibitors (SSRIs) in late pregnancy has been associated with various adverse neonatal outcomes, most recently persistent pulmonary hypertension of the newborn (PPHN), a rare but serious condition with substantial infant mortality and morbidity. Although the increase in absolute risk is small on a population level, it could still be of concern to many patients. It remains unclear, however, whether the increased risks reported for PPHN could be explained by the underlying maternal illness rather than the use of SSRIs. Antenatal depression carries a serious risk on both the mother and the baby and discontinuing antidepressant treatment during pregnancy is associated with a high risk of relapse. It is recommended that pregnant women who require treatment for depression receive comprehensive counseling on a case-by-case basis. Health care providers should be aware of the higher risk for the development of PPHN outcomes amongst mothers on antidepressants in late gestation in order to provide better surveillance and more timely interventions.

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STEPHEN JM[1,2], FLYNN L[1], VAN METER J[1,2], LOWE J[2], BAKHIREVA LN[2]. [1]The Mind Research Network, Albuquerque, NM, United States, [2]University of New Mexico, Albuquerque, NM, United States. Effects of Opioid Maintenance Therapy on Infant Brain Development

While withdrawal effects of prenatal opioid exposure are well documented in infants, it is currently unknown whether there is an enduring impact on infant brain development. This study is part of the larger prospective ENRICH cohort which aims to understand the effects of prenatal alcohol and opioid exposure on infant brain development. In this analysis, we describe our initial results comparing infants exposed to opioid maintenance therapy (OMT; N=5) relative to healthy controls (N=12) assessed at six months of age. Data obtained during the first three study visits (prenatal, at delivery, when an infant was six months of age) were incorporated into this analysis. The women in the OMT group might have exposure to other opioids but no evidence of alcohol or other substance use other than nicotine during pregnancy; the women in the control group had no lifetime use of illicit drugs and no alcohol/tobacco use during pregnancy. Infant brain function was assessed using magnetoencephalography (MEG), a noninvasive measure of neurophysiologic activity, while performing a motor observation task. Periods of rest were identified based on video-coding of behavior. Spectral analysis of these periods of rest was compared statistically using repeated measures ANOVA. Based on previous results indicating frontal asymmetry in substance-exposed infants, we compared left and right frontal power in the five physiologic frequency bands (delta, theta, alpha, beta, and gamma). There was as significant frequency band by hemisphere by group interaction (Greenhouse-Geisser corrected $p = 0.004$). This three-way interaction was driven by significant group by hemisphere interactions in the delta and beta frequency bands ($p = 0.006$ and $p = 0.018$, respectively). The interaction pattern revealed greater delta band power in left hemisphere for controls relative to OMT with the opposite pattern in right hemisphere and greater beta band power in right hemisphere in controls relative to OMT. There was no significant group difference in socioeconomic status ($p > 0.1$). These results provide evidence for enduring effects of prenatal opioid exposure on infant brain development that cannot be explained by simple socioeconomic factors.

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GHASSEMI JAHANI S-A, DANILESSON A, KARLSSON J, BRISBY H. Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Department of Orthopaedic, Gothenburg, Sweden. The Need of Orthopedic Care and Physical Activity Level in a Group of Middle-Aged Individuals with Thalidomide Embryopathy

Background: The incident of congenital limb defects and malformations is 4–6 per 10,000, except the amount caused by teratogenic substances among those Walproac Acid, Misoprostol, or Thalidomide. Thalidomide is in this aspect one of the most notorious teratogenic drugs, known to have induced feature malformations named Thalidomide Embryopathy (TE) in over 10,000 liveborn children worldwide during 1957–1962. Aim: The aim of the study was to investigate the need of orthopaedic surgery and limb orthosis in relation to function in a group of middle-aged individuals with TE. Methods: 13 women/18 men, mean ages 45.8 (SD 1.1), with TE were included. Information about limb surgeries, use of orthotic devices, job, accommodation, and possible need of disable adjustments or personal assistant and time needed for activities of daily life, ADL, in the morning and in the evening before bedtime was collected. The function was measured by general function score, GFS. Individuals with Proximal Focal femoral deficiency, PFFD, with severe malformations on the lower limbs (n=5) were compared with those without PFFD. Participants with the need of home or job disable adjustments (n= 12) were compared with the rest of the group. Result: 3/31 individuals were in need of personal assistance and 7/31 had disabled adjusted homes. A majority of the individuals, 28/31, had a job and 24/31 reported participation in light to heavy exercise/training in their leisure time. The group with PFFD had significantly lower function score and needed significantly longer time for ADL in the morning, compared with the no-PFFD individuals ($p=0.001$ and $p=0.011$ respectively). The group needing home or work adjustments had significantly lower disability score and needed longer time for morning ADL than the rest of the group ($p=0.012$ and $p=0.025$ respectively). Discussion: Overall the middle-aged TE individuals, despite their limb malformations, were active workers, had a good physical function, and participated in physical activities in their spare time to a relatively high extent. The individuals with more severe limb malformations such as PFFD and those in the need of disable adjustment had somewhat lower physical function and required longer time for ADL than the rest of the group.

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DANILESSON AJ, GHASSEMI JAHANI S-A. Institute of Clinical Sciences Sahlgrenska Academy, University of Gothenburg, Department of Orthopaedic, Gothenburg, Sweden. Health Related Quality of Life and Socio-Demographics in Middle-Aged Individuals with Thalidomide Embryopathy

Introduction: The aim was to evaluate the health related quality of life (HRQOL) and function in middle-aged individuals with thalidomide embryopathy (TE). Methods: 31 individuals with TE underwent a full clinical examination including computer tomography of the lower limbs to evaluate musculoskeletal manifestations. SF-36 was answered for evaluation of general HRQOL. Sixteen individuals had no major deformities of the four extremities and were compared with the 15 who had major deformities affecting function of at least one extremity (1, 3, or 4 extremities namely). Results: The mean age of the study group was 46 years and 42% were female. Malformations of the hand occurred in 25 individuals, but despite that, 27 had some sort of grip function. Five patients (16%) had severe malformations of one or both legs (proximal focal femoral deficiency) with limb shortening and need of orthosis/wheelchair. The group with major deformities worked to the same extent, had the same level of strain during working or spare time, and admitted the same amount of stress as the group without any major deformities. The attained level of school education, marital status, and number of children were similar. The physical aspects of QOL were significantly reduced for the full study group compared to the national norms; the Physical Composite score (PCS) /SF-36 was mean 40.6 for the whole group (p=0.0027). Subgroup analysis revealed that it was the group with major deformities of the limbs, who reported a significantly reduced physical QOL, with reductions of all four subscores, leading to a PCS score of mean 34.6 (p=0.0067). Even if the Vitality Score was reduced (mean 59.2 for the whole group and 55.3 for the subgroup with major deformities), the Mental Composite Summary Score, which reflects a more general view of the mental well-being and QOL, was not significantly reduced compared to the national norms. Discussion: The physical quality of life was significantly reduced in this study group of middle-aged individuals with thalidomide embryopathy, but this did not affect the mental quality of life. The findings were more pronounced for those with major deformities of the limbs.

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KARUNAMUNI G[1], GU S[1], DOUGHMAN YQ[1], SHEEHAN MM[1], MA P[1], PETERSON LM[1], LINASK KK[2], JENKINS MW[1], ROLLINS AM[1], WATANABE M[1]. [1]Case Western Reserve University, Cleveland, OH, United States, [2]University of South Florida, St. Petersburg, FL, United States. Betaine Supplementation Reduces Congenital Defects Induced by Prenatal Alcohol Exposure

Over 500,000 women per year in the United States drink during pregnancy, and one in five of this population also binge drink. As high as 20–50% of live-born children with prenatal alcohol exposure (PAE)-induced disorders present with congenital heart defects including outflow and valvuloseptal anomalies that can be life threatening. Previously, we established a model of PAE (modeling a single binge drinking episode during the early first trimester) in the avian embryo and used optical coherence tomography (OCT) imaging to assay early-stage cardiac function and structure and late-stage cardiac defects. At early stages, ethanol-exposed embryos had smaller cardiac cushions and increased retrograde flow. At late stages, they presented with gross morphological defects of the head and chest wall, and also exhibited abnormal atrio-ventricular (AV) valves, thinner interventricular septae (IVS), and smaller vessel diameters for the aortic trunk branches. In other animal models, the methyl donor betaine (found in many foods such as wheat bran, quinoa, beets, and spinach) ameliorates neurobehavioral deficits associated with PAE but the effects on heart structure are unknown. In our model of PAE, betaine supplementation led to a reduction in gross structural defects and prevented certain types of cardiac defects such as ventricular septal defects and abnormal AV valves. Furthermore, great vessel diameters, IVS thicknesses and mural AV leaflet volumes were normalized while the septal AV leaflet volume was increased. To track effects on DNA methylation, histological analysis was performed within 24 hours of saline, ethanol or ethanol and betaine injections by immunofluorescent staining for 5-methylcytosine in transverse embryo sections at the level of the cardiac neural crest. DNA methylation levels were reduced by ethanol exposure and normalized by co-administration of betaine. Together these findings highlight the potential for betaine, a methyl donor, to be used in the prevention of PAE-related birth defects. This research is supported in part by the National Institutes of Health (RO1HL083048). GK was supported by a postdoctoral fellowship from American Heart Association. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or American Heart Association.

Platform Session 4
Epidemiology

Chairpersons: José F. Cordero, University of Georgia and
Peter Langlois, Texas Department of State Health Services

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'T MANNETJE AM[1], BORMAN B[1], ENG AJ[1], ELLISON-LOSCHMANN L[1], DOUWES JE[1], PEARCE N[2]. [1]Centre for Public Health Research, Massey University, Wellington, New Zealand, [2]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom. Hair Dye Use and the Risk of Congenital Malformations: Results from a New Zealand Birth Defects Case-Control Study

Hair dye use is common in women of reproductive age, but studies into reproductive risks associated with this exposure are lacking. Here we present findings from a national case-control study on birth defects conducted in New Zealand during 2009–2014. A total of 648 mothers of children born during 2007–2009 and registered to the New Zealand's National Birth Defects Monitoring Programme, and 504 mothers of children without congenital malformations selected from the Maternity and Newborn Information System, participated in the first case-control study on congenital malformations conducted in New Zealand. A telephone or face-to-face interview with a trained research nurse collected information from the mother on a wide range of potential risk factors, including the use of hair dyes during pregnancy. Logistic regression analyses were conducted to assess the association between hair dye use and congenital malformations, adjusting for maternal age, education, deprivation, smoking, body mass index, and alcohol consumption. In the three months prior to conception, 20% of control mothers had hair dyes applied at the hairdressers, 15% had applied hair dyes themselves at home and <1% had done both. For case mothers, these percentages amounted to 20%, 21% and <1%, respectively. Hair dye use at the hairdressers during the three months prior to pregnancy was not associated with congenital malformations (Odds Ratio (OR) 0.9; 95% Confidence Interval (95%CI) 0.7-1.3). The OR for hair dye use at home was 1.4 (95%CI 1.0-2.0) for all congenital malformations combined and 2.1 (95%CI 1.3-3.5) for circulatory system defects and 1.8 (95%CI 1.0-3.2) for genital organ defects. In the first trimester of pregnancy the prevalence of hair dye use had dropped by a third for both cases and controls, but risk remained elevated for hair dye use at home (OR 1.5; 95%CI 1.0-2.3). These preliminary results suggest that the self-application of hair dyes at the home may be associated with an increased risk of congenital malformations, but that having hair dyes applied professionally is not. These results also indicate that many women reduce their hair dye use after becoming pregnant, suggestive of their consideration of potential health impacts of this exposure on the unborn child.

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NEMBHARD WN[1,2], TANG X[3,2], HU Z[3,2], MACLEOD S[1,2], STOWE Z[4], WEBBER D[1], THE NATIONAL BIRTH DEFECTS PREVENTION STUDY[1]. [1]Division of Birth Defects Research, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, United States, [2]Arkansas Children's Hospital Research Institute, Little Rock, AR, United States, [3]Division of Biostatistics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, United States, [4]Department of Psychiatry, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, United States. Maternal and Infant Genetic Variants in Folate, Homocysteine and Trans-Sulfuration Pathways Modify the Association between Prenatal Selective Serotonin Reuptake Inhibitors Use and Risk of Congenital Heart Defects

Prenatal maternal use of selective serotonin reuptake inhibitors (SSRIs) may increase congenital heart defects (CHDs) risk in offspring. In this study we evaluated whether the association between prenatal SSRI use and CHD risk was modified by maternal and/or fetal genetic variants in the folate, homocysteine, or transsulfuration pathways. We used National Birth Defects Prevention Study data on live-born 1,180 case and 1,644 control infants, born between October 1997 and August 2008. Case infants had selected conotruncal or obstructive heart defects and control infants had no major structural anomalies. Maternal, paternal, and infant DNA was genotyped using an Illumina® Golden Gate custom single nucleotide polymorphism (SNP) panel. Relative risk (RR) and Bayesian False Discover Probability (BFDP) were calculated to identify variants associated with CHDs through interaction with prenatal SSRI using a log-linear model-based hybrid design. Statistical significance was set at BFDP <0.8. Among women taking SSRIs periconceptionally, the maternal SHMT1 (rs9909104) TT and CT genotypes were associated with a 5.9 and 2.4 increased risk of CHD, respectively, compared to the CC homozygous genotype (BFDP=0.69). The BHMT (rs492842 and rs542852) GG and A>G genotypes had greater than a two-fold increased risk of CHD compared to the homozygous AA genotype (BFDP=0.74 and 0.79, respectively). The MGST1 (rs2075237) TT and G>T genotypes were associated with an 8.0 and 2.8 increased risk of CHDs compared to the homozygous GG genotype (BFDP=0.79). We also identified several SNPs in fetal genes involved in the folate (MTHFS rs12438477), homocysteine (TRDMT1 rs6602178 and GNMT rs11752813) and transulfuration (GSTP1 rs7941395 and MGST1 rs7294985) pathways that were associated with increased risk of CHDs. Common variants in maternal or fetal genes involved in folate, homocysteine or transsulfuration pathways may increase CHD risk among offspring of women who take SSRIs during early stages of fetal development.

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KANCHERLA V, OAKLEY GP. Emory University Rollins School of Public Health, Atlanta, GA, United States. Contribution of Total Prevention of Folic Acid Preventable Spina Bifida and Anencephaly towards Achieving Health-Related Sustainable Development Goals in India

Background: Birth defects contribute to a large proportion of neonatal, infant, and under-five mortality. Their burden is underestimated in developing countries. Folic acid preventable spina bifida and anencephaly (FAP SBA) are serious birth defects that are epidemic in many countries, including India. The objective of our study was to estimate the percent reduction in neonatal, infant, and under-five mortality rates in India if we prevented FAP SBA, and the proportional contribution of this reduction in achieving India's health-related Sustainable Development Goals (SDG) for 2030. Methods: Using data from the United Nations International Children's Emergency Fund, the March of Dimes, and published studies from India, we calculated for the year 2012: 1) the number of neonatal, infant, and under-five deaths among those born with FAP SBA; 2) the number of deaths that can be prevented in each of the three mortality categories through mandatory folic acid fortification; and 3) the proportional contribution of FAP SBA prevention towards achieving SDG. Results: In the year 2012, 128,200 babies (5 per 1,000 live births) were affected with spina bifida and anencephaly in India; 90% of them would have been folic acid preventable. The total number of preventable deaths associated with FAP SBA were 72,120 in the neonatal period (100% anencephaly; 25% spina bifida), 86,540 in the first year of life (100% anencephaly; 50% spina bifida), and 100,965 in the under-five years age category (100% anencephaly; 75% spina bifida). Primary prevention of FAP SBA can achieve a reduction of 9.1%, 7.7%, and 7.0% in the current neonatal, infant, and under-five mortality rates, respectively, in India. The proportional contributions of this prevention towards achieving the SDG for 2030 in neonatal (12 per 1,000 live births) and under-five mortality rates (25 per 1,000 live births) are 16% and 13%, respectively. Conclusions: Total prevention of FAP SBA in India could lead to 7–9% reduction in its child mortality and 13–16% of the reduction needed for India to achieve SDG Target 3.2 for child mortality. Mandatory folic acid fortification programs for primary prevention of FAP SBA are both proven and cost-effective, and urgently needed in India.

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CANFIELD MA[1], LANGLOIS PH[1], MARENGO LK[1], HOYT AT[1], ETHEN MK[1], SCHEUERLE AE[2]. [1]Texas Department of State Health Services, Austin, TX, United States, [2]UT Southwestern Medical Center, Dallas, TX, United States. Descriptive Epidemiology of Microcephaly in Texas

There has recently been increased interest in microcephaly because of its association with the Zika virus spreading through Latin America. Our purpose with this study was to describe the epidemiology of microcephaly in Texas before the possible arrival of Zika. Case data were taken from the Texas Birth Defects Registry from 1999, the first year of statewide surveillance, through 2012, the most recent complete year. Detailed analyses focused on the recent five-year period 2008–2012. Statistical methods included calculating percentages and birth prevalence with 95% confidence intervals. In 1999–2012, there were 6,085 cases of microcephaly; its prevalence was 11.37 cases per 10,000 live births. Prevalence has risen roughly three-fold, from 6.62 cases per 10,000 in 1999 (231 cases) to 19.79 per 10,000 in 2012 (757 cases). Among all cases, 5.1% were considered "possible/probable" and 33.0% had co-occurring conditions that might explain the microcephaly (e.g., chromosomal, prenatal cytomegalovirus infection). In 2008–2012, there were 2,009 definitive unexplained cases. The distribution by pregnancy outcome was 99.6% live birth, 0.4% fetal death, and 0.1% pregnancy termination. Also, 34.6% of cases were preterm deliveries. Approximately 55.8% of the cases were considered isolated (i.e., no co-occurring major birth defects). The most common co-occurring birth defects appeared to be other defects of the brain, skull and jaw, and heart defects. Of live-born cases with head circumference information, 24.9% were at least two standard deviations below average and 12.0% were at least three standard deviations, which are considered more objective criteria for "microcephaly" and "severe microcephaly." Birth prevalence rates were significantly higher in female infants and for mothers living in the Dallas/Ft Worth, South Central (San Antonio), and Far West Texas. Rates were significantly lower for non-Hispanic Whites and for mothers with greater than high school education. Maternal age showed a U-shaped pattern. The above results provide a baseline for the occurrence of microcephaly in Texas. In light of Zika virus concerns, next steps for the Texas Birth Defects Registry are to implement rapid case ascertainment of microcephaly, 100% clinical review, and a case-control study of old vs. new cases.

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BOUKHRIS T[1,2], SHEEHY O[2], BERARD A[1,2]. [1]Faculty of Pharmacy, University of Montréal, Montréal, QC, Canada, [2]Research Center, CHU Sainte-Justine, Montréal, QC, Canada. Antidepressant Use in Pregnancy and the Risk of Attention Deficit with or without Hyperactivity Disorder in Children

The association between antidepressant (AD) use during pregnancy and the risk of attention deficit with or without hyperactivity disorder (ADHD) in children is controversial. We sought to evaluate the risk of ADHD associated with overall and class-specific antidepressant exposure *in utero*. We performed a register-population-based cohort study, using an ongoing population-based cohort, the Quebec Pregnancy/Children Cohort (QPC), which includes data on all pregnancies and children in Quebec from 1998–2009. Cox proportional hazards regression models were used to estimate crude and adjusted hazard ratios (HRs) with 95% confidence intervals. During 542,897.28 person-years of follow-up, 4564 infants (3.16%) were diagnosed with ADHD. The mean age at first ADHD diagnosis was 6.35 ± 2.33 years (median, 7.00 years) and the mean age at first ADHD medication was 7.00 ± 1.54 years (median, 7.03 years). AD use during the 2nd or 3rd trimester of pregnancy was significantly associated with an increased risk of ADHD (aHR= 1.28; 95% CI 1.03-1.59; 134 exposed cases) event after adjusting for potential confounders, including maternal history of depression and ADHD; tricyclic ADs use was significantly associated with an increased risk of ADHD (aHR=1.76; 95% CI 1.01-3.06; 16 exposed cases); SSRI and SNRI use were increasing the risk of ADHD but estimates were nonstatistically significant. Our findings suggest that use of ADs during the second or third trimester of pregnancy, specifically tricyclic antidepressants, is an independent risk factor for ADHD in children above and beyond the risk associated with maternal depression or ADHD. Our results are suggesting that medications with serotonergic effect during pregnancy have an impact on the risk of ADHD.

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MUTCHINICK OM[1], AGUAYO A[1], ORTIZ G[1], MUÑOZ LA[1], LUNA L[1], SÁNCHEZ ME[1], BERUMEN E[2]. [1]Genetics Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, Mexico, [2]Fundación Teletón, Estado de México, Mexico. Multicentric Study of Genetic and Environmental Risk Factors Associated to Myelomeningocele in a Sample of 500 Trios of the Mexican Mestizo Population

Background: Although much effort has been devoted to understand the etiology of NTDs, research in humans showed that it is more what we ignore that what we really know. Genomic research alternatives are now the current approach in this field. Although decreasing significantly due to FAF programs in México, NTDs prevalence still remains higher than in many other populations. The lack of representative genomic studies on myelomeningocele (MMC) in our country, we decided to develop a multicenter research project on candidate genes variants. Objective: The aim of the project was to study known and unknown MMC associated risk gene variants to investigate allelic and genotypic associations, allele transmission disequilibrium, gene-gene interactions (GGI), genotype-phenotype correlation, and some environmental risk factors. Material and Methods: 500 trios and 500 controls from 16 Centros de Rehabilitación Infantil Teletón (CRIT) from 16 different States of México were included. DNA was obtained from blood or saliva samples and two questionnaires (clinical-genetic and food-frequency-intake) were applied to case and control mothers. A custom 768 variants Golden-Gate microarray (Illumina®) including 656 variants of 395 candidate genes of diverse signaling, structural, and metabolic pathways plus 112 gene variants for ancestry analysis was used for genotyping. Statistics were performed with PLINK software. For genotype-phenotype correlations, MMC was stratified in high MMC (H-MMC-thoracic-vertebrae-affected) and low (L-MMC-lumbar-sacral-vertebrae-affected). A $p<0.01$ was considered statistically significant. Results: Association analysis showed significant statistical differences (SSD) for two genes variants in H-MMC: *SHROOM3* and *VANGL2*, different from those observed in L-MMC: *DVL2, LAMA5, INVS, PAX3, CSNK1G3.* TDT revealed SSD in *NCAM1, C2CD3, GATAD2A, ERCC5* gene alleles in H-MMC and in *PSMB9, LRP5, PSMB4* in *L-MMC*. GGI results for folate, Wnt-Notch-Hh, cytoskeleton, ciliogenesis-PCP, and glucose-fatty-acid pathways genes showed 19 H-MMC GGI, completely different of 49 GGI seen in L-MMC. Comments: Our findings strongly suggest that some of the 656 gene variants studied represents a risk for MMC occurrence. Furthermore, the characterization in severe (H-MMC) and less severe (L-MMC) phenotypes disclose a quite different panel of associated allelic risk variants, finding that was confirmed by the association, TDT and GGI analysis performed, advocating for a significant genotype-phenotype correlation.

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BERARD A[1,2], SHEEHY O[1], GIRARD S[1,2], ZHAO J[1]. [1]Research Center CHU Sainte-Justine, Montréal, QC, Canada, [2]University of Montréal, Montréal, QC, Canada. Risk of Preterm Birth following Late Pregnancy Exposure to Medications used in the Treatment of Autoimmune Diseases

Introduction: The number of women of childbearing age with autoimmune diseases has increased over the past decades; women using antiinflammatory drugs have also been increasing given their potential availability over-the-counter. The modulation of the inflammatory process associated with these diseases during pregnancy leads to high frequency of perinatal complications such as prematurity. However, treatment might change these risks. Given the potential public health impact, this study aims to quantify the risk of prematurity associated with late pregnancy exposure to antiinflammatory medications. Methods: A cohort study was conducted within the Quebec Pregnancy Cohort (1998–2009). All pregnancies with medication insurance coverage of at least 12 months before and during pregnancy, ending with a liveborn infant were included. Late pregnancy exposure was defined as having filled at least one prescription for selective or nonselective NSAIDs (excluding: indomethacin and sulindac) or biologic agents (infliximab or etanercept) filled in the three months prior to delivery. Prematurity was defined as less than 37 weeks of gestation. Crude and adjusted risk ratios (RR) were obtained using Generalized Estimation Equation (GEE) models. Covariates included maternal demographics (age, welfare recipient, place of residence, and education), maternal autoimmune diseases, pregnancy complications, and other comorbities. Results: A total of 156,531 pregnancies met inclusion criteria. In the three months before delivery, 393 (0.25%) of women used nonselective NSAIDs, 56 (0.036%) used selective NSAIDs, and 13 (0.008%) used biologic agents. Adjusting for maternal autoimmune diseases, and other potential confounders, selective NSAID use in late pregnancy was associated with a 2.42 fold increased risk of prematurity (OR: 2.42 95% CI 1.24-4.70; ten exposed cases) as compared to nonuse. More specifically, late pregnancy exposure to celecoxib was found to increase the risk of prematurity by more than three-fold (OR: 3.17 95% CI 1.18-8.52; six exposed cases). No other statistically significant associations were found. Conclusion: This study showed that selective NSAIDs, more specifically celecoxib, use during late pregnancy was increasing the risk of prematurity even after taking into account the effect of maternal autoimmune disease. These findings suggest that pregnant women with autoimmune diseases should also be closely monitored.

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SHRESTHA S[1], JIMENEZ EY[2], CANO S[1], WILLIAMS S[1], STEPHEN JM[1], BAKHIREVA LN[1]. [1]University of New Mexico Health Sciences Center and the Mind Research Network, Albuquerque, NM, United States, [2]Center for Education Policy Research, University of New Mexico, Albuquerque, NM, United States. Folate, Iron, and Choline Intake in Pregnant Women with Substance Use Disorders

Introduction: Women with substance use disorders could be at a high risk for poor nutrition during pregnancy due to irregular eating habits, unstable housing, food insecurity, comorbid mental health disorders, tobacco use, poverty, poor social support, and a history of abuse. Previous studies in adults have indicated that both alcohol and opioid use can negatively affect dietary intake patterns. The objective of this study was to evaluate folate, iron, and choline intake, important micronutrients for maternal and child health, in opioid-dependent and alcohol-using pregnant women. Methods: Nutrition data was collected using the Block Brief 2000 Food Frequency Questionnaire from 102 pregnant women enrolled in the ENRICH prospective cohort study at the University of New Mexico. Participants were classified into four study groups based on self-reported information and biomarkers: opioid maintenance therapy (OMT; n=26), alcohol (n=22), OMT+ alcohol (n=27), and abstaining controls (n=27). Micronutrient intake was energy adjusted (Willett method) and then log-transformed for multivariate analysis. Effect size was calculated as percentage difference in dietary micronutrient intake when compared with controls. We estimated the proportion of participants in each group with intakes below the Estimated Average Requirements (EAR) based on diet alone and then with diet and supplements. Results: In energy-adjusted analyses, significantly lower intakes of iron (-13.8%, p=0.03) and folate (-19.6%, p=0.003) were observed in the OMT group, and a significantly lower intake of choline (-13.9%, p=0.02) was observed in the OMT+alcohol group. After adjusting for BMI, ethnicity, smoking, employment, and marital status participants on OMT had lower intake of iron (-15.0%, p=0.04) and folate (-16.8%, p=0.03). Based on dietary intake alone, 78.4%, 50%, and 76.5% of women across all groups had intakes below the EAR for iron, folate, and choline respectively. Discussion: Pregnant women with opioid dependency, with or without concurrent alcohol use, may have a dietary pattern with relatively poor nutrient density compared to controls, highlighting a potential need for nutrition intervention in OMT programs. The results also emphasize the need for supplementation of essential micronutrients during pregnancy, and initiatives to promote use of multivitamins prior to conception and throughout pregnancy.

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LIU Y, LI Z, WANG B, REN A. Institute of Reproductive and Child Health, Ministry of Health Key Laboratory of Reproductive Health, Peking University, Beijing, China. Indoor Air Pollution and Orofacial Clefts in a Rural Population of Northern China

We investigated the effect of maternal exposure to indoor air pollution (IAP) from coal combustion and tobacco smoke on the risk of having a newborn baby with orofacial clefts (OFCs) in Chinese population. Data were derived from an on-going population-based case-control study of major external structural birth defects in Shanxi Province. Subjects included 213 cases with orofacial clefts (OFCs) and 1,319 healthy babies delivered during Nov. 2002 and Dec. 2014 in four rural counties. Exposure information was collected by face-to-face interview with women within one week after delivery or pregnancy termination following prenatal diagnosis. The authors derived an exposure index by integrating a series of IAP-related characteristics concerning dwelling and lifestyle. Unconditional logistic regression model was used to adjust for potential confounding factors. We found that an increased risk of OFCs was associated with IAP exposure from heating (adjusted OR=2.4, 95%CI:1.2,4.5), and from smoking (adjusted OR=1.8, 95%CI:1.3,2.5), but not with exposure from cooking (adjusted OR=0.9, 95%CI:0.6,1.4). Compared with women without IAP exposure, the adjusted odd ratio (OR) of OFC was 1.1(95%CI: 0.6, 1.8), 1.4(95%CI: 0.8, 2.4), 1.8(95%CI:1.0,3.2), and 3.4(95%CI: 1.6, 7.4) for those of women with exposure index of 1, 2, 3, and ≥4, respectively, demonstrating a clear dose-response trend ($P<0.001$). Periconception exposure to IAP from coal combustion and tobacco smoking exposure may increase the risk of OFCs in the offspring in Shanxi Province women.

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TERATOLOGY SOCIETY

POSTER ABSTRACTS

(Presenter designated by underlined author.)

Poster Session 1

P1

NEAL-KLUEVER AP[1], AUNGST J[1], WU Y[1], LIU J[2], SHACKELFORD M[1], OGUNGBESAN A[1], GU Y[1], JACOBS K[1]. [1]US Food and Drug Administration, CFSAN/OFAS/DFCN, College Park, MD, United States, [2]Oak Ridge Institute for Science and Education, Oak Ridge, TN, United States. Regulatory Research to Support Food-Contact Infant Safety Assessment at US Food and Drug Administration

The US FDA Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety (OFAS), Division of Food Contact Notifications (DFCN) performs infant lifestage safety assessments for food packaging intended to contact breast milk or infant formula. To advance regulatory science in this area, DFCN has initiated several regulatory research efforts to evaluate developmental and reproductive toxicology (DART) protocols for use in infant safety assessments. DFCN is currently investigating the performance of the internationally validated one- and two-generation DART (Gen-DART) protocols, as well as other juvenile animal study protocols. Our goal is to determine the utility of different types of protocols for predicting the safety of infant food products, including infant food packaging. All available Gen-DART studies submitted to US FDA in support of food additive safety, direct and indirect, were reviewed and compared to available subchronic systemic toxicity studies conducted in adult animals. Metrics were captured and analyzed to assess cohort sensitivity (parental vs. offspring), study sensitivity (Gen-DART vs. subchronic), and effect sensitivity (reproductive, developmental, and systemic endpoints). To date our work indicates that food additive chemicals demonstrate a low order of toxicity. When cohort-specific sensitivity was observed in Gen-DART studies, the parental generation was more likely to exhibit higher sensitivity to food additive chemicals, although higher F1 (juvenile) sensitivity was also observed in a few cases. Additionally, systemic toxicity appeared to provide the most conservative points of departure in Gen-DART studies for the majority of cases. Expanding the Gen-DART test set may provide additional information to allow predictive toxicology approaches regarding potential heightened juvenile toxicity. Ongoing efforts are underway to expand the test set to include reports from the US EPA, ATSDR, ECHA, COSMOS, JECFA, and JMPR.

P2

HILBISH KG[1], BRESLIN WJ[1], CANNADY EA[1], EDWARDS TL[2]. [1]Lilly Research Laboratories, Corporate Center, Indianapolis, IN, United States, [2]WIL Research, Ashland, OH, United States. Pre- and Postnatal Toxicity Assessment in Rabbits with Evacetrapib, a Cholesteryl Ester Transfer Protein (CETP) Inhibitor

Evacetrapib, a potent and selective inhibitor of cholesteryl ester transfer protein (CETP), was under development for the treatment of cardiovascular disease. The purpose of this pre- and postnatal study in rabbits was to evaluate the effects of evacetrapib on pregnancy maintenance, parturition, and lactation of the maternal animals and on the growth, viability, and development of the F1 offspring. Reproductive and behavioral performance of the F1 generation were also assessed. Evacetrapib was administered daily by oral gavage starting on Gestation Day (GD) 7 and continuing through Lactation Day (LD) 41. Dose levels of evacetrapib were 0, 10, 30, and 100 mg/kg using 35 animals per group. Toxicokinetics were assessed in satellite animals. There were no adverse effects on maternal survival, clinical signs, gestation length, parturition, and number of F1 kits born. There were no effects in the F1 kits on clinical observations, body weight, attainment of sexual maturation landmarks, conditioned eye blink response, functional observational battery, or macroscopic necropsy findings. Lower F1 postnatal survival was noted in the 100 mg/kg group during postnatal days 1–7. There were also reductions in F1 mating, fertility and copulation/conception indices for males and females in the 100 mg/kg group, which were considered of uncertain relationship to treatment. There were no changes in sperm parameters, organ weight, F1 maternal reproductive parameters, or in F2 survival. In conclusion, the maternal no-observed-adverse-effect (NOAEL) level following evacetrapib administration in female rabbits was 100 mg/kg. Based on the decreased F1 postnatal survival and the potential effect on reproductive indices at 100 mg/kg, the NOAEL for F1 neonatal developmental and reproductive toxicity was 30 mg/kg.

P3

YUAN YZ. Shengjing Hospital, China Medical University, Shenyang, China. Identification of the Novel Serum Biomarkers for the Prenatal Noninvasive Diagnosis of Neural Tube Defects

Neural tube defects (NTDs) are severe congenital malformations affecting approximately 0.6–6 in every 1,000 pregnancies. To identify candidate serum molecule biomarkers for the noninvasive early prenatal diagnosis of NTDs, we performed a comprehensive maternal serum proteomics assessment in 50 pregnant women with NTDs fetuses and all-trans retinoic acid-induced rat models with spina bifida aperta. An isobaric tagging for relative and absolute quantification (iTRAQ) proteomic approach was used first to compare protein profiles in pooled serum collected from pregnant women with NTDs fetuses or normal fetuses, and 16 proteins displayed significant differential expressions. After further verification, ceruloplasmin (CP) has good sensitivity and specificity in the diagnosis of neural tube defects and it is better than AFP. The area under the receiver operating characteristic curve (AUC) for CP and AFP distinguishing NTD cases from normal controls was 0.979 and 0.938 respectively. Meanwhile, we analyzed the proteomic changes in serum samples from embryonic day (E) 11 and E13 pregnant rats with spina bifida aperta, and 40 proteins at E11 and 26 proteins at E13 displayed significant differential expression in the SBA groups. After confirmation in serum of pregnant women with NTDs fetuses by ELISA, we observed the space-time expression changes of proprotein convertase subtilisin/kexin type 9 (PCSK9) have better diagnostic efficacy (AUC, 0.763). The discovery of serum biomarkers in maternal serum not only could help us in prenatal diagnosis of NTDs, but also may shed new light on NTDs embryogenesis studies.

P4

HOANG TT[1], MARENGO LK[2], MITCHELL LE[1], CANFIELD MA[2], AGOPIAN AJ[1]. [1]University of Texas School of Public Health, Houston, TX, United States, [2]Texas Department of State Health Services, Houston, TX, United States. The Association between Maternal Diabetes and Congenital Heart Defect Phenotypes in Texas and Updated Meta-Analysis

Congenital heart defects (CHDs) are the most common type of birth defect. The etiology of CHDs remains largely unknown, but maternal diabetes has been consistently reported to increase the risk of CHD. CHDs, however, are an etiologically heterogeneous group, so maternal diabetes may have different effects on different aspects of heart development. The mechanisms underlying the association between maternal diabetes and CHD malformations may also differ between women with pregestational versus gestational diabetes. We analyzed the association of maternal diabetes and 17 specific CHD phenotypes (e.g., atrial septal defect, Tetaralogy of Fallot) using data from the Texas Birth Defects Registry and statewide vital records for 1999–2009 deliveries (N=48,249 cases). We used Poisson regression to calculate prevalence ratios for the associations between maternal diabetes and each CHD phenotype, adjusting for maternal age, race/ethnicity, hypertension, previous live births, and smoking. Texas vital records were revised in 2005 to include information on type of diabetes (pregestational or gestational) and maternal body mass index. For 2005–2009 deliveries, analyses were repeated by type of diabetes and further adjusted for body mass index. To address the potential for misclassification bias, we performed logistic regression, using malformed controls. We also conducted meta-analyses on the association between pregestational diabetes and 14 different CHD phenotypes, combining our estimates with previous estimates. In Texas, the prevalence of every CHD phenotype was greater among women with any diabetes compared to nondiabetic women (adjusted prevalence ratios (aPRs): 1.48–5.28). Compared to the any diabetes associations, the associations observed for women with pregestational diabetes were stronger and all statistically significant (aPRs: 2.47–13.20). Associations were slightly attenuated for many CHD phenotypes among women with gestational diabetes (aPRs: 1.15–2.78). The observed associations do not appear to be the result of misclassification bias. In our meta-analysis, pregestational diabetes was significantly associated with each of 14 CHD phenotypes. The largest association was observed for truncus arteriosus (combined relative risk = 14.49). The remaining combined relative risks ranged from 2.75–5.78. These findings contribute towards a better understanding of the teratogenic effects of maternal diabetes and improved counseling for risk of specific CHD phenotypes in offspring.

P5

BAILEY GP[1], VAN HEERDEN M[1], ROOSEN W[1], NDIFOR A[2]. [1]PD&S, Janssen Research and Development, Beerse, Belgium, [2]Janssen Research and Development, La Jolla, California, United States. Seeing Spots in Front of Your Eyes?—Investigating Nuclear Cataracts in Fetal Rats

Fetal examinations in embryo-fetal developmental (EFD) studies are structurally based and histopathology is rarely performed other than to confirm macroscopic finding. Fetal lens examination is therefore generally limited to the presence, size, shape, and colour. Bouins examinations of Day 21 fetuses from a rat EFD study for a new molecular entity at Janssen Preclinical Development & Safety revealed an unusually high incidence of granular foci within the lens. These were observed in all treated groups and were greatest in the high-dose group where almost 70% of the litters were affected. Histopathology was performed on all lenses showing granular foci and revealed nuclear cataracts with swelling, degeneration, and fragmentation of the primary lens fibres. In a second study, performed to establish a no effect level, where all the lenses were examined histopathologically, low incidences of similar findings were observed in all groups including the controls. To understand the background incidences of these findings, histopathology was performed on the lenses of the remaining fetuses from the original study. These results indicated that primary fibre swelling and degeneration was regularly recorded, in control and dosed fetuses in the absence of gross lesions. There was a large variation in the histopathological findings of the control groups with incidences as high as 75 and 70 % of litters with either primary fibre swelling or degeneration, respectively. Investigations are ongoing in control animals into the postnatal outcome by comparing the histopathological incidence of fetal cataracts on Day 21 of pregnancy against ophthalmology performed at 18 days of age and ophthalmology and histopathological findings at 35 days of age. The optimal postnatal method for detecting and classifying lenticular changes (or opacities) is by ophthalmoscopy but this is not routinely performed on pre- and postnatal studies which is the only regulatory study where littering occurs. Therefore we conclude that while there is a significant background incidence of these changes, (0–37% per study, pretreatment ophthalmoscopy at Janssen), it is unlikely to be detectable in routine reproductive toxicity testing unless a treatment effect in fetuses is accompanied by a macroscopic change.

P6

LAMM SH[1,2], POLIFKA JE[3], FERDOSI H[1]. [1]Center for Epidemiology and Maternal and Child Health, Consultants in Epidemiology and Occupational Health (CEOH), Washington, DC, United States, [2]Georgetown University School of Medicine, Washington, DC, United States, [3]University of Washington School of Medicine, Seattle, WA, United States. The WHO Essential Medicines List Ignores the Concerns of the Pregnant Women

Since 1977, the WHO has been publishing biannually a list of medicines that it considers essential (Essential Medicines List, [EML]) for all countries and since 1997 a similar list of medicines for children [EMLc]. However, the teratogenicity of these essential medicines does not appear to have been considered. Further, while the EML specially notates medicines that are restricted to use in children with a [c], there is no similar notation, i.e., a [p], for the special medicinal concerns of pregnant or lactating women. In order to assess the proportion of medicines on the EML that might need special consideration for pregnant women, we sought expert opinions from four published compendia that assess the teratogenic risks of medicines used during pregnancy: TERIS, Reprotox, Briggs et al., and Schaefer et al. Five risk strata were set based on the available information 1) reasonably safe, 2) suggestive risk, 3) hazardous, 4) insufficient information, and 5) no information. For drugs found to be hazardous, alternative medicines known to be safe in pregnant women were sought. The 2015 EML includes 408 medicines. For 36% of these, there is sufficient information to assess them as being reasonably safe for pregnant women. 22% have sufficient information to suggest that they might be hazardous during pregnancy, and 3% [n = 12] have sufficient information to assess them as being hazardous during pregnancy. The remaining medicines have either inadequate (26%) or no (13%) information for assessing their risk. An additional 24 medicines known to be relatively safe for pregnant women were identified for inclusion in subsequent updates. Treatment during pregnancy requires special consideration because of the physiological, pharmacokinetic, and toxicological changes and their subsequent risks to the embryo or fetus. The current EML contains medicines that are inappropriate for use during pregnancy. Information about the potential teratogenicity of medicines and the availability of safer alternatives is not provided. We recommend that the EML that expertise on the EML panels be extended to include risks of medicines during pregnancy and that a notation of [p] be included to indicate medicines known to be hazardous in pregnancy.

P7

FADEL RA[1,2], DESSOUKI SK[2], MOSTAFA NM[2], DAOUD AW[2]. [1]Arabian Gulf University, Manama, Bahrain, [2]Suez Canal University, Ismailia, Egypt. Skeletal Development in the Fetuses Following Administration of Diazepam to Pregnant Rats

Diazepam is a commonly used anxiolytic drug that can be used during pregnancy. The aim of the present study is to provide some insight regarding the pattern of skeletal development in 20-day albino rat fetuses following maternal exposure to high and low therapeutic doses of diazepam. 36 pregnant albino rats were divided equally into three groups: Control group, LDD group (0.45 mg /kg BW), and HDD group (0.9mg /kg BW). Treatment was given daily to pregnant dams intragastrically from day 6–15 of gestation. Fetuses were collected by caesarian section at the 20th day of gestation. Bones were stained by alizarin red using Dawson's technique then ossification of 70 intact fetuses was assessed. The results revealed that low-dose diazepam administration had mild suppressive effects on ossification of fetal bones, while high-dose diazepam delayed ossification markedly. Delay ossification affected the length and shape of the ossified part of the bones. The most affected ossification centers were the supraoccipital, presphenoid, sternum, cervical arches, sacral arches, and centra in the axial skeleton as well as metacarpal, metatarsal, and pubic centers in the appendicular skeleton. No apparent skeletal malformations were detected. In conclusion, diazepam affects passively bone development and delays ossification in albino rat fetuses in a dose-related manner. The mechanism of restriction of ossification could be related to Frost's mechanostat theory for bone development.

P8

GHASSEMI JAHANI S-A[1], DANILESSON A[1], AB-FAWAZ R[2], HEBELKA H[2], DANIELSON B[2], BRISBY H[1]. [1]Institute of Clinical Sciences Sahlgrenska Academy, Department of Orthopedics, University of Gothenburg, Gothenburg, Sweden, [2]Institute of Clinical Sciences Sahlgrenska Academy, Department of Radiology, Gothenburg, Sweden. Degenerative Changes in the Cervical Spine Are More Common in Middle-Aged Patients with Thalidomide Embryopathy Than in Healthy Individuals

Purpose: The aim of the study was to compare the degree of degenerative changes in the cervical spine of thalidomide embryopathy (TE) patients, in whom upper limb malformations often necessitate help with grip function through the mouth or by head motion, and may thereby add extra load to the spine, with that in a control group (CTR). Methods: 27 middle-aged TE patients and 27 age- and gender-matched healthy CTR were examined by cervical MRI. The presence of malformations, disc herniations, osteophytes, nerves, and medullary compression were evaluated. Disc degenerations (DD) were graded according to the Pfirrmann classification. Results: Similar frequencies of disc herniation and disc space narrowing were observed in both groups, but there was more foraminal narrowing in the TE group ($\rho < 0.002$). Significantly more DD were seen in the TE group than in the controls ($\rho < 0.001$). Evaluation of all discs ($n = 135$ per group) showed Pfirrmann grade I in 0% of the TE group and 2% of the controls. Grade II was found in 3% and 36%, respectively, grade III in 46% and 50%, grade IV in 38% and 11%, and grade V in 13% and 1% ($\rho < 0.001$). DD were observed frequently at all levels for the TE group, however mainly in the two lower levels for the CTR. Conclusions: The more frequently observed degenerative changes of foraminal narrowing and disc signal changes in the TE group support the theory that a higher load on the cervical spine leads to earlier development of DD.

P9

CHIMA HS[1], URIU-ADAMS JY[1], CHAMBERS CD[2], COLES CD[3], YEVTUSHOK L[4], ZYMAK-ZAKUTNYA N[5], WERTELECKI W[6], KEEN CL[1]. [1]University of California, Davis, Davis, CA, United States, [2]University of California, San Diego, San Diego, CA, United States, [3]Emory University, Atlanta, GA, United States, [4]Rivne Oblast Medical Diagnostic Center and OMNI-Net, Rivne, Ukraine, [5]Khmelnytsky Perinatal Hospital and OMNI-Net, Khmelnytsky, Ukraine, [6]University of South Alabama, Mobile, AL, United States.

Prenatal Alcohol Exposure: Impact on Child Nutritional Outcomes

The effects of prenatal alcohol exposure on the nutritional status of the offspring are largely unknown. Our ongoing study, conducted in Ukraine, recruits alcohol-consuming and control women during pregnancy. Neurobehavioral assessments of infants are performed at six and twelve months. Infants are classified as having Fetal Alcohol Spectrum Disorder (FASD) if they present with both physical features and one standard score of Bayley Scales of Infant Development II below 85. Plasma samples from control children (N=31), alcohol-exposed children with FASD (N=7) or without FASD (N=8), (overall mean age 3.6 ± 0.9 y) were analyzed for select micronutrients. Using ANCOVA, preliminary data showed no differences in plasma levels of soluble transferrin receptor, soluble transferrin receptor-ferritin index, high-sensitivity C-reactive protein, homocysteine, and cortisol among the three groups. Children displaying features of FASD had significantly lower plasma ferritin levels (1.17±0.10 log ng/mL) compared to control children (1.49±0.05 log ng/mL, p=0.028) but were not different than unaffected children with prenatal alcohol exposure (1.38±0.09 log ng/mL). All children's study visits occurred in summer months. While Vitamin D levels were adequate in all children, there was a nonsignificant trend indicating that children with prenatal alcohol exposure with FASD had higher levels of Vitamin D (2.05±0.05 log nmol/L) compared to unaffected children with prenatal alcohol exposure (1.88±0.05 log nmol/L, p=0.071). However, there was no difference in Vitamin D levels of control children (1.94±0.02 log nmol/L) compared to FASD children. Preschool cognitive testing is currently being assessed. The extent to which the child's nutritional status is associated with neurodevelopmental performance and growth will be explored in the future. (Supported by NIAAA-U01-AA014835-12)

P10

SCALZO AJ[1,2], BRADDOCK SR[1,3]. [1]Department of Pediatrics, Saint Louis University School of Medicine, St. Louis, MO, United States, [2]Division of Medical Toxicology, St. Louis, MO, United States, [3]Division of Medical Genetics, St. Louis, MO, United States.

Normal Offspring of 22 Year Old Male and 17 Year Old Female Recreationally Abusing Synthetic Cannabinoid K2 and Cathinone "Bath Salts"

Since the introduction of synthetic cannabinoids (K2) and cathinones as recreational drugs, little is known about the potential teratogenic and/or development effects. Classical studies dating back to the 1970s have reached disparate conclusions on the teratogenic and/or spermatogenic effects of the natural phytocannabinoid THC in animal models. It is known that THC readily crosses the placenta although its metabolite 11-nor-9-carboxy-THC may not in primates. The degree to which the synthetic cannabinoids or cathinones cross the human placenta is largely unknown. We report the case of a healthy full-term male born to a 17-year-old female and a 22-year-old male who were heavily abusing K2 (JWH018) and also "bath salts" (methylenedioxypyrovalerone). At the time of conception, the father was smoking 9 to 12 grams/day of K2 and was on a six-day binge of bath salt use in late January 2011. The mother also recreationally abused K2 and bath salts. In early February 2011, we received a communication from the paternal grandmother after discovering that her son had impregnated the 17 year old while they were both using the drugs. The father had used marijuana since age 17. The maternal grandparents suggested that their daughter abort the fetus. In consultation with Medical Genetics and Toxicology, the family was counseled and proceeded with the pregnancy based upon the lack of clear data suggesting adverse outcomes. A healthy, full-term male was born weighing 7 lbs, 14 oz with normal phenotype and mild left esotropia. The child underwent strabismus surgery at age two and is thriving. The endocannabinoid system is intricately involved in normal embryogenesis. THC has shown variable teratogenic or developmental effects on the fetus in animal models. Some reports in humans on the affects of THC are conflicting. Very little is known about the teratogenic effects of synthetic cannabinoids and/or cathinones. While this case has had a good outcome, further research is needed to explore the potential adverse effects and teratogenicity of these ubiquitous xenobiotics. We conclude that despite heavy use of synthetic cannabinoids and cathinones by both parents, it is important to offer proper genetic counseling to families.

P11

HIXON M, BEYER L. Gradient, Cambridge MA, United States. Evaluation of Reproductive Health Effects for the Caffeine in an Energy Drink

We evaluated the safety of caffeine in an energy drink in a manner consistent with a Generally Recognized as Safe (GRAS) determination. The product label recommends that women pregnant or nursing should not use the supplement. For this reason, we only reviewed literature addressing the possible effects of caffeine on conception. To do this, we conducted a comprehensive literature search using PubMed and reviewed key studies from 2011 to 2014 on reproductive health effects related to caffeine consumption in humans. We retrieved studies based on search terms including coffee and/or caffeine combined with male and female reproductive health endpoints. We combined the 90th percentile typical daily caffeine ingestion (380 mg/day) with caffeine ingested in the energy drink, resulting in a combined high-end ingestion rate of approximately 780 mg caffeine/day to 880 mg caffeine/day. Based on our analysis, no adverse effects were found for chronic caffeine consumption and male reproductive function, even at doses ≥ 800 mg/day. Limited evidence of reduced fertility was observed in women consuming > 100 mg of caffeine per day. No association was found for menstrual irregularities in women with low (100–199 mg/day), moderate (200–299 mg/day), or high (> 300 mg/day) caffeine intakes. These findings are consistent with a recent evaluation of data for pregnant women, which recommended consumption of one to two cups of coffee a day (i.e., caffeine consumption of <300 mg/day), as a general rule based on fertility as well as adverse pregnancy and neurodevelopmental outcomes. Overall, when used as recommended, caffeine intake up to 250 mg in an energy drink is not harmful to human reproductive health.

P12

PACE ND. University of North Carolina at Chapel Hill, Chapel Hill, NC, United States. Where We've Come from: A Historical Review of Infant Survival of Spina Bifida

In the past century, infant mortality, death of a live born child during the first year of life, has decreased in the US from 10 to 0.6%, a 94% reduction in mortality. Great efforts both to prevent and to treat disease have made this possible. Among the monumental achievements in perinatal clinical care over the last 50 years, is the increased survival of infants born with a birth defect. Despite birth defects being the leading cause of infant mortality, advancements in treatment and clinical decision-making have made defects, like spina bifida, a congenital anomaly that rarely results in death. Spina bifida occurs in 1 out of every 3,000 live births in the US. We aim to present how survival of infants born with spina bifida has increased over time. We reviewed population-based and hospital-based studies on survival among infants with spina bifida and present synthesized results of survival juxtaposed to historical advancements in clinical care. Whether or not to even treat an infant with spina bifida or when to treat was debated for several decades. Prior to the 1960s, only 11–30% of untreated infants with spina bifida survived beyond six months, while 24–41% of treated cases survived beyond one year. Use of shunts to treat and prevent hydrocephalus paralleled spina bifida infant survival rising to 60% in the 1960s. Improved shunts and antibiotic use in the 1970s led to 60–86% survival. During the 1980s, survival incrementally rose to 89%. From the 1990s to the present, survival of spina bifida has gradually improved to be between 92–97% due primarily to improvements in surgery and postoperative care as well as antenatal detection and monitoring. We observed that differences in survival estimates during similar time periods seemed likely due to variation in study design (e.g., geographical location, hospital-based vs. population-based sample, inclusion of spina bifida cases with other co-occurring defects). Shunt use and clinical guidelines to perform treatment soon after birth have likely resulted in the largest improvement in survival. Spina bifida is a model for how other birth defects can improve survival through both medical device advancements and improved clinical guidelines.

P13

MEMON S, BANO U. Liaquat University of Medical & Health Sciences, Jamshoro, Sindh, Pakistan. Effects of Micronutrient Deficient Diet on Maternal Health during Pregnancy

Pregnant women are prone to certain vitamin and mineral deficiencies, due to increase metabolic demands, which results in unfavourable maternal and fetal health effects. Micronutrient deficient diet during critical periods of pregnancy has adverse effects on disease progression later in the life. This study was aimed to detect the possible role of deficient diet in chromium, manganese, and zinc during intrauterine life on maternal health of pregnant mice. Adult female mice were divided in four groups, each comprised of six female mice. Animals were housed individually in polypropylene cages, in standard lighting, controlled temperature and humidity conditions. Control group was fed *ad libitum*. Second group was fed a diet restricted in the chromium (0.51mg/kg diet), third with manganese restricted (0.33mg of Mn/ Kg), and fourth with a diet restricted in the zinc (10 mg/ kg diet). The animals were kept on these diet regimens for four weeks. Plasma levels of these trace elements were determined at the end of four weeks of feeding regimen using spectrophotometer. After ensuring the levels, the animals were allowed mating with control males of same species; the day vaginal plug was detected, counted as day one of pregnancy. The pregnant mice were fed on same diet throughout pregnancy. Daily food intake and weekly body weight was monitored throughout the duration of study, and the effects of these trace elements were observed on pregnant mice. Grossly weight of treated mice was significantly more than control after the treatment as compared to their weight before micronutrients were restricted. Mortality rate was also higher in restricted groups. The pups of restricted diet group were also growth retarded and died within few days of birth. This animal study has provided a clue those micronutrients, although required in minute quantities, are essential components of diet during pregnancy and have adverse effects on maternal and fetal health. Further studies need to be conducted to examine the affects of these micronutrients on offspring with advancing age.

P14

CABRERA RM, VICHIER-GUERRE C, PARKER M, POMERANTZ Y, FINNELL RH. University of Texas at Austin, Austin, TX, United States. Impact of SSRI Exposure on Neural Crest Stem Cells

An estimated 7.5% of pregnancies in the United States are exposed to antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are currently the most common antidepressant prescribed to pregnant women. The teratogenic effects of serotonin are well established, but SSRI teratogenicity is debated. As an alternative to epidemiological and animal studies, embryonic stem cell testing provides a human-based experimental model to examine the risks of prenatal SSRI exposure. Neural crest stem cells (NCSCs) play an important role in craniofacial and cardiac development as precursors to craniofacial bones and heart septa. This study examines the effects of paroxetine and sertraline exposure on NCSC. Our results demonstrate that paroxetine and sertraline alter normal NCSC behavior and may thereby disrupt cardiac and craniofacial development.

P15

FERNANDEZ GANCEDO A, SERRANO GARZA AM, AMARO LARA MK, IBARRA RAMIREZ M, MARTINEZ DE VILLARREAL L. Departamento de Genética, Facultad de Medicina y Hospital Universitario, Universidad Autónoma de Nuevo León, Monterrey, Nuevo Leon, Mexico. Report of Congenital Birth Defects in a Third Level University Hospital from the North of México: Cases from 2013 to 2015

Congenital birth defects are a primary cause of morbidity and mortality on newborns all around the world. It has been calculated that between two and three percent of all newborns will have a congenital birth defect of any kind. In Mexico, these cases are often subdiagnosed, and by addition sub-reported. It is the purpose of this article to generate knowledge about the incidence and prevalence of congenital birth defects in Mexico. For this purpose, we took a sample from a pre-stablished birth defect program database, filled with the information from both parents and the newborn, which in hand had already been diagnosed by both a pediatrician and a clinical geneticist, as a newborn with an either isolated or multiple congenital birth defect. Both genetic and environmental factors were taken in consideration during the data collection as well as the prenatal care and birth conditions for the newborn. The information was then analyzed to get the general incidence of birth defects in our hospital, as well as specific incidence of the most prevalent birth defects according to our own statistic and global prevalence expectations. A total of 310 congenital birth defects were reported during a three year period, with almost 8,500 newborn births per year. The most frequently reported defects were craniofacial malformations (19% of the total reports). Other birth defects highly reported were congenital heart defects (9%): gastrointestinal defects (14%), one third of which were gastroschisis; and CNS birth defects (8%). Down's Syndrome was the most frequently reported multiple defects abnormality, accounting to 11% of the total reports. The incidence of congenital birth defects in our hospital was 12 for every 1,000 newborns although the statistic is lower than the global incidence, the case could be made that there are still newborns who are subdiagnosed, and hence were not reported for inspection and were not added to the report. During the bibliographical research for this article, there was an evident lack of statistic from Mexican hospitals. Lastly, it should be noted that emerging environmental factors like Zika virus could also be identified by congenital birth defect report programs.

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HINOJOSA AMAYA AB, FERNANDEZ GANCEDO A, IBARRA RAMÍREZ M, MARTINEZ DE VILLARREAL L. Departamento de Genética, Facultad de Medicina y Hospital Universitario, Monterrey, Nuevo León, Mexico. Maternal Overweight and Obesity as Risk Factors for Congenital Cardiac Disease in a Third-Level Care Hospital from Northeast Mexico

Congenital cardiac disease is the most common congenital defect worldwide. The prevalence reported ranges from 2.1 to 12.3 in every 1,000 live births. It accounts for almost a third of all congenital defects. In Mexico, there is not a reliable incidence data of these defects due to a lack of a systematic congenital defect registry. It is thought that ventricular septal defects and arterial ductus persistency are the most common congenital cardiac defects in Mexico. The Mexican prevalence of overweight and obesity in childbearing-aged women is 33–39.4% and 20.5–34.7% respectively, both factors being known to increase heart defects incidence. The aim of this study is to correlate relationship between the prenatal maternal body mass index and weight gain during pregnancy with cases of congenital cardiac disease. We collected the cases of newborns with a congenital cardiac defect from the congenital defects electronic registry of the University Hospital, of children born from January 2014 to December 2015. We collected the pregestational and postgestational weight from the mothers of these infants. We calculated the pregestational body mass index and weight gain from the mothers. Finally, we compared those children whose mothers had these risk factors and the ones who did not have them in order to determine if there was a relationship between these risk factors and congenital cardiac defects. A total of 31 cases of congenital cardiac disease were reported during the two year period. This accounted for 9% of all congenital defects. The most prevalent were septal defects (30%) and the second was dextrocardia (19%). The relationship between overweight, obesity, and congenital cardiac disease is discussed in the article, but it should be noted, that the prevalence of obesity during pregnancy was highly observed. It is important to recognize that congenital cardiac disease as a cause of morbidity and mortality in infancy. Maternal weight, as a factor, should be taken into account by gynecologist, and pediatricians, and thus strictly controlled during pregnancy. This study describes Mexican data that show a relationship between overweight, obesity, and congenital cardiac disease, something that has not much data at the moment.

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DANDJINOU M[1,2], SHEEHY O[2], BÉRARD A[1,2]. [1]University of Montréal, Montréal, QC, Canada, [2]CHU Ste Justine, Montréal, QC, Canada. Should We Treat or Not Mildly to Moderately Depressed Pregnant Women during Pregnancy?

Depression is prevalent in women of reproductive age and antidepressants (ADs) are widely used. Given that the majority of depressed pregnant women are mildly to moderately depressed, there is no current consensus on whether treatment with antidepressants is beneficial in this subgroup. The objective of this study was to investigate whether AD use during pregnancy was associated with the risk of postpartum depression (PPD) in mildly to moderately depressed pregnant women. A cohort study was performed using data from the Quebec Pregnancy Cohort (QPC). All pregnancies with a diagnosis of depression or anxiety, or exposed to antidepressants in the 12 months before pregnancy and ending with a delivery were included. Exposure during pregnancy was classified in five groups (not exposed (reference), exposed throughout pregnancy, first trimester exposure only, second/third trimester exposure only; and intermittent). PPD was defined as having a hospital diagnosis from one month after delivery until 12 months postpartum. Cox proportional hazard models were used to estimate crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CI), adjusting for potential confounders including severity of the depression. 20,647 pregnancies met inclusion criteria. When adjusting for potential confounders, women exposed to antidepressants throughout pregnancy (aHR=1.59; 95% CI: 0.52–4.79; 4 exposed cases), those exposed in the first trimester only (aHR=1.90; 95% CI: 0.86–4.22; 8 exposed cases), and those exposed in the second/third trimester only (aHR=1.72; 95% CI: 0.43–6.97; 2 exposed cases) were comparable to depressed pregnant women that did not take antidepressants during gestation in terms of their risk of PPD. However, pregnancies with intermittent exposure were at higher risk of PPD when compared to nonexposures (aHR =2.85; 95% CI: 1.31–6.21; 10 exposed cases). This study showed that antidepressant use in mildly to moderately depressed pregnant women was not associated with lower risk of PPD compared to nonuse. Women with intermittent exposure, however, were at higher risk of PPD, suggesting potential residual confounding by severity of depression in this subgroup.

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EULING S[1], MAKRIS S[1], WALKER T[1], GRAY JR LE[2], IYER P[3]. [1]NCEA/ORD, US EPA, Washington, DC, United States, [2]NHEERL/TAD, US EPA, Research Triangle Park, NC, United States, [3]California EPA, OEHHA, Sacramento, CA, United States. A Systematic Review of Transgenerational Toxicological Studies after Gestational Exposure to Environmental Chemicals

Studies of transgenerational effects after *in utero* exposure to environmental chemicals reported in the literature have mixed findings; some multigeneration rodent studies have reported effects on F2 and subsequent generations after exposures solely to F0 dams. The differences in findings among studies of similar chemical exposures has fueled both an interest in transgenerational epigenetics and a debate about the appropriate study design methods for assessing transgenerational effects. To address these issues, a systematic review of the available transgenerational toxicology literature was conducted. We performed a literature search of PubMed, Toxline, and Web of Science and screened approximately 1,000 studies to identify rat or mouse studies with only F0 gestational exposure that evaluated developmental or reproductive toxicity endpoints in F2 and subsequent generations. For each study that met these criteria, the methods and effects were characterized. Our preliminary analysis identified a number of developmental and reproductive endpoints assessed in F1 to F4 generation offspring including puberty timing, steroid hormone levels, organ weights, and histopathology. This analysis identified some study reporting and design issues. Some studies reported procedures to eliminate biases (e.g., randomization procedures, avoiding sibling or cousin matings, and independent multiple reviews of histopathology data), but other studies did not clearly report the number of control and test group litters and "blind" testing procedures. Study design issues include the use of high-dose levels, suboptimum windows of exposure, or routes of exposure lacking human relevancy; insufficient study power, or inappropriate statistical analyses (e.g., lack of nested statistical analyses to address litter effects). While current regulatory reproductive toxicity testing guidelines are designed to identify chemicals of concern for reproductive and developmental effects by assessing the F1 (and preweaning F2) offspring after F0 and/or F1 parental exposure, the current reproductive and development guideline study data do not assess potential transgenerational effects in the F2 and later generations. This investigation has provided an approach for evaluating transgenerational studies for inclusion in the hazard weight-of-evidence for risk assessment. *The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the US Environmental Protection Agency or California EPA.*

Poster Session 2

P19

BRESLIN WJ[1], NEWCOME DL[2], CHELLMAN GJ[2], MARTIN JA[1], BLACKBOURNE JL[1]. [1]Lilly Research Laboratories, Indianapolis, IN, United States, [2]Charles River Laboratories, Reno, NV, United States. A Six-Month Juvenile Toxicity Study in Cynomolgus Monkeys with Tabalumab: A Human IgG4 Monoclonal Antibody

Tabalumab, a human IgG4 monoclonal antibody with neutralizing activity against soluble and membrane bound B-Cell activating factor (BAFF), has been under development for the treatment of autoimmune diseases. The purpose of this study was to investigate the toxicity and toxicokinetics of tabalumab in juvenile cynomolgus monkeys, 11–12 months of age at the start of dosing, when treated for six months, followed by a six-month recovery period. This study was requested by regulatory agencies due to the concern for affects of tabalumab on the developing immune system in pediatric patients six to less than 18 years of age. Tabalumab was administered by subcutaneous injection, once every two weeks, to groups of seven males and seven females, at doses of 0 (vehicle), 0.3, and 30 mg/kg. At the end of the six-month treatment period, three males and three females/group were retained for the six-month recovery period. Following six months of treatment, there were no adverse treatment-related effects on clinical or neurological signs, body weight or body weight gains, and clinical or morphologic pathology. Expected, nonadverse pharmacologic findings included decreased peripheral blood B-lymphocytes (B-cells) and decreased spleen weights, germinal centers and CD20 immunopositive cellularity at ≥0.3 mg/kg. Despite the reductions in peripheral blood B-cell counts, all tabalumab-treated animals were capable of generating primary and secondary IgM and IgG responses to KLH immunization. After a six-month recovery period, decreased spleen weights persisted at ≥ 0.3 mg/kg and correlated to minimal decreased germinal centers and CD20 immunopositive cellularity at 30 mg/kg. The findings in juvenile cynomolgus monkeys were similar to the findings in more mature (2–4 years of age) and adult, sexually mature (4–12 years of age) monkeys, following up to six months of treatment with tabalumab. In conclusion, the no-observed adverse effect level was 30 mg/kg, the highest dose tested. Exposures at 30 mg/kg provided a margin of safety of 8X the exposure at the highest anticipated clinical dose.

P20

ROBERTS JE[2], SCHWARTZ TS[3], GOHLKE JM[1]. [1]Virginia Tech, Blacksburg, VA, United States, [2]University of Alabama at Birmingham, Birmingham, AL, United States, [3]Auburn University, Auburn, AL, United States. Seleno-L-methionine Toxicity and Maternal Age in the Model Organism *Daphnia pulex*

Selenium is a micronutrient that, in humans, is predominantly obtained via consumption of plant matter in the organic form (Seleno-L-methionine or SeMet). Selenium is found naturally in soils and also enters into the environment from coal ash producing power plants, other manufacturing industries, and agriculture and can be transformed into SeMet and bioaccumulate in plants and animals. Chronic high doses of SeMet have been linked to oxidative stress, reproductive toxicity, and developmental toxicity. As the average human lifespan continues to lengthen, later life births are becoming more common. Maternal age is positively associated with a higher incidence of adverse reproductive outcomes. However, there is limited information concerning the response of offspring from young versus aged mothers to SeMet. The goal of this project is to evaluate whether the effects of SeMet dose are altered by maternal age in the model system *Daphnia pulex*. We hypothesized SeMet toxicity, expressed as mortality rate and reproductive success, will be amplified in the offspring that are taken from the late life brood in comparison to the offspring taken from the early life brood. We also hypothesized the effect of SeMet dose on stress response, expressed as a lower threshold for heat stress, will be exacerbated in the offspring taken from the late life brood in comparison to the offspring taken from the early life brood. Offspring were obtained from maternal populations (N=4, 20 individuals in each population) when the mothers were 8-days old and when the mothers were 32-days old. The offspring were randomized into 0 μg Se/L, 1 μg Se/L, and 4 μg Se/L dose groups. A clear effect of SeMet was seen on reproduction, with those in the 4 μg Se/L dose group producing no viable offspring. No effect of maternal age was seen in the lifespan measures. Offspring from older mothers were more resistant to heat-induced stress (N=80; $p<0.0001$) and had a larger presence of living offspring post heat stress (N=8; $p<0.0001$). In conclusion, these results suggest maternal age and SeMet dose may interact in *D. pulex* to determine offspring reproductive outcomes and resistance to heat stress.

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Testing the Waters to Account for Metabolism in the T47D-kbluc Estrogen Receptor Transcriptional Activation Assay

With the advent of Toxicity Testing in the 21st Century, high-throughput *in vitro* screening assays have gained increasing momentum in the area of predictive toxicology. Despite these advances, a critical challenge faced in moving toward *in vitro*-based assays for compound screening and safety testing is accounting for chemical metabolism. There is a vast body of literature describing compounds that are activated or inactivated for endocrine disrupting activity through *in vivo* metabolic processes. Therefore, screening of a compound in a metabolically incompetent *in vitro* assay does not provide a complete representation of its potential endocrine activity. We tested the hypothesis that incubating a compound with primary rat hepatocytes and subsequently transferring the metabolite-containing hepatocyte media into an estrogen receptor transcriptional activation (ER-TA) reporter assay (T47D-kbluc) will recapitulate metabolism-dependent *in vivo* ER activity. A series of assessments were performed using the T47D-kbluc ER-TA to determine cell viability, ER-responsiveness, and background estrogenic potential in the presence of hepatocyte media. Several positive controls consisting of known proestrogen compounds (methoxychlor (MXC), chalone, trans-4-Phenyl-3-buten-2-one (t-PBO), diphenylpropane (DPP), trans-stilbene, trans-stilbene oxide) and estrogenic compounds known to be inactivated through metabolism (benzyl butyl phthalate (BBP), bisphenol S (BPS)) were assessed in this format. Results from the ER-TA assay demonstrated that estrogenic activity of the test compounds was altered following incubation with hepatocytes, suggestive of metabolic activation or inactivation. Specifically, a shift in the dose response curve was observed for high concentrations of MXC following incubation with hepatocytes, suggesting conversion to the more potent metabolite, 2,2-bis-(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE). Conversely, estrogenic activity of BBP was completely ablated following incubation with hepatocytes, indicative of cleavage of the parent compound to the nonestrogenic metabolites. Efforts are ongoing to analytically identify metabolites in both hepatocyte-treated and ER-TA assay media. This approach provides a solid starting point for confronting the inherent challenge of accounting for metabolism in *in vitro* toxicology and considering the impact of metabolism on endocrine activity in an ER responsive *in vitro* screening assay.

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CHAN MY[1,2,3,4], MCKENZIE EM[1,3,4], WILLIAMS A[1,4], MCINTOSH TG[1,2,4], SMITH MA[1, 2,3, 4]. [1]Department of Environmental Health Science, Athens, GA, United States, [2]Center for Food Safety, Athens, GA, United States, [3]Regenerative Bioscience Center, Athens, GA, United States, [4]University of Georgia, Athens, GA, United States.

Possible Infant Exposure Reservoirs of *Cronobacter* Species in Households

Cronobacter spp. is associated with cases of severe life-threatening infections of necrotizing enterocolitis, bacteremia, and meningitis with case fatalities as high as 80% in premature and full-term infants. The gram-negative bacteria has been isolated from food processing plants, home environments, and suspected to be widely distributed in nature. The first identified cases of *Cronobacter* spp. have been associated with contaminated powdered infant formula and with contaminated utensils used in formula preparation. The purpose of our study was to 1) determine if *Cronobacter* spp. are found in the home environment, and 2) if found in a home, to determine the locations where *Cronobacter* spp. are most likely to reside. Over sixty households were sampled including at least 20 each from urban, nonurban, and farm areas based on data provided by the United States 2010 Census. Thirty samples were collected from each home. The samples were enriched and tested for the presence of *Enterobacteriaceae* and *Cronobacter* spp.; *Enterobacteriaceae* were isolated as an indicator of potential favorable growth conditions for *Cronobacter* spp. within the home. Surveys assessed socioeconomic status and other factors that may correlate with the presence and prevalence of *Cronobacter* spp. in homes. There have been a total of 148 isolates of *Cronobacter* spp. recovered from separate locations across the 65 houses. *Cronobacter* spp. were found in 80% and *Enterobacteriaceae* were found in 100% of homes sampled. There was no significant difference in finding *Cronobacter* spp. between urban, suburban, and farm homes ($P>0.05$). Samples from which *Cronobacter* spp. were frequently isolated included vacuum dust (45%), garage floor (35%), front entrance floor (26%), main walking routes (22%), and kitchen floor (22%). When found in a home, *Cronobacter* spp. was found most frequently on samples taken from floors ($P<0.05$). *Cronobacter* spp. can be found in homes, particularly on floors, providing a possible reservoir for contamination to occur. This is a concern for infants who play or crawl on the floor with typical hand-to-mouth childhood behaviors, which may increase the child's risk of exposure to *Cronobacter* spp. as compared to an adult.

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KIM ST[1], SIEBER S[1], SCHATZ A[2]. [1]Ashland Inc., Dublin, OH, United States, [2]Ashland Inc., Bridgewater, NJ, United States. A Combinational Approach of Literature Search, (Q)SAR, Read Across, Chemical Grouping, and Professional Judgement in Assessing Developmental Toxicity Potential of Personal Care Ingredients and Their Manufacturing Reagents in Screening for Safer and Innovative Alternatives

In order to compete in the current economic climate, personal care product companies are required to produce large numbers of new, innovative, and effective products whilst significantly reducing development time and costs without compromising the consumer safety. The use of (Q)SARs is an effective/efficient approach for faster screening of innovative candidates. In doing so, developmental toxicity is one of the critical toxicological endpoints that are being evaluated with (Q)SARs. We find that the use of (Q)SARs by themselves provides an unbalanced and poor accuracy, but integrating literature search, read across, chemical grouping (via mode-of-action), and professional judgement, together with (Q)SAR, significantly increases the specificity and sensitivity of developmental toxicity endpoint prediction. We have compared the reliability of widely used (Q)SARs (CAESAR and T.E.S.T.) with two sets (N > 50 for each set) of selected chemicals: one set of chemicals with positive experimental data and the other set with negative experimental data. CAESAR and T.E.S.T. models provided 15% and 40% false positive prediction when compared to the experimental data of nondevelopmental toxicants, respectively. On the other hand, CAESAR and T.E.S.T. models provided 30% and 15% false negative prediction when compared to those of the experimental data of developmental toxicants, respectively. The reliability has been significantly improved by supplementing read across, action mechanism, and professional judgement to the (Q)SAR outcome. For example, both CAESAR and T.E.S.T. analyses of diethylene glycol diethyl ether, dipropylene glycol methyl ether, and tetraethylene glycol dimethyl ether predicted that all of these glycol ethers are nondevelopmental toxicants. The known developmental toxicity of this class of substances is due to metabolite 2-methoxyacetic acid, which is generated from 2-methoxyethanol that is formed from the cleavage of center ether bond by enzymatic *O*-dealkylation. When compared, the three glycol ethers, diethylene glycol diethyl ether and tetraethylene glycol dimethyl ether had structural features that can generate metabolite 2-methoxyacetic acid, while dipropylene glycol methyl ether does not. Thus, it is concluded that dipropylene glycol methyl ether is not a developmental toxin, while other two glycol ethers are developmental toxins. This conclusion is supported by experimental data.

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STEELE JW, SENGAL AG, CABRERA RM, FINNELL RH. Dell Pediatric Research Institute, Department of Nutritional Sciences, University of Texas at Austin, Austin, TX, United States. An *In Vitro* Teratogen Screen Using 3-D Neuroepithelial Organoids

Assessing the teratogenic potential of pharmaceuticals or environmental chemicals remains a challenging, but essential undertaking. It has recently been estimated that there are 100,000 chemicals in commonly used products, and we lack reproductive toxicity data on approximately 90 percent of these compounds. *In vivo* animal model studies are slow, expensive, and do not always yield data that is relevant to human physiology. As a solution, many *in vitro* assays have been developed to screen for reproductive/developmental toxicity; however, these techniques typically over-generalize by using undifferentiated stem cells and broad, nondefinitive readouts for toxicity, such as gene expression or metabolic changes. However, the toxic activities of any one teratogen are cell-type specific and ultimately result in birth defects through cellular or tissue-level damage to particular embryonic structures. Therefore, any *in vitro* screen for teratogenic potential should have relevance to the cellular mechanisms of morphogenesis observed *in vivo*. Here, we use a three-dimensional (3-D), cell culture-derived model of neuroepithelium to measure teratogenic phenotypes specifically for the neural tube and developing nervous system. We screened several teratogens known to result in human neural tube defects, and measured the effects of these toxins on cellular functions that influence morphogenesis of the neural tube: proliferation, apoptosis, apicobasal polarity, cell-to-cell contacts, and oxidative stress. We then applied statistical analyses to compare these results to a set of benign, nonteratogenic chemicals. Our results demonstrate the ability of the assay to differentiate teratogens from nonteratogens across various chemical categories. Furthermore, our screen identified novel mechanisms of action for well-established teratogens, such as Valproic Acid (Depakote). Ultimately, these assays provide a rapid and relatively inexpensive phenotypic readout at the cellular level, which could be used to predict potential teratogenic activities of new pharmaceutical, occupational, or environmental chemicals. Our approach should also be applicable for any 3-D cell culture system that models an embryonic structure.

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TUCKER DK[1,2], FENTON SE[2], BOUKNIGHT SA[3]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2]NTP Laboratory, NIEHS, Research Triangle Park, NC, United States, [3]Pathology Associates, Inc., Charles River Laboratories, Durham, NC, United States. Increased Susceptibility to Mammary Carcinogenesis following a Prenatal Exposure to BPA Analogs

The continued efforts to phase out Bisphenol A (BPA) from consumer products have been met with the challenges of finding safer alternatives. Several replacement analogs have been implemented including, Bisphenol AF (BPAF) and Bisphenol S (BPS); however, both possess estrogenic characteristics very similar to BPA and may equally pose a risk to the developing mammary gland, including an increased susceptibility to developing later life diseases. This study aimed to determine whether the affects of an early life exposure to BPAF and BPS on the mammary gland persisted into adulthood. Timed pregnant CD-1 mice were exposed to vehicle, BPA (0.5–50 mg), BPAF and BPS (0.05–5 mg/kg) via oral gavage between gestational days 10–17. Mammary glands were collected at 8 and 14 months for whole mount, histo-pathological evaluation and qPCR. At eight months, mammary whole mounts exhibited varied morphology that included hyperplastic and inflammatory lesions within and surrounding the ducts and stroma. This was especially prominent in the BPAF 5 mg and BPS 0.5 mg group. By 14 months, lesion incidence within these groups had increased (50% BPAF and 89% BPS) but was also shown to increase within all treated groups. H&E sections identified these lesions as perivascular inflammation, tubuloalveolar or papillary hyperplasia, adenocarcinoma, squamous cell carcinoma, and squamous metaplasia. Interestingly, analysis of serum estradiol and progesterone levels as well as mammary mRNA levels of the estrogen receptor alpha, progesterone receptor, and the androgen receptor at 8 and 14 months revealed no changes compared to vehicle control. Altogether, this data may suggest that early exposure to bisphenol analogs may shift the window of development to make the gland more susceptible to preneoplastic formations in a similar manner to BPA. It also suggests that earlier life events and nonclassical estrogen pathways may play a critical role in mediating these phenotypes, however, further studies will be required to pinpoint the exact timing and pathways involved.

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WALKER L, SPARKS N, ZUR NIEDEN N. University of California, Riverside, Riverside, CA, United States. Aberrant Upstream Kinase Signaling Negatively Impacts Osteogenesis by Impairing FOXO-Mediated Oxidative Stress Response

Exposure to toxicants such as tobacco products can increase cellular levels of reactive oxygen species (ROS) and alter both transcriptional networks and cell fate. Previous work in mature tissues found increased nuclear activity of transcription factor FOXO3 under elevated ROS, triggering increased oxidative stress fighting response. Moreover, ROS activation of the cJun N-terminal kinase (JNK) signal transduction pathway encouraged posttranslational modification and nuclear translocation of FOXO3. In developing cells, however, the relationship between ROS manipulation of transcriptional networks and altered cell fate has yet to be clearly elucidated. This study examined the link between altered activity of upstream kinase regulators of FOXO3 and osteogenic cell fate under elevated ROS. Embryonic stem cells (ESCs) were employed as a model system to study development. ESCs were differentiated into osteoblasts and treated with tobacco product extracts to induce ROS. Decreased osteogenic calcification as well as decreased nuclear FOXO3 protein and FOXO3 interaction with cofactor β-catenin was observed in high ROS doses. Preliminary coimmunoprecipitation of β-catenin/FOXO3 in JNK knockout cells revealed decreased overall interaction of β-catenin and FOXO3 in high ROS cultures, suggesting the importance of posttranslational modification of FOXO3. Treatment of high ROS wild type cultures with anisomycin, a JNK activator, produced a synergistic decrease in calcification, suggesting that JNK was already active in high ROS cultures. Subsequent western blot analysis revealed comparable JNK activation between low and high ROS cultures whereas AKT activation levels were found to be elevated in high ROS cultures. Follow up treatment of wild type cultures with AKT inhibitor demonstrated a rescue of calcification in high ROS cultures. Overall, our results suggest that aberrant upstream kinase signaling during oxidative stress may induce altered β-catenin/FOXO3 interaction leading to subsequent ROS accumulation and inhibited osteogenesis during development.

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MILLER L, GILBERT KS. Southern Research, Birmingham, AL, United States. Acetylsalicylic Acid: Oral (Gavage) Developmental Toxicity in Sprague-Dawley Rats

A positive control study was conducted with Acetylsalicylic acid (ASA) for training on identification of fetal anomalies in rats. ASA was administered to timed mated rats (Sprague-Dawley; Charles River, Raleigh, NC) as a single dose of 500 or 750 mg/kg on gestation day (GD) 9, 10, 11, or 12. The dose volume of vehicle (0.2% CMC) or ASA was 5 mL/kg. A laparohysterectomy was conducted on GD 21 and all fetuses were weighed and examined for external, soft tissue (viscera, head), and skeletal anomalies.

P28

EULING S[1], GLENN B[1], ALCALA C[2]. [1]NCEA/ORD, US EPA, Washington, DC, United States, [2]Association of Schools and Programs of Public Health Environmental Health Fellow at NCEA/ORD, US EPA, Washington, DC, United States. The Role of Environmental Factors in Pubertal Gynecomastia

Proliferation of grandular tissue in the male breast during puberty, or pubertal gynecomastia, is a common condition that is usually benign and reversible. Since not all boys develop gynecomastia during puberty, we were interested in whether environmental factors play a role. We were also interested in whether transient pubertal gynecomastia, while not malignant, may lead to breast tissue alterations that increase susceptibility to breast disease. To address the first question, a systematic literature search, querying Toxline, Pubmed, and Web of Science was performed. In order to understand the epidemiology of gynecomastia, we conducted a preliminary review of a subset of ~10 available studies of healthy, population-based participants within the pubertal age range and found a wide range, 4–69%, of reported incidence or prevalence. Reported estimates may vary by diagnostic definitions, number and frequency of examinations (e.g., this transient condition may be missed in studies with one exam or annual exams), country, age, and other demographic characteristics. Numerous case reports of environmental exposures and pubertal gynecomastia were identified and support a role for environmental factors in pubertal gynecomastia. Fewer than 10 epidemiological studies that assessed either chemical exposure (e.g., phthalates) or surrogates for environmental exposure levels (e.g., urban/rural residence, diet) were identified. While some associations were found, the very small epidemiological database makes it difficult to draw conclusions about the role of environmental factors. Rodent toxicology studies reporting male mammary gland developmental effects after environmental chemical (e.g., methoxychlor) exposures were identified but the developmental stage concordance of the reported effects to human pubertal gynecomastia is unclear. Recent studies investigating the mechanism of pubertal gynecomastia in humans have reported an increased serum levels of estradiol, FSH, leptin, and IGF-1 in boys with pubertal gynecomastia, consistent with a role for a variety of hormonal pathways underlying gynecomastia. Ongoing efforts include comparisons and integration of human and animal model findings. To address the second question, longitudinal studies of pubertal gynecomastia and later life male breast cancer are needed. *The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the US Environmental Protection Agency.*

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DESAI A, SEQUEIRA J, QUADROS E. SUNY Downstate Medical Center, Brooklyn, NY, United States. A Rat Model for Folate Receptor Antibody-Mediated Behavioral Deficits: Implications of Folate Receptor Autoantibodies in Autism

This study examines the role of antibodies against the folate receptor alpha (FRa) on brain development and function to determine if a similar mechanism could operate in autism spectrum disorders (ASD) and other neurodevelopmental disorders. A previous study in our laboratory found that >70% of children with ASD are positive for serum FR-autoantibodies. Consequently, we developed a rat model to study the behavioral and cognitive deficits induced by exposure to FR-antibody during gestation and weaning. We focused particularly on behavioral deficits that mirror those seen in ASD. We studied the transfer of FR-antibodies from mother to fetus and identified regions of the brain affected most by this antibody accumulation, which could potentially lead to the identification of regions involved in the functional and behavioral changes seen in ASD. Effective interventions to help in the treatment of those with ASD and FR-antibodies were considered, looking specifically at the efficacy of folinic acid and dexamethasone in preventing the behavioral deficits induced by FR antibodies in the rat model. Our results demonstrate that rats exposed to FR antibodies during gestation or weaning display core ASD symptoms such as deficits in communication, socialization, and set-shifting tasks. They also have learning and memory deficits. Treatment with folinic acid and dexamethasone results in significant improvement of the deficits. FR antibody exposure during gestation decreases folate transport from mother to fetus with antibody localizing to embryo, placenta, uterine wall, yolk sac, and amnion. Overall, these studies were aimed at understanding the affect of FR antibodies on fetal and infant brain development and function. The outcome of these studies could herald a paradigm shift in our understanding of ASD and other developmental disorders associated with FR autoimmune disorder.

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BALOGUN WG[1,2], ADEBAYO IA[1], KAMALDIN J[1], ENAIBE BU[2]. [1]Universiti Sains Malaysia, Kepala Batas, Penang, Malaysia, [2]University of Ilorin, Ilorin, Kwara, Nigeria. Effect of Prenatal Oral Administration of *Vernonia amygdalina* on the Mothers and Litters of Wistar Rats

Background: *Vernonia amygdalina*, commonly called bitter leaf, is widely consumed by pregnant women in Africa for the treatment of various pregnancy related illness. It is uncertain whether the oral consumption of *Vernonia amygdalina* the treatment is deleterious to the development of prefrontal cortex, an area of the brain that is important in the child learning process. The study investigated effects of aqueous *Vernonia amygdalina* extract on the activities of glucose-6-phosphate dehydrogenase (G6PDH) and lactate dehydrogenase (LDH) are measured to determine the normality of the prefrontal cortex function in producing ATP. Methods: 25 female Wistar rats with an average weight of 200g (± 10g) were inseminated and equally divided into five groups, namely group A (control, no dosing), group B (repeated dosing on days 1–7 of gestation), group C (repeated dosing on days 8–14 of gestation), group D (repeated dosing on days 14–21 of gestation), and group E (repeated dosing on days 1–21 of gestation). Each rat was dosed with 400 mg/kg of *Vernonia amygdalina* (10:1) crude aqueous extract according to the designated treatment regimen. After parturition, three litters were selected in each group and sacrificed every week until the postnatal week five. The prefrontal cortices of each rat were homogenized separately in chilled 5% sucrose solution and centrifuged, the supernatant aliquoted to assay for the enzyme activities of G6PDH and LDH using spectrophotometric analysis. Results: There was a decrease in G6PDH activity among the litters exposed to *Vernonia amygdalina* in groups C and E when compared with the control in contrast there was an increase in LDH activity. The litters in groups B and D were comparable to the control. Conclusions: The above findings suggest that prenatal exposure to *Vernonia amygdalina* could affect glucose metabolism although the effect was subsequently normalised in the Wistar rats. Keywords: *Vernonia amygdalina*, LDH, G6PDH, ALP, and prefrontal cortex.

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NAROTSKY MG[1], MANLEY AL[2], OLA O[3]. [1]US Environmental Protection Agency, Research Triangle Park, NC, United States, [2]Oak Ridge Institute for Science and Education (ORISE), Oak Ridge, TN, United States, [3]Student Services Contractor, Raleigh, NC, United States. Assessment of Iodoform Effects on Pregnancy Maintenance and Eye Malformations in a Developmental Toxicity Screen with F344 Rats

Iodoform (triiodomethane) is a drinking water disinfection by-product (DBP) formed when oxidizing disinfectants (e.g., chlorine) react with iodide-containing organic material in source waters. Previously, we have shown that brominated trihalomethanes (bromoform, bromodichloromethane) cause pregnancy loss (i.e., full-litter resorption; FLR) when administered to F344 rats, apparently due to disruption of luteinizing hormone (LH) during the LH-dependent period of pregnancy. Trihalomethanes, however, have not been shown to cause eye malformations in F344 rats, an inbred strain particularly sensitive to toxicant-induced anophthalmia and microphthalmia. Here, we administered iodoform, in corn oil vehicle, by gavage to timed-pregnant F344 rats at 0, 60, 90, and 120 mg/kg on gestation days (GD) 6–10 (plug = GD 0); 10–12 dams were treated per group. This exposure period encompasses the maternal LH-dependent period (GD-7–10), as well as the critical period for embryonic eye development. Dams were allowed to deliver and litters were examined on postnatal days 1 and 6. Uteri of nongravid rats were stained with 2% ammonium sulfide to confirm cases of FLR. Maternal toxicity was evidenced by weight loss after the first dose at the mid- and high-dose levels. Pregnancy loss (i.e., FLR) was observed in zero, one (10%), two (17%), and two (20%) of the dams in the control, low-, mid-, and high-dose groups respectively; these incidences were significant at the two highest dose levels. Anophthalmia or microphthalmia was observed in zero, one (11%), one (10%), and two (25%) litters of the respective groups; based on historical control data, the high-dose incidence was marginally significant (p=0.08). There were no effects on prenatal or postnatal viability, and pup weights were comparable in all groups. All animals that maintained their pregnancies delivered normally on GD 21 or 22; however, a slight, but significant, delay in parturition was evident at the mid-dose level. Thus, dose-related trends of both FLR and eye malformations were observed; further investigation is necessary to confirm these findings. Although FLR has been reported for other trihalomethanes, this is the first indication of trihalomethane-induced eye malformations. *This abstract does not necessarily reflect US EPA policy.*

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WOLF CJ, BECKER C, DAS KP, WATKINS AM, BELAIR DG, ABBOTT BD. US Environmental Protection Agency, Research Triangle Park, NC, United States. Development of a 3-D Co-Culture Model Using Human Stem Cells for Studying Embryonic Palatal Fusion

Morphogenetic tissue fusion is a critical and complex event in embryonic development and failure of this event leads to birth defects, such as cleft palate. Palatal fusion requires adhesion and subsequent dissolution of the medial epithelial layer of the mesenchymal palatal shelves, and is regulated by the growth factors EGF and TGF_{β}, and others, although the complete regulatory mechanism is not understood. Three-dimensional (3-D) organotypic models allow us to mimic the native architecture of human tissue to facilitate the study of tissue dynamics and their responses to developmental toxicants. Our goal was to develop and characterize a spheroidal model of palatal fusion to investigate the mechanisms regulating fusion with exposure to growth factors and chemicals in the ToxCast program known to disrupt this event. We present a spheroidal model using human umbilical-derived mesenchymal stem cells (hMSC) spheroid cores cultured for 13 days and then coated with MaxGel™ basement membrane and a layer of human progenitor epithelial keratinocytes (hPEK) (hMSC+hPEK spheroids). We characterized the growth, differentiation, proliferation, and fusion activity of the model. Spheroid diameter was dependent on hMSC seeding density, size of the seeding wells, time in culture, and type of medium. hMSC spheroid growth was enhanced with osteogenic differentiation medium. Alkaline phosphatase activity in the hMSC spheroid, indicating osteogenic differentiation, increased in intensity throughout culture to day 14. Preliminary results showed EGF exposure at 2 or 4 ng/ml in hMSC+hPEK spheroid cultures increased cell proliferation by almost two-fold. In a pilot fusion study, hMSC spheroids when placed in contact began to merge within 8 hrs, while hMSC+hPEK spheroids began to fuse at a later time point, 40–48 hrs, and were completely merged at four days. This model will enable us to study the regulation of fusion by manipulation of spheroid activity with growth factors and to evaluate the effects of exposure to ToxCast chemicals associated with cleft palate. Additionally, this model can be implemented in the study of other embryonic fusion events that involve mesenchymal and epithelial tissues. *This abstract does not necessarily reflect US EPA policy.*

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HILBISH KG[1], BRESLIN WJ[1], CANNADY EA[1], EDWARDS TL[2]. [1]Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, United States, [2]WIL Research, Ashland, OH, United States. Fertility and Developmental Toxicity Assessment in Rats and Rabbits with Evacetrapib, a Cholesteryl Ester Transfer Protein (CETP) Inhibitor

Evacetrapib, a potent and selective inhibitor of cholesteryl ester transfer protein (CETP), has been under development for cardiovascular disease. The purpose of these studies was to evaluate the effects of evacetrapib on male (M) and female (F) fertility and on embryo-fetal development (EFD). Evacetrapib was administered daily by oral gavage starting two (F) or four (M) weeks prior to mating, during cohabitation, and until necropsy in the M rat fertility study or through gestation day (GD) 17 in the F rat combined fertility/EFD study. For the rabbit EFD study, animals were dosed from GD 7–19. Dose levels of evacetrapib ranged from 60–600 mg/kg for rats and from 10–100 mg/kg for rabbits with 20 animal/group. Parental findings in rats were limited to decreased BW and FC and moribund euthanasia (2F) in animals given 600 mg/kg and decreased food consumption at 300 mg/kg. There were no adverse effects on estrus cycling, fertility indices, sperm parameters, maternal reproductive parameters, male reproductive tissue, or fetal viability, growth, or external/visceral morphology. An increase in the incidence of 14th rudimentary ribs, considered nonadverse, was the only significant developmental finding in rats given 600 mg/kg. There were no adverse maternal effects in rabbits. A dose-responsive increase in the incidence of lung lobular agenesis was noted at all dose levels (10, 30, and 100 mg/kg) in the rabbit. Although lung lobular agenesis is a common background observation in rabbits, this finding was considered potentially treatment-related and adverse pending further confirmation in a repeat study. In conclusion, no adverse effects on fertility or EFD were observed in rats at doses up to 600 mg/kg. In the rabbit EFD study, a dose-responsive increase in lung lobular agenesis was observed at all doses. The reproducibility and no effect level for lung lobular agenesis is being assessed in a repeat study.

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MEMON S[1], PRATTEN M[2]. [1]Liaquat University of Medical and Health Sciences, Jamshoro, Sindh, Pakistan, [2]The University of Nottingham, Nottingham, United Kingdom. Retinoic Acid and Maternal Diabetes Developmental Toxicity is Mediated by Gap Junction Disruption in Cardiomyocytes in Culture

Gap junctions are responsible for intercellular communication between adjacent cells. These in the heart are not only responsible for impulse coordination, but are also involved in the development of the heart. Congenital cardiac defects are the leading cause of infant mortality and morbidity. Maternal excessive consumption of retinoic acid (RA) or maternal diabetes mellitus, are one of the major etiological factors of such defects. Additionally, nutritional deficiency prenatally is also considered to be an important risk factor for birth defects. This study aims to investigate the potential for retinoic acid and diabetic conditions to disrupt gap junction protein Cx43 as a mechanism of teratogenesis, and also to investigates potential preventive role of folic acid and vitamin C. Embryonic hearts were dissected from five day old white Leghorn chick embryos and the cells were isolated and cultured in eight well chamber slides. The cells were exposed to 20μM retinoic acid or diabetic condition (20mM glucose+ 15mM β hydroxybutyric acid) only or with 100μM vitamin C and 1mM folic acid in addition on day two of incubation. *12-O-Tetradecanoylphorbol-13-acetate* (TPA) a positive control for phosphokinase C (PKC) activated pathway was added at 50nM and dibutyryl cAMP (as a control for phosphokinase A activated pathways) was added at 100μM. Day six samples were incubated with primary antibody Cx43 at 4°C overnight. The next day, the secondary antibody was applied and incubated at room temperature for one hour in dark. Slides were washed with BSA and water and mounted in Vectashield™ containing DAPI and were viewed under a confocal microscope. RA and diabetes cause a reduction in expression of Cx43 in cardiomyocytes, which is not evident when vitamin C or folic acid is co-administered. There is also an evident redistribution of the label from the cell surface to a juxtanuclear location, with addition of RA and diabetic conditions. Addition of TPA also showed a similar intracellular distribution whereas addition of cAMP increased the surface expression of Cx43. It is therefore likely that both RA and DM act via PKC and their effects can be negated by vitamin supplementation.

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JOHANSSON HKL, LUND SP, KYJOVSKA Z, JACKSON P, WALLIN H, VOGEL U, HOUGAARD KS. Danish Nanosafety Centre, National Research Centre for the Working Environment, Copenhagen, Denmark. Estrous Cyclicity Is Altered Following Lung Exposure to Multiwalled Carbon Nanotubes in Mice

Carbon nanotubes attract huge industrial interest due to their unique properties. They are constructed from graphite carbon into different molecular-scale tubes. Multiwalled carbon nanotubes (MWCNT) consist of several concentric grapheme tubes with diameters of up to 100 nm. Exposure is anticipated to be of concern in occupational settings primarily by inhalation. Airway exposure to nanoparticles causes lung inflammation in experimental studies. Experimental animal studies show that inflammation may interfere with the female hormonal reproductive axis. Lung exposure to nanoparticles may therefore potentially impair female fertility. We aimed to study the effects of lung exposure to MWCNTs on female reproductive capacity. Female C57BL/6J mice were exposed once to 67 μg of MWCNTs, by deposition directly into the airways by intratracheal instillation. Estrous cyclicity was monitored for 14 days pre-exposure and 14 days post-exposure, by measuring cycle length by microscopic examination of daily vaginal lavage samples. Data were analyzed by including all measured cycle into a parametric mixed model, allowing for comparison between and within groups. Upon termination of the study, four weeks after exposure, lung inflammation was assessed by differential cell count of bronchoalveolar lavage fluid. Lung inflammation was evident in exposed females four weeks after exposure, as judged by the differential cell counts. The mixed model analysis, which included all pre-exposure estrous cycle values from all females indicated differential and highly statistical significant effects of the exposure. Exposure prolonged the length of estrous cycle in which exposure took place by two days compared to the pre-exposure cycle. The subsequent cycle was however significantly shortened. Both exposure and post-exposure values varied statistically significantly from cycle lengths in control females. The changes observed in estrous cyclicity are concordant with findings in studies of inflammation and female reproduction. Exposure to MWCNTs could potentially interfere with the female reproductive cycle, and thereby affect the ability to achieve pregnancy.

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KANCHERLA V[1], ARTH A[1], PACHÓN H[1,2], ZIMMERMAN S[2], JOHNSON Q[2], OAKLEY G[1]. [1]Emory University Rollins School of Public Health, Atlanta, GA, United States, [2]Food Fortification Initiative, Atlanta, GA, United States. A 2015 Global Update on Folic Acid-Preventable Spina Bifida and Anencephaly

Background: Spina bifida and anencephaly are two major neural tube defects. They contribute substantially to perinatal, neonatal, infant, and under-five mortality and life-long disability. To monitor the progress toward the total prevention of folic acid-preventable spina bifida and anencephaly (FAP SBA), we examined their global status in 2015. Methods: Based on existing data, we modelled the proportion of FAP SBA that are prevented in the year 2015 through mandatory folic acid fortification globally. We included only those countries with mandatory fortification that added at least 1.0 ppm folic acid as a fortificant to wheat and maize flour, and had complete information on coverage. Our model assumed mandatory folic acid fortification at 200 mcg/day is fully protective against FAP SBA, and reduces the rate of spina bifida and anencephaly to a minimum of 0.5 per 1,000 births. Results: Our estimates show that in 2015, 13.2% (35,500 of about 268,700 global cases) of FAP SBA were prevented in 58 countries through mandatory folic acid fortification of wheat and maize flour. Most countries in Europe, Africa, and Asia were not implementing mandatory fortification with folic acid. Conclusion: Knowledge that folic acid prevents spina bifida and anencephaly has existed for 25 years, yet only a small fraction of FAP SBA is being prevented worldwide. Several countries still have 5- to 20-fold epidemics of FAP SBA. Implementation of mandatory fortification with folic acid offers governments a proven and rapid way to prevent FAP SBA-associated disability and mortality, and to help achieve Sustainable Development Goals.

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REN AG, LIN SS, WANG LL, HUANG Y. Peking University, Beijing, China. Vitamin E Decreases the Incidence of Neural Tube Defects Induced by Benzo(a)pyrene in ICR Mice

We have shown that maternal exposure to polycyclic aromatic hydrocarbons is associated with an elevated risk of neural tube defects (NTDs) in offspring, and benzo(a)pyrene (BaP) could induce NTDs in mice. The objective of this study was to examine whether dietary supplementation with vitamin E could reduce the incidence of NTDs induced by BaP in ICR mice. Pregnant ICR mice were assigned to the control group, the BaP group, or the vitamin E supplemented BaP group. Beginning on the day that a copulation plug was found (GD 0.5), mice in the control and BaP group were fed with control chow, while mice in the supplemented BaP group were fed with chow supplemented with the water-soluble (±)-α-tocopherol succinate form of vitamin E (0.125%, w/w). Chow was provided ad libitum. Mice in the two BaP groups were treated intraperitoneally with BaP dissolved in corn oil from GD 7 through GD 10 (250 mg/kg/d). On GD 10.5, pregnant mice were sacrificed by cervical dislocation and fetuses were removed by cesarean section. The numbers of implantation sites, living fetuses, and reabsorbed or dead fetuses were recorded. All alive fetuses were inspected for visible external malformations. NTD-affected embryos were classified as showing distinct evidence of failed closure of the neural tube. No obvious malformations were observed in embryos in the control group. The BaP group had an NTD rate of 9.09%, compared with a rate of 1.03% in the vitamin E supplemented BaP group ($p<0.01$). Most of the NTDs induced by BaP were closure failure at the hindbrain or the midbrain, with a few closure failures along the neural tube from the cranial to the spinal region. Split face accompanied by forebrain anencephaly was also observed. In addition to NTDs, embryos in both BaP groups showed different degrees of disrupted neural tube closure (33.12% vs. 11.69%, $p<0.01$). The incidence of heart defects was 39.61% in the BaP group, compared with 22.08% in the supplemented BaP group ($p<0.01$). Supplementation with vitamin E confers a protective effect against BaP-induced NTDs and other malformations in ICR mice. (Supported by the National Natural Science Foundation of China, grant no. 31371523.)

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FERNANDEZ GANCEDO A, HINOJOSA AMAYA AB, IBARRA RAMIREZ M, MARTINEZ DE VILLARREAL L. Departamento de Genética, Facultad de Medicina y Hospital Universitario, Universidad Autónoma de Nuevo León, Monterrey, Nuevo Leon, Mexico. BMI and Pregnancy Weight Gain As Risk Factor for NTD: A Case Study in a Northeast Mexican Third Level Hospital

Neural tube defects (NTD) have been highly associated with maternal nutritional state, specially folate intake. Overweight and obesity may be related to reduction of basic nutriments, but they could also have a teratologic effect by themselves. Worldwide incidence of NTD has been calculated from 0.2 to 10 per 1,000 births, with an average of 1 out of every 1,000 births. In Mexico, this incidence is estimated to be 14 for every 10,000 births. The purpose of this article is to analyze BMI and weight gain during pregnancy, based on cases of NTD reported in our hospital, and the risk factors associated. A sample was taken from a pre-stablished birth defects program database. The information was obtained through a conscious clinical history, focused on risk factors during pregnancy associated with the defects, as well as familiar history of previous similar congenital defect. This data was compared to the medical records of the hospital medical archives. There was special interest in BMI and pregnancy weight gain to determine whether an association between them could be made with NTD development. During a two-year period from 2014 to 2015 a total of 13 newborns with neural tube defects were born, which resulted in an incidence of 7 for every 10,000 newborns. Maternal weight gain was on most cases greater than expected for a normal pregnancy, whereas there was one case in which weight gain was less than expected, due to the severity of the malformation. We found maternal overweight and obesity in more than half of the cases. NTDs have been widely studied because of the morbidity and mortality they have. Their prevention through folate supplementation of foods and additional folate supplements for pregnant women has been successful worldwide, however, it is important to determine if another factor is playing role on the physiopathology of NTD. Prevalence of overweight and obesity has been increasing in the last decades. The effects of this condition to the development of diseases is important, but it has been mostly studied for adult onset diseases, however its role in congenital birth defects should be further studied.

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PARK JJ[1,2], KIM HY[1,2], WEGNER SH[1,2], VAN NESS KP[1], PACHECO SE[2], WORKMAN T[2], HONG S[1], GRIFFITH W[2], FAUSTMAN EM[1,2]. [1]University of Washington, Seattle, WA, United States, [2]Institute of Risk Analysis and Risk Communication, Seattle, WA, United States. Histone Modifications in Proliferating and Differentiating Human Neural Progenitor Cells after Acute Chlorpyrifos and Arsenic Exposures

Epigenetic gene regulation including histone modification has been shown to play an important role in directing differentiation potential and fate specification of neuronal stem cells. Changes in histone modifications are likely to be specific to differentiation state as chromatin structure changes throughout normal differentiation. The objective of this study was to investigate the "windows of susceptibility" for histone modifications in proliferating and differentiating human neural progenitor cells (hNPCs) after exposures to the well-known neurotoxicant, chlropyrifos (CP). Sodium arsenite (As) was used as a positive control. We examined morphology, cell viability, and histone H3 modifications after CP or As exposure for 72 hours *in vitro*. In a cell viability assay, differentiating hNPCs were impacted more than proliferating cells after 72 hours of CP or As exposures. We also observed differential susceptibility of cells to CP or As in proliferating and differentiating conditions. Western blots of specific histone modifications indicated that di-methyl Histone H3 lysine 4 (DMH3Lys4) was significantly increased after CP treatment in both proliferating and differentiating hNPCs. Phosphorylated acetyl Histone H3 serine 10 (pAH3Ser10) also showed a significant increase in its expression; however, this was only seen in proliferating hNPCs exposed to CP for 72 hours while HDAC4 showed a significant decrease only in differentiating hNPCs with 72 hours of CP exposures. Following As exposure, both proliferating and differentiating hNPCs had increased expression of acetylated Histone H3 lysine 9 (AH3Lys9). As exposed differentiating cells also had increased expression of pAH3Ser10 while As-exposed proliferating hNPCs showed decreased expression of di-methyl Histone H3 lysine 79 (DMH3Lys79). In conclusion, our study demonstrates differential effects of CP and As on histone methylation in proliferating and differentiating *in vitro* hNPCs, illustrating the importance of developmental timing on the effect of toxicants on histone modifications. Furthermore, the consistency of histone modification sites targeted by CP and As across previous *in vivo* studies and our *in vitro* model demonstrates the ability of our hNPC differentiation model to detect context-specific epigenetic changes. This study was supported by US EPA and NIEHS.

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WELLS CB[1], CARNEY ME[1], MILLER BM[1], LAM XT[1], KEPKO DS[1], MUELLER ML[1], HOOD RD[2], BAILEY MM[1]. [1]Emporia State University, Emporia, KS, United States, [2]Ronald D. Hood & Associates, Northport, AL, United States. Maternal Psychological Stress and Cyclophosphamide Teratogenisis in CD-1 Mice

Psychological stress can cause a variety of adverse effects on fertility and prenatal development. Physical restraint can be used to induce consistent psychological stress during the gestational period and has been shown in specific instances to cause cleft palate, rib variations, and complications during organogenesis. Cyclophosphamide (CP) is an anticancer agent and model proteratogen that causes limb, digit, and cranial defects if fetal exposure occurs during the window of susceptibility. This study focused on determining the effects of psychological stress induced by repeated restraint on CP teratogenesis. Mated CD-1 mice were randomly assigned to one of four treatment groups: control (saline only), restraint only, CP only 20mg/kg, or a combined CP 20mg/kg + restraint group. Mice were restrained in decapicones for three one-hour sessions per day from GD 8–13. Restraint treatments were conducted at 8:15 am, 12:15 pm, and 4:15 pm. CP or saline were given via intraperitoneal injection on GD 10. Dams were sacrificed on GD 17 and their litters were examined for gross defects and skeletal defects. Maternal weight gain was significantly adversely affected by restraint both in the control and CP-exposed dams ($p<0.05$). Fetal weight was adversely affected by restraint in the control dams ($p<0.05$) but not in the CP-exposed dams. Maternal restraint does not appear to affect litter size or embryolethality. Reduced incidences of limb, digit, tail, body, cephalic, and eye defects were observed in fetuses in the restraint+CP group compared to CP alone. Restraint alone did not increase the incidence of these malformations compared to fetuses in the unrestrained control group. Preliminary skeletal data revealed an apparent increase in rib variation (supernumerary and rudimentary ribs) with exposure to restraint stress. Stress induced by maternal restraint reduces the incidence of cyclophosphamide-induced malformations, but further study is needed to clarify possible underlying mechanisms. This research was supported by NIH grant number P20GM103418 from the INBRE Program of the National Center for Research Resources to Emporia State University.

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WILDER CS[1,2], WEGNER SH[1,2], SMITH MN[1,2], HARRIS S[1,2], HONG SW[1,2], GRIFFITH WC[1,2], FAUSTMAN EM[1,2]. [1]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, United States, [2]Institute for Risk Analysis and Risk Communication, University of Washington, Seattle, WA, United States. Organotypic Modeling Platform for Adverse Outcome Pathways of Male Reproductive and Developmental Processes

This project will develop a systems-based platform for integrating normal and adverse responses across testicular development in rodents *in vivo* and *in vitro*. Specifically, we have developed transcriptomic tools for anchoring proliferation, steroid regulation, and spermatogenesis processes for integration of dose response in an organotypic three-dimensional testicular culture system. The objective is to develop a context for interpreting Adverse Outcome Pathways (AOP) for these *in vitro* systems and provide biologically informed metrics for dose-response modeling. We have identified *in vivo* developmental processes using our transcriptomic analysis in combination with a detailed literature search to create a framework for identifying morphological, steroid regulation, transcriptional, and cell cycle events comparing developmental processes in rats and mice across time. Control transcriptomic profiles were generated for *in vivo* and *in vitro* development for rats and these were used to anchor our responses. Based on our transcriptomic analysis and developmental framework we have identified postnatal days (PND) 9–25 as a critical window of susceptibility in rodent testis development that would link hypothesized key events in AOPs for testicular impact. To evaluate the ability of the *in vitro* culture to capture dynamic developmental processes we characterized long-term viability, testosterone production, and morphology up to 21 days in culture. Western blotting revealed expression of cell type-specific protein markers of Sertoli, Leydig, and spermatogonial cells and immunofluorescence indicated changes in morphology including cell migration, proliferation, and differentiation. Testosterone detected in the culture indicated a switch in production from fetal to adult Leydig cells. A model testicular toxicant, cadmium was used during this critical window of susceptibility. We dosed the culture on days *in vitro* 2, 6, and 15 and measured the effects of cadmium after 24 hours at 2.5, 5, and 10 μM concentrations. Our initial studies have observed dose-dependent disruption in germ cell morphology observed at 5 and 10 μM after a 24-hour exposure for all three-time points. These quantitative results have been interpreted within our Organotypic Modeling Platform and demonstrate the potential of our model to capture adverse outcomes in proliferation, steroid regulation and spermatogenesis pathways of male reproductive development. Supported by the US EPA and NIEHS.

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SOLOMON HM, MURZYN S, SKEDZIELEWSKI T, RENDEMONTI J, CHAPMAN S, ALSAID H. GlaxoSmithKline Pharmaceuticals, King of Prussia, PA, United States. Comparing Micro-CT Imaging and Alizarin Red Staining Methods to Examine Fetal Rabbit Skeletons (Dutch Belted) Obtained on Day 29 of Gestation

Micro-computed tomography (micro-CT) has been used to examine fetal rabbit skeletons as an alternative to alizarin red staining in developmental toxicity studies (Winkelmann and Wise 2009). In our lab, we are in the process of evaluating the use of micro-CT using a higher resolution acquisition protocol and fetuses obtained later in gestation. A Siemens Inveon micro-CT scanner was used with settings of: voltage/current: 55kVp/400uA, exposure time: 400ms, projection bin factor: 4, and pixel size "resolution": 82.5um. Dutch Belted rabbit fetuses were obtained by cesarean section on gestation day (GD) 29 (mating = GD 0) and stored frozen. The fetal skeletons were thawed, imaged, and then stained with Alizarin Red S. 53 fetuses (totaling 13,453 skeletal elements) were examined by both methods and the results compared. Every skeletal malformation was detected by both methods. Differences in the extent of ossification were found in only 44 out of 13,453 skeletal elements. In the majority of cases, ossification was detected by stain but not by micro-CT (e.g., medial phalanx forepaw, 16th/17th caudal vertebrae, parietal or frontal of the skull). The extent of ossification of the medial phalanx and caudal vertebrae are normally quite variable when obtained on GD 29 making them unreliable when determining overall ossification of the skeletons. There was a slightly increased incidence of incomplete ossification of the parietals and frontals by micro-CT, relative to staining. The influence of this difference will be examined further. Overall, the results of the two methods were identical in 99.7% of the fetal skeletal elements examined making micro-CT imaging a realistic alternative to skeletal staining.

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MARIEN D, VAN DEN HEUVEL J, CLAESSEN J, SAS C, FEYEN B. Janssen Research & Development, Preclinical Development & Safety, Beerse, Belgium. Microsampling and Microdosing in Mini Rodents

With the increasing need for juvenile animal toxicity studies in support of pediatric drug development comes increasing complexity in study design and animal handling. Depending on the clinical program, treatment duration, and development of organs of pharmacological or toxicological interest, each juvenile animal toxicity study needs to be specifically designed, using animals of a developmentally representative age correlating to the intended pediatric patient population (i.e., using preweaned rats when there is a clinical need for drug administration to children during the first year of life). These studies entail many restrictions related to the small size of the immature test system and its need for nursing and continuous maternal care within the litter. It becomes even more challenging when it concerns preterm neonatal patients, requiring a juvenile rat study starting at the representative age of less than postnatal day (PND) 8. This starting age should only be considered if absolutely required for the pediatric drug development and it requires elegant and ethically acceptable solutions for test article administration and obtaining data on toxicity and toxicokinetic parameters as routinely assessed in adult general toxicity studies. In this regard, we developed in-house juvenile rodent expertise to facilitate the successful application of oral gavage dosing of newborn PND 1 rat pups. Dosing the fragile PND 1 rat pups was found to be feasible using appropriate sized flexible soft plastic gavage (feeding) tubes with a bulb shaped tip although still challenging in terms of avoiding preterm pup mortality. Furthermore, implementation of capillary microsampling (32 to 60µl) for toxicokinetic purposes from as early as PND 8 pups via the tail vein was successfully applied and eliminated the need for terminal bleeds from satellite animals, which is more cost-effective (i.e., man-hours, resources, and test article required), but moreover significantly contributes to the 3R principles as it resulted in a > 50% reduction (i.e., > 200 animals) in experimental animal use in just one single experiment. In addition, more detailed age-related exposure profiles can be obtained, assisting better assessment and prediction of the often-observed ADME differences between juvenile and adult animals.

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WAN H, MCPHERSON S, JIN Y. WuXi AppTec, Suzhou, China. Comparison of Juvenile and Adult Rat Study on Toxicokinetics and Toxicity

The test article (TA) currently is being explored as antivirus candidate in pediatrics. In support of pharmaceutical development, nonclinical studies were performed to investigate whether oral administration of TA could cause a different response in juvenile rats versus adult rats. Juvenile rats were treated with TA via oral gavage at the dosages of 50, 150, and 450 mg/kg/day from postnatal day (PND) 4 to 31. In addition to in-life parameters and postmortem evaluations, toxicokinetics were investigated. After single oral dosing, exposure level in juvenile rats was slightly higher than in adult rats. C_{max} on PND 4 was up to 1.7-fold higher and $AUC_{0\text{-}24h}$ on PND 4 was up to 3.4-fold higher than adults at eight weeks of age. After repeated dosing for 28 days, exposure represented by C_{max} and $AUC_{0\text{-}24h}$ was similar in juvenile rats on PND 35 and adult animals at 12 weeks of age. As same as seen in adult animals, no treatment related clinical signs were observed in juvenile rats after single dosing on PND 4at doses up to 450 mg/kg/day. After 28-day repeated dosing on PND 31, treatment related but nonadverse and slight decreases in body weights and food consumptions, slight increases in organ weights of liver, spleen and thyroid correlating with minimal microscopic changes in these organs were observed in juvenile rats at 450 mg/kg/day. These were similar to those observed in adult rats at the same dosage. In conclusion, the exposure and the findings in juvenile rats were very similar to those observed in previously performed adult rats at the same dose levels, same route, and same dose duration. The no observed adverse effect-level (NOAEL) of TA was considered to be 450 mg/kg/day either in juvenile rats or in adult rats.

P45

DERFLER K, KNEPLEY P, FETTER A, PARSONS P. Covance Research Products, Inc, Denver, PA, United States. Impacts of Social Housing on Time-Mated Rabbits

Sixty female NZW rabbits housed in a commercial production facility were randomized into a group of thirty single housed rabbits and a group of 30 pair housed rabbits (15 pairs). Every effort was made to eliminate other variables between the two groups: same caging design, same location within building, same caretakers, same feed program, and same microenvironment. From age 15 weeks until breeding at age 25 weeks, all pair housed rabbits remained compatible, but exhibited a 20% incidence of minor cosmetic defects (hair barbering, skin nicks) associated with normal social interactions. Upon breeding, 14 of the 15 pairs rapidly became socially incompatible. Effort to achieve 100% conception rates in the socially housed rabbits was double that of individually housed rabbits. Conclusions: Socially housed female pairs may exhibit minor cosmetic defects from normal social interactions and time-mated rabbits are not a social species.

P46

HENWOOD SM, LUETJENS CM, FUCHS A, WEINBAUER G. Covance Laboratories Inc., Madison, WI, United States. Enhanced Pre- and Postnatal Development Studies in the Nonhuman Primate Model: Experiences with Social Housing

Regulatory guidance for preclinical safety assessment of biopharmaceuticals (e.g., monoclonal antibodies) by ICH M3(R2) and ICH S6(R1) is associated with frequent demand for nonhuman primate (NHP) models as the relevant species for developmental toxicity testing. Typically, an enhanced pre- and postnatal development (ePPND) study is conducted. Although studies involving pregnant animals are still considered a special challenge, moving toward social housing has had a positive impact on fetal loss and infant mortality. Here we report our cumulative experience from 2007–2015 for the conduct of developmental toxicity studies in the cynomolgus monkey. Overall, data from more than 700 pregnant animals including >200 control animals and >150 infants have been collected. Social housing was based on continuous comingling of 2–3 pregnant animals/cage. Maternal animals delivered in the home cage and infants were raised in the group home cage. Across all animals and over the entire time period, social housing proved feasible. Cumulative pregnancy loss in control animals was 15% compared to 19% under single housing (>1,000 control animals and >120 control infants, Jarvis et al. 2010, *BDRB* 89:175). Most notably, stillbirth rate was 6% vs. 11% under single housing. These data refer predominantly to mainland Asian origin animals. In 40 Mauritian origin control animals, pre- and postnatal losses appeared comparable. In another study with 45 undosed females, prenatal loss was also 15% and no stillbirths occurred. Meanwhile, social housing of large breeder males was achieved in over 20 pairs. In conclusion, our data demonstrate that continuous social housing throughout all phases of an ePPND study is entirely feasible in cynomolgus monkeys, including social housing of breeder males, and is associated with overall lower fetal and infant losses (e.g., abortion and stillbirth rates) compared to single housing. Albeit based upon a limited dataset, NHP origin may not be relevant in this context. Finally, loss rates in nondosed animals were comparable to those dosed with control substances indicating that administration procedure might not contribute to pregnancy losses.

Author Index

Fortieth Anniversary Annual Meeting of the Developmental Neurotoxicology Society Held in Conjunction with the 56th Annual Meeting of the Teratology Society

Grand Hyatt San Antonio, San Antonio, Texas

June 25–29, 2016

DNTS 2016 Program

SATURDAY, JUNE 25, 2016

8:00 AM–12:00 Noon	**TERATOLOGY SOCIETY EDUCATION COURSE SESSION I—Texas Ballroom D** *(Separate Registration Required)* **Embryology in Modern Times**
12:00 Noon–5:00 PM	**DNTS REGISTRATION—Texas Ballroom F Foyer**
1:00 PM–2:00 PM	**DNTS PUBLIC AFFAIRS COMMITTEE MEETING—Republic B**
1:30 PM–5:00 PM	**TERATOLOGY SOCIETY EDUCATION COURSE SESSION II—Texas Ballroom D** *(Separate Registration Required)* **Development and Teratology of the Heart**
2:00 PM–3:00 PM	**DNTS PUBLICATIONS COMMITTEE MEETING—Republic B**
3:00 PM–4:00 PM	**DNTS STRATEGIC PLANNING COMMITTEE MEETING—Republic B**
4:00 PM–6:00 PM	**DNTS COUNCIL MEETING—Republic B**

SUNDAY, JUNE 26, 2016

7:30 AM–8:00 AM	**MORNING COFFEE AND PASTRIES—Texas Ballroom A** (Joint with the Teratology Society)
8:00 AM–5:00 PM	**DNTS REGISTRATION—Texas Ballroom F Foyer**
8:00 AM–8:15 AM	**DNTS PRESIDENT'S WELCOME—Texas Ballroom F** *President: Lynn Singer, Case Western Reserve University*
8:15 AM–9:00 AM	**JOSEF WARKANY LECTURE—Texas Ballroom D** (Joint with the Teratology Society and OTIS) **DNTS 01: Framing Our Birth Defects Questions with Systems Biology: Learning from Our Mentors** *Chairperson: Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.* *Lecturer: Elaine M. Faustman, University of Washington*

9:00 AM–10:00 AM **DNTS 40TH ANNIVERSARY CELEBRATING OUR PAST AND FUTURE—Texas Ballroom F**

9:00 AM–9:05 AM **Introduction**
Lynn Singer, Case Western Reserve University

9:05 AM–9:35 AM **DNTS 02: Origins of the Developmental Neurotoxicology Society**
Charles Vorhees, Cincinnati Children's Research Foundation and University of Cincinnati, Cincinnati, OH, United States

9:35 AM–9:45 AM **DNTS 03: Discussant**
Jane Adams, University of Boston

9:45 AM–9:55 AM **DNTS 04: Discussant**

10:00 AM–10:15 AM **Break** (Joint with the Teratology Society)**—Texas Ballroom A**

10:15 AM–11:00 AM **DNTS 05: Reversal of Neurobehavioral Teratogenicity with Cell Transplantation: Animal Models and the Prospect for Translation**
Joseph Yanai[1,2], Adi Pinkas[1], Asher Ornoy[3], Itamar Altman[1], Dana Pulver[4], Gadi Turgeman[4]
[1]The Ross Laboratory for Studies in Neural Birth Defects, Department of Medical Neurobiology, IMRIC, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, [2]Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, United States, [3]Department of Medical Neurobiology, IMRIC, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, [4]Department of Molecular Biology, Ariel University, Ariel, Israel

11:00 AM–11:30 AM **DNTS 06: Marijuana and Development of the Brain**
Diana Dow-Edwards, State University of New York, Downstate Medical Center, Brooklyn, NY, United States

10:00 AM–11:00 AM **SPOUSE AND GUEST MEET-AND-GREET*—Republic A**

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

1:30 PM–5:30 PM **SYSTEMATIC EVALUATIONS OF MECHANISTIC—Texas Ballroom F**

Data for Developmental Neurotoxicity Outcomes
Chairperson: Andrew Craft, US Environmental Protection Agency

1:30 PM–1:35 PM **Introduction: Challenges in the Systemic Evaluation of Mechanistic Data for Developmental Neurotoxicity Risk Assessment**
Andrew Craft, US EPA

1:35 PM–2:00 PM **DNTS 07: The Critical Role of Context in Defining Developmental Neurotoxicity**
Deborah Cory-Slechta, University of Rochester School of Medicine, Rochester, NY, United States

2:00 PM–2:35 PM **DNTS 08: Epigenetic Effects of Prenatal Exposures: Issues of Timing, Tissue, and Sex**
Frances Champagne, Columbia University, New York, NY, United States

2:35 PM–3:20 PM **DNTS 09: Phenotypic Screening for Developmental Neurotoxicity: Mechanistic Data at the Level of the Cell**
William Mundy, Integrated Systems Toxicology Division, US Environmental Protection Agency, RTP, NC, United States

3:20 PM–4:00 PM **DNTS 10: Incorporating New Knowledge and Known Complexity for Systematic Evaluation of Mechanistic Data for Developmental Neurotoxicity: Considering Behavioral Outcome as a Primary Organizing Principle**
Christina Sobin, University of Texas, El Paso, TX, United States

4:00 PM–4:15 PM	**Break** (Joint with the Teratology Society and OTIS)**—Texas Ballroom A**
4:15 PM–5:00 PM	**DNTS 11: Developmental Neurotoxicity: Structured Frameworks for Evaluation** *Elaine M. Faustman, University of Washington, Seattle, WA, United States*
5:00 PM–5:30 PM	**Panel Discussion**

5:30 PM–6:00 PM **PATRICIA RODIER MID-CAREER AWARD FOR RESEARCH AND MENTORING—Texas Ballroom D**

(Joint with the Teratology Society)

Chairpersons: Bruce K. Beyer, Sanofi U.S. Inc. and Patricia Janulewicz, Boston University

Lecturer: Christina D. Chambers, University of California, San Diego

6:00 PM–7:30 PM **WELCOME RECEPTION, STUDENT AND POSTDOCTORAL FELLOW RESEARCH SHOWCASE**, AND EXHIBITS ATTENDED—Texas Ballroom B**

(Joint with the Teratology Society)

MONDAY, JUNE 27, 2016

7:30 AM–8:00 AM **MORNING COFFEE AND PASTRIES—Texas Ballroom B**

(Joint with the Teratology Society)

8:00 AM–5:00 PM **DNTS REGISTRATION—Texas Ballroom F Foyer**

9:00 AM–12:00 Noon **WILEY-BLACKWELL SYMPOSIUM—Texas Ballroom D**

(Joint with the Teratology Society)

Neurodevelopmental Deficits from Fetal Exposure to Methamphetamine, Cocaine and Alcohol: Emerging Mechanisms and Human Consequences
(See Page 333 for Session Details)

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

12:00 Noon–1:30 PM ***NTT* EDITORIAL BOARD LUNCHEON—Crockett C**

(For Board Members Only)

1:30 PM–5:30 PM **INTEGRATIVE *IN VITRO* MODELS FOR NEUROVASCULAR DEVELOPMENT FUNCTION SYMPOSIUM—Texas Ballroom D**

(Joint with the Teratology Society)

(See Page 335 for Session Details)

5:30 PM–7:30 PM **POSTER SESSION 1 AND EXHIBITS ATTENDED—Texas Ballroom B**

(Joint with the Teratology Society and OTIS)

DNTS P01: Behavioral Consequences following Deletion of the Dopamine D2 Receptor in Forebrain GABAergic or Glutamatergic Neurons

Devon Graham, Taylor Trammell, Lisa Anderson, Gregg Stanwood
Florida State University College of Medicine, Biomedical Sciences, Tallahassee, FL, United States

DNTS P02: Comparison of Developmental Effects across Multiple Phthalate Esters

Erin Yost[1], Xabier Arzuaga[2], Brandiese Beverly[1], Todd Blessinger[2], Susan Euling[2], Andrew Hotchkiss[1], Susan Makris[2], Teneille Walker[2], Andre Weaver[1]
[1]National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Research Triangle Park, NC, United States, [2]National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Washington, DC, United States

DNTS P03: Single and Repeated Exposures to the Volatile Anesthetic Isoflurane Do Not Impair Operant Performance in Aged Rats

Jennifer Walters, John Chelonis, Charles Fogle, Merle Paule
National Center for Toxicological Research (NCTR)/FDA, Jefferson, AR, United States

DNTS P04: High-Taurine Consumption by Adolescent C57BL/6J Mice Alters Biogenic Amines in a Sex-Dependent Manner

Christine Curran, Jamie Weimer, Clare Ludwig, Josephine Brown
Northern Kentucky University, Highland Heights, KY, United States

DNTS P05: Prioritization of Polychlorinated Biphenyl Congeners to Support Human Health Risk Assessment

Laura Macaulay[1], Jenny Li[2], Geniece Lehmann[1]
[1]National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Research Triangle Park, NC, United States, [2]National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Washington, DC, United States

DNTS P06: Circadian Disruption, Cognitive Function and Neurotransmission in a Rodent Model

Rekha Balachandran[1], Michael Leventhal[1], Audrey Robertson[1], Stephane Beaudin[2], Megan Mahoney[1], Paul Eubig[1]
[1]University of Illinois at Urbana-Champaign, Urbana, IL, United States, [2]University of California Santa Cruz, Microbiology and Environmental Toxicology, Santa Cruz, CA, United States

DNTS P07: Identifying Attention Problems in Children and Adolescents with the Behavioral Assessment and Research System (BARS)

Clara Sears[1], Lonnie Sears[2], Carol Hanchette[3], Barbara Polivka[4], Kristina Zierold[1]
[1]University of Louisville School of Public Health and Information Sciences, Louisville, KY, United States, [2]Department of Pediatrics, Louisville, KY, United States, [3]Department of Geology and Geosciences, Louisville, KY, United States, [4]School of Nursing, Louisville, KY, United States

DNTS P08: Dopamine Transporter (DAT) and Vesicular MOnoamine Transporter (VMAT) expression in the Striatum and Medial Prefrontal Cortex in Weanling and Adult, Cocaine-Exposed Rats is Altered by Perinatal PCB Exposure

Mellessa Miller, Jenna Sprowles, Abby Meyer, Helen Sable
University of Memphis, Memphis, TN, United States

DNTS P09: Gender-Specific Effects of Prenatal Cocaine Exposure of Emotional Behavior in Adolosecent Rats: Implications for Antidepressant Efficiay
Elijah Clark Jr.[1], Sonya K. Sobrian[2]
[1]Howard University, Washington, DC, United States, [2]Howard University College of Medicine, Washington, DC, United States

DNTS P10: The Relation between Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) and Performance on the Ages and Stages Questionnaire (ASQ)
Jolene Borchelt[1], Kerri Bertrand[1], Patricia Janulewicz Lloyd[2], Anna Rosofsky[2], Jocelyn Lutes[3], Kelly Kao[1], Christina Chambers[1], Kenneth Jones[1], Jane Adams[3]
[1]University of California San Diego, San Diego, CA, United States, [2]Boston University, Boston, MA, United States, [3]University of Massachusetts Boston, Boston, MA, United States

DNTS P11: Effects of Prenatal Cocaine Exposure on Responses to Stress in Adolescence
Meeyoung Min, Sonia Minnes, June-Yung Kim, Adelaide Lang, Lynn Singer
Case Western Reserve University, Cleveland, OH, United States

DNTS P12: Prenatal Tobacco and Cannabis Exposure: Effects on Infant Regulation via Fetal Growth, Maternal Stress, and Anger/Hostility
Rina Eiden[1], Pamela Schuetze[1], Marilyn Huestis[2]
[1]University at Buffalo, State University of New York, Buffalo, NY, United States, [2]National Institute on Drug Abuse, Baltimore, MD, United States

7:30 PM–10:00 PM **TERATOLOGY SOCIETY AND MARTA STUDENT CAREER EVENT—Texas Ballroom A**

(Open to Teratology Society, DNTS, and OTIS Student and Postdoctoral Fellows)

TUESDAY, JUNE 28, 2016

8:00 AM–5:00 PM **DNTS REGISTRATION—Texas Ballroom F Foyer**

8:00 AM–8:30 AM **MORNING COFFEE AND PASTRIES—Texas Ballroom B**

(Joint with the Teratology Society)

9:00 AM–12:30 PM **PUBLIC AFFAIRS SYMPOSIUM—Texas Ballroom D**

(Joint with the Teratology Society and OTIS)

Depression and Its Treatment in Pregnancy
(See Page 336 for Session Details)

12:30 PM–2:00 PM **LUNCH ON YOUR OWN**

2:00 PM–3:00 PM **DNTS 24: ELSEVIER DISTINGUISHED LECTURER—Texas Ballroom F**

Mouse Models of Autism to Identify Genetic Causes and Discover Therapeutics
Chairperson: Lynn Singer, Case Western Reserve University

Lecturer: Jacqueline Crawley, Robert E. Chason Endowed Chair in Translational Research, University of California, Davis

3:00 PM–4:30 PM **PLATFORM SESSION 1—Texas Ballroom F**

Chairperson: Jerold Meyer, University of Massachusetts, Amherst

3:00 PM–3:30 PM **DNTS 25: Hair Cortisol in Newborn Macaque Monkeys: Use As a Biomarker of Prenatal Cortisol Exposure and Relationship to Infant Behavior**

Jerrold Meyer[1], Melinda Novak[1], Kimberly Grant[2], Tom Burbacher[2], Julie Worlein[2], Rose Kroeker[2]
[1]University of Massachusetts Amherst, Amherst, MA, United States, [2]Washington National Primate Research Center, Seattle, WA, United States

3:30 PM–3:45 PM **Break** (Joint with the Teratology Society and OTIS)**—Texas Ballroom A**

3:45 PM–4:10 PM **DNTS 26: Long-Lasting Cognitive Deficits in Rhesus Monkeys after Neonatal General Anesthesia Induced by Isoflurane/Nitrous Oxide: Protection by Acetyl-L-carnitine**

Merle Paule[1], Mi Li[1], Xuan Zhang[1], Shuliang Liu[1], Joseph Hanig[2], William Slikker[1], Cheng Wang[1]
[1]National Center for Toxicological Research US FDA, Jefferson, AR, United States, [2]Center for Drug Evaluation and Research US FDA, Silver Spring, MD, United States

4:10 PM–4:30 PM **DNTS 27: Associations of Prenatal Exposure to Phthalates and Bisphenol A with Measures of Cognitive Function in 7.5-Month-Old Infants**

Kelsey Dzwilewski[1,2], Andrea Aguiar[2,3], Mahsa Yazdy[4,5], Susan Korrick[4,6], Susan Schantz[2,3]
[1]Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana, IL, United States, [2]Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, IL, United States, [3]Department of Comparative Biosciences, University of Illinois at Urbana-Champaign, Urbana, IL, United States, [4]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States, [5]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, United States, [6]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, United States

4:30 PM–5:30 PM **DNTS BUSINESS MEETING AND AWARDS PRESENTATION—Texas Ballroom F**

6:00 PM–8:00 PM **DNTS SOCIAL EVENT**

WEDNESDAY, JUNE 29, 2016

7:30 AM–8:00 AM **MORNING COFFEE AND PASTRIES—Texas Ballroom A**

(Joint with the Teratology Society)

9:00 AM–10:30 AM **PLATFORM SESSION 2—Texas Ballroom F**

Chairperson: Rina Eiden, State University of New York, Buffalo

9:00 AM–9:30 AM **DNTS 28: Impact of Gestational Serotonin Availability on Brain Function and Social Behavior**

Valentina Garbarino, Marshall Edwards, Anjuli Goring, Tyler Pryzbyla, Lynette Daws, Georgianna Gould
UTHSCSA, San Antonio, TX, United States

9:30 AM–10:00 AM **DNTS 29: Perinatal Citalopram Exposure Alters Spatial Learning and Memory, Acoustic Startle Response, Anxiety, and Sociability in Adult Sprague-Dawley Rats**

Jenna Sprowles[1], Jillian Hufgard[1,2], Arnold Gutierrez[1,2], Rebecca Bailey[1,2], Sarah Jablonski[1], Michael Williams[1,2], Charles Vorhees[1,2]
[1]Cincinnati Children's Research Foundation, Division of Neurology, Cincinnati, OH, United States, [2]University of Cincinnati College of Medicine, Cincinnati, OH, United States

10:00 AM–10:30 AM **DNTS 30: Developmental Outcomes for Infants of Mothers with Major Depressive Disorder or Bipolar Disorder**

Aimee Santucci[1], Lynn Singer[2], Stephen Wisnewski[3], James Luther[3], Heather Eng[3], Dorothy Sit[3], Katherine Wisner[4]
[1]St Jude Children's Research Hospital, Memphis, TN, United States, [2]Case Western Reserve University, Cleveland, OH, United States, [3]University of Pittsburgh, Pittsburgh, PA, United States, [4]Northwestern University, Chicago, IL, United States

10:30 AM–11:00 AM **Warkany Tea** (Joint with the Teratology Society)**—Texas Ballroom A**

11:00 AM–11:30 AM **DNTS 31: Interactive Effects of Prenatal Tobacco Exposure, Prenatal Maternal Depression, and Child Sex on Attention Problems at Preschool Age**

Rina Eiden, Danielle Molnar, Pamela Schuetze, Shannon Shisler
University at Buffalo, State University of New York, Buffalo, NY, United States

11:30 AM–12:00 Noon **DNTS 32: Effects of Prenatal Cocaine Exposure on Self-Reported Mental Health at Age 17**

Sonia Minnes, Lynn Singer, Meeyoung Min, Adelaide Lang
Case Western Reserve University, Cleveland, OH, United States

12:00 Noon **DNTS 2016 FORMALLY ADJOURNED**

Thank you for coming. Have an excellent and productive year ahead.
See you in Denver in 2017.

***Spouse and Guest Meet-and-Greet:** The Spouse and Guest Meet-and-Greet event is a great opportunity to meet fellow travelers, touch base with past friends, and coordinate your plans for exploring everything that San Antonio has to offer. Please join us at 10:00 am on Sunday, June 26 in the Republic A room at the Grand Hyatt San Antonio. The event will provide an opportunity for you to ask city experts suggestions for must-see attractions in San Antonio or have them answer any questions you may have about the city and its history. This event is free and open to guests of all registered attendees of the Teratology Society, DNTS, and OTIS meetings.

****Student and Postdoctoral Fellow Research Showcase:** The Student and Postdoctoral Fellow Research Showcase is new and exciting opportunity for students and postdoctoral fellows to showcase their research. The showcase is open to all students and postdoctoral fellows assigned to a Poster or Platform Session.

29th Annual Education Meeting for Organization of Teratology Information Specialists Members and MotherToBaby Affiliates

Grand Hyatt San Antonio, San Antonio, Texas

June 25–28, 2016

SATURDAY, JUNE 25, 2016

8:00 AM–10:00 AM **OTIS BOARD OF DIRECTORS MEETING—Crockett B**

Presiding: OTIS President: Robert Felix, University of California, San Diego

10:00 AM–10:15 AM **BREAK**

10:15 AM–12:30 PM **OTIS EDUCATION/PUBLIC AFFAIRS COMMITTEE MEETING—Crockett C**

Presiding: Christine Colon, University of Arizona

12:30 PM–12:45 PM **BREAK**

12:45 PM–2:45 PM **RESEARCH COMMITTEE MEETING—Crockett C**

(OTIS Research Committee Members Only)

Presiding: Gerald G. Briggs, MemorialCare Center for Women and Janine E. Polifka, University of Washington and TERIS

2:45 PM–3:00 PM **BREAK**

3:00 PM–6:00 PM **OTIS RESEARCH TEAM MEETING—Texas Ballroom E**

(OTIS Research Coordinators and Committee Members Only)

Presiding: Gerald G. Briggs, MemorialCare Center for Women and Janine E. Polifka, University of Washington and TERIS

3:00 PM–3:05 PM	**Welcome** *Janine E. Polifka, University of Washington and TERIS*
3:05 PM–3:25 PM	**Autoimmune Diseases in Pregnancy** *Diana Johnson, University of California, San Diego*
3:25 PM–3:45 PM	**Postmarketing Surveillance for Safety of Vaccines and Medications in Pregnancy—VAMPSS** *Diana Johnson, University of California, San Diego*
3:45 PM–3:55 PM	**New Projects and Progress on Manuscripts** *Christina D. Chambers, University of California, San Diego*
3:55 PM–4:10 PM	**Break**
4:10 PM–4:30 PM	**Update on Motherisk Studies** *Anna Pupco, The Hospital for Sick Children*
4:30 PM–4:50 PM	**Quebec Pregnancy Cohort Studies** *Anick Berard, University of Montréal*

4:50 PM–5:10 PM	**OTIS/ENTIS Collaboration** *Richard K. Miller, University of Rochester School of Medicine and Dentistry*
5:10 PM–5:25 PM	**Drugs in Lactation Analysis Consortium** *Shinya Ito, The Hospital for Sick Children*
5:25 PM–5:50 PM	**HRSA Geographic Outreach Effort** *Nicole Chavez, Nicole Greer, and Elizabeth Wasternack, OTIS National Office*
5:50 PM–6:00 PM	**Summary of Research Committee Meeting** *Janine E. Polifka, University of Washington and TERIS*

4:30 PM–6:30 PM **OTIS MEETING REGISTRATION—Texas Ballroom E Foyer**

SUNDAY, JUNE 26, 2016

7:00 AM–8:00 AM **OTIS WEBSITE/MARKETING COMMITTEE MEETING—Crockett B**

Presiding: Lori Wolfe, UNT Dept. of Biology Texas TIS and Jennifer A. Zellner, University of California, San Diego

7:00 AM–8:00 AM **OTIS OCCUPATIONAL COMMITTEE MEETING—Crockett C**

Presiding: Ginger Nichols, UConn Health

7:00 AM–8:15 AM **OTIS MEETING REGISTRATION—Texas Ballroom E Foyer**

8:15 AM–9:00 AM **JOSEF WARKANY LECTURE—Texas Ballroom D**

(Joint with the Teratology Society)

Framing Our Birth Defects Questions with Systems Biology: Learning from Our Mentors
Chairperson: Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.

Lecturer: Elaine M. Faustman, University of Washington

9:00 AM–9:15 AM **BREAK**

9:15 AM–10:30 AM **THOMAS H. SHEPARD LECTURE—Texas Ballroom E**

An Evolution of Labeling Information for Pregnant Women and Nursing Mothers: One Year in for the Pregnancy and Lactation Labeling Rule Introduction with President's Welcome: OTIS President: Robert Felix, University of California, San Diego
Speaker: Melissa S. Tassinari, US Food and Drug Administration

10:00 AM–10:30 AM **SPOUSE AND GUEST MEET-AND-GREET—Republic A**

(Open to the Teratology Society, DNTS, and OTIS Spouses and Guests)

10:30 AM–10:45 AM **BREAK**

10:45 AM–12:30 PM **GERALD G. BRIGGS RESEARCH SYMPOSIUM—Texas Ballroom E**

Maternal Infection During Pregnancy
Presiding: Gerald G. Briggs, MemorialCare Center for Women and Janine E. Polifka, University of Washington and TERIS

10:45 AM–10:50 AM	**Welcome** *Gerald G. Briggs, MemorialCare Center for Women*
10:50 AM–11:20 AM	**Overview of Congenital Infections** *Dee Quinn, University of Arizona*
11:20 AM–11:50 AM	**Hemorrhagic Fever Viruses in Pregnancy and Risks of Vertical Transmission** *Anita McElroy, Emory University*

11:50 AM–12:20 PM	**Maternal Zika Virus Infection and Microcephaly** *Lavinia Schuler-Faccini, Universidade Federal do Rio Grande do Sul, Brazil*
12:20 PM–12:30 PM	**Discussion**

12:30 PM–2:30 PM **LUNCH ON YOUR OWN**

1:00 PM–2:15 PM **OTIS MEETING PLANNING COMMITTEE MEETING—Republic A**

Presiding: Anna Pupco, The Hospital for Sick Children and Alfred Romeo, MotherToBaby Utah

2:30 PM–5:30 PM **PREGNANCY REGISTRY UPDATES SYMPOSIUM—Texas Ballroom E**

(Joint with the Teratology Society)

(See Page 331 for Session Details)

5:30 PM–6:30 PM **OTIS MEMBERSHIP COMMITTEE MEETING—Crockett B**

Presiding: Alfred Romeo, MotherToBaby Utah and Mark Roth, Pregnancy Risk Network

6:30 PM–8:00 PM **OTIS WELCOME RECEPTION—OFF-SITE (PAT O'BRIEN'S)**

MONDAY, JUNE 27, 2016

7:00 AM–8:00 AM **OTIS/ENTIS RESEARCH CONSORTIUM COMMITTEE MEETING—Crockett B**

Presiding: Richard K. Miller, University of Rochester School of Medicine and Dentistry

8:00 AM–8:15 AM **BREAK**

8:15 AM–9:15 AM **OCCUPATIONAL AND ENVIRONMENTAL—Texas Ballroom E**

Exposures: Occupational Committee Training
(Serving OTIS Members and MotherToBaby Affiliates)

Presiding: Richard K. Miller, University of Rochester School of Medicine and Dentistry

9:15 AM–9:30 AM **BREAK**

9:30 AM–10:50 AM **OTIS SPECIAL LECTURE—Texas Ballroom E**

Medical Marijuana, Substances of Abuse, Laws
Speakers: Robert Felix, University of California, San Diego
Anthony Scalzo, Saint Louis University School of Medicine

10:50 AM–11:00 AM **BREAK**

11:00 AM–12:00 Noon **OTIS SPECIAL LECTURE—Texas Ballroom E**

Consumer Products and Reproductive Safety
Speakers: Wafa Harrouk, Food and Drug Administration

12:00 Noon–2:15 PM **LUNCH ON YOUR OWN**

12:15 PM–2:00 PM **OTIS BOARD OF DIRECTORS MEETING—Crockett B**

Committee Reports
Presiding: OTIS President: Robert Felix, University of California, San Diego

2:15 PM–3:30 PM **OTIS BUSINESS MEETING—Texas Ballroom E**

Presiding: OTIS President: Robert Felix, University of California, San Diego

3:30 PM–5:30 PM **OTIS ABSTRACT SESSION—Texas Ballroom E**

Moderator: Anick Berard, University of Montréal

3:30 PM–3:50 PM **Goldenhar Syndrome Following First Trimester PTU Exposure: How Do We Counsel Patients Now?**
Kennedy D[1,2,3], Roscioli T[2,3], Turner A[2,3]. [1]MotherSafe Royal Hospital for Women Randwick, Australia, [2]Department of Medical Genetics Sydney Children's Hospital, Randwick Australia, [3]School of Women's and Children's Health, UNSW NSW Australia.

3:50 PM–4:10 PM **Evaluating the Impact of Linking an Electronic Medical Record Referral for Teratogen and Contraceptive Counseling with a Physician Contraceptive Provision Appointment on the Use of Highly Effective Contraception among Reproductive Aged Women Taking Teratogenic Medications: A Multi-Site Randomized Controlled Pilot Trial**
Batra P[1], Ornelas M[2], Salas-Wallace E[2], Kernahan C[2], Felix R[2], Kao K[2], Mody S[3]. [1]Department of Obstetrics and Gynecology, University of California, Los Angeles, Los Angeles, CA, United States, [2]Department of Pediatrics, University of California, San Diego, La Jolla, CA, United States, [3]Department of Reproductive Medicine, University of California, San Diego, La Jolla, CA, United States.

4:10 PM–4:30 PM **Break**

4:30 PM–4:50 PM **Lead Exposures and Management during Pregnancy: A Thirty Year Perspective**
Miller RK. MotherToBaby UR Medicine, Finger Lakes Children's Environmental Health Center, Obstetrics/Gynecology, University of Rochester School of Medicine and Dentistry, Rochester, NY, United States.

4:50 PM–5:10 PM **Zika Virus Infection in Brazil and Brain Anomalies Defects**
Schuler-Faccini L[1], Ribeiro E[2], Pessoa A[2].[1]Teratogen Information Service, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, [2]Hospital Albert Sabin, Fortaleza, Ceara, Brazil.

5:10 PM–5:30 PM **Pregnancy Outcome Following Maternal Use of Methylphenidate during Pregnancy: A Multicentre, Prospective, Comparative, Observational Cohort Study**
Dian-Citrin O[1,2], Shechtman S[1], Arnon J[1], Wajnberg R[1], Borisch C[3], Beck E[3], Richardson JL[4], Bozzo P[5], Nulman I[5], Ornoy A[2]. [1]The Israeli Teratology Information Service, Ministry of Health, Jerusalem, [2]The Hebrew University Hadassah Medical School, Jerusalem, Israel, [3]Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy, Berlin, Germany, [4]The United Kingdom Teratology Information Service, Newcastle upon Tyne, England, [5]The Motherisk Program, the Hospital for Sick Children, Toronto, Canada.

5:30 PM–7:30 PM **POSTER SESSION 1 AND EXHIBITS ATTENDED—Texas Ballroom B**

(Joint with the Teratology Society and DNTS)

7:30 PM–10:00 PM **TERATOLOGY SOCIETY AND MARTA STUDENT CAREER EVENT—Texas Ballroom A**

(Open to the Teratology Society, DNTS, and OTIS Student and Postdoctoral Fellows)

TUESDAY, JUNE 28, 2016

7:00 AM–8:00 AM **OTIS/ENTIS RESEARCH CONSORTIUM COMMITTEE MEETING—Crockett B**

Presiding: Richard K. Miller, University of Rochester School of Medicine and Dentistry

8:00 AM–8:30 AM **OTIS MEETING REGISTRATION—Texas Ballroom E Foyer**

8:30 AM–9:00 AM **ROBERT L. BRENT LECTURE: TERATOGEN UPDATE—Texas Ballroom D**

(Joint with the Teratology Society)

Preventing the Preventable: Where Do We Stand on Fetal Alcohol Spectrum Disorders in 2016?

Chairperson: Sonja A. Rasmussen, Centers for Disease Control and Prevention

Speaker: Christina D. Chambers, University of California, San Diego

9:00 AM–12:30 PM **PUBLIC AFFAIRS SYMPOSIUM—Texas Ballroom D**

(Joint with the Teratology Society and DNTS)

Depression and Its Treatment in Pregnancy

(See Page 336 for Session Details)

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

1:30 PM–5:30 PM **ADVANCES IN PLACENTAL RESEARCH SYMPOSIUM—Texas Ballroom D**

(Joint with the Teratology Society)

(See Page 338 for Session Details)

5:30 PM **ADJOURN**

Birth Defects Research (Part A) 106:441–444 (2016)

OTIS

PLATFORM ABSTRACTS

(Presenter designated by underlined author.)

1

KENNEDY D[1,2,3], ROSCIOLI T[2,3], TURNER A[2,3]. [1]MotherSafe Royal Hospital for Women, Randwick, Australia, [2]Department of Medical Genetics Sydney Children's Hospital, Randwick, Australia, [3]School of Women's and Children's Health, UNSW NSW Australia. Goldenhar Syndrome following First Trimester PTU Exposure: How Do We Counsel Patients Now?

A male infant was born at term (birth weight 3.2kg) to a 27-year-old G1P0 mother following a pregnancy complicated by hyperthyroidism. The mother was diagnosed with hyperthyroidism one year prior to conceiving. She chose to remain unmedicated in view of a planned pregnancy but commenced propylthiouracil (PTU) 100mg daily at six weeks amenorrhoea because of increasing symptoms of hyperthyroidism including anxiety, palpitations, and weight loss. She was advised to use PTU for the first trimester and then to switch to carbimazole as per current recommendations. She switched from PTU to carbimazole at 13 weeks amenorrhoea. Second trimester morphology ultrasound revealed bilateral preauricular skin tags but no other anomalies. At birth, in addition to bilateral preauricular skin tags he was noted to have mild facial asymmetry (left hemifacial microsomia) with a misshapen left ear (overfolded left concha) and micrognathia. An epibulbar dermoid was noted in the upper outer quadrant of his right eye. Further investigations revealed a small perimembranous VSD. X-rays showed a cervico-thoracic scoliosis as well as apparent fusion of T6/7 vertebrae and hemivertebrae at C6 and T4. Audiometry revealed mild-moderate right conductive hearing loss and severe/profound sensori-neural hearing loss on the left. No clinically significant CNV was noted on SNP array. MRI showed dysplastic left inner ear structures (semi-circular canal, vestibule and cochlear nerve) with normal appearance of right cochlea and semi-circular apparatus. A clinical diagnosis of Goldenhar syndrome/OAV spectrum was made. Discussion: This case suggested an association between the Goldenhar syndrome phenotype and exposure to PTU in early pregnancy. Most cases of Goldenhar syndrome are considered to be sporadic although there are reports of associated chromosomal anomalies as well as exposure to retinoids and thalidomide in the literature. A series of possible PTU-associated birth defects affecting the urinary tract and face and neck, and specifically the first and second branchial arches, was recently published (Andersen et al. *Thyroid* 2014; 24(10):1533–1540). Although generally less severe than the birth defects reported following carbimazole/methimazole this still raises the question about how best to counsel women about the optimal management of hyperthyroidism at various stages of pregnancy.

2

BATRA P[1], ORNELAS M[2], SALAS-WALLACE E[2], KERNAHAN C[2], FELIX R[2], KAO K[2], MODY S[3]. [1]Department of Obstetrics and Gynecology, University of California, Los Angeles, Los Angeles, CA, United States, [2]Department of Pediatrics, University of California, San Diego, La Jolla, CA, United States, [3]Department of Reproductive Medicine, University of California, San Diego, La Jolla, CA, United States. Evaluating the Impact of Linking an Electronic Medical Record Referral for Teratogen and Contraceptive Counseling with a Physician Contraceptive Provision Appointment on the Use of Highly Effective Contraception among Reproductive Aged Women Taking Teratogenic Medications: A Multi-Site Randomized Controlled Pilot Trial

Purpose: Despite the risks of harmful exposures in unplanned pregnancies, women prescribed teratogenic medications do not use more highly effective contraception than the general population. This multisite randomized controlled pilot trial investigated whether the combination of electronic medical record (EMR) referrals for teratogen and contraception counseling by MotherToBaby California counselors, and a dedicated contraception physician appointment would increase the use of effective contraception among women of reproductive age taking potential teratogens. Methods: In this pilot study, women ages 18–45 years prescribed or currently taking a potential teratogen and seen at a family medicine or internal medicine clinic were referred via EMR for teratogen and contraception counseling by MotherToBaby California counselors. The contraception counseling used the Contraceptive CHOICE Project script promoting long-acting reversible contraceptives (LARCs). Subjects were randomized to either an in-person dedicated contraception physician appointment (intervention) or no dedicated contraception physician appointment (control). Randomization was stratified by whether the patient was seen in a family medicine or internal medicine clinic. Nonparametric tests of association (Wilcoxon rank-sum test, chi-square test) were used given small sample size, and nonnormal underlying distributions. Analysis was conducted with intention to treat. Results: A total of 16 participants were recruited; six were randomized to the control, and ten to the intervention. There were no differences at baseline between the two groups with respect to: age, body mass index, number of baseline conditions, number of baseline medications, and proportion using a LARC/sterilization. There was no difference in the proportion of LARC/sterilization use between control and intervention participants at three months (40.0% versus 37.5%, p=0.93) or six months (33.3% versus 22.2%, p=0.63). LARC/sterilization use was increased at three months (31.3%) and six months (25.0%) compared to baseline (12.5%) in the entire study population. Conclusion: Linking enhanced contraception counseling using the Contraceptive CHOICE script to patient education regarding teratogenic medication exposures in pregnancy via the EMR was associated with increases in patient-reported use of LARC methods and sterilization. Providing coordinated contraception follow up appointments with physicians did not significantly increase the use of highly effective contraceptive methods. Findings were limited by sample size in this pilot study.

3

MILLER RK[1]. MotherToBaby UR Medicine, Finger Lakes Children's Environmental Health Center, Obstetrics/Gynecology, University of Rochester School of Medicine and Dentistry, Rochester, NY, United States. Lead Exposures and Management during Pregnancy: A Thirty-Year Perspective

Lead poisoning has been a human health risk for the millennia. A major focus has been lead intoxication in children, which is an important health focus with screening programs implemented early in life. However, of importance is detecting whether the women of reproductive age have histories of lead intoxication/exposure especially as they become pregnant. Recent concern has arisen in Flint, Michigan concerning the exposure of the population to lead through leaching of the conduits for their potable water supply. Yes, this type of exposure is certainly a major concern because old piping can have lead solder joints. However, there are many other reasons to screen mothers or women intending pregnancies to identify the myriad of other exposures to lead, which can lead to elevated blood lead levels (BLL) in excess of 25–65 ug/dl. For twenty years, New York State has required of health care providers that they screen each pregnant woman via a questionnaire and/or blood lead analysis at her first prenatal visit. Examples will be discussed involving women who have had screening with elevated levels (>5 ug/dl) due to drinking water exposure, hair dyes, gunshot fragments retained, immigrants from countries with leaded gasoline, pica eating, contaminated foods prepared in leaded containers, urine drinking, ayurvedic medicines, herbal products, occupations, gardening, and home remodeling. Often when one is exploring a point source, one finds multiple exposures, which must be remediated. Superimposed on these exposures are mothers who have been lead intoxicated in the past and during their second and third trimesters may be pulling the lead along with the needed calcium for the fetus from her skeleton. BLLs and K X-ray fluorescence (K-XRF) monitoring may be required. In practically all instances, chelation is counter-indicated and concentrating upon removing the source of exposure is critical and must be monitored monthly with BLL. Other interventions will be discussed on a case-by-case basis. (Support: HRSA, New York State DOH.)

4

SCHULER-FACCINI L[1], RIBEIRO E[2], PESSOA A[2].[1]Teratogen Information Service, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, [2]Hospital Albert Sabin, Fortaleza, Ceara, Brazil. Zika Virus Infection in Brazil and Brain Anomalies Defects

Introduction: At the beginning of 2015, an outbreak of Zika virus (ZIKV) was identified in Northeast Brazil. ZIKV is a RNA flavivirus transmitted by *Aedes* spp. mosquitoes. As from August 2015, an increased number of children born with microcephaly were observed in the same regions where ZIKV was circulating. ZIKV RNA was identified in amniotic fluid samples and in brain tissues from babies with severe brain abnormalities. Therefore a possible ZIKV embryopathy was proposed. At this moment, no specific serological test (IgM or IgG) is available in Brazil. The exposure to ZIKV is performed by RT-PCR, which detects the genome of the ZIKV only during the acute period of infection. In this communication we present the phenotypical findings in children included as suspected cases of ZIKV infection during pregnancy in the State of Ceará, Brazil. Methods: Suspected cases of ZIKV prenatal infection were defined as children born from August 2015 to January 2016, with head circumference (HC) under the 3rd centile OR with suspected maternal ZIKV infection during pregnancy. For this communication, we included the children referred to Hospital Albert Sabin in Fortaleza for investigation by medical geneticists, and including STORCHES and brain image exams. Results: From 91 examined children, 27 (30%) were excluded because normal neurological/brain ultrasound; and other four were also excluded because they were diagnosed with a genetic/storch condition and 13 (14%) are still under investigation. The 47 remaining cases were therefore considered probable cases of ZIKV infection. Head circumference was below 3 SD from the mean in 25/47 (53%); 16 (34%) were between <2SD and >3SD, 6 (12%) were >2DP but below the 3rd centile and other 6 (12%) had HC above 3rd centile but maternal history of infection compatible with ZIKV and/or neurological abnormality. Nine CT scans are already available and all presented anomalies: brain calcifications, lissencephaly/polymicrogiria, cortical atrophy, ventricular enlargement, and corpus callosum agenesis. At the physical exam, craniofacial disproportion was striking along with head skin folds. Neurological signs of hypertonia and cortical impairment were observed. Conclusion: The authors conclude that there is a characteristic phenotype possibly associated to prenatal maternal Zika virus infection.

5

DIAN-CITRIN O[1,2], SHECHTMAN S[1], ARNON J[1], WAJNBERG R[1], BORISCH C[3], BECK E[3], RICHARDSON JL[4], BOZZO P[5], NULMAN I[5], ORNOY A[2]. [1]The Israeli Teratology Information Service, Ministry of Health, Jerusalem, Israel, [2]The Hebrew University Hadassah Medical School, Jerusalem, Israel, [3]Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy, Berlin, Germany, [4]The United Kingdom Teratology Information Service, Newcastle upon Tyne, England, [5]The Motherisk Program, the Hospital for Sick Children, Toronto, ON, Canada. Pregnancy Outcome following Maternal Use of Methylphenidate during Pregnancy: A Multicentre, Prospective, Comparative, Observational Cohort Study

Introduction: Methylphenidate is a central nervous system stimulant medicinally used in the treatment of attention deficit disorders. Data on its use in human pregnancy are limited. The primary objective of this study was to evaluate the rate of major congenital anomalies after pregnancy exposure to methylphenidate for medical indications. Design: Prospective, comparative, multicentre, observational cohort study. Methods: Callers who contacted one of the four participating Teratology Information Services (Jerusalem, Berlin, Newcastle-upon-Tyne, and Toronto) between 1996 and 2013 regarding methylphenidate exposure during pregnancy were prospectively collected and followed-up. The outcome was compared to that of pregnancies from the same services after nonteratogenic exposure (NTE), matched by maternal age, gestational age, and year at initial contact. Results: 382 methylphenidate-exposed pregnancies [89.5% in the first trimester] were followed-up. There was no significant difference in the overall rate of major congenital anomalies between the groups [10/309=3.2% (methylphenidate) vs. 13/358=3.6% (NTE), p=0.780]. Similarly, after exclusion of genetic or cytogenetic anomalies and limiting methylphenidate exposure to the period of organogenesis (weeks 4-13 after the last menstrual period), the rates of major congenital anomalies [6/247=2.4% (methylphenidate) vs. 12/358=3.4% (NTE), p=0.511] and cardiovascular anomalies [2/247=0.8% (methylphenidate) vs. 3/358=0.8% (NTE), p=0.970] were similar. There was a higher rate of miscarriage and elective termination of pregnancy in the methylphenidate group. Using Cox proportional hazards model, significant predictors for miscarriage included methylphenidate exposure (adjusted HR=1.98, 95% CI 1.23-3.20, p=0.005) and past miscarriage (adjusted HR=1.35, 95% CI 1.18-1.55, p<0.001). Conclusion: The present study suggests that methylphenidate use in the first trimester does not seem to increase the risk for major malformations. However, due to limitations including a high rate of early pregnancy therapy discontinuation and no comparison with a disease-matched group, further studies are required to establish its pregnancy safety and its possible association with increased risk of miscarriage. The study has been accepted for publication in the *Journal of Clinical Psychiatry*.

Birth Defects Research (Part A) 106:445–452 (2016)

OTIS

POSTER ABSTRACTS

(Presenter designated by underlined author.)

1

NULMAN I[1], BARRERA M,[2] BREZDEN-MASLEY C[3], COLAPINTO N[4], KASSIRIAN S[4], MAXWELL C[5], KOREN G[6], MADARNAS Y[7], SERMER M[8], SRIDHAR S[9], TOZER R[10], WARNER E[11], YU J[12]. [1]Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [2]Division of Haematology/Oncology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [3]Division of Hematology/Oncology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada, [4]General Surgery, North York General Hospital, University of Toronto, Toronto, ON, Canada, [5]Maternal Fetal Medicine, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [6]Motherisk Program, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [7]Department of Oncology, Quinte Health Care, Queen's University, Kingston, ON, Canada, [8]Medical Disorders of Pregnancy Program, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [9]Medical Oncology, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada, [10]Hamilton Juravinski Hospital and Cancer Centre, Department of Oncology, McMaster University, Hamilton, ON, Canada, [11]Medical Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada, [12]Medical Oncology, North York General Hospital, University of Toronto, Toronto, ON, Canada. Cancer and Pregnancy Outcomes: An Overview of Existing Knowledge and Preliminary Results of a Multicenter Study

Purpose: Pregnancy associated cancer is a dramatic and stressful event for the patient and medical care providers, creating a conflict between optimal maternal treatment and fetal reproductive safety. Limited knowledge exists on pregnancy course, maternal and child's immediate and long-term outcomes following *in utero* exposure to maternal cancer and its cure. Management guidelines are inconsistent. The objectives of this report are to present an overview of existing knowledge on solid and hematological malignancies during pregnancy and to present preliminary results of a multicenter study on pediatric and neurodevelopmental outcomes of children following prenatal chemotherapy for breast cancer. Methods: A systematic overview was performed. Preliminary results on pediatric health and neurodevelopmental outcomes were documented and compared to healthy age and gender-matched controls. Children's neurodevelopment was assessed using standardized psychological tests. Results: 17 exposed children (aged 40 to 112 months) and their matched controls were assessed. There were more premature deliveries in the chemotherapy-exposed group (ten vs. one in controls). Children from both groups were similar in their rates of neonatal complications, allergies, oral thrush, and atopic dermatitis. Exposed children were not different in developmental milestones and anthropometric measurements at the time of testing. There were no cases of autoimmune cytopenia. 30% of exposed mother/child pairs (vs. 6% in controls) came from families where English is the second language. Full Scale IQs (FSIQs), WIPPSI_III, of younger children were confounded and significantly predicted by maternal Verbal IQ (R2=32; β=0.41; p=0.36). In contrast, the older children scored similarly to controls on the WISC-IV test (WISC-IV; 112 vs. 111; p=0.98). The FSIQs of premature and term children were similar in this cohort. The number of chemotherapy cycles did not predict any cognitive outcomes at this stage of research. Conclusion and Clinical Implications: This is the first study designed to assess children's cognition following prenatal exposure to chemotherapy for breast cancer. Chemotherapy was not found to be neurotoxic in this cohort. Thorough considerations should be given to potential confounding factors. Although these results are reassuring and may assist in weighing the benefits of timely versus postponed breast cancer treatment, more research is needed to support our findings.

2

CHALLIS S[1], HILL M[2], MIZIA K[2], GOMEZ-POULIN C[1], CUPITT D[2], KENNEDY D[1,2]. [1]School of Women's and Children's Health, University of New South Wales, Kensington, Australia, [2]MotherSafe Royal Hospital for Women, Randwick, Australia. Changing Patterns of Calls to MotherSafe Regarding Alcohol and Drugs of Dependence in the Period 2006–2015

Aim: To examine the trends and characteristics of calls made to MotherSafe (the NSW statewide teratogen information service) regarding alcohol and drugs of abuse from 2006 to 2015 and to compare them with trends seen in the general population. Methods: A retrospective database review of calls to MotherSafe regarding drugs of dependence was undertaken for the period January 2006 to December 2015. Each call was reviewed for exposure type, reason for call, and area of residence. Results: A total of 206,382 calls were made to MotherSafe in the ten-year period. Compared with calls in other categories, including antidepressants and antipsychotics, which remained steady, there was a significant decrease in calls regarding alcohol and drugs of abuse over the study period: 416/15,537 (2.86%) in 2006 compared with 176/22,057 (0.8%) in 2015. Overall the number of calls regarding alcohol fell by over 50%, from 252 calls in 2006 to 122 in 2015. The steepest fall was between 2008 and 2009 which coincided with publication of the latest Australian NHMRC guidelines regarding alcohol use and pregnancy. There was also a steady decline in the number of calls regarding marijuana, heroin, ecstasy, and amphetamines, reflecting population trends. Conversely, however, there was an increase in calls regarding the prescription drugs with potential for abuse including temazepam, dexamphetamine, and especially oxycodone. A significant number of women calling about drugs of abuse had associated psychiatric conditions requiring psychotropic medications. The majority of calls about cocaine, amphetamines, and smoking/NRT were regarding multiple exposures while calls about alcohol, methadone, and dexamphetamine were more likely to be regarding the single exposure. The commonest associated exposures included other drugs of abuse as well as antidepressants, benozodiazepines, and antipsychotics. Women calling regarding drugs of dependence were less likely to have planned the pregnancy and were more likely to consider termination of pregnancy compared to women calling MotherSafe about other exposures. Conclusion: Despite fewer calls overall regarding drugs of dependence, there was a significant increase in calls about exposure to prescription drugs of dependence, which reflects nationally reported trends. Strategies need to be implemented to ensure women on prescription medications of addiction and abuse receive appropriate counseling ideally prior to a planned pregnancy.

3

TRESENG L[1], BROCHET MS[1], FERREIRA E[1,2]. [1]Pharmacy Department, CHU Sainte Justine, Montréal, QC, Canada, [2]Faculté de Pharmacie, Université de Montréal, Montréal, QC, Canada. Clonidine Use for the Treatment of Sialorrhea Gravidarum: A Case Series and Literature Review

Background: Sialorrhea gravidarum is often related to nausea and vomiting, as well as to gastroesophageal reflux. Clonidine has been used to treat sialorrhea associated with various conditions and could potentially be an interesting option for sialorrhea gravidarum. Purpose: To describe the use of clonidine for sialorrhea gravidarum with regard to efficacy and safety outcomes. Methods: Retrospective case series of all hospitalized pregnant women at CHU Sainte-Justine between January 2010 and February 2015 with a prescription for clonidine to treat sialorrhea gravidarum were included. The patients were identified using the pharmacy software. Clonidine used only for hypertension or sedation was excluded. Maternal demographics, clinical and medication history data for each patient and medical charts of each newborn were reviewed and demographic and clinical (congenital or abnormal outcomes) data were collected. Literature search was conducted using EMBASE. The MESH terms "pregnancy", "clonidine", "hyperemesis gravidarum", "sialorrhea", "hypersalivation", and "ptyalism" were used. Articles written in French and English between 1974 and 2015 were used. Case reports and letters to the editor were included. Results: Ten pregnant women were treated with clonidine for sialorrhea gravidarum during the evaluation period. Clonidine was prescribed when sialorrhea continued despite the use of standard hyperemesis gravidarum treatment. The patients' symptoms were considered to have improved enough for discharge after the addition of clonidine. All ten infants were examined and the only birth defect reported was a simian crease dysmorphism in a newborn exposed to clonidine after organogenesis. Although there is no publication regarding the use of clonidine in sialorrhea gravidarum, it has been studied in the context of hypertension during pregnancy and hyperemesis gravidarum. Six studies have not shown an increase in malformations following the use of clonidine during any trimester but only one publication reported use during the first trimester (59 infants). Conclusions: Clonidine has not been shown to be teratogenic in humans and could potentially be a treatment for sialorrhea gravidarum. This case series expands on the information available regarding clonidine use during pregnancy.

4

BROCHET MS[1], DAHDOUH EM[2]. [1]CHU Sainte-Justine, Centre IMAGe, Department of Pharmacy, University of Montréal, Montréal, QC, Canada, [2]Assisted Reproduction Center, CHU Sainte-Justine, Department of Obstetrics and Gynecology, University of Montréal and Procrea Clinics, Montréal, QC, Canada. Letrozole Treatment for Infertility and the Risk of Congenital Malformations: A Systematic Review

Background: Recent evidence suggests that the aromatase inhibitor, letrozole (LTZ), might be more effective as an oral agent for ovulation induction in a subgroup of women with polycystic ovary syndrome and that it is equivalent to clomiphene citrate (CC) in treating women with unexplained infertility. However, its safety has been questioned following an oral presentation at the American Society for Reproductive Medicine meeting in 2005, which suggested that LTZ might be associated with higher risk of congenital malformations, mainly cardiac and locomotor, compared to natural conceptions. As a result, the manufacturer issued a black box warning about the potential teratogenicity of LTZ and released a statement that contraindicates its use for infertility. Purpose: To conduct a systematic review of publications and evaluate the safety of LTZ. Methods: Search was conducted using electronic databases Pubmed, MEDLINE, Embase, Google Scholar, and COCHRANE database as well as RCT registry (www.clinicaltrials.gov) for possible relevant articles published in English or French up to February 2016 with no date limitations using the following Boolean search criteria: ("Pregnancy Outcome"[Mesh]) AND "letrozole" [Supplementary Concept]. Only studies with comparison groups (other ovulation induction drugs or spontaneous pregnancy among infertile women population) including birth defects as primary or secondary outcomes were examined. Results: Out of 526 citations identified, 120 articles met initial eligibility criteria and were further analyzed. Of these, only six studies (three observational and three randomized controlled trials) met full inclusion criteria. Newborns and malformations following maternal LTZ treatment used for ovulation stimulation were evaluated. Out of these, malformations were reported resulting in a rate of 0 to 6.6% (6/514, 0/112, 5/201, 2/30, 4/102, 2/56) of total congenital malformations. Cardiac and locomotor defects were not a pattern of birth defect. Overall malformation rates were not higher than in comparison groups. Conclusions: The rate of congenital malformation associated with LTZ is low and is comparable to the rate with natural conceptions, CC and spontaneous pregnancy among infertile women population. In addition, no specific pattern of congenital anomalies was identified when LTZ was used for ovulation stimulation.

5

BERTRAND K[1], CHAMBERS C[1], SAUBERAN J[2], ANDERSON P[1], BODE L[1], KIM JH[1,3], BOYLE D[1]. [1]University of California San Diego, La Jolla, CA, United States, [2]Sharp Mary Birch Hospital for Women and Newborns, San Diego, CA, United States, [3]Rady Children's Hospital of San Diego, San Diego, CA, United States. Marijuana Use in Women Participating in the University of California San Diego (UCSD) Human Milk Biorepository Cohort

Background: The benefits of human milk on growth, cognitive development, and protection against disease have been well documented; however, little is known about the excretion of recreational drugs into human milk. Specifically, marijuana use in breastfeeding women is not well studied. Only two case reports have been published. They indicated that tetrahydrocannabinol (THC) is excreted in human milk and can be absorbed by the infant. Because the brain rapidly develops during the first three years of life, marijuana use among breastfeeding women needs more research. The purpose of this study is to investigate the prevalence of marijuana use among breastfeeding women. Methods: Participants were enrolled in the Human Milk Biorepository located at The Center of Better Beginnings through the UCSD Department of Pediatrics. Breastfeeding women 18 years or older were eligible for participation. Women were recruited through social media, the UCSD Pediatric Clinic, the UCSD Medical Center NICU, and two satellite sites. Participants completed an in-person interview on demographics, health history, and lifestyle habits (i.e., medications, recreational drugs, tobacco, alcohol). Each participant provided a 50 mL sample of breast milk using a closed system breast pump and sterile collection kit. Samples were aliquoted and stored in a -80°C freezer. Results: As of February, 135 participants provided human milk samples. Of the women enrolled, 14 (10.4%) reported using marijuana within the seven days prior to sample collection. The median age of these children was 12 months (3–20). Of those women who smoked marijuana, eight (57.1%) had a mental illness diagnosis, such as anxiety or depression. Of women who smoked marijuana, 12 (85.7%) had also consumed alcohol within the prior seven days. Conclusions: Ten percent of participants used marijuana in the prior seven days and of those, about 86% used marijuana in combination with alcohol. More research is needed to understand the long-term effects on children who are breastfed by mothers who use marijuana. Future research includes analyzing human milk marijuana compounds using mass spectrometry. These results will help researchers understand what compounds a nursing infant would be exposed to if the mother is using marijuana. References: 1. Perez-Reyes M, Wall ME. Presence of Δ9-Tetrahydrocannabinol in Human Milk. *N Engl J Med* 1982;307:819-820. Letter.

6

ALWAN S[1], BANDOLI GB[2], CHAMBERS CD[2]. [1]University of British Columbia, Vancouver, BC, Canada, [2]University of California, San Diego, La Jolla, CA, United States. Maternal Use of Selective Serotonin-Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn: An Update of the Current Evidence and Clinical Implications

Maternal use of selective serotonin reuptake inhibitors (SSRIs) in late pregnancy has been associated with various adverse neonatal outcomes, most recently persistent pulmonary hypertension of the newborn (PPHN), a rare but serious condition with substantial infant mortality and morbidity. Although the increase in absolute risk is small on a population level, it could still be of concern to many patients. It remains unclear, however, whether the increased risks reported for PPHN could be explained by the underlying maternal illness rather than the use of SSRIs. Antenatal depression carries a serious risk on both the mother and the baby and discontinuing antidepressant treatment during pregnancy is associated with a high risk of relapse. It is recommended that pregnant women who require treatment for depression receive comprehensive counseling on a case-by-case basis. Health care providers should be aware of the higher risk for the development of PPHN outcomes amongst mothers on antidepressants in late gestation in order to provide better surveillance and more timely interventions.

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SHERMAN S[1], WOLFE L[2], CESSAC N[2]. [1]MotherToBaby North Texas, Denton, TX, United States [2]The University of North Texas, Denton, TX, United States. Meeting the Needs of Underserved Populations through Technology

At MotherToBaby North Texas, we have seen an increasing need for our service to be available to more people through the use of new and innovative technology beyond our normal weekday working hours. As always, we are looking for ways to expand our services to underserved populations that have not traditionally utilized teratogen services. It is imperative that pregnant and nursing women have information on exposures in order to reduce the numbers of spontaneous abortions, preterm deliveries, premature births, and low birth weight babies that are possibly caused by the adverse effects of teratogens. We realize the importance of reaching out to the people who work during the hours our services are available. They do not have the time necessary for us to take the comprehensive history that is needed in order to counsel them concerning the teratogenic agents to which they are exposed. They are looking or quick and easily accessible answers. Since an increasingly large number of Americans have devices with access to cellular services, we believe that reaching out with new and increasingly-improving technologies is the best way for us to reach new and underserved populations. Studies have shown that the under-25 population of Americans is increasingly using cellular devices to access information. The MotherToBaby North Texas Teratogen Information Service is currently participating in the Texting Pilot Program that began in the fall of 2015. We were off to a good start in September with approximately 100 text messages and the number of messages has increased significantly each month. In this short time, we see that the texting service is going to be a great tool in helping us achieve our goal of reaching out to a historically underserved population of women, who will benefit from the information we have to offer.

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LYNCH ME, KABLE JA, PAIGE S, COLES CD. Emory University School of Medicine, Department of Psychiatry, Atlanta, GA, United States. Prenatal Alcohol Exposure and Behavior Problems in a Prospective Longitudinal Sample of Young Adults

Little research is available on the relation between prenatal alcohol exposure (PAE) and behavior problems in adulthood. Studies of clinically-referred adults suggest serious problems (e.g., Streissguth et al., 1996). A recent study of young adults with low to moderate levels of PAE also showed that behavior problems occurred (Day et al., 2013). The present analysis describes self-reported behavior problems in a prospectively-followed sample of young adults experiencing a wide range of PAE. We expected that adults more severely affected by PAE would report more behavior problems. The sample included 234 young adults (average age = 22.77) in five groups and was drawn from a predominantly African-American, low-income population. Exposure was based on maternal report prenatally. The exposed young adults were grouped by dysmorphia score and IQ score into three groups: 1) Exposed/Physically Dysmorphic (most severely affected); 2) Exposed/Cognitively Affected (Not Dysmorphic/IQ < 84); and 3) Exposed/Not Cognitively Affected (Not Dysmorphic/ IQ > 84). Control groups for SES and disability were included. Adults responded to the Adult Self Report (ASR) (Achenbach & Rescorla, 2003) and the LISRES-A (Moos & Moos, 1994), a self-report measure of life stresses and resources. Analyses of ASR T scores for dependent variables (Total Problems, Internalizing, Externalizing) were completed with Group and Gender as the independent variables and T score for Negative Life Events from the LISRES-A as a covariate. Results for all three variables were significant for Group; the Exposed/ Cognitively Affected group showed the highest scores. Negative Life Events T score was a significant covariate for each variable. Gender was significant only for Externalizing T score (males > females). The Exposed/Not Cognitively Affected group scores were similar to the control group for all three variables. Contrary to our expectation, the adults who were cognitively (but not physically) affected were most likely to report behavior problems. As they were not dysmorphic, they may have been less likely to be diagnosed and to receive referrals for services. This finding is similar to results of Streissguth et al. (1996) and to those found for other adaptive functioning variables in this sample (Lynch et al., 2015).

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ETWEL F[1,2], FAUGHT LH[1,2], RIEDER M[1,2], KOREN G[1,2]. [1]University of Western Ontario, London, ON, Canada, [2]Motherisk, Israel. Risk of Adverse Pregnancy Outcome after First Trimester Exposure to H1 Antihistamines: An Updated Meta-Analysis

H1-blockers are used for the treatment of nausea and vomiting during pregnancy (NVP), as well as the symptomatic relief of asthma, urticaria, allergy, and common cold. Although they are overall felt to be safe in pregnancy, recently several studies challenged this assumption. As millions of women are exposed to them in the first trimester. Methods: Following the guidelines of Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group, a systematic review was performed to retrieve all published articles involving H1-blocker exposure during pregnancy. Electronic databases including PubMed, SCOPUS, and EMBASE were searched for possibly relevant articles published in any language up to December 2015. Results: After removing duplicate publications, excluding animal studies, case studies; and review articles without original data, 56 articles were reviewed in detail and 37 studies fulfilled the inclusion criteria for the meta-analysis. In cohort studies the risk of congenital malformation in the offspring of women exposed to H1 antihistamines was not higher than that of the control population (OR 1.067; 95% CI 0.979-1.162). The Q-statistic for heterogeneity of effects was not significant ($P > 0.05$, $I2 < 25\%$) and there was no evidence of publication bias. Similar results were achieved with case-control studies (OR 1.053; 95% CI 0.899-1.232). Similarly, H1 blockers were not associated with more prematurity (OR 0.956 (0.764-1.198), miscarriage (OR0.996 (0.826-1.201), LBW (OR 1.202 (0.630-2.294). Similar results were achieved with case-control studies. Conclusions: The safety of H1 blockers has been confirmed with over 1.3 m cases and controls.

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LÉVEILLÉE D[1], IGLESIAS MH[2], BROCHET MS[1], FERREIRA E[1,3]. [1]Pharmacy Department, CHU Sainte Justine, Montréal, QC, Canada, [2]Department of Obstetrics and Gynaecology, CHU Sainte Justine, Montréal, QC, Canada, [3]Faculté de Pharmacie, Université de Montréal, Montréal, QC, Canada. Sildenafil Use during Pregnancy for Intrauterine Growth Restriction: A Case Series and Review of Literature

Background: Intrauterine growth restriction (IUGR) is defined as an estimated fetal weight of <10th percentile and is a major cause of neonatal and maternal morbidity and mortality. Currently, there is no evidence-based treatment option for severe early-onset IUGR. In the majority of IUGR cases, a vascular placental insufficiency is probably the cause of the growth restriction. Sildenafil citrate, a selective inhibitor of phosphodiesterase 5 (PDE-5) that induces vasodilatation has been shown to increase uterine blood flow and potentiates estrogen induced vasodilatation. Purpose: To describe the use of sildenafil in pregnant women with severe early-onset IUGR. Methods: Retrospective case series of all hospitalized pregnant women with known pregnancy outcomes who received sildenafil for severe IUGR at the CHU Sainte-Justine from January 2012 to November 2015. Patients were identified using the Pharmacy software program. For the purposes of analysis, a standardized data collection sheet for all demographic, biological, pharmaceutical and clinical data was developed. In addition, a review of the medical literature on the use of sildenafil for IUGR during pregnancy was conducted. Results: We identified 19 hospitalized pregnant women who had received sildenafil for severe IUGR. Sildenafil was started at an average of 25 weeks+3 days (median: 25, [20+1, 30+6]). Uterine artery notching was observed 95% of pregnancies and abdominal circumference was inferior to 5th percentile in most pregnancies (79%). Absent or reversed umbilical artery Doppler was present in six pregnancies before sildenafil. Gestational age increased by 24 days (median: 17, [5, 47]) during the admission-to-delivery interval. Before the initiation of sildenafil, estimated average fetal weight was 558g [237, 1208] and increased by an average of 807 g (median: 820, [320, 1360]) at delivery after sildenafil's initiation and with an average weight gain of 249g (median: 123, [-46, 732]). A majority (74%) of women developed pre-eclampsia. Preterm delivery occurred in all pregnancies. Gestational age at delivery was on average 28 weeks+6 days (median: 29+2, [24+2, 33]). The survival rate at birth was 17/19 live births and 15/19 survival at hospital discharge. Sildenafil was well tolerated by mothers. Conclusions: Our case series suggests that sildenafil is well tolerated and may offer an option to improve perinatal outcomes for pregnancies complicated by severe IUGR.

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RAEMAEKERS BC[1], VORSTENBOSCH S[1], VAN PUIJENBROEK EP[1,2]. [1]Teratology Information Service and Netherlands Pharmacovigilance Centre Lareb's-Hertogenbosch, The Netherlands, [2]Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, The Netherlands. Teratology in a Pharmacovigilance Context: Five Years of Experience in The Netherlands

Background: The Dutch Teratology Information Service (TIS) became part of the Netherlands Pharmacovigilance Centre Lareb in 2011. Lareb is the Dutch national reporting centre for suspected adverse drug reactions (ADRs), which include effects on the (unborn) child after using medicines during pregnancy and/or lactation. Since the transition, the case-by-case assessment of these retrospective reports has been conducted by TIS staff rather than Lareb pharmacovigilance assessors. The aim of this overview is to describe the ADR reports assessed thus far, as well as to explore the potential added value of these reports to the standard practices of collecting data by TIS. Methods: The Lareb ADR database was searched for reports received between 2011 and 2015, regarding effects on the (unborn) child after using medicines during pregnancy and/or lactation. The relevant reports were evaluated by type of ADR and by type of suspect drug. Results: A total of 192 reports comprising 271 suspected ADRs were located in the database. Of these, only five reports (11 ADRs) concerned exposure of the child through breast milk. The 260 pregnancy-related ADRs consisted of 15 spontaneous abortions, 12 stillbirths, nine other fetal complications, 66 neonatal conditions (including PPHN, respiratory depression and withdrawal syndrome), 95 congenital malformations and 63 other disorders (including developmental delay). The pregnancy-related ADRs were most commonly reported in association with SSRI's, followed by other antidepressants, antiepileptics, diethylstilbestrol, TNF-α inhibitors, antipsychotics and proton pump inhibitors. Conclusion: Due to the retrospective nature of ADR reports, it is difficult to establish causality from these data. However, detailed analysis of ADR reports may result in a preliminary signal, prompting further studies in a prospective setting. The potential added value of ADR reports is also illustrated by the diethylstilbestrol cases, as effects can occur many years after intrauterine exposure, which is beyond the follow-up period of most prospective teratology studies. In addition, ADR reports are likely to reflect the type of drugs that are perceived to be teratogenic by healthcare professionals and patients, providing TIS with the opportunity to address any recurring misperceptions.

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FORTIN G, VALLÉE M, BROCHET MS. Centre IMAGe, Sainte-Justine University Hospital, Montréal, QC, Canada. Tramadol during Pregnancy and the Postnatal Period: A Case Report of Chronic Therapy throughout Pregnancy and Review of the Literature

Background: Tramadol is a synthetic opioid that has been on the North American market for over 15 years. Little data is available on its use during pregnancy and neonatal outcomes. In adults, tramadol has a lower risk of adverse effects and dependence, hence rare withdrawal symptoms when stopped abruptly compared to traditional opioids, making it a valuable option for patients with chronic pain syndromes. All publications on neonatal outcomes following chronic tramadol use during pregnancy describe neonatal withdrawal syndromes. Purpose: To describe a case of chronic tramadol therapy throughout pregnancy that did not lead to a withdrawal syndrome in the newborn, and to review medical literature on tramadol use during pregnancy and the postnatal period. Methods: We obtained the mother's written consent to consult her and her daughter's medical charts. We performed a literature search up to February 2016 in Pubmed, MEDLINE, and Embase, using the key words "tramadol," "pregnancy," and "neonatal abstinence syndrome", and retrieved all relevant English and French language abstracts and articles. Results: Case-report: The patient had been taking six years prior to her pregnancy tramadol extended release 200 mg daily for chronic pain following a complicated urologic surgery. She continued it throughout her pregnancy, which was uneventful except for threatened preterm labour at 30 weeks which responded successfully to tocolysis. Her daughter was born by C-section at 38 + 4/7 weeks with a normal Apgar and no major congenital anomalies. Finnegan scores were done and as the baby showed no signs of drug withdrawal, she and her mother were discharged in good health three days after delivery. Literature search: Two studies describe pregnancy outcomes after first trimester exposure to tramadol, for a total around 1,900 exposures, showing mostly reassuring results. Ten cases of neonatal withdrawal syndromes are reported, mainly in newborns exposed to chronic maternal treatment. Conclusions: To our knowledge, this is the first written report of a baby chronically exposed to tramadol *in utero* who did not present a neonatal withdrawal syndrome. More data on the safety of tramadol use during pregnancy is needed.

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SIMON TA, DOMINIQUE A, YU HELEN. Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb, Hopewell, NJ, United States. What Is the Proportion of Abatacept Users Who Are Women with Child-Bearing Potential in the Ongoing Epidemiology Post Marketing Commitment Studies?

Background: Abatacept is a selective T cell costimulation modulator approved for the treatment of rheumatoid arthritis (RA). The abatacept adult RA epidemiology post marketing commitment (PMC) program consists of seven RA cohorts, and a North American pregnancy Organization of Teratology Information Specialists (OTIS) Registry. We evaluated the proportion of women of child bearing potential (WOCBP) in the abatacept PMC program to determine if the low number of pregnancies in OTIS Registry may be due to the age of the treated population. Methods: Data from the PMC program, commercial sales, and the US census was used. Five (5) PMC studies provided the age distribution of WOCBP. Two United States (US) claims databases (United Health Care and MarketScan) and three registries: the National DataBank for Rheumatic Diseases, the Swedish ARTIS registry and the German RABBIT registry provided data. A WOCBP defined as female 18 to 45 years. WOCBP exposed to commercial abatacept is estimated using available sales data and compared to the WOCBP in the US using census data. Results: The abatacept PMC program (N=16,068: mean age ~ 53 years) has 82.6%>18 year old females; of these, ~6%:18 to 35 and ~ 11%:36 to 45 years. Using abatacept commercial sales data, the cumulative number of patients treated through 22-Jun-2015 is approximately 308,256; using the PMC data it's estimated that ~6% are 18 to 35 years in the US. The US Vital statistics reported 63 million WOCBP (16 to 44 years) and four million births in 2012. 84% of the births occurred in 18 to 34; ~1% have RA and of those only ~ 25% are on a biologic (~0.25% of general WOCBP population). Conclusion: Although the age groups are slightly different, it seems unlikely that a WOCBP with RA and treated with abatacept will choose to become pregnant. Therefore the few number of abatacept exposed pregnancies in the pregnancy registry may be reflective of the actual pregnancies in this RA population. Pregnancy registries are an important component of post marketing monitoring however alternative data collection measures like health care claims should be considered in a RA population of WOCBP with few pregnancies.

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.

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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
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. (**www.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. (**www.toxsci.oxfordjournals.org**)

4. Teratology Society website. (**www.teratology.org**)