Society for
Birth Defects Research & Prevention
EST. 1960 AS THE TERATOLOGY SOCIETY

VIRTUAL

61ST ANNUAL MEETING

June 24–July 1, 2021

Building Bridges** in Birth Defects Research and Prevention: **From Innovation to Application

Virtual 33rd Annual Eduction Meeting for Organization of Teratology Information Specialists Members and MotherToBaby Affiliates

June 22–July 1, 2021

Virtual 45th Annual Meeting of the Developmental Neurotoxicology Society

February 4–June 30, 2021

Society for
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Program & Abstracts

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Building Bridges** in Birth Defects Research and Prevention: **From Innovation to Application

Education Courses • July 15, 22, 29, 2021

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The work of the Society for Birth Defects Research and Prevention is done mainly through the activities of its committees and the dedicated members who serve on and lead those committees. There is room for you—volunteer to serve on a committee!

Email bdrp@birthdefectsresearch.org if you're interested in getting involved.

Program Overview

All times listed in the agenda are Eastern Daylight Time (US).

Thursday, June 24, 2021

11:00 AM–11:10 AM **President's Welcome**

11:10 AM–11:45 AM **Josef Warkany Lecture (L1)**
Reactive Oxygen Species and DNA Damage/Repair in Developmental Disorders

11:45 AM–12:30 PM **Robert L. Brent Lecture—Teratogen Update (L2)**
Identifying New Human Teratogens: Revisiting Shepard's Criteria

12:30 PM–1:00 PM **Break**

1:00 PM–3:30 PM **Graduate Student and Postdoctoral Fellow Platform Session 1**

3:30 PM–4:00 PM **Break**

4:00 PM–5:00 PM **President's Welcome Social**

Friday, June 25, 2021

11:00 AM–11:30 AM **F. Clarke Fraser New Investigator Award (L3)**
Consequentialist Epidemiology of Birth Defects: Early Career Experiences and Key Findings from National and Global Research

11:30 AM–12:00 Noon **James G. Wilson Publication Award**
Exploratory analysis of machine learning approaches for surveillance of Zika–associated birth defects

12:00 Noon–12:30 PM **Patricia Rodier Mid-Career Award for Research and Mentoring (L4)**
Manganese Overexposure during Development: Environmental and Genetic Effects
(Joint with DNTS)

12:30 PM–1:00 PM **Agnish Fellowship Lecture (L5)**
Education, Service, and Career Paths in the Multidisciplinary Science of Birth Defects Causation and Prevention

1:00 PM–1:30 PM **Break**

1:30 PM–3:00 PM **Multidisciplinary Research Needs Workshop**

1:30 PM–3:00 PM **Professional Development Workshop**

Monday, June 28, 2021

11:00 AM–11:45 AM **Keynote Lecture (L6)**
Pregnancy and the Perils of Precaution: Toward a New Paradigm for the Ethics of Including Pregnant People in Vaccine Research and Deployment
(Joint with OTIS)

11:45 AM–12:30 PM **BDRP and European Teratology Society (ETS) Exchange Lecture**
Covid-19 in Pregnancy and Lactation: US and European Perspectives on Research and Public Health
(Joint with OTIS)

12:30 PM–1:00 PM **Break**

1:00 PM–3:00 PM **Wiley Symposium**
Approaches for Mechanistic Evidence Analysis in Hazard Evaluation of Reproductive Toxicology Data

1:00 PM–3:00 PM **The Effects of Water Fluoridation on Neurodevelopment and Other Health Outcomes Symposium**
(Joint with DNTS)

1:00 PM–3:00 PM **Neglected Diseases/Neglected Patients Symposium**

3:00 PM–3:30 PM **Break**

3:30 PM–4:30 PM **Poster Session 1**
Attended for Questions & Answers
Posters P1–P17

7:00 PM–9:00 PM **BDRP Trivia Night Social**
(Space is limited for this event)

Program Overview (continued)

All times listed in the agenda are Eastern Daylight Time (US).

Tuesday, June 29, 2021

10:00 AM–10:45 AM New and Prospective Member Meet and Greet

11:00 AM–12:30 PM Platform Session 2

11:00 AM–12:30 PM Platform Session 3

11:00 AM–12:30 PM Platform Session 4

12:30 PM–1:00 PM Break

1:00 PM–3:00 PM Cannabis in Pregnancy and Through Generations Symposium

1:00 PM–3:00 PM HESI Symposium
Nonclinical Considerations for Inclusion of Pregnant and Lactating Women in Clinical Trials

1:00 PM–3:00 PM Current Topics and Updates for Pregnancy Registries Workshop
(Joint with OTIS)

3:00 PM–3:30 PM Break

3:30 PM–4:30 PM Poster Session 2
Attended for Questions & Answers
Posters P18–P34

Wednesday, June 30, 2021

11:00 AM–12:00 Noon Innovator Award Finalists Platform Session 5

12:00 Noon–12:30 PM Warkany Tea

12:30 PM–1:00 PM Break

1:00 PM–3:00 PM Molecular Mechanisms of Fetal Alcohol Spectrum Disorders (FASD) in Humans and Animal Models Symposium
(Joint with DNTS)

1:00 PM–3:00 PM Refining Toxicology Testing to Detect Endocrine Disrupting Chemicals Symposium

3:00 PM–3:30 PM Break

3:30 PM–4:30 PM Poster Session 3
Attended for Questions & Answers
Posters P35–P51

4:30 PM–5:30 PM BDRP 40th Annual Volleyball Game, A Virtual NETworking Event

Thursday, July 1, 2021

11:00 AM–12:30 PM Transforming Women's Health Through Better Information on the Safety of Medications During Pregnancy and Lactation Symposium
(Joint with OTIS)

11:00 AM–12:30 PM Hot Topic Symposium
Assessing Reproductive Risks from Fracking and Mountaintop Mining

12:30 PM–1:00 PM Break

1:00 PM–3:00 PM New Frontiers in Developmental Toxicity Testing for Environmental Chemicals Workshop

3:00 PM–3:30 PM Break

3:30 PM–4:30 PM Annual Meeting Awards Presentation and Business Meeting

Education Courses

Thursday, July 15, 2021

11:00 AM–2:30 PM Education Course Session 1
Development and Disorders of the Gastrointestinal (GI) Tract
(Separate Registration Required)

Thursday, July 22, 2021

11:00 AM–2:30 PM Education Course Session 2
Craniofacial Morphogenesis and Teratogenesis
(Separate Registration Required)

Thursday, July 29, 2021

11:00 AM–1:00 PM Mini Course
Single-Cell RNA Sequencing in Understanding Normal and Abnormal Development
(Separate Registration Required)

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(as of May 17, 2021)

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Invitation from the President

PRESIDENT'S INVITATION TO THE 61ST ANNUAL MEETING

I am pleased to invite you to attend the 61st Annual Meeting of the Society for Birth Defects Research and Prevention, a fully online, virtual experience that will take place weekdays from June 24 to July 1, 2021, with three Education Courses scheduled later in July. We believe this meeting format is the safest approach for the well-being of our members and speakers, and we are excited that we can build on the successes and lessons learned through our impactful 2020 virtual meeting.

The Program Committee, chaired by Susan Makris, has put together an outstanding program around the meeting theme which is "Building Bridges in Birth Defects Research and Prevention: From Innovation to Application." The Keynote Lecture will be given by Carleigh Krubiner, Johns Hopkins Berman Institute of Bioethics. Dr. Krubiner's research focuses on ethical issues surrounding the equitable development and delivery of health interventions in low and middle-income settings. For the past several years, Dr. Krubiner has co-led work focusing on how epidemic vaccine development and deployment can be more responsive to the health interests of pregnant women, with more recent work focusing on COVID-19 vaccine R&D and distribution.

The 61st Annual Meeting program offers an exciting variety of scientific sessions on topics including:

- Approaches for Mechanistic Evidence Analysis in Hazard Evaluation of Reproductive Toxicology Data
- The Effects of Water Fluoridation on Neurodevelopment and Other Health Outcomes
- Neglected Diseases/Neglected Patients
- Cannabis in Pregnancy and Through Generations
- Nonclinical Considerations for Inclusion of Pregnant and Lactating Women in Clinical Trials
- Current Topics and Updates for Pregnancy Registries
- Refining Toxicology Testing to Detect Endocrine Disrupting Chemicals
- Transforming Women's Health Through Better Information on the Safety of Medications During Pregnancy and Lactation
- Assessing Reproductive Risks from Fracking and Mountaintop Mining
- New Frontiers in Developmental Toxicity Testing for Environmental Chemicals

Our virtual annual meeting will also include a Research Needs Workshop and a Professional Development Workshop plus several platform sessions, including the Graduate Student and Postdoctoral Fellow Platform and the Innovator Award Finalists Platform. This year the Poster Sessions will allow attendees to interact with poster authors in a face-to-face virtual setting so they can showcase their research and generate a discussion. As in previous years, the best trainee platform and poster presentations will be recognized with special awards.

Networking is a cornerstone of our annual meeting, and this year attendees will have more opportunities to partake in interactive and engaging experiences through a dynamic virtual platform, all while connecting from the comfort and safety of your home or office. In addition, our trainees and early career professionals will have an opportunity to learn more about our Society through mentorship.

The Education Committee, chaired by Christina Carruthers, has developed three exciting Education Courses pertaining to Craniofacial Morphogenesis and Teratogenesis, Development and Disorders of the Gastrointestinal Tract, and Single-Cell RNA Sequencing in Understanding Normal and Abnormal Development. These courses will take place on Thursdays throughout the month of July.

Thank you to our **Annual Meeting Sponsors** for their continued support of our meeting in its new virtual format. Their financial support has allowed us to use the best available technology for an enhanced, interactive meeting while keeping registration fees manageable for all participants. Additionally, I would like to thank our **Sustaining Members** for their continued support of the year-round operations of the Society.

Our Annual Meeting provides us with the opportunity to promote our shared vision and scientific identity as researchers focused on the causes, manifestations, intervention, and prevention of birth defects, both structural and functional. It is also a celebration of our scientific diversity as a Society of clinicians, scientists, and science policy regulators from academic, industrial, and government sectors, and an opportunity to bring a truly multidisciplinary perspective to important and emerging scientific issues. We hope you will join us online for what promises to be an informative and engaging virtual meeting!

Sincerely,
Elise Madison Lewis, PhD
Society for Birth Defects Research and Prevention President

General Information

AWARDS/LECTURES

Josef Warkany Lecturer

This lecture recognizes Josef Warkany's contributions to the Society for Birth Defects Research and Prevention. 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 over his/her career. This year's lecture will be presented by **Peter Wells**, University of Toronto. Dr. Wells will deliver the Josef Warkany Lecture during the virtual meeting on June 24, 2021.

Robert L. Brent Lecture

This lecture recognizes Robert L. Brent's contributions to the Society and particularly for 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. This year's Robert L. Brent Lecture will be presented by **Sonja A. Rasmussen**, University of Florida College of Medicine. Dr. Rasmussen will deliver the Robert L. Brent Lecture during the virtual meeting on June 24, 2021.

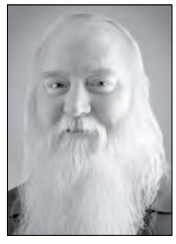
F. Clarke Fraser New Investigator Award

This award honors F. Clarke Fraser, one of the founding members of the Society, for his many contributions to the field of developmental toxicology. The award recipient must be an active member of the Society for Birth Defects Research and Prevention with evidence of a successful, independent research career in birth defects research. This year's award recipient is **Vijaya Kancherla**, Emory University. Dr. Kancherla will give her presentation during the virtual meeting on June 25, 2021.

James G. Wilson Publication Award

This award honors James G. Wilson, one of the founding Society members, and is presented in recognition of the best paper accepted or published in the journal *Birth Defects Research* during the prior year. The dual purpose of the award is to provide recognition to the author(s) 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 *Exploratory analysis of machine learning approaches for surveillance of Zika–associated birth defects*. *Birth Defects Research*, 112.18:1450–1460 (2021). **Richard Lusk**, Deloitte Consulting, LLP, **John Zimmerman**, Deloitte Consulting, LLP, and **Nicole M. Roth**, Centers for Disease Control and Prevention. Drs. Lusk, Zimmerman, and Roth will give their presentation during the virtual meeting on June 25, 2021.

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 past Council member of the Society for Birth Defects Research and Prevention. The purpose of the award is to recognize a mid-career individual who has demonstrated successful, independent research in neurobehavioral teratology, birth defects, or related fields; and has demonstrated a commitment to mentorship of students, postdoctoral fellows, young investigators, and/or trainees. This year's award recipient is **Michael T. Williams**, Cincinnati Children's Research Foundation. Dr. Williams will give his presentation during the virtual meeting on June 25, 2021.

Narsingh Agnish Fellowship

This award recognizes Narsingh Agnish's contributions to the Society, particularly the implementation of the Education Courses. The Narsingh Agnish Fellowship is awarded to a long-standing member who has made a major contribution to education in the field. This year's recipient is **Ronald Hood**, The University of Alabama. Dr. Hood will give his presentation during the virtual meeting on June 25, 2021.

Keynote Lecture

The Society is honored to have **Carleigh Krubiner** present the 2021 Keynote Lecture. Dr. Krubiner is a Policy Fellow at the Center for Global Development in Washington, DC, and associate faculty at the Johns Hopkins Berman Institute of Bioethics. Her research focuses on ethical issues surrounding the equitable development and delivery of health interventions in low and middle-income settings. For the past several years, Dr. Krubiner has co-led work focusing on how epidemic vaccine development and deployment can be more responsive to the health interests of pregnant women, with more recent work focusing on COVID-19 vaccine R&D and distribution. Dr. Krubiner will present *Pregnancy and the Perils of Precaution: Toward a New Paradigm for the Ethics of Including Pregnant People in Vaccine Research and Deployment* on June 28, 2021.

Distinguished Scholar Awards

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 our journal, *Birth Defects Research* .

2021 Award Recipients

De-Kun Li, MD, PhD, for research associated with A Systematic Review to Calculate Background Miscarriage Rates using Life Table Analysis; *BDRA*, 94.6: 417–423 (2012) and *In Utero* Exposure to Bisphenol-A and Anogenital Distance of Male Offspring, *Birth Defects Research–Part A*, 91.10: 867–872 (2011)

Marilyn H. Silva, PhD, DABT, and **Lauren Zeise**, PhD, for research associated with 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; *Birth Defects Research–Part B*, 104.2:71–89 (2015)

Society for Birth Defects Research and Prevention Innovator Award

This award recognizes innovative and translational research at the intersection of at least two of the following areas: basic science, new technologies, clinical research, policy, and outreach. The three finalists for this year's award are **Hao H. Chen**, who will present *Transcriptomic and Proteomic Profiling of Alternative Flame Retardant Exposures in Human Embryonic Stem Cell Neural Derivatives*; **Georgia G. Pitsava**, who will present *Exome Sequencing Findings in 115 Children with Annular Pancreas*; and **Philip J. Lupo**, who will present *Newborn Screening Analytes and Structural Birth Defects: Evaluating Novel Associations using a Phenotypic Spectrum Analysis*. The abstracts will be presented during the Innovator Award Finalist platform session in the virtual meeting on June 30, 2021.

Edward W. Carney Distinguished Service Award

This award honors Edward W. Carney, Past President of the Society for Birth Defects Research and Prevention, for his exemplary dedication and service to the Society and the field. This year's Edward W. Carney Distinguished Service Award recipient is **John M. Rogers**, US Environmental Protection Agency and ToxStrategies, Inc. Dr. Rogers' has demonstrated a long-term and unwavering commitment to birth defects research. He has over 100 peer reviewed papers; 40 book chapters and reviews; numerous achievement awards; and countless acknowledgements from peers for the vision, quality, and impact of his research. His knowledge and expertise are recognized not only by the US EPA, but also by other agencies and organizations, who seek his participation in scientific working groups and discussion panels. He has made it a tenet of his career to share insight, research findings, time, and energy with his fellow scientists and student members in the Society by participating in continuing education courses, developing and/or chairing symposia, and presenting lectures and posters at annual meetings.

Wilson Presentation Award

The Graduate Student/Postdoctoral Platform Session on June 24, 2021, showcases the work of eight students and postdoctoral fellows. The participants in this session were selected by the Student Affairs Committee from submitted abstracts. The presenters in this session will compete for the Wilson Presentation Award. This award was established in honor of James G. Wilson, one of the founding members of the 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.

HIGHLIGHTS

Poster Sessions

Electronic posters will be available online throughout the virtual meeting and for a period of time following the meeting. Virtual poster sessions will provide attendees with the opportunity to interact with poster presenters in real time. Virtual poster sessions are scheduled to take place Monday, June 28, Tuesday June 29, and Wednesday, June 30, from 3:30 pm to 4:40 pm Eastern (US).

Opportunities to Socialize and Network!

The virtual meeting platform will provide attendees ample opportunities to connect with other attendees. Daily microcommunities will provide a chance for small group networking, mentoring, and discussion. Poster Sessions will provide opportunities for face-to-face discussion with poster authors. In addition, the following special events are planned:

On Thursday, June 24 from 4:00 pm to 5:00 pm Eastern (US), join us for the virtual President's Welcome Reception.

On Monday, June 28 from 7:00 pm to 9:00 pm Eastern (US), the Student Affairs Committee will host a virtual Trivia Night. Space is limited for this event.

On Tuesday, June 29 at 10:00 am Eastern (US), new and prospective members are encouraged to attend a Meet and Greet hosted by the Membership Committee to network and learn more about the Society and ways to get involved.

On Wednesday, June 30 from 12:00 noon to 12:30 pm Eastern (US), break out your favorite mug as we gather to celebrate the Society's virtual Warkany Tea.

On Wednesday, June 30 from 4:30 pm to 5:30 pm Eastern (US), join us for the BDRP 40th Annual Volleyball Game, A Virtual NETworking Event, a creative twist on the Society's Annual Volleyball Game, now in its 40th year!

On Thursday, July 1 from 3:30 pm to 4:30 pm Eastern (US), attend the Awards Presentation and Annual Business Meeting to find out who won this year's BDRP Innovator Award and trainee awards and to learn about the business of your scientific society!

Make sure to use your smartphone or a computer outfitted with a webcam and microphone for these special events!

Program Agenda

All times listed in the agenda are Eastern Daylight Time (US).

Thursday, June 24, 2021

11:00 AM–11:10 AM **President's Welcome**

BDRP President, Elise Madison Lewis, Charles River Laboratories

11:10 AM–11:45 AM **Josef Warkany Lecture (L1)**

Reactive Oxygen Species and DNA Damage/Repair in Developmental Disorders

Chairperson: Elise Madison Lewis, Charles River Laboratories

Lecturer: Peter Wells, University of Toronto

11:45 AM–12:30 PM **Robert L. Brent Lecture—Teratogen Update (L2)**

Identifying New Human Teratogens: Revisiting Shepard's Criteria

Chairperson: Elise Madison Lewis, Charles River Laboratories

Lecturer: Sonja A. Rasmussen, University of Florida College of Medicine

12:30 PM–1:00 PM **Break**

1:00 PM–3:30 PM **Graduate Student and Postdoctoral Fellow Platform Session 1**

Organized by the Student Affairs Committee

Chairpersons: Paul B. Bushdid, Covance Laboratories Inc. and Laura Carlson, US Environmental Protection Agency

Presenting author is underlined.

1:00 PM–1:05 PM		**Introduction**
1:06 PM–1:24 PM	**1**	**Enhanced Ethanol-initiated, Reactive Oxygen Species-dependent Embryopathies in Breast Cancer 1 (Brca1) Knockout Mouse Embryos in Culture** *Afsharian K, Wells PG. University of Toronto, Toronto, ON, Canada*
1:24 PM–1:42 PM	**2**	**COVID-19 and Its Effects on the Newborn: A Rapid Review of Available Data** *Valladares DA, Kramer EF, Powell MM, Pomputius A, Rasmussen SA. University of Florida, Gainesville, FL, United States*

Thursday

1:42 PM–2:00 PM	**3**	**The Effects of Bisphenols on Endochondral Ossification in Murine Limb Bud Cultures** *Iskandarani L[1], Hales BF[2], Robaire B[2]. [1]Department of Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada*
2:00 PM–2:18 PM	**4**	**A Novel Molecular Basis for Breast Cancer 1 Protein (BRCA1) Protection of the Fetal Brain from Developmental Disorders Mediated by Reactive Oxygen Species** *Drake DM, Wells PG. University of Toronto, Toronto, ON, Canada*
2:18 PM–2:36 PM	**5**	**Evaluation of Viral Entry and Cellular Passage of Zika Virus Immune Complexes in a Tissue Culture Model of the Maternal-Fetal Interface** *Momben Abolfath S, Xu Y, He Y, Eller N, Norton M, Struble E. US Food and Drug Administraition, Silver Spring, MD, United States*
2:36 PM–2:54 PM	**6**	**Exploring Airshed and Watershed Exposure Pathways as Mediators of the Association between Proximity to Surface Mining and Adverse Birth Outcomes in Central Appalachia** *Ruktanonchai CW[1], McKnight M[2], Marr L[1], Krometis L-A[1], Buttling L[2], Ranganathan S[1], Kolivras K[1], Gohlke J[1]. [1]Virginia Tech, Blacksburg, VA, United States, [2]Mitre, McLean, VA, United States*
2:54 PM–3:12 PM	**7**	**Sex and Strain-Dependent Effects of Prenatal Alcohol Exposure on Craniofacial and Brain Development in Mice** *Boschen KE, Fish EW, Cannizzo MD, Dragicevich CJ, Peterson RL, Steensen MC, Parnell SE. University of North Carolina, Chapel Hill, NC, United States*
3:12 PM–3:30 PM	**8**	**Standardization and Validation of a Scalable Human Neural Rosette Microarray Assay for Assessment of Neural Tube Defect Risk and Developmental Neurotoxicity** *Knight GT, Fedorchak N, Lundin B, Ashton RS. University of Wisconsin, Madison, WI, United States*

3:30 PM–4:00 PM **Break**

4:00 PM–5:00 PM **President's Welcome Social**

Friday, June 25, 2021

11:00 AM–11:30 AM **F. Clarke Fraser New Investigator Award (L3)**

Consequentialist Epidemiology of Birth Defects: Early Career Experiences and Key Findings from National and Global Research

Chairperson: Philip Lupo, Baylor College of Medicine

Lecturer: Vijaya Kancherla, Emory University

11:30 AM–12:00 Noon **James G. Wilson Publication Award**

Exploratory analysis of machine learning approaches for surveillance of Zika–associated birth defects

Chairperson: Russell S. Kirby, USF College of Public Health

Lecturers: Richard Lusk, Deloitte Consulting, LLP; John Zimmerman, Deloitte Consulting, LLP; and Nicole M. Roth, Centers for Disease Control and Prevention

12:00 Noon–12:30 PM **Patricia Rodier Mid-Career Award for Research and Mentoring (L4)**

Manganese Overexposure during Development: Environmental and Genetic Effects
(Joint with DNTS)

Chairpersons: Philip Lupo, Baylor College of Medicine and Sonia Minnes, Case Western Reserve University

Lecturer: Michael T. Williams, Cincinnati Children's Research Foundation

12:30 PM–1:00 PM **Agnish Fellowship Lecture (L5)**

Education, Service, and Career Paths in the Multidisciplinary Science of Birth Defects Causation and Prevention
Chairperson, Christina M. Carruthers, Janssen Pharmaceuticals

Lecturer: Ronald Hood, The University of Alabama

1:00 PM–1:30 PM **Break**

1:30 PM–3:00 PM **Multidisciplinary Research Needs Workshop**

Chairpersons: Dana L. Shuey, Incyte and William Slikker Jr., National Center for Toxicological Research, US FDA

1:30 PM–1:45 PM	**Overview of Workshop Goals and Progress**
1:45 PM–2:25 PM	**Concurrent Breakout Sessions**
2:25 PM–3:00 PM	**Reassemble to Discuss Progress from Breakout Sessions**

1:30 PM–3:00 PM **Professional Development Workshop**

Organized by the Membership Committee and Student Affairs Committee

Chairpersons: Paul B. Bushdid, Covance Laboratories Inc. and Deirdre K. Tucker, Charles River Laboratories

1:30 PM–1:35 PM	**Introduction** *Paul B. Bushdid, Covance Laboratories Inc.*
1:35 PM–1:55 PM	**Career Options for Trainees** *Tacey E.K. White, Aclairo Pharmaceutical Development Group, Inc.*
1:55 PM–2:15 PM	**Changing Professional Paths Mid-Career** *Christine Perdan Curran, Northern Kentucky University*
2:15 PM–2:35 PM	**Balancing Career and Family** *Terry C. Hrubec, E. Via Virginia College of Osteopathic Medicine*
2:35 PM–2:55 PM	**Career Challenges** *Ida M. Washington, West Virginia University*
2:55 PM–3:00 PM	**Closing Remarks**

Monday, June 28, 2021

11:00 AM–11:45 AM **Keynote Lecture (L6)**

Pregnancy and the Perils of Precaution: Toward a New Paradigm for the Ethics of Including Pregnant People in Vaccine Research and Deployment
(Joint with OTIS)

Chairperson: Susan L. Makris, US Environmental Protection Agency

Speaker: Carleigh Krubiner, Center for Global Development and Johns Hopkins Berman Institute of Bioethics

11:45 AM–12:30 PM **BDRP and European Teratology Society (ETS) Exchange Lecture**

Covid-19 in Pregnancy and Lactation: US and European Perspectives on Research and Public Health
(Joint with OTIS)

Chairpersons: Susan Makris, US Environmental Protection Agency and Manon Beekhuijzen, Charles River

BDRP
Christina D. Chambers, University of California San Diego

ETS
David Baud, Centre Hospitalier Universitaire Vaudois (CHUV)

12:30 PM–1:00 PM **Break**

1:00 PM–3:00 PM **Wiley Symposium**

Approaches for Mechanistic Evidence Analysis in Hazard Evaluation of Reproductive Toxicology Data
Chairpersons: Xabier Arzuaga, US Environmental Protection Agency and Erin Yost, US Environmental Protection Agency

1:00 PM–1:05 PM		**Introduction** *Xabier Arzuaga, US Environmental Protection Agency*
1:05 PM–1:25 PM	**S1**	**The Hazards of Endocrine Disrupting Chemicals Partially Overlap with the Hazards of Reproductive Toxicants** *Michele La Merrill, University of California, Davis*
1:25 PM–1:45 PM	**S2**	**A New Approach Methods-Based Integrated Assessment of Estrogenicity of Alkylphenols** *Fabian Grimm, ExxonMobil Biomedical Sciences, Inc.*
1:45 PM–2:05 PM	**S3**	**Application of Key Characteristics in Support of Identifying Chemicals with Reproductive Hazard Traits** *Lauren Zeise and Francisco Moran, California Environmental Protection Agency*
2:05 PM–2:25 PM	**S4**	**Application of the Key Characteristics Approach to Female Reproductive Hazard Identification: Benzo[a]pyrene as a Case Example** *Ulrike Luderer, University of California, Irvine*
2:25 PM–2:45 PM	**S5**	**Applying the Key Characteristics Approach to Evaluate Mechanistic Evidence for Qualitative and Quantitative Weight of Evidence to Support Risk Assessment: A Case Study with Benzo[a]Pyrene-Induced Male Reproductive Toxicity** *Ingrid Druwe US Environmental Protection Agency*
2:45 PM–3:00 PM		**Discussion**

1:00 PM–3:00 PM **The Effects of Water Fluoridation on Neurodevelopment and Other Health Outcomes Symposium**
(Joint with DNTS)

Chairpersons: Kembra L. Howdeshell, National Institute of Environmental Health Sciences and Kyla Taylor, National Institute of Environmental Health Sciences

1:00 PM–1:05 PM		**Introduction** *Kembra L. Howdeshell, National Institute of Environmental Health Sciences*
1:05 PM–1:30 PM	**S6**	**Fluoride Intake and Exposure and Oral Health Effects** *E. Angeles Martinez Mier, Indiana University School of Dentistry*
1:30 PM–1:55 PM	**S7**	**Early-Life Exposures to Fluoride and Child Neurodevelopmental Outcomes** *Christine Till, York University*
1:55 PM–2:20 PM	**S8**	**Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects** *Kyla Taylor, National Institute of Environmental Health Sciences*
2:20 PM–2:45 PM	**S9**	**Fluoride Exposure and Neuroendocrine Outcomes among Youth in the United States** *Ashley Malin, Keck School of Medicine, University of Southern California*
2:45 PM–3:00 PM		**Discussion**

1:00 PM–3:00 PM **Neglected Diseases/Neglected Patients Symposium**

Chairpersons: Jane Stewart, Apconix, Melissa S. Tassinari, Consultant, and Belen Tornesi, Medicine for Malaria Medicine

1:00 PM–1:05 PM		**Introduction** *Melissa S. Tassinari, Consultant*
1:05 PM–1:30 PM	**S10**	**Global Efforts for Eradication of Malaria: A Focus on Pregnant and Lactating Women** *Belen Tornesi, Medicine for Malaria Medicine*
1:30 PM–1:55 PM	**S11**	**The Use of a Humanized Mouse Model to Assess Antimalarial Efficacy and Identify Optimal Drugs Combinations** *Claudia Demarta-Gatsi, Medicines for Malaria Venture*
1:55 PM–2:20 PM	**S12**	**Working in Operationally Challenging Situations: How Do We Get Malarial Drugs to Pregnant Women in the Real World?** *Bhargavi Rao, Médecins Sans Frontières (MSF) UK*
2:20 PM–2:45 PM	**S13**	**Above All Do No Harm: How Can Pregnancy Outcomes for Malarial Patients Be Monitored and How Can Benefit-Risk Be Assessed?** *Stephanie Dellicour, Liverpool School of Tropical Medicine*
2:45 PM–3:00 PM		**Discussion**

3:00 PM–3:30 PM **Break**

3:30 PM–4:30 PM **Poster Session 1**

Attended for Questions & Answers
Posters P1–P17

7:00 PM–9:00 PM **BDRP Trivia Night Social**

Organized by the Student Affairs Committee

(Space is limited for this event)

Tuesday, June 29, 2021

10:00 AM–10:45 AM **New and Prospective Member Meet and Greet**

Organized by the Membership Committee

11:00 AM–12:30 PM **Platform Session 2**

Chairpersons: Maia M. Green, ExxonMobil Biomedical Sciences, Inc. and Kristal A. Rychlik, Johns Hopkins University Bloomberg School of Public Health

Presenting author is underlined.

11:00 AM–11:15 AM **9** **Tracking Development in the First Two Years of Life Among Children with Possible Congenital Zika Virus Exposure: 50 US States and the District of Columbia**

Neelam V[1], Woodworth K[1], Chang DJ[1], Roth NM[1], Reynolds MR[1], Tong VT[1], Anderson K[1], Mulkey SB[2], DeBiasi OO[2], Biddle C[2], Lee EH[3], Lash MK[3], Godred-Cato S[1], Gilboa SM[1], Honein MA[1], Moore CA[1]. [1]Centers for Disease Control, Atlanta, GA, United States, [2]Children's National Hospital, Washington, DC, United States, [3]New York City Department of Health and Mental Hygiene, Long Island City, NY, United States

11:15 AM–11:30 AM **10** **Risk of Birth Defects by Pregestational Type 1 or Type 2 Diabetes: National Birth Defects Prevention Study, 1997–2011**

Marchincin SL[1], Howley MM[2], Van Zutphen AR[2], Fisher SC[2], Nestoridi E[3], Tinker S[4], Browne ML[2]. [1]New York State Department of Health, Buffalo, NY, United States, [2]New York State Department of Heath, Albany, NY, United States, [3]Massachusetts Center for Birth Defects Research and Prevent, Department of Public Health, Boston, MA, United States, [4]National Center on Birth Defects and Developmental Disabilities; CDC, Atlanta, GA, United States

11:30 AM–11:45 AM **11** **Co-Occurring Birth Defects in Children with Nonsyndromic Microtia**

Schraw JM[1], Benjamin RH[2], Scott DA[3], McLean SD[4], Northrup H[5], Langlois PH[6], Canfield MA[6], Scheuerle AE[7], Schaaf OO[1], Ray, JW[8], Chen H[9], Swartz MD[10], Agopian AJ[11], Lupo PJ[12]. [1]Baylor College of Medicine, Houston, TX, United States, [2]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States, [3]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, Houston, TX, United States, [4]Baylor College of Medicine, San Antonio, TX, United States, [5]University of Texas Health Science Center at Houston, Houston, TX, United States, [6]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, United States, [7]Department of Pediatrics, Division of Genetics and Metabolism, University of Texas Southwestern Medical Center, Dallas, TX, United States, [8]University of Texas Medical Branch, Galveston, TX, United States, [9]Center for Precision Health, UTHealth School of Public Health and UTHealth School of Biomedical Informatic, Houston, TX, Unites States, [10]Department of Biostatistics and Data Science, UTHealth School of Public Health, Houston, TX, Unites States, [11]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX United States, [12]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX, United States

11:45 AM–12:00 Noon **12** **The Association between the Occurrence of Gastroschisis and Maternal Chlamydia Infection among Cases in the Texas Birth Defects Registry, 2013–2017**

Shumate CJ[1], Russell K[2], Navarro Sanchez ML[3], Le M[1], Canfield MA[4]. [1]Texas Department of State Health Services, Austin, TX, United States, [2]Maternal and Child Health Epidemiology, Texas Department of State Health Services, Austin, TX, United States, [3]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States, [4]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, United States

12:00 Noon–12:15 PM **13** **Maternal Vitamin D Status and Risk of Select Birth Defects in the National Birth Defects Prevention Study (1997–2011)**

Adrien N[1], Yazdy M[2], Nestoridi E[2], Carmichael SL[3], Orta OR[4]. [1]Department of Epidemiology, Boston University School of Public Health, Boston, MA, United States, [2]Massachusetts Center for Birth Defects Research and Prevent, Department of Public Health, Boston, MA, United States, [3]Department of Pediatrics and Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, United States, [4]Boston University School of Public Health, Department of Epidemiology, Boston, MA, United States

12:15 PM–12:30 PM **14** **Unique Clusters of Sudden Unexpected Infant Death (SUID) Decedents Revealed Through Machine Learning Epidemiological Analyses**

Blackburn J[1], Chapur VF[2], Stephens JA[3], Zhao J[3], Shepler A[4], Pierson CR[5], Otero JJ[6]. [1]The Ohio State University, Columbus, OH, United States, [2]Instituto de Ecoregiones Andinas (INECOA)/ Consejo Nacional de investigaciones científicas y técnicas, San Salvador de Jujuy, Argentina, [3]The Ohio State University, Center for Biostatistics, Columbus, OH, United States, [4]Franklin County Forensic Science Center, Columbus, OH, United States, Nationwide Children's Hospital, Department of Pathology and Laboratory Medicine, Columbus, OH, United States, [6]The Ohio State University, Department of Pathology, Division of Neuropathology, Columbus, OH, United States

11:00 AM–12:30 PM Platform Session 3

Chairpersons: William Slikker Jr., National Center for Toxicological Research, US FDA and Bevin Blake, National Institute of Environmental Health Sciences

Presenting author is underlined.

11:00 AM–11:15 AM **15** ***In Vitro* to *In Vivo* Extrapolation for Developmental Toxicity Potency of Valproic Acid Analogues**

Chang X[1], Kleinstreuer NC[2], Casey WM[3], Allen DG[4], Ceger P[4], Bell S[4], Mansouri K[2], Palmer J[5], Donley OO[5], Lumen A[6], Lee UJD[7]. [1]Integrated Laboratory Systems, LLC, Morrisville, NC, United States, [2]NIH/NIEHS/ DNTP/NICEATM, Research Triangle Park, NC, United States, [3]NIH/ NIEHS/DNTP, Research Triangle Park, NC, United States, [4]Integrated Laboratory Systems, LLC, Morrisville, NC, United States, [5]Stemina Biomarker Discovery Inc., Madison, WI, United States, [6]US FDA/ NCTR, Jefferson, AR, United States, [7]Albert Einstein College of Medicine, Bronx, NY, United States

11:15 AM–11:30 AM **16** **Does Nrf2 Play a Role in the Developmental Toxicity of the Sulfate Metabolite of3,3'-dichlorobiphenyl(PCB-11)**

Roy MA, Gridley CK, Li S, Park Y, Timme-Laragy AR. University of Massachusetts Amherst, Amherst, MA, United States

Tuesday

11:30 AM–11:45 AM **17** **A Data-Driven Model Analysis of Retinoid Signaling in Skeletal Dysmorphogenesis and Potential Adverse Outcome Pathways**
Pierro JD[1], Baker NC[2], Richard AM[1], Kleinstreuer NC[3], Knudsen TB[1]. [1]US EPA, Research Triangle Park, NC, United States, [2]Leidos, Research Triangle Park, NC, United States, [3]NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, NC, United States

11:45 AM–12:00 Noon **18** **The Effects of Low Dose Cadmium on Mouse Embryo Vascular Development *In Vitro***
Erwin NJ[1], Liu J[2], Kapron CM[3]. [1]Environmental & Life Sciences, Peterborough, ON, Canada, [2]Shandong University / School of Medicine, Jinan, China, [3]Trent University, Peterborough, ON, Canada

12:00 Noon–12:15 PM **19** **Transcriptome Analysis Reveals Toxicant-Induced miRNA Signatures Associated with Aberrant Human Embryonic Stem Cell Osteoblast Differentiation**
Sparks NRL[1], Williams D[2], zur Nieden NI[1]. [1]University of California, Riverside, Riverside, CA, United States, [2]Department of Molecular, Cell, and Systems Biology, College of Natural and Agricultural Sciences, Riverside, CA, United States

12:15 PM–12:30 PM **20** **ReproTracker: A Human Stem Cell-Based Biomarker Assay for *In Vitro* Assessment of Developmental Toxicity**
Jamalpoor A, Hartvelt S, Zwetsloot T, Ghoussain N, Osterlund T, Hendriks G. Toxys B.V., Leiden, Netherlands

11:00 AM–12:30 PM Platform Session 4

Chairpersons: Barbara F. Hales, McGill University and Madhumita Basu, Nationwide Children's Hospital

Presenting author is underlined.

11:00 AM–11:15 AM **21** **Effects of Bisphenol A and Bisphenol AF on the Murine Limb Bud Transcriptome**
McHattie TJ[1], Iskandarani L[1], Robaire B[1,2], Hales BF[1]. [1]Department of Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada; [2]Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada

11:15 AM–11:30 AM **22** **A New Entity: Vascular-Induced Skeletal Dystrophisms of the Lower Limb**
Hootnick D[1], DeSesso JM[2]. [1]SUNY Upstate Medical University, Syracuse, NY, United States, [2]Exponent and Georgetown University School of Medicine, Alexandria, VA, United States

11:30 AM–11:45 AM **23** **Alteration of the Expression of Proteins Associated with Radical Glial Scaffold Development in Ethanol-Exposed Forebrain Organoids Derived from Human Embryonic Stem Cells**
Chen S-y[1], Lu L[1], Yuan F[1], Liu J[1], Wilkey DW[2], Merchant ML[2]. [1]Department of Pharmacology and Toxicology, University of Louisville Health Science Center, Louisville, KY, United States, [6]Department of Medicine, University of Louisville Health Science Center, Louisville, KY, United States

11:45 AM–12:00 Noon **24** **Using Live Imaging and FUCCI ESC to Provide QC for a DevTox HTS and to Define Stressful Doses of PFOA and DEP**
Rappolee DA[1], Abdulhasan M[1], Ruden X[1], You Y[1], Harris S[2], Ruden D[1], Awonuga A[1], Alvero A[1], Puscheck O[1]. [1]Wayne State University, Detroit, MI, United States, [2]University of Michigan, Ann Arbor, MI, United States

12:00 Noon–12:15 PM **25** **Aryl Hydrocarbon Receptor Mediated Disruption of Dopaminergic and Serotonergic Signaling in the Hippocampus and Prefrontal Cortex of Mice Exposed to Benzo[a]pyrene during Development**
Foster E, Clough K, Curran CP. Northern Kentucky University, Highland Heights, KY, United States

12:15 PM–12:30 PM **26** **Exposure to Flame Retardants and Surfactants *In Utero* and Biomarkers of Human Placental Development and Disease**
Varshavsky J[1], Robinson JF[1], Zhou Y[1], Puckett K[1], Buarpung S[1], Aburajab R[1], Gaw S[1], Sen O[2], Crispo Smith S[3], Frankenfield J[3], Park J-S[3], Fisher S[1], Woodruff T[1]. [1]University of California, San Francisco, San Francisco, CA, United States, [2]The University of Tennessee Health Science Center, Memphis, TN, United States, [3]Department of Toxic Substances Control, Berkeley, CA, United States

12:30 PM–1:00 PM **Break**

1:00 PM–3:00 PM **Cannabis in Pregnancy and Through Generations Symposium**

Organized by the Public Affairs Committee

Chairpersons: Poorni R. Iyer, California EPA and Marlissa Campbell, California EPA

1:00 PM–1:05 PM **Introduction**
Poorni R. Iyer, California EPA and Marlissa Campbell, California EPA

1:05 PM–1:30 PM **S14** **A Review of Epidemiological Evidence in Humans of the Effects of Prenatal Exposure to Cannabis (Smoke and Δ9-THC).**
Farla Kaufman, California EPA

1:30 PM–1:55 PM **S15** **A Clinical Perspective on Cannabis Use During Pregnancy**
Torri Metz, University of Utah Health

1:55 PM–2:20 PM **S16** **Perinatal Exposure to Δ9-tetrahydrocannabinol Alters Immune Functions in Fetal and Postnatal Stages of Life: Role of Epigenetic Pathways**
Prakash Nagarkatti, University of South Carolina School of Medicine

2:20 PM–2:45 PM **S17** **Epigenetic Effects of Cannabis on the Developing Brain**
Anissa Bara, Icahn School of Medicine at Mount Sinai

2:45 PM–3:00 PM **Discussion**

1:00 PM–3:00 PM **HESI Symposium**

Nonclinical Considerations for Inclusion of Pregnant and Lactating Women in Clinical Trials

Chairpersons: Kary Ellen Thompson, Janssen Pharmaceuticals and Dinesh J. Stanislaus, GlaxoSmithKline

1:00 PM–1:05 PM **Introduction**
Kary Ellen Thompson, Janssen Pharmaceuticals

1:05 PM–1:30 PM **S18** **The Time Is Now: Why We Must Include Pregnant and Lactating Women in Drug Development**
Belen Tornesi, Medicine for Malaria Medicine

1:30 PM–1:55 PM **S19** **Nonclinical Evaluation of Medicines Used in Pregnancy/Lactation: Looking Back to Move Forward**
Dinesh J. Stanislaus, GlaxoSmithKline

1:55 PM–2:20 PM **S20** **Considerations for Evolution of the Nonclinical Toxicology Paradigm to Enable Clinical Trials in Pregnant/Lactating Patients**
Kary Ellen Thompson, Janssen Pharmaceuticals

Tuesday

2:20 PM–2:45 PM **S21** **Making Nonclinical Data Meaningful: Communicating Data and Risk Assessment with HCP and Women**
Wendy Halpern, Genentech

2:45 PM–3:00 PM **Discussion**

1:00 PM–3:00 PM **Current Topics and Updates for Pregnancy Registries Workshop**
(Joint with OTIS)

Chairpersons: Lewis B. Holmes, MassGeneral Hospital for Children and Keele Elise Wurst, GlaxoSmithKline

1:00 PM–1:05 PM **Introduction**

1:05 PM–1:25 PM **W1** **Criteria Used for Classifying Abnormalities Identified in the Antiretroviral Pregnancy Registry**
Angela Scheuerle, UT Southwestern Medical Center

1:25 PM–1:45 PM **W2** **The Inclusion/Exclusion Criteria Used by the North American Antiepileptic Drug (AED) Pregnancy Registry**
Lewis B. Holmes, MassGeneral Hospital for Children

1:45 PM–2:05 PM **W3** **An Update on the Use of Social Media to Recruit Pregnant People into Pregnancy Registries**
Nicole Chavez, Nicole Chavez Public Relations

2:05 PM–2:25 PM **W4** **Trends in Antiepileptic Drug Use and individual Treatment Pattern during the First Trimester of Pregnancy: An Evaluation of the German Embryotox Cohort**
Hoeltzenbein M, Slimi S, Fietz AK, Onken M, Dathe K, Schaefer C. Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt Universität zu Berlin, and Berlin Institute of Health, Institut für Klinische Pharmakologie und Toxikologie, Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie, Berlin, Germany

2:25 PM–2:45 PM **W5** **The Development of a Belgian Prospective Data Registration System on Perinatal Medication Use and Mother-Infant Outcomes: An Introduction to the BELpREG Initiative**
Sillis L[1], Ceulemans M[1], Van Calsteren K[2,3], Smits A[3,4], Hompes T[5,6], Bogaerts A[3,7,8], Allegaert K[1,3,9], De Vos M[3,10], Verbakel JY[11,12], Foulon V[1]. [1]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Belgium, [2]Department of Obstetrics and Gynecology, University Hospitals Leuven Gasthuisberg, Belgium, [3]Department of Development and Regeneration, KU Leuven, Belgium, [4]Department of Pediatrics and Neonatology, University Hospitals Leuven Gasthuisberg, Belgium, [5]Adult Psychiatry UPC, KU Leuven, Belgium, [6]Department of Neurosciences, KU Leuven, Belgium, [7]Faculty of Medicine and Health Sciences, University of Antwerp, Belgium, [8]Faculty of Health, University of Plymouth, Devon, United Kingdom, [9]Department of Clinical Pharmacy, Erasmus MC Sophia's Children Hospital, the Netherlands, [10]Department of Electrical Engineering (ESAT), KU Leuven, Belgium, [11]Department of Public Health and Primary Care, KU Leuven, Belgium, [12]Nuffield Department of Primary Care Health Sciences, University of Oxford, United Kingdom

2:45 PM–3:00 PM **Discussion**

3:00 PM–3:30 PM **Break**

3:30 PM–4:30 PM **Poster Session 2**

Attended for Questions & Answers
Posters P18–P34

Wednesday, June 30, 2021

11:00 AM–12:00 Noon **Innovator Award Finalists Platform Session 5**

Chairperson: Kembra L. Howdeshell, National Institute of Environmental Health Sciences

Presenting author is underlined.

11:00 AM–11:20 AM **27** **Transcriptomic and Proteomic Profiling of Alternative Flame Retardant Exposures in Human Embryonic Stem Cell Neural Derivatives**

Chen H[1], Robinson JF[1], Jigmeddagva U[1], Williams KE[1], Hunter CL[2], Yan CD[1], Iyer NS[1]. [1]University of California, San Francisco, San Francisco, CA, United States, [2]SCIEX, San Francisco, CA, United States

11:20 AM–11:40 AM **28** **Exome Sequencing Findings in 115 Children with Annular Pancreas**

Pitsava G[1], Pankratz N[2], Lane J[2], Yang W[3], Rigler S[4], Shaw GM[5], Mills JL[1]. [1]NICHD, NIH, Bethesda, MD, United States, [2]Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, MN, United States, [3]Department of Pediatrics, Stanford University School of Medicine, Standford, CA, United States, [4]Department of Neonatology, Naval Medical Center Portsmouth, Portsmouth, VA, United States, [5]Standford University School of Medicine, Standford, CA, United States

11:40 AM–12:00 Noon **29** **Newborn Screening Analytes and Structural Birth Defects: Evaluating Novel Associations using a Phenotypic Spectrum Analysis**

Lupo PJ[1], Archer NP[2], Marengo LK[2], Hoyt AT[2], Drummond-Borg M[2], Freedenberg D[2], Langlois PH[3], Canfield MA[3]. [1]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX, United States, [2]Texas Department of State Health Services, Austin, TX, United States, [3]Birth Defects Epidemiology and Surveillance, Texas Department of State Health Services, Austin, TX, United States

12:00 Noon–12:30 PM **Warkany Tea**

12:30 PM–1:00 PM **Break**

1:00 PM–3:00 PM **Molecular Mechanisms of Fetal Alcohol Spectrum Disorders (FASD) in Humans and Animal Models Symposium**

(Joint with DNTS)

Chairpersons: Peter G. Wells, University of Toronto and Rajesh C. Miranda, Texas A&M Health Science Center

1:00 PM–1:05 PM **Introduction**

Peter G. Wells, University of Toronto

1:05 PM–1:30 PM **S22** **Oxidative DNA Damage and Repair and Epigenetic Mechanisms in Fetal Alcohol Spectrum Disorders (FASD)**

Peter G. Wells, University of Toronto

1:30 PM–1:55 PM **S23** **Epigenetic Mechanisms: Endocrine miRNAs in Pregnant Women, Predictive of FASD Infant Outcomes, Inhibit Placental Maturation, and Result in Fetal Growth Restriction**

Rajesh C. Miranda, Texas A&M Health Science Center

1:55 PM–2:20 PM **S24** **Neural Stem Cell Modeling of FASD: Mouse Strain- and Sex-dependent Effects of Alcohol on DNA Methylation**

Mojgan Rastegar, University of Manitoba

2:20 PM–2:45 PM **S25** **Transcriptomic Analyses Identify Genetic Modifiers of Adult Cardiometabolic Disease Risk in Zebrafish Following Embryonic Alcohol Exposure**

Wolfram Goessling, Brigham and Women's Hospital, Harvard Medical School

2:45 PM–3:00 PM **Discussion**

Wednesday

1:00 PM–3:00 PM **Refining Toxicology Testing to Detect Endocrine Disrupting Chemicals Symposium**

Chairpersons: Kembra L. Howdeshell, National Institute of Environmental Health Sciences and Heather B. Patisaul, North Carolina State University

1:00 PM–1:05 PM		**Introduction** *Kembra L. Howdeshell, National Institute of Environmental Health Sciences*
1:05 PM–1:30 PM	**S26**	**Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA): Findings and Considerations for Future Guideline Toxicity Testing of Endocrine Disrupting Chemicals** *Kembra L. Howdeshell, National Institute of Environmental Health Sciences*
1:30 PM–1:55 PM	**S27**	**Detecting Endocrine Disruption of Brain and Behavior** *Heather B. Patisaul, North Carolina State University*
1:55 PM–2:20 PM	**S28**	**Validation of *In Vitro* Thyroid Mechanistic Methods Based on the Organization of Economic Co-operation and Development Scoping Document** *Sandra Coecke, European Commission*
2:20 PM–2:45 PM	**S29**	**Case-Study Applications Using Evidence-Based Approaches to Assess Endocrine Activity for Risk Assessment** *Daniele Wikoff, ToxStrategies, Inc.*
2:45 PM–3:00 PM		**Discussion**

3:00 PM–3:30 PM **Break**

3:30 PM–4:30 PM **Poster Session 3**

Attended for Questions & Answers
Posters P35–P51

4:30 PM–5:30 PM **BDRP 40th Annual Volleyball Game, A Virtual NETworking Event**

Thursday, July 1, 2021

11:00 AM–12:30 PM **Transforming Women's Health Through Better Information on the Safety of Medications During Pregnancy and Lactation Symposium**
(Joint with OTIS)

Chairpersons: Janet R. Hardy, Biohaven Pharmaceuticals and Elizabeth A. Conover, University of Nebraska Medical Center

11:00 AM–11:05 AM		**Introduction** *Elizabeth A. Conover, University of Nebraska Medical Center*
11:05 AM–11:25 AM	**S30**	**Overview of PRGLAC** *Leyla Sahin, US Food and Drug Administration*
11:25 AM–11:45 AM	**S31**	**Introduction to the ConcePTION Initiative** *Marie Teil, UCB Biopharma*
11:45 AM–12:05 PM	**S32**	**PRGLAC: Data Gaps and Strategies** *Janet R. Hardy, Biohaven Pharmaceuticals*
12:05 PM–12:30 PM		**Discussion** *Melissa S. Tassinari, Consultant*

11:00 AM–12:30 PM **Hot Topic Symposium**

Assessing Reproductive Risks from Fracking and Mountaintop Mining
Chairpersons: Christine Perdan Curran, Northern Kentucky University and Philip Lupo, Baylor College of Medicine

11:00 AM–11:05 AM		**Introduction** *Philip Lupo, Baylor College of Medicine*
11:05 AM–11:20 AM	**S33**	**Intensity of Oil and Gas Well Site Activities in Early Pregnancy and the Risk of Structural Birth Defects** *Lisa McKenzie, Colorado School of Public Health*
11:20 AM–11:35 AM	**S34**	**Drinking Water Vulnerability and Neonatal Health Outcomes in Relation to Oil and Gas Production in the Appalachian Basin** *Nicole Deziel, Yale University School of Public Health*
11:35 AM–11:50 AM	**S35**	**Using Animal Studies to Understand Reproductive Risks Associated with Inhalation Exposures to Particles** *Timothy Nurkiewicz, West Virginia University*
11:50 AM–12:05 PM	**S36**	**Fuel for Thought: Summing Up the Risks from Unconventional Energy Extraction** *Christine Perdan Curran, Northern Kentucky University*
12:05 PM–12:30 PM		**Discussion**

12:30 PM–1:00 PM **Break**

1:00 PM–3:00 PM **New Frontiers in Developmental Toxicity Testing for Environmental Chemicals Workshop**

Organized by the Science Committee

Chairpersons: Thomas B. Knudsen, US Environmental Protection Agency and Susan Y. Euling, US Environmental Protection Agency

1:00 PM–1:05 PM		**Introduction** *Susan Y. Euling, US Environmental Protection Agency*
1:05 PM–1:30 PM	**W6**	**Challenges and Opportunities: Building NAMs to Reflect Developmental Stage Complexity** *Elaine M. Faustman, University of Washington*
1:30 PM–1:55 PM	**W7**	**Scaling Up: Zebrafish Social Interaction as Scalable Phenotype for Identifying Neurodevelopmental Toxicants and Their Mechanisms** *Randall T. Peterson, University of Utah*
1:55 PM–2:20 PM	**W8**	**Single-Cell RNA-Sequencing Analysis of Early Cardiogenesis Reveals Cell-Type-Specific Perturbations that Drive Organ-Level Developmental Defects upon Hand2 Loss** *Yvanka De Soysa, Boston Children's Hospital*
2:20 PM–2:45 PM	**W9**	**Predictive Developmental Toxicity with Pluripotent Stem Cell Models and ToxCast/Tox21 Assay Batteries** *Thomas B. Knudsen, US Environmental Protection Agency*
2:45 PM–3:00 PM		**Discussion**

3:00 PM–3:30 PM **Break**

Thursday

3:30 PM–4:30 PM **Annual Meeting Awards Presentation and Business Meeting**

Wilson Presentation Awards
Marie Taubeneck Award
James C. Bradford Memorial Student Poster Awards
BDRP Innovator Award
Birth Defects Research Distinguished Scholar Award
Edward W. Carney Distinguished Service Award
Recognition of Other Awards Presented throughout the Week
Annual Business Meeting

Education Courses

All times listed in the agenda are Eastern Daylight Time (US).

Thursday, July 15, 2021

11:00 AM–2:30 PM **Education Course Session 1**

Development and Disorders of the Gastrointestinal (GI) Tract
(Separate Registration Required)

Organized by the Education Committee

Chairperson: Christina M. Carruthers, Janssen Pharmaceuticals

11:00 AM–11:05 AM	**Course Overview** *Education Committee, Chairperson, Christina M. Carruthers, Janssen Pharmaceuticals*
11:05 PM–11:45 AM	**Early Development of the GI Tract** *Wendy Halpern, Genentech*
11:45 AM–12:25 PM	**Mechanisms of Gut Stem Cell Niches in Early Postnatal Gut Development and Necrotizing Enterocolitis** *Tae-Hee Kim, The Hospital for Sick Children, University of Toronto*
12:25 PM–12:40 PM	**Discussion**
12:40 PM–12:55 PM	**Break**
12:55 PM–1:35 PM	**Embryology and Pathogenesis of Gastroschisis** *Marcia Lynn Feldkamp, University of Utah*
1:35 PM–2:15 PM	**Clinical Management** *Suna Seo, US Food and Drug Administration*
2:15 PM–2:30 PM	**Discussion**

Thursday, July 22, 2021

11:00 AM–2:30 PM **Education Course Session 2**

Craniofacial Morphogenesis and Teratogenesis

(Separate Registration Required)

Organized by the Education Committee

Chairperson: Christina M. Carruthers, Janssen Pharmaceuticals

11:00 AM–11:05 AM	**Course Overview** *Education Committee, Chairperson, Christina M. Carruthers, Janssen Pharmaceuticals*
11:05 PM–11:45 AM	**Early Development** *John DeSesso, Exponent*
11:45 AM–12:25 PM	**Control and Dysregulation** *Robert Lipinski, University of Wisconsin*
12:25 PM–12:40 PM	**Discussion**
12:40 PM–12:55 PM	**Break**
12:55 PM–1:35 PM	**Models of Disease** *Brian Johnson, Michigan State University*
1:35 PM–2:15 PM	**Clinical Management** *Marilyn Jones, Rady Children's Hospital*
2:15 PM–2:30 PM	**Discussion**

Thursday, July 29, 2021

11:00 AM–1:00 PM **Mini Course**

Single-Cell RNA Sequencing in Understanding Normal and Abnormal Development

(Separate Registration Required)

Sponsored by Alan M. Hoberman, in memory of Robert L. Brent

Organized by the Education Committee

Chairperson: Christina M. Carruthers, Janssen Pharmaceuticals

11:00 AM–11:05 AM	**Course Overview** *Education Committee, Chairperson, Christina M. Carruthers, Janssen Pharmaceuticals*
11:05 AM–11:30 AM	**Single-Cell Profiling for Advancing Birth Defects Research and Prevention** *Thomas B Knudsen, US EPA*
11:30 AM–11:55 AM	**Technical Considerations for Single-Cell RNAseq Workflows** *David Gallegos, US EPA*
11:55 AM–12:20 PM	**Analytical Approaches to Dissect Dysregulated Gene Expression and Developmental Trajectories** *Yvanka de Soysa, Boston Children's Hospital*
12:20 PM–12:45 PM	**Prospects for Profiling Developmental Toxicity with Single-Cell Resolution** *Joshua F. Robinson, University of California, San Francisco*
12:45 PM–1:00 PM	**Discussion**

Society for Birth Defects Research and Prevention

LECTURE ABSTRACTS

(Presenter designated by underlined author.)

Josef Warkany Lecture

Chairperson:
Elise Madison Lewis,
Charles River Laboratories

L1

WELLS PG, BHATIA S, AFSHARIAN K, DRAKE DM. University of Toronto, Toronto, ON, Canada. Reactive Oxygen Species and DNA Damage/Repair in Developmental Disorders

Reactive oxygen species (ROS) like hydrogen peroxide, superoxide, and hydroxyl radicals are essential components of many physiological cellular processes, but can cause disease by adversely altering the structure and function of cellular macromolecules (lipids, proteins, DNA, RNA). ROS-initiated developmental disorders can arise in biochemically predisposed progeny that have enhanced pathways for ROS formation, and/or deficiencies in antioxidative enzymes that detoxify ROS, or proteins that repair ROS-initiated DNA damage. Moreover, ROS formation and ROS-initiated developmental disorders are enhanced by numerous drugs (e.g. phenytoin, thalidomide, ethanol, methamphetamine) and environmental chemicals (e.g. benzo[a]pyrene). Developmental disorders likely occur at least in part via nonmutational mechanisms involving epigenetic changes caused by oxidative lesions in DNA and RNA, and particularly the DNA lesion 8-oxoguanine (8-oxoG). "Tumor" suppressor genes, including those that repair DNA damage, are widely known for their role in suppressing cancer. However, throughout most of evolution, animals including humans died before they could develop most cancers, so the evolutionary pressure for DNA repair genes likely arose from the developmental necessity to produce healthy progeny. Knockout mice deficient in DNA repair proteins like p53, ataxia telangiectasia mutated (ATM), oxoguanine glycosylase 1 (OGG1) and breast cancer 1 (BRCA1) exhibit enhanced susceptibility to ROS-initiated embryonic oxidative DNA damage and disorders in developmental morphology and/or postnatal neurodevelopment, potentially relevant to some components of autism and other developmental disorders. Moreover, neurodevelopmental disorders in progeny deficient in the above DNA repair proteins or Cockayne Syndrome B (CSB) are further enhanced by *in utero* exposure to ROS-initiating xenobiotics including phenytoin and ethanol, which may contribute respectively to the mechanism of disorders like fetal hydantoin syndrome (FHS) and fetal alcohol spectrum disorders (FASD). In addition to genetic predisposition, susceptibility also can be enhanced by environmental factors, exemplified by a substantial reduction in embryonic BRCA1 caused by *in utero* ethanol exposure. Remarkably, epigenetic changes initiated in fetal brain by 8-oxoG and mediated by OGG1 may be reversible postnatally, raising the potential for therapeutic mitigation of some neurodevelopmental disorders.

Robert L. Brent Lecture—Teratogen Update

Chairperson:
Elise Madison Lewis,
Charles River Laboratories

L2

RASMUSSEN SA. University of Florida, Gainesville, FL, United States. Identifying New Human Teratogens: Revisiting Shepard's Criteria

In 2015, a sharp increase in the number of babies born with microcephaly was noted in Brazil, leading to concern that Zika virus might be a new cause of birth defects. However, this hypothesis was met with much skepticism by the general public, as well as by many in the medical and public health communities. This led us to review previously developed criteria for establishing pregnancy exposures as causes of birth defects. Application of those criteria to the association between Zika virus and birth defects resulted in confirmation of Zika virus as a cause of microcephaly and other serious birth defects in April of 2016 (Rasmussen et al., *N Engl J Med* 2016; 374:1981–1987). In this presentation, the criteria developed by Shepard and Bradford Hill used to confirm Zika virus as a cause of birth defects will be reviewed, along with discussion of other criteria for causation in teratology. Application of these criteria to future potential teratogens will be discussed.

F. Clarke Fraser New Investigator Award

Chairperson:
Philip Lupo,
Baylor College of Medicine

L3

KANCHERLA V. Emory University, Atlanta, GA, United States. Consequentialist Epidemiology of Birth Defects: Early Career Experiences and Key Findings from National and Global Research

Consequentialist epidemiology, proposed by Dr. William Foege in 1983, advocates for epidemiological research that aims at informing and promoting public health interventions and improving population health. Thus, consequentialist epidemiology goes beyond identifying causes and distributions of disease, and takes a "so what" approach. It expands the boundaries of epidemiology to include implementation science and translational research. Birth defects epidemiology will require a consequentialist approach to actively enable primary prevention, improve data quality, influence surveillance and policy, eliminate disparities, and enhance the quality of life of those affected in a global context. In this presentation in honor of Dr. F. Clarke Fraser, I will share highlights of my research in birth defects epidemiology over the past eight years. The period signifies my early career investigator phase as a faculty at a leading School of Public Health in the United States. I will present my experiences contributing in various areas directly impacting those affected by birth defects: etiological studies, surveillance and trend analyses, needs assessment, predictive modelling studies, mortality and health outcomes, health economics, health services research, global health, and studies exploring factors influencing race/ethnic and socio-economic disparities in birth defects. I will share key findings from selected national and international studies informing services and policy. Applying a consequentialist approach, I will also discuss multi-disciplinary collaborations I have developed with various organizations sharing the common goal of preventing major birth defects globally. I will highlight opportunities where I could publish and contribute to national and international policy discussions on folic acid fortification of staple foods. As consequential epidemiologists, we need to bring birth defects into the discussions of reproductive, maternal, newborn, and child health sectors at multinational agencies that have the power to influence policy in developing countries. My learnings as an early career investigator include keeping an open mind, staying motivated, asking right questions, participating and presenting in conferences, collaborating, teaching and mentoring, and seeking multiple mentors who are able to provide complementary guidance. I will close the presentation by sharing about major boosts and challenges I faced as an early career investigator.

Patricia Rodier Mid-Career Award for Research and Mentoring

(Joint with DNTS)

Chairpersons:
Philip Lupo,
Baylor College of Medicine and Sonia Minnes,
Case Western Reserve University

L4

WILLIAMS MT. Cincinnati Children's Research Foundation, Cincinnati, OH, United States. Manganese Overexposure During Development: Environmental and Genetic Effects

Manganese (Mn) is an essential element, however when too much intake occurs through contaminated sources such as drinking water or polluted air, it can produce neurotoxicity. Mn-overexposure (MnOE) during early development is especially problematic, since homeostatic systems for Mn are not fully developed. Children of lower social economic status are at increased risk since soy-based baby formulas can contain up to 10 times the amount of Mn compared with dairy-based formulas and 100 times more than in human milk. These children are also more likely to be exposed to Mn in air, soil, and water from industrial or groundwater sources. MnOE in children is associated with decreased IQ, reduced school performance, and behavioral disinhibition. A rat model of MnOE was used, where MnCl (100 mg/kg, free metal) was delivered once daily, every other day, from postnatal day (P)4 to P28. This regimen of MnOE increases blood Mn levels similar to those found in MnOE children. When rats are tested as adults, there are deficits in learning and memory assessed in the Cincinnati water maze (CWM) and the Morris water maze (MWM). Reductions of striatal dopamine in adulthood with the neurotoxin 6-OHDA resulted in greater deficits in the CWM in MnOE rats compared with controls, with a lesser effect on the MWM. We then created a rat model with a floxed Slc30a10, the Mn exporter, gene and crossed it with a Th-cre rat. The rats were maintained on NIH-7 chow without any supplemental Mn and were tested in adulthood. In a preliminary analysis, the Slc30a10 x Th-cre rats performed worse in the CWM than controls. These data demonstrate that environmental and genetic manipulations of Mn have similar effects on egocentric learning and memory as tested in the CWM. The data also show that body burden of MnOE is not a necessary requirement for Mn-related learning and memory deficits.

Agnish Fellowship Lecture

Chairperson,
Christina M. Carruthers,
Janssen Pharmaceuticals

L5

HOOD RD. Retired, Vedra, FL, United States. Education, Service, and Career Paths in the Multidisciplinary Science of Birth Defects Causation and Prevention

The Agnish Fellowship was established in recognition of Dr. Narsingh Agnish's contributions to the Society, and especially for his initiation and development of the Education Courses. Continuing education and service are important to a multidisciplinary society, such as BDRP, and to its individual members. Those activities offer opportunities for Society members to learn and to become recognized, while contributing and networking. And some Society members have followed unexpected paths to professional careers and BDRP membership. Examples of education and service to our Society and profession, both typical and atypical, will be given. In addition, how the speaker and some former doctoral students, Joe Lary, Jane Rasco, and Elise Lewis, eventually came to be involved in birth defects research and education will be presented as examples of the varied and often circuitous career paths that have led to BDRP membership.

Keynote Lecture

(Joint with OTIS)

Chairperson:
Susan L. Makris,
US Environmental Protection Agency

L6

KRUBINER CB. Center for Global Development, Washington, DC, United States. Pregnancy and the Perils of Precaution: Toward a New Paradigm for the Ethics of Including Pregnant People in Vaccine Research and Deployment

Zika virus, H1N1, Ebola, and now COVID-19 have shown how outbreaks can severely and—in some cases—uniquely affect pregnant women and their offspring. These threats highlight the critical need to proactively consider pregnant people in vaccine research agendas and deployment efforts, both as a matter of public health and health equity. New vaccines are rarely designed with pregnant women in mind, and evidence about safety and efficacy in pregnancy is often limited and late in coming. Consequently, in numerous outbreaks and epidemics, pregnant women have been denied vaccines that would have protected them and their offspring from severe infectious disease threats. In the case of COVID-19, we are already seeing the policy implications of the failure to include pregnant people in vaccine trials, with highly variable vaccine guidance and access for pregnant people across countries as vaccines are being rolled out. A new paradigm is needed for vaccine research to responsibly and equitably address the health interests of pregnant people, particularly in the context of epidemic threats. The field must move away from the single guiding principle of precaution, and adopt approaches that protect pregnant people through research, rather than from it. This keynote presentation will provide an overview of how a precautionary stance in vaccine research has failed pregnant people and their offspring; present an ethics framework relying on the presumption of inclusion with risk-benefit assessment; and review concrete recommendations from the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group to fairly include the health interests of pregnant people and their offspring in vaccine research and deployment activities. The PREVENT Guidance was developed by a multidisciplinary, international team of 17 experts specializing in bioethics, maternal immunization, maternal-fetal medicine, obstetrics, pediatrics, philosophy, public health, and vaccine research and policy, and informed by consultations with over 100 additional experts in ethics, public health, vaccine science, maternal and child health, and regulatory affairs. While this guidance focuses on vaccines for emerging and re-emerging pathogens, the underlying ethics framework and many of the recommendations are also relevant to the inclusion of pregnant people in the broader context of biomedical research.

Society for Birth Defects Research and Prevention

SYMPOSIUM ABSTRACTS

(Presenter designated by underlined author.)

Wiley Symposium
Approaches for Mechanistic Evidence Analysis in Hazard Evaluation of Reproductive Toxicology Data

Chairpersons: Xabier Arzuaga, US Environmental Protection Agency and Erin Yost, US Environmental Protection Agency

S1

LA MERRILL MA. University of California, Davis, Davis, CA, United States. The Hazards of Endocrine Disrupting Chemicals Partially Overlap with the Hazards of Reproductive Toxicants

Endocrine-disrupting chemicals (EDCs) are exogenous chemicals that interfere with hormone action, thereby increasing health risks, such as reproductive impairment, cancer, and obesity. A complex literature of mechanistic studies provide evidence on EDC hazard, yet there has been no widely-accepted, systematic method to integrate these data to help identify EDC hazards. Inspired by work to improve hazard identification of carcinogens using key characteristics (KCs), we have developed 10 KCs of EDCs based on our knowledge of hormone actions and EDC effects as follows: 1) interacts with or activates hormone receptors, 2) antagonizes hormone receptors; 3) alters hormone receptor expression; 4) alters signal transduction in hormone receiving cells; 5) induces epigenetic modifications in hormone producing or receiving cells; 6) alters hormone synthesis; 7) alters hormone transport across cell membranes; 8) alters hormone distribution or circulating hormone levels; 9) alters hormone metabolism or clearance; and 10) alters fate of hormone producing or receiving cells. We describe how the KCs of EDCs compare to the KCs of reproductive toxicants. We reflect on how these KCs can be used to identify, organize and utilize mechanistic data when evaluating teratogenic chemicals as EDCs, and use *in utero* exposure to the pesticide DDT as an example to illustrate this approach.

S2

GRIMM FA. ExxonMobil Biomedical Sciences, Inc., Annandale, NJ, United States. A New Approach Methods-Based Integrated Assessment of Estrogenicity of Alkylphenols

The inclusion of new approach methods (NAM) data in weight of evidence evaluations presents a promising opportunity to improve chemical safety assessments and decrease reliance on animal testing. Despite significant progress in the development and application of NAMs, confidence in these new data streams is challenged by their often limited ability to capture complex chemical-biological interactions. This is particularly discernible in the case of chemical interactions with the endocrine system, which are a toxicologic interest for many entities globally. In order to elicit an adverse response, including reproductive effects, endocrine-disrupting chemicals (EDCs) need to be able to perturb one or more key signaling events at the cellular level. Among the best studied mechanisms of chemical-induced endocrine disruption are modulations of the estrogen receptor pathway with chemical interactions with the estrogen receptor (ER) being regarded as the key initiating event. Among identified chemical xenoestrogens are certain alkylphenols, a group of chemicals with a wide range of industrial and consumer product applications. In this study, we tested the hypothesis that estrogen receptor activity for alkylphenols can be predicted using a mechanistically-based integration of evidence from multiple data sources, including QSAR models, available bioactivity screening data from the ToxCast inventory, and curated uterotrophic assay data. Individual data streams were subject to comparative assessment to evaluate concordance, and also provided inputs for the development of a virtual Adverse Outcome Pathway (vAOP) model that can provide screening level ER activity predictions for prioritizing alkylphenols.

S3

ZEISE L, MORAN F. OEHHA/CalEPA, Sacramento, CA, United States. Application of Key Characteristics in Support of Identifying Chemicals with Reproductive Hazard Traits

Biology of reproduction involves a complex and dynamic set of physiological processes that work in coordination. Alterations in these physiological processes can potentially lead to adverse outcomes such as impotence, menstrual disorders, reduced fertility, low birthweight, and spontaneous abortion. Several environmental factors, including natural and man-made chemicals alone or in combination with other stressors, may adversely perturb normal reproductive processes with adverse consequence. Often the precise nature of chemical interactions that lead to adverse outcomes are unknown but critical biological traits of chemicals associated with adverse reproductive outcomes can be observed. Such Key Characteristics, or KCs, have been proposed for female reproductive toxicity (Luderer et al., *Environmental Health Perspectives*, 2019, CID: 075001) and male reproductive toxicity (Arzuaga et al., *Environmental Health Perspectives*, 2019, CID: 065001). These KCs provide a way of organizing and integrating mechanistic data in support of identifying chemicals for public health and regulatory attention. In performing "hazard identification", there are to two general types of chemicals in terms of the amount of available evidence—the "data rich" and "data poor" chemicals. For the first type there is a rich body of evidence from whole animal testing and epidemiology studies, along with mechanistic data, that support conclusions about whether or not the chemical should be classified as a male or female reproductive toxicant. For the data poor chemicals animal and human evidence is sparse; here, mechanistic toxicology studies and structural modeling provide insight on whether the chemical should be prioritized for further research or ultimately treated as a reproductive risk. We reflect on the application of the KCs for female reproductive toxicity for data rich chemicals, taking a retrospective look at the 58 chemicals listed under California's Proposition 65 as "known to the State to cause reproductive toxicity" because they are recognized as causing female reproductive toxicity. We also consider how to capitalize on the use of KCs for non-Proposition 65 activities for the data sparse case. We present a few examples on how the KCs approach could help in the identification of "new" chemicals as having the hazard trait of female reproductive toxicity. We conclude by discussing the advantages and challenges of using the KCs to identify female reproductive toxicants.

S4

LUDERER U. University of California Irvine, Irvine, CA, United States. Application of the Key Characteristics Approach to Female Reproductive Hazard Identification: Benzo[a]pyrene as a Case Example

The vast majority of chemicals in commerce have not been tested for female reproductive toxicity, in part because traditional *in vivo* toxicology and epidemiological studies are time and resource intensive. The Key Characteristics (KCs) provide a uniform approach to search, organize, integrate, and evaluate mechanistic evidence for hazard identification. This approach was recently applied to female reproductive toxicants, resulting in the identification of 10 KCs that occur in cells or tissues of the female reproductive system: 1) alters hormone receptor signaling; alters reproductive hormone production, secretion, or metabolism; 2) chemical or metabolite is genotoxic; 3) induces epigenetic alterations; 4) causes mitochondrial dysfunction; 5) induces oxidative stress; 6) alters immune function; 7) alters cell signal transduction; 8) alters direct cell–cell interactions; 9) alters survival, proliferation, cell death, or metabolic pathways; and 10) alters microtubules and associated structures (Luderer et al., 2019, *Environ Health Perspect*). The polycyclic aromatic hydrocarbon (PAH) benzo[a]pyrene (BaP) serves as an example to illustrate the utility of the KCs of female reproductive toxicants. *In vivo* studies have clearly demonstrated that BaP is a developmental and adult female reproductive toxicant. PubMed searches identified mechanistic *in vivo* or *in vitro* studies of BaP effects in cells and tissues of the female reproductive system. Endpoints were examined for alignment with the KCs of female reproductive toxicants. Studies were identified that associate BaP and/or its metabolites with all 10 of the KCs. Identified endpoints include: estrogen receptor agonism and inhibition of androstenedione and estradiol synthesis (KC1); DNA adducts, DNA strand breaks and mutations in ovaries and fetuses (KC2); epigenetic alterations in GnRH-related genes and uterus (KC3); mitochondrial dysfunction (KC4) and increased reactive oxygen species in oocytes (KC5); increased inflammatory cytokine expression in uterus (KC6); altered PI3K/AKT signaling in human placental cell lines (KC7); decreased oocyte-sperm binding (KC8); induced apoptosis in germ cells and inhibited growth of antral follicles (KC9); disrupted oocyte meiotic spindle formation (KC10). While BaP exhibits all 10 female reproductive KCs, it is not necessary for a chemical to exhibit all or even a majority of the KCs to be considered a possible female reproductive toxicant and prioritized for further testing.

S5

DRUWE I[1], BLAKE BE[1], DAVIS A[1], DEAN J[2], GIBBONS C[3], LAMBERT J[2], LIZARRAGA LL[2], ARZUAGA X[3]. [1]US EPA, Research Triangle Park, NC, United States, [2]US EPA, Cincinnati, OH, United States, [3]US EPA, Washington, DC, United States. Applying the Key Characteristics Approach to Evaluate Mechanistic Evidence for Qualitative and Quantitative Weight of Evidence to Support Risk Assessment: A Case Study with Benzo[a]Pyrene-Induced Male Reproductive Toxicity

In order to derive health protective reference dose values (RfD), a qualitative evaluation and integration of toxicological, epidemiological, and mechanistic evidence must first be performed in order to identify potential hazard(s) and their operative mode(s) of action (MOA). In particular, consideration of mechanistic studies in this evaluation process may inform biological plausibility along with human relevance of effects observed in experimental animal models, identify database uncertainties, and facilitate decision-making that impacts quantitative assessment. Here we integrate eight proposed key characteristics of male reproductive toxicants with established pathways for loss of reproductive function to identify and analyze the mechanistic evidence on benzo[a] pyrene (B[a]P)-induced male reproductive effects. The weight of evidence for support of each key event (KE) and key event relationship (KER) along the proposed MOA for reduced male fertility were evaluated for biological plausibility and human relevance. The quantitative data informing the KE and KER in this putative MOA were further appraised for dose response modeling and where the data allowed, Points of Departure (PODs) for KE along the MOA continuum were derived using EPAs Benchmark Dose Modeling Software (BMDS). Qualitative and quantitative evaluations of mechanistic studies are ongoing to identify potential causal pathways of B[a] P-induced male reproductive toxicity, inform biological plausibility, and facilitate dose response interpretation and assessment. This B[a]P case study demonstrates that the key characteristics approach serves as a practical and objective tool for identifying and organizing mechanistic evidence as well as quantitative information along key event continuums in male reproductive toxicity in support of human health risk assessment.

The Effects of Water Fluoridation on Neurodevelopment and Other Health Outcomes Symposium

(Joint with DNTS)

Chairpersons: Kembra L. Howdeshell, National Institute of Environmental Health Sciences and Kyla Taylor, National Institute of Environmental Health Sciences

S6

MARTINEZ-MIER E[1], CASTIBLANCO GA[2], CANTORAL A[3]. [1]School of Dentistry, Indiana University, Indianapolis, IN, United States, [2]Indiana University-Purdue University Indianapolis, Indianapolis, IN, United States, [3]Universidad Iberoamericana, Mexico City, Mexico. Fluoride Intake and Exposure and Oral Health Effects

At appropriate levels, fluoride has been well established as an effective agent in the prevention of dental caries. The available evidence indicates that fluoridation programs reduce both the proportion of individuals with caries and the number of teeth with caries per individual. For that reason, fluoride levels have been adjusted in community water supplies for more than 70 years. Despite advances in the reduction of oral diseases, dental caries remains common among both children and adults worldwide, especially among underserved populations. Dental caries can negatively affect an individuals' overall health and quality of life, and often results in reduced productivity. While death as a direct result of dental caries remains rare, its presence often results in years lived with disability. In addition, its traditional treatment is costly. The prevention of caries and the subsequent preservation of functional dentition often results in better nutritional outcomes in late adulthood and decreased disability-adjusted life years (DALYs). On the other hand, when individuals are exposed to excessive amounts of fluoride, negative side effects are seen. Dental enamel fluorosis, a condition that results from excessive intake of fluoride during tooth development, has increased its prevalence worldwide, raising questions regarding a potential excessive intake of and exposure to fluoride in children. This presentation will review the evidence supporting fluoride's role in lowering the prevalence and incidence of dental caries. Trends on the prevalence of dental caries in different segments of the population, as well as the number of people with untreated disease will also be presented. The presentation will also discuss trends on the prevalence of dental enamel fluorosis over the last four decades, with an emphasis on US data. The detailed analysis of this evidence will be useful to inform public policy aiming at optimizing the beneficial effects of fluoride while minimizing its detrimental effects.

S7

TILL C. York University, Toronto, ON, Canada. Early-Life Exposures to Fluoride and Child Neurodevelopmental Outcomes

Fluoride is considered a developmental neurotoxicant at high exposure levels. What remains disputed is whether fluoride added to drinking water for the prevention of dental caries contributes to neurotoxic effects to the developing brain. One of the main concerns about indiscriminately delivering fluoride through drinking water relates to uncontrolled dose. One litre of fluoridated water per day provides the same dose of 0.7 mg to an adult as it does to a pregnant woman or to an infant who consumes formula reconstituted with fluoridated tap water. This presentation will discuss recently published studies that have been conducted in populations with optimal fluoridation of salt and drinking water. The presentation will examine how fluoride exposures measured in different periods of development (pregnancy, infancy, childhood) are associated with IQ and behavioral outcomes in young children. Emerging evidence suggests that early-life exposure to fluoride may be associated with lower IQ scores and higher risk of ADHD in children living in areas with optimal fluoridation. Results also show that the neurotoxic effects of fluoride may vary depending on the timing of exposure and biologic sex of the fetus. The presentation will conclude with a discussion of areas of current investigation, the process of communicating hazard conclusions to the public, and some of the challenges associated with researching a controversial topic.

S8

TAYLOR KW, National Institute of Environmental Health Sciences, Morrisville, NC, United States. Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

People of all ages are exposed to fluoride from a variety of sources including dental products, drinking water, food, beverages, and pharmaceuticals. In some developed countries, fluoride is added to municipal water systems to prevent tooth decay. The National Toxicology Program (NTP) conducted a systematic review of the human, experimental animal, and mechanistic literature to evaluate the extent and quality of the evidence about whether fluoride exposure is associated with neurodevelopmental and cognitive effects. The literature search and screening process identified 159 published human studies, 339 published experimental animal studies, and 60 *in vitro*/mechanistic studies. While the animal data provide some evidence of effects of fluoride on neurodevelopment, the human evidence base is large, directly addresses cognitive neurodevelopmental effects, and is most informative concerning the effects of fluoride on cognitive neurodevelopment in children. The human body of evidence provides a consistent and convincing pattern of findings that higher fluoride exposure (e.g., >1.5 mg/L in drinking water) is associated with lower measures of cognitive neurodevelopment, primarily in measures of children's IQ. When focusing on findings from studies with fluoride exposures in ranges typically found in drinking water in the United States (0.7 mg/L for optimally fluoridated community water systems), effects on cognitive neurodevelopment of children are inconsistent, and therefore unclear. The evidence for effects of fluoride exposures on cognition in adults is also limited. The evidence from animal studies is difficult to directly relate to the observed cognitive effects in humans, and the mechanisms underlying fluoride-associated cognitive neurodevelopmental effects are not well characterized.

S9

MALIN AJ, Keck School of Medicine at USC, Los Angeles, CA, United States. Fluoride Exposure and Neuroendocrine Outcomes among Youth in the United States

Fluoride exposure is ubiquitous in the United States. Approximately 74% of the population on public water distribution systems receives fluoridated water for tooth decay prevention. Fluoride exposure can also occur via fluoridated dental products, tea, pesticides, and pharmaceuticals. While the dental benefits of fluoride are well-established, there is emerging evidence that chronic fluoride exposure at US population-relevant levels may contribute to adverse effects on neurodevelopment and endocrine function. However, research examining effects of fluoride exposure on neuroendocrine outcomes in the US is scarce. Fluoride accumulates preferentially in the pineal gland which produces melatonin, the hormone that regulates the sleep-wake cycle and may influence pubertal onset. We examined associations of fluoride exposure with sleep and reproductive health outcomes among older adolescents participating in the National Health and Nutrition Examination Surveys (NHANES). We found that adolescents with higher household tap water fluoride levels had higher odds of reporting symptoms suggestive of sleep apnea, later bedtime and wake time, and among males, lower odds of reporting snoring. We also found that higher water fluoride concentrations were associated with earlier age of menarche among adolescent females. Furthermore, among non-Hispanic black females, higher plasma fluoride concentrations were associated with earlier age of menarche. Recent studies conducted in Canada and Mexico have also found that greater childhood and/or prenatal fluoride exposure is associated with poorer neurodevelopmental outcomes. However, there are no published studies examining individual-level fluoride exposure in relation to neurodevelopment among youth living in the US. This talk will present findings from a pilot study of 4–6-year-old children living in New York City, including results on the associations of fluoride exposure with attention, executive function, and structural and functional changes in the brain. Additionally, it will discuss future research examining prenatal fluoride exposure in relation to neurodevelopmental outcomes in a US prospective pregnancy and birth cohort.

Neglected Diseases/Neglected Patients Symposium

Chairpersons: Jane Stewart, Apconix, Melissa S. Tassinari, Consultant, and Belen Tornesi, Medicine for Malaria Medicine

S10

TORNESI B. MMV, Geneva, Switzerland. Global Efforts for Eradication of Malaria: A Focus on Pregnant and Lactating Women

An estimated 125 million pregnancies per year are at risk of malaria around the world. For both mother and child, malaria is potentially life-threatening. Malaria is caused by a parasite, transmitted through the biting of certain species of mosquitos in parasite-endemic regions. Those at greatest risk of severe forms of the disease, and death, are children under the age of five years and pregnant women. Common risk factors are maternal anemia, premature labor, and poor birth outcomes such as low birthweight, which are associated with a negative impact on early childhood development. WHO reported that in 2018 around 11 million pregnancies were exposed to malaria, resulting in high levels of maternal anaemia and the delivery of around 872,000 children with low birthweight. Unfortunately, pregnant women are actively excluded from trials and if pregnancy occurs during the trial, treatment is discontinued and follow-up on the pregnancy outcomes is ensured. This practice aims to protect women and the foetus, but it also prevents generation of data. We should protect by research not by exclusion. Data to support the use of medicines during pregnancy is typically collected only after the product is marketed and its efficacy is established, in order to balance potential risks if used in pregnancy. Data on drug exposure in lactating in women, is also collected in a postapproval setting, if at all. In the context of malaria-endemic countries, this means that there is often a long delay in access to medicines by pregnant and lactating women. The paucity of data leads many patients and practitioners to uninformed decision making during this lag-period. Similarly, there is a lack of data to support the use of malaria medicines in the youngest of infants. Medicine for Malaria Venture has developed a platform call MiMBa (malaria in mothers and baby). It is a strategy that aims to raise the standard of care for pregnant women and their newborns affected by malaria. How? Ensuring drug supplies for children and pregnant women; Generating data on existing compounds to inform on their use in pregnant women and neonates; developing new antimalarial medicines to address the needs of pregnant women and neonates; strengthening the capture of safety data from routine clinical use of antimalarial medicines during pregnancy; and advocating for changes in drug development that promote the safe inclusion of pregnant women into clinical studies.

S11

DEMARTA-GATSI C[1], ANGULO-BARTUREN I[2], JIMÉNEZ-DÍAZ M-B[2], TORNESI B[3], MÖEHRLE J[3]. [1]Medicine for Malaria Venture, Geneva, Switzerland, [2]The Art of Discovery (TAD), Derio, Spain, [3]MMV, Geneva, Switzerland. The Use of a Humanized Mouse Model to Assess Antimalarial Efficacy and Identify Optimal Drugs Combinations

New antimalarial medicines are urgently needed to counter the emergence of resistance and contribute to malaria's global elimination. These medicines should be developed as fixed-dose combinations of two drugs, each with different mechanisms of action and compatible PK profiles. Unlike in the past, these medicines are now usually deliberately developed as fixed-dose combinations of two (or more) agents, where at least one of the agents is novel. However, the selection and ranking of optimal combination candidates is a complex scientific challenge because of the high number of biological, pharmacological and pharmacodynamic variables involved as well as the high number of potential drug combinations that can be formulated out of the set of antimalarials currently in preclinical development. In our current drug development model, new drug combinations are prioritized based on their efficacy in the *P. falciparum*-infected humanized mouse model (NODscidIL2Rynull, NSG) in which mice are engrafted with human erythrocytes allowing *in vivo* growth of human *Plasmodium* providing a means of measuring the efficacy of novel agents to kill the human parasite. *In vivo* drug combination studies are run to investigate, understand, and gauge the individual contribution and mechanistic interactions of the partner drugs. So far, thirty combinations have been studied using this animal model. Our results indicate that the data generated in the falciparum-infected NSG model effectively translates to the human volunteer infection study model. Therefore, the development of humanized mouse models has emerged as a powerful enabling technology to assess new candidate drug combinations.

S12

RAO B[1], DE SMET M[2], MORRISON C[1], STERK E[3]. [1]Medecins sans Frontieres (UK), London, United Kingdom, [2]Medecins sans Frontieres (Belgium), Bruxelles, Belgium, [3]Medecins sans Frontieres (Switzerland), Geneva, Switzerland. Working in Operationally Challenging Situations: How Do We Get Malarial Drugs to Pregnant Women in the Real World?

MSF treats over 2.5 million malaria patients a year, across a range of endemic humanitarian contexts, including through ante-natal care implementing both case management and preventative measures for pregnant women (intermittent preventative treatment in pregnancy, or IPTp, and vector control). In 2018, we added prevention and treatment guidelines for malaria in pregnancy practices and the barriers to implementing them in humanitarian contexts. In summary, two thirds of MSF projects reported following MSF guidance on chemoprevention, whilst over 75% of projects followed the correct treatment protocol across all trimesters for malaria in pregnancy. Although 63% treated uncomplicated malaria patients with Quinine in first trimester, we found that only 54% for of projects managed severe malaria with intravenous Artesunate in the first trimester. Barriers to implementing chemoprevention in pregnant women: access, with 72% of projects highlighted women did not attend regular ANC and 56% stated women attended too late in their pregnancy to access preventative services. Additionally, 63% reported chemoprevention was not possible since women regularly attended with a positive malaria rapid diagnostic test (mRDT) and therefore needed case management. Stockouts of sulphadoxine-pyremethamine (SP) and mRDTs were identified as challenges in 25% and 9% of projects respectively. In comparison, for management of severe malaria in pregnancy, 48% of the projects cited a lack of staff training, 35% a lack of family facilities, 26% drugs shortage and 22% a lack of appropriate equipment. Pregnant women with severe malaria were often manage outside reproductive health facilities with limitations on the personnel permitted to administer nonoral preparations. Only half of projects managed severe malaria in 1 trimester correctly with IV Artesunate, and the main reason was confusion with guidelines for the management of uncomplicated malaria (where oral Quinine is recommended). Addressing external factors is undoubtedly difficult, but several barriers identified were internal to SF and need be urgently addressed such as adequate supplies and staff training. Community engagement, improvement in access to ANC and policy alignment will require longer-term strategic focus to overcome barriers to preventing and treating malaria in pregnancy.

S13

DELLICOUR S. LSTM, London, United Kingdom. Above All Do No Harm: How Can Pregnancy Outcomes for Malarial Patients Be Monitored in the Field and How Can Benefit-Risk Be Assessed?

As pregnant women are often excluded from preregistration trials, information on the safety of medicines in pregnancy is obtained in the postmarketing phase. A range of pharmacovigilance tools exists to monitor the benefits and risks of medicines in pregnancy. For medicines with anticipated use in women of childbearing potential, dedicated postauthorisation studies are needed. In high-income countries, this information can be derived from electronic health records and health insurance claims. As such electronic records are not available in most malaria endemic countries, specific systems need to be developed to collect the required data. The purpose of this presentation is to summarise the key issues to generate robust data on antimalarial exposures in pregnancy and pregnancy outcomes in resource-constrained settings. Methodological considerations will be highlighted including approaches to capture antimalarial drug exposure, choice of endpoints and comparison groups, sample size implications, and analytical approaches. The presentation will discuss the main criteria that should be considered in the benefit-risk assessment of malaria treatment in the first trimester of pregnancy, considering the potential risk to the fetus and the benefits to the woman and fetus of an effective antimalarial treatment.

Cannabis in Pregnancy and Through Generations Symposium

Organized by the Public Affairs Committee

Chairpersons: Poorni R. Iyer, California EPA and Marlissa Campbell, California EPA

S14

KAUFMAN FL[1], KIM A[2], SANDY MS[2], HAMMER A[3], KUMARAVEL J[3], ZEISE K[3]. [1]CalEPA, Sacramento, CA, United States, [2]OEHHA/CalEPA, Oakland, CA, United States, [3]OEHHA/CalEPA, Sacramento, CA, United States. A Review of Epidemiological Evidence in Humans of the Effects of Prenatal Exposure to Cannabis (Smoke and Δ9-THC)

In spite of evidence from both animal and human studies of adverse effects of prenatal cannabis exposure, more women than ever are using cannabis during pregnancy. Along with this increase in use, the potency (as measured by the concentration of Δ9-THC) of cannabis has increased greatly over the past few decades from less than 1.5% in 1980 to 17.1% in 2017. As the legal market for cannabis has grown, pregnant women inquiring at dispensaries are often told that cannabis is safe to use during pregnancy. This review will present a summary of the epidemiologic evidence for adverse neurodevelopmental and somatic outcomes in children exposed to cannabis *in utero*. A comprehensive literature search was conducted in November 2018 for studies examining developmental effects of prenatal exposure to cannabis smoke and Δ9-THC in preparation of a hazard identification document (HID) under California's Proposition 65. This presentation will include the findings from the HID, as well as an update from some more recent literature. Multiple neurodevelopmental outcomes have been examined. Central nervous system maturation was assessed as maturation of visual pathways. Significant findings in infants prenatally-exposed to cannabis included decreased maturation of the visual system, increased sleep problems and decreased habituation to light in neonates. Studies of cognitive function have assessed visual function and processing, attention, and intelligence and academic achievement. Studies evaluating visual function and processing reported adverse effects on higher order cognitive processes related to visual analysis in exposed offspring, with no effects on basic visual functions. Studies of attention reported increased impulsivity in offspring prenatally exposed. Associations between exposure and deficits in sustained attention in offspring were observed through varying methods. In some studies, these attention problems were also linked to outcomes later in life such as delinquency and lower school achievement. Studies of intelligence and academic achievement reported decreases in language comprehension, learning and memory, verbal and quantitative reasoning, intelligence scores and school achievement. Substance use, mood disorders, and behavior problems were also associated with prenatal exposure. Findings for somatic outcomes will also be presented. As of December 2019, cannabis smoke and Δ9-THC are listed under California's Proposition 65 as developmental toxicants.

S15

METZ TD. University of Utah Health, Salt Lake City, UT, United States. A Clinical Perspective on Cannabis Use During Pregnancy

The prevalence and perceived safety of marijuana use in pregnancy are increasing with expanding legalization in the United States. Marijuana crosses the placenta and passes into breastmilk. Some women cite reasons for marijuana use in pregnancy and while breastfeeding such as nausea, pain, and anxiety. Despite a large volume of literature on this topic, there remain many unanswered questions related to the safety of marijuana use for the pregnant mother and fetus. This is predominantly a result of lack of adequate ascertainment of exposure to cannabis with biological sampling, and lack of adjustment for other socioeconomic factors and tobacco use, which are known to be associated with the outcomes of interest. A National Academies of Sciences report on the health effects of cannabis concluded that marijuana use is associated with poor fetal growth but that evidence for the association between marijuana use and other perinatal outcomes is inconclusive. Two recent systematic reviews and meta-analyses found an association between marijuana use and adverse perinatal outcomes, especially with heavy marijuana use. In addition, there are four longitudinal studies examining the relationship between prenatal marijuana exposure and childhood neurodevelopment. While early childhood neurodevelopmental outcomes are similar, investigation later in life demonstrates decreased attention, verbal reasoning, and cognitive function. With the high prevalence of marijuana use among reproductive age individuals, it is critical for healthcare providers to query women regarding use and provide information regarding potential harms and safe alternatives. Given the available evidence, women should be advised to refrain from marijuana use during pregnancy and while breastfeeding. Studies to better delineate the impact of legal marijuana on mothers and children are needed for policy, public health, treatment, and informed decision-making.

S16

NAGARKATTI PS. University of South Carolina School of Medicine, Columbia, SC, United States. Perinatal Exposure to Δ9-tetrahydrocannabinol Alters Immune Functions in Fetal and Postnatal Stages of Life: Role of Epigenetic Pathways

Marijuana has been legalized for recreational use in many states because of which its use is becoming increasingly prominent among pregnant women. Although marijuana cannabinoids have been shown to exert immunosuppression in adults, not much research has been pursued on the effect of marijuana use during pregnancy on the developing immune system of the fetus and during postnatal life. In the current study, we used a mouse model to address the effect of exposure to Δ(9)-tetrahydrocannabinol (THC) during pregnancy on the immune system of the fetus and as well as during postnatal life. We found that murine fetal thymus expressed high levels of the cannabinoid receptors CB1 and CB2. Perinatal exposure to THC caused marked decrease in thymic cellularity on gestational days 16, 17, and 18 and postgestational day one and marked alterations in T cell subpopulations. This effect was reversed by administration of CB1/CB2 antagonists, thereby suggesting that THC acted through the cannabinoid receptors. Thymic atrophy induced in the fetus by THC was caused by caspase-dependent apoptosis in thymocytes. The perinatal exposure to THC also altered the immune response during postnatal life. Peripheral T cells from such mice showed decreased T cell proliferative response to mitogens and to antigens such as HIV-1 p17/p24/gp120. Mechanistically, THC modulates the immune response through epigenetic regulation involving histone modifications and changes in the miRNA. THC treatment led to histone modification signals to Th2 cytokine genes and suppressive modification signals to Th1 cytokine genes, thereby causing a shift from Th1 to Th2. THC treatment during the delayed-type hypersensitivity response inhibited Th1/Th17 activation via regulation of microRNA expression. Together, our data demonstrate that perinatal exposure to THC triggers significant T cell dysfunction through epigenetic modulations, thereby suggesting that marijuana use during pregnancy may suppress the immune functions in the fetus and thereby increasing the susceptibility to infections during postnatal life.

S17

BARA A. Icahn School of Medicine at Mount Sinai, New York, NY, United States. Epigenetic Effects of Cannabis on the Developing Brain

In spite of increasing awareness, cannabis preparations remain the most widely abused illicit drugs by pregnant women in many societies worldwide. Cannabinoids readily cross the placenta barrier during gestation and our research has previously demonstrated that exposure to the principal psychoactive component, Δ9-tetrahydrocannabinol (THC), during the prenatal period results in enduring consequences for the offspring. Using an animal model, here we show that adult male progeny of mothers exposed to THC during pregnancy exhibited abnormal motivation for food, a depression-like phenotype and altered stress-sensitivity. To explore the underlying neurobiological mechanisms, a panel of epigenetic regulators was investigated in the offspring's nucleus accumbens (NAc), a key brain area mediating responses to rewarding experiences. This analysis identified a highly robust increase in the expression of Histone-Lysine N-Methyltransferase 2A (Kmt2a) that targets lysine 4 on histone H3 (H3K4me) in cellular chromatin. Importantly, normalizing Kmt2a in the NAc restored the motivational phenotype of prenatally THC-exposed animals. To gain insight into the gene expression disturbances of the NAc and their relationship to Kmt2a upregulation, we measured *in vivo* NAc transcriptome alterations, H3K4me3 enrichment, and developed a CRISPR-based *in vitro* overexpression model. Comparison of sequencing data sets on prenatal THC-related mRNA and epigenetic alterations with the specific consequences of Kmt2a upregulation in the CRISPR model revealed significant changes in pathways related to synaptic plasticity and neurotransmission. Altogether these studies provide direct evidence for the enduring effects of gestational cannabis exposure that can cause epigenetic deviations in the NAc via Kmt2a dysregulation and enhance psychiatric vulnerability.

HESI Symposium
Nonclinical Considerations for Inclusion of Pregnant and Lactating Women in Clinical Trials

Chairpersons: Kary Ellen Thompson, Janssen Pharmaceuticals and Dinesh J. Stanislaus, GlaxoSmithKline

S18

TORNESI B. MMV, Geneva, Switzerland. The Time Is Now: Why We Must Include Pregnant and Lactating Women in Drug Development

Unfortunately, during the clinical development of most new medicines, pregnant and lactating women are actively excluded from trials and if pregnancy occurs during the trial, treatment is discontinued and follow-up on the pregnancy outcomes is ensured. This practice aims to protect women and the foetus, but it also prevents generation of data. Data to support the use of medicines during pregnancy is typically collected only after the product is marketed and its efficacy is established, in order to balance potential risks if used in pregnancy. Data on drug exposure in lactating women, is also collected in a postapproval setting, if at all. PK studies in pregnant women should be incorporated into drug development programs and prioritized to obtain important information about safe and appropriate doses of a drug when used during pregnancy. The paucity of data leads many patients and practitioners to uninformed decision making during this lag-period. Another key issue is that many women in their first trimester of pregnancy may be unaware that they are pregnant, placing them at even greater risk and effectively broadening the high-risk category to include all sexually active women of reproductive potential. Off-label use is common and data capture on safety and efficacy in pregnancy or birth outcomes is challenging for many national health systems. The time is now to protect pregnant/lactating women by research not by exclusion. The COVID-19 pandemic is a prime example of why pregnant people must be included in research. The inclusion of pregnant women and breastfeeding women in medical research is long overdue. With almost four million women in the US giving birth each year, 80 percent of whom will breastfeed their infants, and about 74 million women of childbearing age in the US, it is time to include pregnant women and breastfeeding women in research. With a health pandemic raging across the globe, a rising maternal mortality rate and wide disparities in health outcomes, women are working every day to protect themselves and their families. We have a good momentum going let's use it.

S19

STANISLAUS D. Glaxosmithkline, Collegeville, PA, United States. Nonclinical Evaluation of Medicines Used in Pregnancy/Lactation: Looking Back to Move Forward

There are only few drugs developed for use specifically during pregnancy or lactation, and the majority of those are designed to address conditions that arise only during these states. Whereas the use of most medications in pregnant or lactating individuals for nonpregnancy related indications appear to be based primarily on a drug's history of safety which is balanced with mothers need for the medication. For these drugs safety information from nonclinical animal studies may or may not play a critical role in that decision to use during pregnancy. During drug development one objective of reproductive toxicology studies is to enable the enrollment of women of reproductive potential so that an appropriate characterization of the risk to fetus could be made to inform on the risk vs the benefit for a patient if she becomes pregnant during a clinical trial. As pregnant women form a unique population of high risk where both the benefit for the mother and the fetus need to be considered there is a general understanding that a comprehensive set of nonclinical studies need to be conducted prior to any exposure of a pregnant woman to an experimental medicine. This discussion will focus on what type of studies have been conducted to enable the enrollment of pregnant women in clinical trials while exploring nonclinical options that would enable the collection of safety and efficacy data from pregnant women during the conduct of clinical trials.

S20

THOMPSON KE. Janssen, Hillsborough, NJ, United States. Considerations for Evolution of the Nonclinical Toxicology Paradigm to Enable Clinical Trials in Pregnant/Lactating Patients

The ICH Guidelines prescribe a series of developmental and reproductive toxicity (DART) studies in animals; the complement of data will characterize potential risks throughout the reproductive lifespan. The timing of DART evaluations for molecules as outlined in ICH M3(R2) are proposed to include people of child-bearing potential in clinical trials, and not those known to be pregnant or lactating. Accordingly, nonclinical data evaluating potential effects on organogenesis, fetal growth, parturition, lactation, and postnatal development are generated in a tiered approach as the number of patients expands in clinical trials, with conduct of the pre- and postnatal development (PPND) study to support registration. The staging of pregnant/lactating women in clinical trials could impact the timing of DART studies, potentially necessitating DART data be available earlier. This could be achieved by continuing dosing through parturition in embryo-fetal development (EFD) studies, conduct of combined EFD/PPND studies, or accelerated scheduling of a dedicated PPND study. Rodents have a short fetal period, representing the minority of pregnancy duration, whereas in humans, the fetal period encompasses the second/third trimesters, exceeding the interval of organogenesis by 2-fold. Continued dosing of an EFD study through parturition in nonrodents, with a proportionally longer fetal period, could permit additional insights into effects during mid and late pregnancy. Toxicokinetic data, including qualification of metabolites, is expected in pregnant animals to inform risk assessment. The modality of drug candidates, as it relates to potential transfer across the placenta or into milk, will also greatly influence the risk assessment. Small molecules, which are able to pass the placenta and into milk by diffusion, and with greater potential for off-target effects, are also more readily evaluated by *in vitro* PBPK models to support risk assessment. Monoclonal antibodies will have limited to no passage across the placenta for a drug intended for use during the first trimester, however the fetus will be extensively exposed during the second half of pregnancy. Similarly, mAbs are excreted into colostrum during early lactation, but are found in irrelevant concentrations in mature milk. As such, the timing of intended clinical use during pregnancy and lactation will be essential to consider.

S21

HALPERN WG. Genentech, South San Francisco, CA, United States. Making Nonclinical Data Meaningful: Communicating Data and Risk Assessment with HCP and Women

This talk will review the place of nonclinical data with the intent of improving the risk:benefit assessment for medicines taken during pregnancy and lactation Historically, we have struggled to enable the use of experimental, or even approved, drugs during pregnancy and lactation. Even when nonclinical data are available, they are often bypassed unless a hazard has been identified. Likewise, when nonclinical safety signals are identified, the species-specific context and assessment may be incomplete. Often the messaging in a drug label is to avoid pregnancy while using the drug, which is even stronger than a recommendation to avoid use of the drug while pregnant. In the case of lactation, the message is often reduced to a choice between the medical benefit of the medicine for the mother, versus the benefit of breastfeeding for the baby. Although there is no easy answer, the vast majority of pregnant and lactating women will use at least one medicine during their pregnancy and/or lactation. Both healthcare providers and women of childbearing potential want to make informed decisions regarding medicines taken during pregnancy, or in choosing to avoid pregnancy; this requires access and interpretation of relevant information, including nonclinical data.

Molecular Mechanisms of Fetal Alcohol Spectrum Disorders (FASD) in Humans and Animal Models Symposium

(Joint with DNTS)

Chairpersons: Peter G. Wells, University of Toronto and Rajesh C. Miranda, Texas A&M Health Science Center

S22

WELLS PG, DRAKE DM, BHATIA S, AFSHARIAN K, CHENG A. University of Toronto, Toronto, ON, Canada. Oxidative DNA Damage and Repair and Epigenetic Mechanisms in Fetal Alcohol Spectrum Disorders (FASD)

This presentation covers molecular mechanisms involving oxidative stress and DNA damage and repair that may contribute to morphological and functional developmental abnormalities, termed fetal alcohol spectrum disorders (FASD), in animal models resulting from exposure to alcohol (ethanol, EtOH) *in utero* or in embryo culture. A brief review will cover mechanisms within the embryo and fetal brain by which EtOH increases the formation of reactive oxygen species (ROS), and critical embryonic/fetal antioxidative enzymes that detoxify ROS. The talk will then focus upon the pathogenic role of EtOH-initiated oxidative DNA damage, and particularly the DNA lesion 8-oxoguanine (8-oxoG), in knockout mice lacking the DNA repair enzyme oxoguanine glycosylase 1 (OGG1) or the DNA repair regulatory protein breast cancer 1 (BRCA1). Potential nonmutational mechanisms by which the 8-oxoG lesion alone or together with OGG1 can directly modulate signal transduction or epigenetically modulate gene expression will be discussed. Particular attention is paid to studies in which chemical and/or genetic manipulation of the above mechanisms alters the ability of EtOH to adversely affect development. Alterations in the above components are also discussed in terms of: 1) individual embryonic and fetal determinants of risk and, 2) potential risk biomarkers and mitigating strategies, including the potential for postnatal reversal of some neurodevelopmental disorders mediated via epigenetic mechanisms. FASD risk is likely increased in progeny that are biochemically predisposed via genetic and/or environmental mechanisms, including enhanced pathways for ROS formation and/or deficient pathways for ROS detoxification or DNA repair.

S23

MIRANDA R[1], PINSON M[2], CHAMBERS C[2]. [1]Texas A&M University, Bryan, TX, United States, [2]UC San Diego, San Diego, CA, United States. Epigenetic Mechanisms: Endocrine miRNAs in Pregnant Women, Predictive of FASD Infant Outcomes, Inhibit Placental Maturation, and Result In Fetal Growth Restriction

Several epigenetic changes, including changes in expression of nonprotein-coding regulatory RNAs like miRNAs, have recently been implicated in teratogenesis due to prenatal alcohol exposure (PAE). We previously reported, in a study of pregnant women in Ukraine, that 11 microRNAs were significantly elevated in plasma of alcohol-exposed mothers whose infants were affected (HEa), compared to mothers who subsequently gave birth to apparently unaffected or unexposed infants. We previously reported that HEamiRNAs inhibited placental trophoblast invasiveness and maturation, and in pregnant women, HEamiRNA expression during the second trimester, explained between 24.5 and 31.8% of growth parameters in their newborn offspring. Moreover, in a mouse model, a single exposure to murine-conserved HEamiRNAs resulted in fetal growth restriction. Here we report that in a mouse model, a single episode of ethanol or HEamiRNAs results in decreased umbilical cord blood flow. RNAseq analysis of placenta showed that HEa miRNAs and ethanol both induce signficant and persistent changes in gene expression. However, the effects of HEamiRNAs do not overlap with the effects of maternal ethanol exposure. Taken together, these data suggest that pathogenic levels of maternal circulating miRNAs may synergize with the effects of ethanol exposure itself, to interfere with placental growth, resulting in fetal growth restriction and thereby contributing to the pathology of Fetal Alcohol Spectrum Disorders (FASD).

S24

RASTEGAR M. University of Manitoba, Winnipeg, MB, Canada. Neural Stem Cell Modeling of FASD: The Mouse Strain- and Sex-dependent Effects of Alcohol on DNA Methylation

Neural stem cells (NSC) are progenitor cells of the central nervous system that differentiate into different brain cell types. During development, the processes of self-renewal and differentiation of neural stem cells can be impacted by environmental insults such as *in utero* alcohol exposure. Independent studies from different groups including us have shown that alcohol (ethanol) alters NSC gene expression program and epigenetic setting. Such molecular damages are well studied, especially on the role of DNA methylation and the main protein that binds to this epigenetic modification, called "MeCP2 (Methyl CpG-Binding Protein 2)". MeCP2 is an important epigenetic factor in the brain and in neurons. Indeed, MECP2 genetic mutations with loss- and gain-of-function lead to neurodevelopmental disorders Rett Syndrome (RTT), and MECP2 Duplication Syndrome (MDS), respectively. Altered MeCP2 expression has recently become an emerging factor involved in Fetal Alcohol Spectrum Disorders (FASD). Although RTT and MDS are rare neurodevelopmental disorders, FASD is a common neurological disorder associated with high economic impact in the society. FASD is the consequence of alcohol consumption by pregnant women, including at an early time when the mothers are still unaware of the pregnancy. FASD refers to a range of neurodevelopmental disorders that are associated with intellectual disabilities, abnormalities in body growth, and malformation of facial characteristics. To identify the important gene regulatory networks that are involved in FASD, we have performed genome-wide RNAseq and candidate-approach analysis in primary brain derived NSC. Our team reported that the deregulatory impact of alcohol on the brain cells is sex-dependent and the outcome may vary depending on the strain of the mice that is used to isolate NSC (Amiri et al., *Molecular Neurobiology* 2020; Xu et al., *Scientific Reports* 2019). Our results highlighted that in modeling neurodevelopmental disorders in mice, sex is an important biological factor that should be considered. Our data would shed light on strain- and sex-specific regulation of MeCP2 and DNA methylation machinery when modeling human disorders in primary neural stem cells. Currently, the potential involvements of specific gene regulatory networks in FASD pathobiology are not fully clear and such studies warrant further investigations.

S25

GOESSLING W. Gastroenterology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States. Transcriptomic Analyses Identify Genetic Modifiers of Adult Cardiometabolic Disease Risk in Zebrafish Following Embryonic Alcohol Exposure

We recently demonstrated that adult patients with fetal alcohol spectrum disorders (FASDs) exhibit increased incidence of metabolic abnormalities, including type 2 diabetes, low HDL, high triglycerides, and female-specific overweight and obesity. Controlled population studies in a zebrafish model of embryonic alcohol exposure (EAE) further confirmed an increased risk for diet-induced obesity and fasting hyperglycemia in adulthood. While EAE larvae initially had embryonic growth restriction and delayed adipocyte maturation, initiation of a high fat high cholesterol (HFHC) diet induced significantly increased visceral adipose tissue size and elevated fasting blood glucose level. The long-term transcriptional consequences of EAE are poorly characterized, and the extent to which specific molecular perturbations or genetic risk factors contribute to these life-long shifts in metabolic disease risk is unknown. To decipher molecular mechanisms underlying altered cardiometabolic health in EAE zebrafish, we performed transcriptomic analyses on pooled control and EAE larvae at multiple developmental stages in the presence and absence of HFHC diet. We identify stage- and diet-specific transcriptional changes that could account for differences in the growth and metabolic health of control and EAE larvae. Forty eight hours after EtOH exposure in seven days post fertilization (dpf) larvae, components of the proteasome were significantly upregulated, combined with evidence of disrupted protein homeostasis. Subsequently, 13 dpf EAE larvae receiving a HFHC diet demonstrated significantly dysregulated genes relevant to metabolism and lipid handling. The transcriptional response to EAE is highly stage-specific and dependent on diet and other environmental factors. No individual gene appears to explain the propensity for metabolic abnormalities following EAE; instead, we identify proteasome dysregulation as a mechanism for EAE-induced growth deficiency and regulators of lipid handling, cholesterol homeostasis, and metabolism as additional candidate modifiers of the observed metabolic effects.

Refining Toxicology Testing to Detect Endocrine Disrupting Chemicals Symposium

Chairpersons: Kembra L. Howdeshell, National Institute of Environmental Health Sciences and Heather B. Patisaul, North Carolina State University

S26

HOWDESHELL KL. National Institute of Health, Research Triangle Park, NC, United States. Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA): Findings and Considerations for Future Guideline Toxicity Testing of Endocrine Disrupting Chemicals

The Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) is a multi-agency research program developed by the National Toxicology Program (NTP) designed to link guideline-compliant and academic research more effectively. BPA, a known endocrine disrupting compound, was selected as a test chemical because of the diverse and challenging-to-interpret body of literature available. The CLARITY-BPA research program combined a perinatal guideline-compliant two-year chronic toxicity study (called the core study) conducted by researchers from the US Food and Drug Administration (FDA) with mechanistic studies and endpoints evaluated by 14 university-based researchers, supported by grants from the National Institute of Environmental Health Sciences (NIEHS). The core study involved a Sprague Dawley rat model orally dosed with vehicle control, BPA in the low dose range (2.5–25,000 μg/kg body weight/day), beginning on gestation day (GD) 6 and continuing through lactation (stop dose) or two years (continuous dose) as well as a positive estrogen control, ethinyl estradiol. The presentation will highlight the published findings and individual authors' conclusions of CLARITY-BPA research program with a focus on the mammary glands and reproductive organ systems. The talk will identify technologies used and endpoints measured among the CLARITY-BPA publications, and the program participants' prior literature, for consideration to detect endocrine disrupting chemicals in future guideline toxicology testing. Finally, the presentation will explore lessons learned from this innovative research program to inform future research collaborations.

S27

PATISAUL H. NC State University, Raleigh, NC, United States. Detecting Endocrine Disruption of Brain and Behavior

Many nonreproductive behaviors are sexually dimorphic and highly dependent on the organizing roles of steroid hormones to fully manifest. Consequently these behaviors and their coordinating neuroendocrine circuitry are vulnerable to endocrine disruption. This talk will illustrate key behaviors, including socioemotional traits of relevance to human neurodevelopmental disorders, and brain endpoints that could be readily examined as part of toxicity testing. Examples from the CLARITY-BPA consortium project and nontraditional animal models will be shown. Focusing on sexually dimorphic traits is critical for understanding how chemical exposures may contribute to neurodevelopmental disorders because most, including autism spectrum disorder and attention deficit hyperactivity disorder, have a strong sex bias.

S28

COECKE S[1], BROWNE P[2], GOURMELON A[2]. [1]European Commission Joint Research Centre, Ispra, Italy, [2]Organisation for Economic Co-operation and Development, Paris, France. Validation of *In Vitro* Thyroid Mechanistic Methods Based on the Organization of Economic Co-operation and Development Scoping Document

Concern over the potential for environmental chemicals to perturb hormone systems has led to the development and implementation of a number of Organization of Economic Co-operation and Development (OECD) Test Guidelines for the screening and testing of endocrine disrupting chemicals. Although a number of methodologies have been developed to interrogate reproductive steroids, incorporation of test methods to evaluate disruptors of thyroid hormone signalling pathways has been limited, owing largely to the complexity of the thyroid system. The thyroid gland plays the central role in the thyroid hormone signalling, which modulates cellular metabolism and signalling pathways at the target tissues and plays a crucial role in the developmental processes, including neurodevelopment. The processes of thyroid hormone biosynthesis, release, uptake at the target tissues and clearance are regulated and interlinked with the hypothalamic-pituitary axis and hepatic metabolism. The European Commission Joint Research Centre's European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM) has joint forces with the OECD to make available 18 Thyroid Hormone Disruption *in vitro* mechanistic methods based on the OECD scoping paper (OECD, 2014). A set of over 100 chemicals selected by a combination of expert input and the use of chemoinformatics tools and Artificial Intelligence-based (AI) tools is being used to assess the reliability and relevance of the battery of *in vitro* mechanistic methods. The presentation will illustrate how global collaboration, harmonisation, interdisciplinary efforts and increasing common awareness of common agreed regulatory information needs can deliver methods and approaches responding to current regulatory challenges for identifying human thyroid disruptors. References: OECD 2014: New scoping document on *in vitro* and *ex vivo* assays for the identification of modulators of thyroid hormone signalling. Series on testing and assessment n° 207, ENV/JM/MONO(2014)23. OECD, Paris.

S29

WIKOFF D[1], FITCH S[2], BORGHOFF S[3]. [1]ToxStrategies, Asheville, NC, United States, [2]ToxStrategies, Katy, TX, United States, [3]ToxStrategies, Research Triangle Park, NC, United States. Case-Study Applications Using Evidence-Based Approaches to Assess Endocrine Activity for Risk Assessment

Risk assessment methods evaluate of a body of evidence to determine the potential for adverse outcomes; however, assessment of endocrine disruption potential requires an extension of the standard paradigm to assess biological pathways, or mechanisms of action. Evidence-based methods, including systematic review, scoping reviews, and systematic generation of evidence inventories facilitate rigorous and transparent assessments of endocrine activity when combined with existing knowledge about estrogen (E), androgen (A), thyroid (T), and steroidogenesis (S) modalities. Collectively, they provide a structured biological platform to organize and integrate evidence in pathway-based assessments. Using case studies of chemicals from consumer products and environmental contaminants, the presentation will demonstrate the challenges and the utilities of applying evidence-based methods in the evaluation of potential endocrine disruption properties. In one example, the ECHA/EFSA guidance was applied to a large and heterogenous evidence base which includes >80 studies of varying design: epidemiological, *in vivo* and *in vitro* guideline-based assays, nonguideline *in vivo* and assays, and high-throughput datasets. Using a structure approach, each experimental dataset was extracted to capture EATS modalities and the weight of evidence was determined for the potential for activity and adversity based on the level (1–5) of the assays, study quality, along with direction of activity, consistency, magnitude. These data were subsequently integrated using a structured approach to assess endocrine-mediated modes of action (hazard), characterize uncertainty, and finally in the development of risk-based conclusions.

Transforming Women's Health Through Better Information on the Safety of Medications During Pregnancy and Lactation Symposium

(Joint with OTIS)

Chairpersons: Janet R. Hardy, Biohaven Pharmaceuticals, Inc. and Elizabeth A. Conover, University of Nebraska Medical Center

S30

SAHIN L. US Food and Drug Administration, Silver Spring, MD, United States. Overview of PRGLAC

Despite there being close to four million births per year in the United States, pregnant and lactating people have been underrepresented in clinical research. In 2016, the 21st Century Cures Act established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to identify and address gaps in knowledge and research on safe and effective therapies for pregnant and lactating people. The PRGLAC task force included representation across federal agencies, industry, academia, and medical societies. This presentation will include an overview of the PRGLAC Task Force recommendations and the implementation plan. Some of the key messages from the PRGLAC Task Force reports include the need for a culture change in the understanding of the importance of including pregnant and lactating people in research, as well as the need to move from automatic exclusion to presumed eligibility for inclusion in clinical trials. This presentation will also discuss the US Food and Drug Administration's efforts to advance data collection in pregnant and lactating people.

S31

TEIL M. UCB Pharma, Brussels, Belgium. Introduction to the ConcePTION Initiative

Pregnant and breastfeeding women have long been overlooked in research due to complex ethical and legal challenges associated with including pregnant and breastfeeding women in clinical trials. However, with more than five million pregnancies per year in Europe, and an average use of three medicines during pregnancy or breastfeeding, women who are pregnant and breastfeeding deserve to have information about the use of medicine during pregnancy and lactation.

ConcePTION is a five-year private-public partnership funded by the Innovative Medicines Initiative (IMI) and composed of a network of more than 80 organizations: universities, pharmaceutical companies, and health authorities, working in partnership towards a collaborative and sustainable goal. ConcePTION builds on novel techniques in biobanking and lactation research, and uses data from various existing and new sources into a common data model in order to provide robust evidence to be used for decision making. The objective is to create a collaborative and sustainable ecosystem to generate robust and rapid scientific evidence to support women, healthcare professionals (HCPs) and regulators globally and address the current knowledge gap. We will describe the ConcePTION structure and the approach to implement this ecosystem. We will share the status of the project and discuss the roles of the eight work packages (WP), and how ConcePTION ensures the engagement of key stakeholders and the sustainability of the ecosystem. This initiative is an important step to inform key stakeholders and to help women make informed decisions about their health during pregnancies and breastfeeding.

S32

HARDY JR[1], TASSINARI MS[2], CONOVER B[3], ROMEO AN[4]. [1]Biohaven Pharmaceuticals, Inc., New Haven, CT, United States, [2]Retired, Harwich Port, MA, United States, [3]Nebraska Teratogen Information Service, Omaha, NE, United States, [4]Pregnancy Risk Line/MotherToBaby, Salt Lake City, UT, United States. PRGLAC: Data Gaps and Strategies

Pregnant women remain underrepresented in research. The Task Force on Research Specific to Pregnant Women and Lactation Women (PRGLAC) was established to advise the Secretary of Health and Human Services (HHS) regarding gaps in knowledge and research specifically on safe and effective therapies for pregnant women and lactating women. Research on the safety of medications and vaccines in pregnancy and lactation has traditionally occurred after products are market approved. Significant time can pass before safety data accrue. The PRGLAC recommends inclusion of pregnant and lactating women in clinical research. The recommendations also include development of research and training programs to expand the availability of preclinical models (e.g., tissue on a chip). The development and implementation of such research models will help support nontraditional methods to estimate risk and evidence-based decision-making. We will describe the PRGLAC identified research gaps and strategies to address them. COVID-19 has increased the urgency for more research on therapy and vaccine safety in pregnancy. We will describe how COVID-19 has advanced the consideration of pregnancy and lactation clinical studies. The safety of medications and vaccines in pregnancy and lactation remains a major public health concern. Research on these topics is foundational to the Society for Birth Defects Research and Prevention (BDRP) and the Organization for Teratology Information Specialists (OTIS). BDRP and OTIS members have the expertise to meaningfully contribute to the discussions regarding research needs and to conduct research needed to help address data gaps that will ultimately help inform provider-patient discussions and policy.

Hot Topic Symposium
Assessing Reproductive Risks from Fracking and Mountaintop Mining

Chairpersons: Christine Perdan Curran, Northern Kentucky University and Philip Lupo, Baylor College of Medicine

S33

MCKENZIE LM. University of Colorado Anschutz Medical Campus, Aurora, CO, United States. Intensity of Oil and Gas Well Site Activities in Early Pregnancy and the Risk of Structural Birth Defects

Teratogens, including benzene, toluene, and xylene, emitted from oil and natural gas well sites may increase structural birth defect risk in infants whose mothers live near the sites during pregnancy. This presentation will summarize the current evidence on the prevalence of structural birth defects in infants of pregnant women living in areas with oil and natural gas activity. We reviewed four observational studies published between January 2014 and March 2021 that evaluated associations between prevalence of congenital heart defects, neural tube defects, oral clefts, and/or gastroschisis and maternal proximity to oil and natural gas well sites. Two studies applied retrospective cohort designs and two studies applied case-control designs. The combined study population includes 1,300,120 infant-mother pairs obtained from the Colorado, Oklahoma, and Texas birth defects and birth registries. To assess exposure, the studies used oil and natural gas well information obtained from the Colorado Oil and Gas Information System, the Oklahoma Corporation Commission, and the Railroad Commission of Texas to calculate either the density of oil and natural gas well sites or intensity of oil and natural gas activity surrounding the maternal residence using inverse distance weighting methods. The studies found that the prevalence of congenital heart and neural tube defects is higher in infants of pregnant woman living in areas with the most oil and natural gas activity than in infants of pregnant women living in areas with no or low oil and natural gas activity. Specifically, these studies indicate odds ratios ranging from 1.36–4.0 for pulmonary artery and valve, aortic artery and valve, conotruncal, and tricuspid valve defects, as well as hypoplastic left heart syndrome. These studies also indicate odds ratios ranging from 1.2–2.4 for anencephaly and spina bifida. The Texas study found evidence of increased prevalence of gastroschisis for infants of older mothers. None of the studies found evidence of an association between oral clefts and maternal proximity to oil and natural gas well sites. The current evidence indicates that infants of mothers that live in areas with high oil and natural gas activity during their pregnancy are at a higher risk of several specific types of congenital heart defects, neural tubes, and gastroschisis. Further study will be necessary to address remaining limitations in exposure specificity and potential confounding.

S34

DEZIEL NC[1], CLARK CJ[1], XIONG B[2], SIEGEL H[3], JOHNSON NP[1], SORIANO M[3], SORRENTINO KK[1], GAUGHAN C[1], GUTCHESS K[3], PLATA D[4], SAIERS J[3]. [1]Yale School of Public Health, New Haven, CT, United States, [2]University of Minnesota, Minneapolis, MN, United States, [3]Yale School of the Environment, New Haven, CT, United States, [4]Massachusetts Institute of Technology, New Haven, CT, United States. Drinking Water Vulnerability and Neonatal Health Outcomes in Relation to Oil and Gas Production in the Appalachian Basin

Epidemiologic studies have observed associations between exposure to unconventional oil and gas (UOG) development and adverse birth outcomes, including reduced fetal growth, preterm deliveries, and congenital malformations These studies have primarily used spatial metrics incorporating distance and density as surrogates of exposure, which are feasible approaches for retrospectively assessing aggregate exposures in large-scale studies. Investigating which exposure pathways may be captured by these metrics can illuminate potential underlying mechanisms. We conducted a groundwater exposure study comparing several spatial metrics with detection frequencies of 47 organic UOG-related chemicals/chemical groups in residential groundwater from 255 homes in two states in the Appalachian Basin (n=94 in Pennsylvania [PA], n=151 in Ohio [OH]). We considered traditional metrics (e.g., inverse distance weighted UOG well count) and a new, water-specific metric, IDups, which represents the inverse distance to the nearest topographically upstream UOG well. Ten chemicals/chemical groups were detected in at least 20% of samples; four had evidence of developmental or reproductive toxicity. However, chemicals were present at concentrations far below health standards. IDups was associated with increased odds of detection for bromomethane (odds ratio [OR]: 2.6, 95% confidence intervals [CI] 1.1–6.1), toluene (OR: 2.6, 95% CI: 1.1–6.5), and xylenes (OR: 3.4, 95% CI: 1.2–9.7) at 1 km and 1,2-dichloroethene and benzene (OR: 2.6, 95% CI 1.0–6.7) at 2 km; associations were not observed for other chemicals. These relationships were relatively consistent across metrics. Our results found that spatial surrogates were not generally associated UOG-related organic chemicals. These findings may indicate that 1) water contamination by UOG occurs with low frequency or is episodic yielding a temporal misalignment between measurements and metrics, 2) more complex groundwater flow and contaminant fate and transport metrics are needed to accurately capture drinking water exposure, and/or 3) spatial surrogates in health studies could be more reflective other stressors (e.g., air pollution, noise, stress).

We are conducting a retrospective birth cohort study of UOG exposure and risk of adverse birth outcomes in OH using both traditional metrics and water-specific metrics in a population of 967,112 children born between 2010–2017 with 6,420 confirmed cases of congenital malformations.

S35

NURKIEWICZ T. West Virginia University, Morgatown, WV, United States. Using Animal Studies to Understand Reproductive Risks Associated with Inhalation Exposures to Particles

Air pollution generated from mountaintop mining operations and hydraulic fracturing is complex, dynamic and frequently occurs in close proximity to diverse populations. This risk is augmented by the geography common to Appalachia. Inhalation is the primary exposure route through which these toxicants alter biologic function. Therefore, particle surrogates (titanium dioxide, carbon black) are frequently used in whole body inhalation exposures with rats and mice. This presentation will discuss the various particle surrogates commonly used in animal studies and the specific physicochemical characteristics of these aerosols. Some of the most relevant characteristics are aerosol concentration, particle size and cumulative aerosol size distribution as these are used to establish lung burden. The role of particle size on deposition will be presented in terms of coarse, fine, and ultrafine particulate matter. Our research program is focused on the impact of these exposures on microvascular function in various systems, most notably the reproductive system. The role of gestational day of exposures, and cumulative dose on reproductive outcomes will be discussed. Specific outcomes will focus on maternal vascular dysfunction, placental dysfunction, and fetal health. Mechanisms of these dysfunctions will also be presented that include: pulmonary inflammation propagating into systemic inflammation, endothelial dysfunction, oxidative stress, placental efficiency, conservation of litter mass. In all these regards a relationship with inappropriate microvascular adaptation to pregnancy will be established.

S36

CURRAN CP. Northern Kentucky University, Highland Heights, KY, United States. Fuel for Thought: Summing Up the Risks from Unconventional Energy Extraction

More than two-thirds of natural gas and nearly 60% of crude oil in the United States is produced by hydraulic fracturing or “fracking.” Mountaintop coal mining has affected more than 1.5 million acres in central Appalachia since the 1970s with ~21,000 more acres affected each year. This talk will review the extent of unconventional natural gas extraction and mountaintop mining as well as recent studies that report an association between these methods and adverse reproductive outcomes. Novel methods for collecting exposure data will be explained. The weight of evidence will be considered for endpoints including preterm births, low birthweights and endocrine disruption. This talk will end with a discussion with all participants about collaborative opportunities and priorities to be explored further in the annual Research Needs Workshop.

Society for Birth Defects Research and Prevention

WORKSHOP ABSTRACTS

(Presenter designated by underlined author.)

Current Topics and Updates for Pregnancy Registries Workshop

(Joint with OTIS)

Chairpersons: Lewis B. Holmes, MassGeneral Hospital for Children and Keele Elise Wurst, GlaxoSmithKline

W1

SCHEUERLE A. UT Southwestern Medical Center, Dallas, TX, United States. Criteria Used for Classifying Abnormalities Identified in the Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry (APR) is designed to identify teratogenic signals in pregnancies exposed to the covered medications. It is tasked by the US FDA to report fetal and neonatal malformations. APR birth defect rates are compared to population-based rates published by the Metropolitan Atlanta Congenital Defects Program (MACDP) and the Texas Birth Defects Registry (TxBDR). In order to facilitate this comparison, the APR uses the same defect definition and classification scheme as the public health entities. However, the data sources and goals of the APR and of public health entities differ and allowances must be made for that. Similarities are the list of defects used and the definitions of major and minor malformations. MACDP and TxBDR use the six-digit or "BPA" code list, which is recommended by the FDA for this work. Use of the list translates to a general protocol for defining defects as "major" or "minor." It must be noted that public health entities are think of defects as those that are of medical importance and are consistently ascertained—"codable"—and those that are inconsistently ascertained—"conditional". Conditional defects may also be those that are surveilled by other programs such as newborn screening. These definitions do not strictly adhere to the medical meaning of "major" and "minor" malformations, though there is substantial overlap. The APR receives much less defect information per case than the model active surveillance systems, and it relies on passive, voluntary reporting usually by physicians for the mother rather than the infant. To compensate for some of these differences, the APR uses a less detailed birth defect list that combines defects of similar embryology. It is considered a case with two minor malformations alone to be a defect case. Also, defects or other medical problems actively excluded by MACDP and TxBDR are coded as "not a defect" or "not a defect – other", respectively within the APR and can be analyzed separately. This talk will review the APR approach for classifying and coding birth defects and other health problems within its database population.

W2

HOLMES LB. MassGeneral Hospital for Children, Boston, MA, United States. Inclusion/Exclusion Criteria Used by North American Antiepileptic Drug (AED) Pregnancy Registry

A common method for identifying human teratogens is to examine the exposed fetus at birth for the presence of malformations. A pregnancy registry uses copies of the pediatricians' written exam findings to confirm the presence of malformations. It is essential to establish, in advance, those physical features included as structural abnormalities and those excluded. In this Registry the definition of a malformation used is a structural abnormality with surgical, medical or cosmetic importance. Exclusions are: 1) minor anomalies (transverse palmar crease); 2) birth marks (hemangiomas); 3) positional deformities (torticollis); 4) transient heart findings (muscular VSD); 5) features of prematurity (undescended testes; PDA); 6) findings in newborn screening (PKU; hearing loss); 7) genetic disorders and chromosome abnormalities (achondroplasia, Down Syndrome); and 8) findings in prenatal screening that are not confirmed at birth by the examining pediatrician. The findings recorded by examining pediatricians in 1,000 consecutive newborn infants showed that the features excluded (n=320) were 18 times more common than the malformations identified (n=18) [Holmes LB, Westgate M-N: Birth Def Res (Part A) 2011; 91:807–812]. Having an unexposed comparison group whose findings are evaluated by the same staff, using the same interviews and requested medical records, provides the most informative comparison in assessing a potential teratogenic effect (Smith CR et al. *Birth Def Res (A)* 2009; 82:311). The frequency of malformations identified increases in the first year of life and thereafter. This makes it essential to establish a "time window" in which the malformations are identified. Population-based studies, like the MACDP at CDC, have shown that the prevalence rates at birth were 2.1% and increased to 2.6% at 6 to 12 months of age (Correa A et al.: *Birth Def Res* 2007; 79:106. Inclusion and exclusion criteria are arbitrary, but if used in both exposed and unexposed infants, the comparison will be informative. The North American AED Pregnancy Registry is supported by: AbbVie, Advanz, Greenwich Biosciences, Janssen, Pfizer, Sunovion, UCB, Apotex, Aurobindo Pharma USA, Cipla, Dr. Reddy's Lab, GlaxoSmithKline, Sandoz and Teva Pharmaceuticals.

W3

CHAVEZ N. Nicole Chavez Public Relations, Madison, CT, United States. An Update on the Use of Social Media to Recruit Pregnant People into Pregnancy Registries

Facebook and its sister site, Instagram, continue to be the platforms of choice for women of childbearing age. Daily, there are more than 1.62 million people active on Facebook and 75% of all women in the United States have profiles on the platform. In July 2018, Instagram reached one billion users. Users under age 35 make up more than 70% of Instagram users. The most active age bracket is 18–29. For these stated reasons, it was likely that Facebook and Instagram were platforms of choice for women of childbearing age. For pregnancy registry recruitment with smaller outreach budgets, it is important to stretch dollars while still generating results. Since it was evident that the Facebook and Instagram social media platforms were potentially where its targeted female audience was spending its time, the North American Antiepileptic Drug (AED) Pregnancy Registry explored Facebook and Instagram advertising campaigns in an effort to increase registry recruitment numbers in both exposed and nonexposed populations. This effort began in 2016. This talk will examine strategies and results of the first few years of the social media effort to recruit women into the registry, and whether it was a cost-effective way of not only recruiting pregnant women into the study, but if it was a platform that resulted in strong retention rates compared to women recruited in more traditional ways, such as through healthcare provider referrals.

W4

HOELTZENBEIN M, SLIMI S, FIETZ AK, ONKEN M, DATHE K, SCHAEFER C. Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt Universität zu Berlin, and Berlin Institute of Health, Institut für Klinische Pharmakologie und Toxikologie, Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie, Berlin, Germany. Trends in Antiepileptic Drug Use and individual Treatment Pattern during the First Trimester of Pregnancy: An Evaluation of the German Embryotox Cohort

Due to their developmental toxicity, some antiepileptic drugs (AEDs) should be avoided during pregnancy. Concerns about adverse fetal effects may lead to discontinuation or switching of AEDs after recognition of pregnancy. Data on AED treatment changes during the first trimester of pregnancy are still scarce. Trends in AED use at conception were analyzed in 3,763 prospectively ascertained pregnancies at the German Embryotox Pharmacovigilance Institute between 2000 and 2018. In addition, treatment pattern during the first trimester in women with epilepsy (n=2,395) including the proportion of recommended (lamotrigine/levetiracetam) and nonrecommended (valproate/phenobarbital/phenytoin/topiramate) AEDs were evaluated. There was an increase in women using AEDs for nonepilepsy indications from 19% in 2000 to 39% in 2018. In women with epilepsy analysis of treatment pattern over time showed a shift from nonrecommended teratogenic AEDs to recommended AEDs. However, at the end of the study period (2017–2018), 13% of women still used nonrecommended AEDs at conception. Despite limited evidence of safety for the unborn, zonisamide, lacosamide, eslicarbazepine, and brivaracetam as newer AEDs with marketing authorization after 2004 were increasingly used, even shortly after their approval. Among women with livebirth and complete information on course of AED use 90% (1,361/1,506) did not change AED treatment during the first trimester, 7% discontinued, and 2% switched to other AEDs. Valproate, oxcarbazepine, and topiramate were more likely discontinued or switched than other AEDs. Focusing on women with AED monotherapy 4% discontinued antiseizure medication, 2% switched to other AEDs, and 1% added an AED during the first trimester. 16% of women with polytherapy at conception reduced the number of concomitantly used AEDs. This first analysis of treatment pattern in AED exposed pregnancies in Germany confirms a trend also observed in other countries towards less teratogenic and newer AEDs. However, it remains questionable whether women still using nonrecommended AEDs with a teratogenic potential or insufficient evidence of safety are refractory to established AEDs of lower risk or if pertinent treatment guidelines and risk minimization measures for women of childbearing age are disregarded. This work was funded by the German Federal Institute for Drugs and Medical Devices (BfArM).

W5

SILLIS L[1], CEULEMANS M[1], VAN CALSTEREN K[2,3], SMITS A[3,4], HOMPES T[5,6], BOGAERTS A[3,7,8], ALLEGAERT K[1,3,9], DE VOS M[3,10], VERBAKEL JY[11,12], FOULON V[1]. [1]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Belgium, [2]Department of Obstetrics and Gynecology, University Hospitals Leuven Gasthuisberg, Belgium, [3]Department of Development and Regeneration, KU Leuven, Belgium, [4]Department of Pediatrics and Neonatology, University Hospitals Leuven Gasthuisberg, Belgium, [5]Adult Psychiatry UPC, KU Leuven, Belgium, [6]Department of Neurosciences, KU Leuven, Belgium, [7]Faculty of Medicine and Health Sciences, University of Antwerp, Belgium, [8]Faculty of Health, University of Plymouth, Devon, United Kingdom, [9]Department of Clinical Pharmacy, Erasmus MC Sophia's Children Hospital, the Netherlands, [10]Department of Electrical Engineering (ESAT), KU Leuven, Belgium, [11]Department of Public Health and Primary Care, KU Leuven, Belgium, [12]Nuffield Department of Primary Care Health Sciences, University of Oxford, United Kingdom. The Development of a Belgian Prospective Data Registration System on Perinatal Medication Use and Mother-Infant Outcomes: An Introduction to the BELpREG Initiative

Recent studies have demonstrated that perinatal medication use is also common in Belgium. As in other countries, this entails safety questions and information needs, among patients as well as healthcare professionals (HCP). The research potential of real-world data regarding medication safety is currently underused in Belgium due to a lack of comprehensive data registration and infrastructure. Therefore, the researchers involved in the future establishment of a Belgian TIS recently founded the BELpREG initiative aimed at developing a prospective data registration system on perinatal medication use and mother-infant outcomes. Both female/male patients and HCPs will be able to register data by using a web interface or mobile application. Linkage with software systems of HCPs will be strived for as this would facilitate data entry by HCPs; the opportunity to collect data on infant development will also be explored. The development of BELpREG mainly focuses on the following four activities: 1) exploring the technical prerequisites of the data collection instrument; 2) defining a list of core variables to be registered; 3) investigating the privacy and ethical considerations for data collection and processing; and 4) investigating the preferences of HCPs and patients on data registration. REDCap software has been chosen as data capturing instrument. To define the core variables, a Delphi study, based on the list of common data elements which has recently been compiled within the ConcePTION project, will be applied. This approach will not only guarantee evidence-based data collection but will also increase the willingness of Belgian HCPs to register data. A collaboration with legal experts has been set-up to ensure optimal adherence to current data protection and ethical regulations. Finally, interviews and 'thinking aloud' experiments with HCPs and patients will contribute to an optimal accessibility and usability.

New Frontiers in Developmental Toxicity Testing for Environmental Chemicals Workshop

Organized by the Science Committee

Chairpersons: Thomas B. Knudsen, US Environmental Protection Agency and Susan Y. Euling, US Environmental Protection Agency

W6

FAUSTMAN EM. University of Washington, School of Public Health, Seattle, WA, United States. Challenges and Opportunities: Building NAMs to Reflect Developmental Stage Complexity

Recognition that normal human development is part of a larger life course across ages which forms along developmental trajectories has provided our discipline with a expanded framing for how we look at windows of susceptibility. When paired with conversations about wellbeing and resilience this life course framework provides both challenges and opportunities to researchers who are interested in evaluating various environmental impacts along this trajectory including both positive and potentially negative impacts. The purpose of this talk will be to set this stage by discussing the life course dynamics and then discuss how new approach methods (NAM) capture developmental trajectories *in vitro* and *in silico* using a series of case studies. The ability of NAM to capture specific developmental trajectories either for cells, tissues or organisms can be thought of in terms of "domain of applicability" where this phrase can be used in this context to mean what developmental processes are captured and replicated in a specific NAM and in example cases within a class of chemicals with replicability of a similar potency gradient (ranking) across methodological applications. For developmental processes this has been especially challenging as many cell signaling processes associated with both normal and perturbed development are shared, for example, apoptosis and inflammation. Case studies evaluating neuro, repro and developmental windows will be discussed as well as examples from *in vitro* organotypic cell cultures, micro physiological systems and *in silico* cell free systems. Domain of applicability will be examined using several levels of biological complexity to explore limitations of application.

W7

PETERSON RT. University of Utah, Salt Lake City, UT, Unites States. Scaling Up: Zebrafish Social Interaction as Scalable Phenotype for Identifying Neurodevelopmental Toxicants and Their Mechanisms

Sociality is widely conserved across the animal kingdom, facilitating cooperation, reproduction, and protection from predation. In humans, disruption of social preference is a hallmark of several neurodevelopmental disorders, including autism. To identify environmental factors that influence development of sociality, we developed an automated screening system to screen for small molecules that disrupt development of social preference behavior in zebrafish. In a screen of 1,120 drugs, we discovered that the α isoform of topoisomerase II (Top2a) is essential for zebrafish social behavior development. This function is conserved in mice, where prenatal exposure to the Top2 inhibitor ICRF-193 caused durable behavioral deficits related to core features of autism. Top2a depletion in zebrafish selectively altered expression level and epigenetic status of autism-associated genes, and mechanistic studies revealed Ezh2 and H3K27me3 as the key mediators of this effect. These findings identify Top2a as a key component of an evolutionarily conserved regulatory mechanism essential for the development of social behavior.

W8

DE SOYSA Y[1], RANADE S[2], GIFFORD C[3], OKAWA S[4], RAVICHANDRAN S[4], DEL SOL A[4], SRIVASTAVA DD[5]. [1]Boston Children's Hospital, Boston, MA, United States, [2]Gladstone Institutes, San Francisco, CA, United States, [3]Stanford University School of Medicine, Stanford, CA, United States, [4]University of Luxembourg, Luxembourg Centre for Systems Biomedicine, Esch-sur-Alzette, Luxembourg, [5]Gladstone Institutes; UCSF, San Francisco, CA, United States. Single-Cell RNA-Sequencing Analysis of Early Cardiogenesis Reveals Cell-Type-Specific Perturbations that Drive Organ-Level Developmental Defects upon Hand2 Loss

Organogenesis involves integration of myriad cell types, each progressing through successive stages of lineage specification, proliferation and differentiation. Establishment of unique gene networks within each cell drives fate determination and behavior, and mutations of the transcription factors that drive such networks can result in birth defects. Congenital heart malformations are the most common defects, and are caused by disruption of discrete subsets of progenitors that contribute to distinct cardiac structures. However, determining the transcriptional changes in individual cells that lead to organ level defects in the heart has not been tractable. Moreover, although genetic analyses are revealing mutations that may contribute to congenital heart defects (CHD), identification of specific cell types and the progenitors from which they are derived that are affected by such mutations has remained a challenge. To address these challenges, we identified the transcriptional features of cardiac cell specification and morphogenesis with single-cell transcriptomics. We sequenced over 36,000 individual cells collected from the cardiogenic region of wild-type mouse embryos at embryonic day (E)7.75, E8.25, and E9.25. Our analyses identified novel cardiac cell-type-specific genes, additional heterogeneity within wild-type progenitor compartments and enrichment of genes with CHD mutations in specific cell populations. A network-based computational method that predicts lineage specifying transcription factors identified Hand2 as a specifier of outflow tract cells but not right ventricular cells, despite failure of right ventricular formation in Hand2-null mice. Temporal single-cell transcriptome analysis of Hand2-null embryos revealed failure of outflow tract myocardium specification, whereas right ventricular myocardium was appropriately specified, but exhibited differentiation defects and failed to migrate into the developing heart. We found dysregulation of retinoic acid signaling that was associated with posteriorization of anterior cardiac progenitors in Hand2-null mutant hearts and ectopic atrial gene expression in outflow tract cells and right ventricle precursors. This work reveals transcriptional determinants in individual cells that specify cardiac progenitor cell fate and differentiation, and exposes mechanisms of disrupted cardiac development and single-cell resolution, providing a framework to investigate congenital heart defects.

W9

KNUDSEN TB. US Environmental Protection Agency, Research Triangle Park, NC, United States. Predictive Developmental Toxicity with Pluripotent Stem Cell Models and ToxCast/Tox21 Assay Batteries

Assessing developmental toxicity during pregnancy has a critical role in setting health and environmental policy. *In vitro* assays and *in silico* models that reflect key aspects of embryo-fetal development will be indispensable for NAM-based detection of developmental hazard potential in animal models of human relevance (e.g., pregnant rats, rabbits). High-throughput screening (HTS) and other *in vitro* platforms using pluripotent stem cell (PSC) lines established from the embryoblast (mouse, human) can recapitulate some of the biology driving embryogenesis during the period covered by guideline prenatal studies (e.g., OECD TG 414). Computational models built on biological knowledge of embryogenesis can extend data-driven models to predict thresholds of developmental toxicity potential or inform mechanistic pathways and processes. This presentation will provide an update on the use of pluripotent and differentiating stem cell models for predictive modeling of developmental toxicity. Learning objectives will include: 1) a compilation of various stem cell modalities for developmental toxicity; 2) synopsis of an ongoing international effort (Europe, Japan, USA) scoping the performance of stem cell models for predictive developmental toxicity in the published literature; 3) performance-based evaluation of stem cell assays in ToxCast/Tox21 for threshold-based determinations of developmental toxicity in pregnant animal studies; 4) improvements in assay sensitivity with deep learning models utilizing >1000 assays from the ToxCast/Tox21 assay portfolio; and 5) applications to *in silico* toxicodynamic models in a virtual embryo platform. This abstract does not represent the views of the Agency.

Society for Birth Defects Research and Prevention

PLATFORM ABSTRACTS

(Presenter designated by underlined author.)

Graduate Student and Postdoctoral Fellow Platform Session 1

Organized by the Student Affairs Committee

Chairpersons: Paul B. Bushdid, Covance Laboratories Inc. and Laura Carlson, US Environmental Protection Agency

1

AFSHARIAN K, WELLS PG. University of Toronto, Toronto, ON, Canada. Enhanced Ethanol-initiated, Reactive Oxygen Species-dependent Embryopathies in Breast Cancer 1 (Brca1) Knockout Mouse Embryos in Culture

The breast cancer 1 (Brca1) gene is widely known for its role in breast cancer, and regulates key enzymes involved in DNA repair and antioxidative signalling pathways, which our lab has shown protects the embryo and fetus from developmental disorders mediated by reactive oxygen species (ROS). Physiological levels of ROS in the developing brain are implicated in postnatal neurodevelopmental deficits in genetically predisposed mice, potentially relevant to autism spectrum disorders (ASD), and ethanol (EtOH)-enhanced ROS levels are implicated in fetal alcohol spectrum disorders (FASD). Our lab has characterized an *in vivo* mouse Brca1 knockout (KO) model in which heterozygous (+/-) progeny exhibit over a 50% reduction in BRCA1 protein and increased neurodevelopmental disorders compared to their wild-type (+/+) littermates. Herein, we established a whole embryo culture model for Brca1 embryos to determine the role of BRCA1 and ROS as risk factors for morphological abnormalities in this strain. Embryos were extracted on gestational day (GD) 8.5 and cultured at 37 ºC in medium containing 2 mg/mL EtOH or saline vehicle. After 24 hr, embryonic gross morphological development was assessed using a dissecting microscope. Compared to saline controls, which developed normally, EtOH increased embryopathies in +/+ embryos ($p<0.05$), and more so in +/- littermates ($p<0.05$), the latter confirming a protective role for BRCA1 in this strain. Specifically, in +/+ embryos, EtOH reduced only head length, turning and somite development ($p<0.05$), whereas +/- littermates exhibited abnormalities in all parameters except anterior neuropore closure ($p<0.05$). In preliminary additional studies, pretreatment with the free radical spin trapping/ROS blocking agent phenylbutylnitrone (PBN) prevented the EtOH-initiated decrease in at least somite development ($p<0.05$), and showed a similar protective trend for blocking EtOH effects on anterior neuropore closure and turning, suggesting that the pathogenic mechanism was ROS-mediated. This strain of Brca1 KO embryos develop normally in culture, and are similar to another type of Brca1 conditional KO embryos in their response to EtOH and PBN. These results corroborate the developmental role of BRCA1 in protecting the embryo from ROS, and will be useful in determining the molecular consequences and morphological developmental impacts of losing one Brca1 allele.

2

VALLADARES DA, KRAMER EF, POWELL MM, POMPUTIUS A, RASMUSSEN SA. University of Florida, Gainesville, FL, United States. COVID-19 and Its Effects on the Newborn: A Rapid Review of Available Data

Background: Recent outbreaks of infectious diseases (e.g., 2009 H1N1 influenza and Zika) have had significant effects on pregnant women and their infants. Thus, understanding the effects of COVID-19 during pregnancy is essential. We conducted a literature review to better understand the frequency of intrauterine transmission of SARS-CoV-2 as well as to understand COVID-19's effects during pregnancy on neonatal outcomes. Methods: To identify reports of SARS-CoV-2 infection during pregnancy, relevant search terms were utilized across PubMed, Cochrane, Embase, and Web of Science to identify articles between January 1 and July 17 of 2020. Two independent reviewers reviewed abstracts of papers identified, with subsequent review of relevant full text articles for inclusion. We evaluated all neonates who tested positive for SARS-CoV-2 using criteria developed by Blumberg et al. to identify cases of possible intrauterine transmission. Results: 1,019 abstracts were screened with 334 articles selected for full text review. Ultimately, 151 articles met our criteria for inclusion. Preterm birth, low five-minute APGAR scores, and low birthweight occurred more often among mothers with severe COVID-19 illness. Among 1,250 neonates tested for SARS-CoV-2, 101 tested positive, with 80 testing positive during the first week of life; of those, eight satisfied Blumberg criteria, although only three were likely to represent intrauterine transmission. Discussion: Adverse pregnancy outcomes were observed more often in mothers with more severe COVID-19 illness. Intrauterine transmission of SARS-CoV-2 occurs but appears to be infrequent, and its effects are inconsistent. Our findings emphasize the importance of preventing SARS-CoV-2 infection during pregnancy.

3

ISKANDARANI L[1], HALES BF[2], ROBAIRE B[2]. [1]Department of Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada. The Effects of Bisphenols on Endochondral Ossification in Murine Limb Bud Cultures

The bisphenols are a family of chemicals commonly used to produce polycarbonate plastics and epoxy resins used in consumer products. Bisphenols often leach out of these products, resulting in widespread exposure and leading to concerns about their possible impact on human health. There is evidence that bisphenol A (BPA) is an endocrine disrupting chemical that is associated with a variety of adverse effects both in humans and in animals. Thus, many alternatives to BPA, such as BPAF, are now emerging in consumer products. It was shown that *in utero* exposure to BPA affected skeletal development in animal models. However, it remains unknown whether BPA and its alternatives specifically disrupt endochondral ossification, the process by which bone is formed. Using an *ex vivo* murine limb bud culture system, we determined the effects of BPA and BPAF on endochondral ossification. The major stages of this process were visualized using triple transgenic mice that express fluorescent markers of collagen: COL2A1-eCFP (proliferative chondrocytes), COL10A1-mCherry (hypertrophic chondrocytes), and COL1A1-YFP (osteoblasts). The forelimbs of gestation day 13 embryos were cultured in the presence of vehicle (DMSO), BPA (1, 10, 50, or 100 μM), or BPAF (0.1, 1, 5, or 10 μM). BPA (≥10 μM) and BPAF (≥1 μM) reduced the differentiation of hypertrophic chondrocytes and osteoblasts, as seen by a reduction in COL10A1-mCherry and COL1A1-YFP fluorescence. Significant suppressions in chondrogenesis, as indicated by decreases in the morphological scores assigned to each limb, were observed after exposure to ≥50 μM BPA or ≥5 μM BPAF. Osteogenesis was almost completely arrested after exposure to 100 μM BPA or 10 μM BPAF. Both BPA and BPAF affected the expression of Sox9, Runx2, and Sp7, the master regulators of endochondral ossification. The expression of Sox9 was downregulated at the 3-hour time point after exposure to 10 or 50 μM BPA and to 1 or 5 μM BPAF. Exposure to 50 μM BPA downregulated the expression of Runx2 at all time points and downregulated the expression of Sp7 at later time points, compared to control limbs. Our data suggest that BPAF, the replacement bisphenol, appears to be more detrimental to endochondral ossification than BPA.

4

DRAKE DM, WELLS PG. University of Toronto, Toronto, ON, Canada. A Novel Molecular Basis for Breast Cancer 1 Protein (BRCA1) Protection of the Fetal Brain from Developmental Disorders Mediated by Reactive Oxygen Species

Reactive oxygen species (ROS) within the fetal brain optimize neurodevelopment, but also can cause pathogenic oxidative DNA damage. The breast cancer 1 (BRCA1) protein facilitates DNA repair, which protects the fetus from ROS-mediated DNA damage and developmental abnormalities caused by physiological and alcohol (ethanol, EtOH)-enhanced levels of ROS , respectively relevant to autism and fetal alcohol spectrum disorders (ASD, FASD) (Drake & Wells, *Birth Defects Res.* 112(11): 793 (No. 2), 2020). Herein we investigated the molecular mechanisms by which BRCA1 deficiency enhances the risk of ASD and FASD. Heterozygous (+/-) Brca1 knockout (KO) females and males were mated, and pregnant dams were treated once on gestational day 17 with either EtOH (4 g/kg i.p.) or its saline vehicle, with or without phenylbutylnitrone (PBN, free radical spin trap/ROS inhibitor) pretreatment. Fetal brains were collected 6 h post-treatment and assessed for ROS formation [NADPH oxidase (NOX) activity], DNA strand breaks (DSBs) and antioxidative capacity (catalase activity). Fetal +/- brains with ~50% less BRCA1 protein exhibited ~37% higher NOX activity ($p<0.0001$), ~50% enhanced DSBs ($p<0.0001$) and ~70% enhanced catalase activity ($p<0.0001$) compared to wild-type (+/+) littermates, independent of treatment. *In utero* EtOH exposure further enhanced NOX activity ($p<0.0001$), DSBs ($p<0.0001$) and catalase activity ($p<0.0001$) by 20, 36 & 35% respectively compared to saline-exposed +/- fetal brains. Pretreatment with the ROS inhibitor PBN reduced EtOH-enhanced NOX activity ($p<0.0001$), DSBs ($p<0.0001$) and catalase activity ($p<0.0001$) by 15, 26 & 28% respectively in +/- fetal brains, confirming ROS-dependent mechanisms. In +/+ fetal brains, EtOH similarly enhanced NOX activity ($p<0.0001$), DSBs ($p<0.0001$) and catalase activity ($p<0.05$) by 43, 20 & 27% respectively. PBN pretreatment similarly reduced +/+ NOX activity ($p<0.0001$), DSBs ($p<0.001$) and catalase activity ($p<0.0001$) by 13, 14 & 37% respectively. The increased NOX activity in +/- Brca1 fetal brains reveals a novel mechanism by which BRCA1 deficiency enhances oxidative DNA damage and neurodevelopmental disorders, which are not prevented by the concomitant increase in catalase activity. The developmental role of BRCA1 in protecting the fetus from both physiological and EtOH-enhanced ROS formation involves the regulation of both NOX and DNA repair.

5

MOMBEN ABOLFATH S, XU Y, HE Y, ELLER N, NORTON M, STRUBLE E. US Food and Drug Administraition, Silver Spring, MD, United States. Evaluation of Viral Entry and Cellular Passage of Zika Virus Immune Complexes in a Tissue Culture Model of the Maternal-Fetal Interface

When acquired during pregnancy, Zika virus (ZIKV), a member of the Flaviviridae family of RNA viruses, is associated with fetal microcephaly and other birth defects of the newborn. Treatment with anti-ZIKV polyclonal antibodies has been proposed as a potential therapy, to benefit both mother and baby. Unlike most biologics, maternal immunoglobulin G (mIgG) passes the placenta, playing a crucial role in protecting the fetus and future newborn from viral infections. This process is mediated by the neonatal Fc receptor (FcRn), widely expressed in placental cells. The potential exists that mIgG may facilitate the transfer of ZIKV pathogen across placenta leading to the enhancement of fetal infection. This process is analogous to antibody-dependent enhancement (ADE) of viral disease, which has been shown to correlate with enhanced viremia and disease severity in other viruses. Thus, before anti-ZIKV IgG therapy can be tested in clinical trials, there is a need to determining whether it could enhance Zika replication and exacerbate disease pathogenesis, especially in the fetus. To evaluate this potential, we developed an *in vitro* model using mammalian placenta cells and cells overexpressing human FcRn to evaluate the role of ADE in viral infection using anti-Zika antibody. We found that ZIKV can enter and be transferred across placental and epithelial cells expressing FcRn. The viral entry in FcRn+ cells was dependent on the IgG concentration in a bimodal way: entry was reduced at the lowest (0.3-3 ng/mL) and highest (3 μg/mL) concentrations, yet it was increased at intermediate concentrations. Enhancement of viral entry was also seen at intermediate IgG concentrations in placental cells. On the other hand, anti-ZIKV antibodies degraded at a faster rate in the presence of ZIKV immunogen. Of the two monoclonal antibodies tested, the preparation with higher aggregation exhibited higher degradation. In conclusion, Zika virus has the potential to be transferred across the placenta and epithelial cells expressing FcRn. Blockage or enhancement of viral entry depends on the anti-ZIKV IgG antibody concentration. Our *in vitro* model could be used as a screening tool to assess the prophylactic and therapeutic antibody treatments against Zika infection. Disclaimer: This presentation represents my own best judgement; it does not bind or obligate FDA.

6

RUKTANONCHAI CW[1], MCKNIGHT M[2], MARR L[1], KROMETIS L-A[1], BUTTLING L[2], RANGANATHAN S[1], KOLIVRAS K[1], GOHLKE J[1]. [1]Virginia Tech, Blacksburg, VA, United States, [2]Mitre, McLean, VA, United States. Exploring Airshed and Watershed Exposure Pathways as Mediators of the Association between Proximity to Surface Mining and Adverse Birth Outcomes in Central Appalachia

Previous work has determined an association between proximity to active surface mining in coal producing counties within Central Appalachia and an increased risk of preterm birth (PTB) and low birthweight (LBW); however, the specific exposure pathway explaining this association remains poorly understood. Multiple potential exposure pathways exist, including inhalation of particulate matter from coal trucks and other surface mining activities (airshed exposure), or via surface mining emissions into local watersheds and subsequent exposure to impacted surface waters (watershed exposure). Here, we explore the relationship between airshed and watershed exposure, and the odds of PTB and LBW births across Central Appalachia. Maternal addresses were geocoded from birth records acquired through health departments in WV, KY, VA, and TN from 1990 to 2015. Yearly active surface mines were identified through remotely sensed Landsat imagery. Airsheds were estimated using the HYSPLIT4 atmospheric trajectory model, while watersheds were assigned through United States Geological Survey (HUC10) watershed boundaries. We used a mixed effects hierarchical model, with age, education, race/ethnicity, tobacco use, and payment status as fixed effects, plus year and ZIP code nested within state as random effects. We iteratively included: 1) the % of active mining landcover within 5 km of residency during the majority gestation year (MGY); 2) the sum of all surface mining airshed exposures during the MGY; and 3) the % of land experiencing active surface mining within the watershed of residency. Our baseline model found that the percent of active mining within a 5 km buffer of maternal residence was associated with an increased odds ratio (OR) of adverse birth outcomes (PTB: 1.08, 1.04–1.13; LBW: 1.07, 1.03–1.12), while controlling for significant predictors. When airshed exposure was added to the base model, the association between active mining within a 5 km buffer and health outcomes reduced (PTB: 1.05, 1.01–1.10; LBW 1.05, 1.01–1.10), and the odds of PTB and LBW increased with airshed exposure (PTB: 1.11, 1.06–1.15; LBW: 1.05, 1.02–1.09), consistent with a mediation hypothesis. Evidence of mediation by watershed was less clear. These results suggest that air pollution resulting from surface mining activities may be the primary exposure pathway explaining the association between maternal residence proximity to active surface mining and PTB and LBW.

7

BOSCHEN KE, FISH EW, CANNIZZO MD, DRAGICEVICH CJ, PETERSON RL, STEENSEN MC, PARNELL SE. University of North Carolina, Chapel Hill, NC, United States. Sex and Strain-Dependent Effects of Prenatal Alcohol Exposure on Craniofacial and Brain Development in Mice

Exposure to alcohol during early gestation is associated with craniofacial abnormalities and a wide range of neurological deficits. While genetics are a known mediator of prenatal alcohol sensitivity, the role of biological sex in determining the incidence and severity of alcohol-related birth defects is not fully understood. The present study compares the effects of gastrulation-stage prenatal alcohol exposure (PAE) in male and female fetuses from several lines of genetically modified mice. For all studies, dams were treated with either two doses of alcohol (PAE) or vehicle 4 hr apart on embryonic day (E) 7.0 and fetuses were observed for craniofacial defects on E17. In addition to C57BL/6J mice obtained from Jackson Labs, we used mice with gene deletions in either p53 (apoptosis pathway), Htt (intracellular signaling), Kif3a (ciliary transport), or Efcab7 (Smo trafficking) on varying background strains. In C57BL/6J mice, PAE females had a higher incidence of severe eye defects (48%) compared to males (30%). A similar effect was observed in the wild-type mice of all transgenic strains: PAE females had significantly more defects compared to males, independent of background strain. In some strains, an additional gene x sex interaction was observed. In the p53 mice, the protective effect of p53+/- and p53-/- was greatest in males. In the Htt strain, Htt+/- males were protected against a moderate alcohol dose and Htt+/- females were protected against a low alcohol dose. Conversely, Htt+/- females were more sensitive to moderate alcohol, indicating a possible sex x gene x dose interaction. In the Efcab7 or Kif3a mice, PAE females had higher rates of eye defects and craniofacial malformations compared to PAE males, regardless of genotype. Kif3a partial deletion did not affect sensitivity to PAE; full deletion of Efcab7 increased the severity of PAE-induced defects in both sexes. Collectively, these data demonstrate that female mice are more sensitive to prenatal alcohol than males and that sex can interact with certain genotypes to impact outcome. Interestingly, the alcohol exposure used in these studies is confined to the period of gastrulation, prior to sexual differentiation. Understanding how early gestational alcohol creates differential outcomes in males and females is an important future direction in the field of prenatal alcohol research, both in animal studies and in the human population. Supported by NIAAA AA021651/ AA026068 (SEP) and K99AA028273 (KEB).

8

KNIGHT GT, FEDORCHAK N, LUNDIN B, ASHTON RS. University of Wisconsin, Madison, WI, United States. Standardization and Validation of a Scalable Human Neural Rosette Microarray Assay for Assessment of Neural Tube Defect Risk and Developmental Neurotoxicity

Neural organoids derived from human pluripotent stem cells (hPSCs) are becoming powerful tools for investigating CNS development, physiology, and disease. However, the innate and spontaneous emergent properties of neurally differentiating hPSC aggregates, which make neural organoids possible, also limit their application due to inconsistencies in organoid tissue cytoarchitecture. We hypothesized that this is caused by the absence of biophysical and biochemical cues normally present within the developing embryo. To exert control *in vitro*, we developed a microarray cell culture platform that enables facile spatiotemporal control of microenvironmental cues to standardize early neural organoid morphogenesis. In this talk, we will detail our success exerting biophysical control over microscale tissue morphology to standardize the derivation of singularly polarized neuroepithelial rosette tissues from various CNS regions with high yield. These rosettes mimic the earliest stage of CNS morphogenesis, i.e., neural tube formation, and are a useful *in vitro* tissue analog to screen for adverse neurodevelopmental outcomes. To validate our neural rosette arrays as a platform for developmental neurotoxicity (DNT) screening and neural tube defect (NTD) risk assessment, we screened a small library of pesticides and substances known to cause clinical NTDs through multiple modes of action. The results of this preliminary validation screen with 30 substances across the pharmaceutical, agrochemical, and industrial chemical spaces will be presented and evaluated in the context of similar *in vitro* alternatives. Finally, we will discuss scale up of this culture platform to create an "off-the-shelf" screen for quantitatively assessing a chemical's DNT and NTD risk. Support for this work was funded by National Science Foundation CCF-1418976 & IIS-1447449 (RMW) and CBET-1651645 (RSA) grants, National Institute of Health 1U54 AI117924-01 (RMW), R21NS082618, R33NS082618, and R21HD103111 (RSA) grants, EPA STAR Award 83573701 (RSA), Burroughs Wellcome Fund Award 1014150 (RSA), and the Wisconsin Alumni Research Foundation through a Draper TIFF, Accelerator, and Fall Competition Awards. Conflict of interest disclosure: RSA, GTK, and RMW are cofounders of Neurosetta LLC which seeks to commercialize the presented technology.

Platform Session 2

Chairpersons: Maia M. Green, ExxonMobil Biomedical Sciences, Inc. and Kristal A. Rychlik, Johns Hopkins University Bloomberg School of Public Health

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NEELAM V[1], WOODWORTH K[1], CHANG DJ[1], ROTH NM[1], REYNOLDS MR[1], TONG VT[1], ANDERSON K[1], MULKEY SB[2], DEBIASI OO[2], BIDDLE C[2], LEE EH[3], LASH MK[3], GODRED-CATO S[1], GILBOA SM[1], HONEIN MA[1], MOORE CA[1]. [1]Centers for Disease Control, Atlanta, GA, United States, [2]Children's National Hospital, Washington, DC, United States, [3]New York City Department of Health and Mental Hygiene, Long Island Ciety, NY, United States. Tracking Development in the First Two Years of Life Among Children with Possible Congenital Zika Virus Exposure: 50 US States and the District of Columbia

The US Zika Pregnancy and Infant Registry (USZPIR) monitors pregnancy and infant outcomes among pregnancies with laboratory evidence of recent possible or confirmed Zika virus infection. We analyzed data from the US states and DC on pregnancies completed during December 2015–March 2018, and child follow-up data up to age two years. We reviewed information from developmental assessments and results of validated developmental screenings that assessed multiple domains (i.e., fine motor, gross motor, language, cognitive, social), or other developmental notations in the medical record. Data were aggregated into age intervals of 0–5, 6–11, 12–17, 18–23, and ≥24 months of age, with children included in ≥1 interval. Developmental delay was classified as confirmed (specialist assessment, receipt of therapy, or multiple notations of delay with supportive neuroimaging findings), possible (failing ≥1 domain on a validated screener at ≥1 timepoint, or ≥ 2 domains noted as abnormal at ≥2 timepoints but not reported as a validated screener), or no developmental delay. As of December 2020, USZPIR had 2,485 liveborn infants reported. Of 2,047 children with developmental data reported, 131 (6.4%) were reported as having a Zika-associated birth defect. Among children with a Zika-associated birth defect, the percentage of children failing at least one domain was 18.9% (18/95) at 0–5, 41.6% (32/77) at 6–12, 43.0% (34/79) at 12–17, 57.6% (34/59) at 18–23, and 50.8% (30/59) at ≥24 months. Among children without a Zika-associated birth defect, the percentage of children failing at least one domain was 1.1% (18/1599) at 0–5, 2.8% (28/1011) at 6–12, 5.0% (53/1068) at 12–17, 11.0% (85/772) at 18–23, and 11.7% (77/656) at ≥24 months. The percentage of confirmed or possible delay was 45.2% (56/124) among children with and 5.0% (91/1804) among those without Zika-associated birth defects. The preliminary data indicate a markedly increased risk for developmental delay among children with Zika-associated birth defects warranting consideration of early developmental evaluation in these children. Longer term follow-up of the development of all children with possible or confirmed exposure to Zika virus *in utero* may improve the accuracy of estimating the proportion with developmental delays.

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MARCHINCIN SL[1], HOWLEY MM[2], VAN ZUTPHEN AR[2], FISHER SC[2], NESTORIDI E[3], TINKER S[4], BROWNE ML[2]. [1]New York State Department of Health, Buffalo, NY, United States, [2]New York State Department of Heath, Albany, NY, United States, [3]Massachusetts Center for Birth Defects Research and Prevent, Department of Public Health, Boston, MA, United States, [4]National Center on Birth Defects and Developmental Disabilities; CDC, Atlanta, GA, United States. Risk of Birth Defects by Pregestational Type 1 or Type 2 Diabetes: National Birth Defects Prevention Study, 1997–2011

Previous studies have examined the relationship between pregestational diabetes, defined as either type 1 or type 2 diabetes, and birth defects. Consistent, increased risks for defects of the cardiovascular, central nervous, and musculoskeletal systems have been observed, including a recent National Birth Defects Prevention Study (NBDPS) analysis of women with pregestational diabetes. There are different underlying biologic mechanisms for pregestational type 1 diabetes (PGD1) and type 2 diabetes (PGD2); however, few studies have examined pregestational diabetes separately by type. The NBDPS was a population-based case-control study of birth defects. PGD1 and PGD2 were self-reported and defined as diagnosed prior to the index pregnancy estimated date of conception. For birth defects with 5+ exposed cases, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for maternal age, race/ethnicity, education, body mass index, and study center. We estimated crude ORs and exact 95% CIs for defects with 3–4 exposed cases. Of the 39,922 women in the analysis (29,024 cases and 10,898 controls), 24 (0.2%) control and 252 (0.9%) case women reported PGD1, and 34 (0.3%) control and 357 (1.2%) case women reported PGD2. PGD1 was associated with 22 of 52 birth defects examined (OR range 2.3–74.0) and PGD2 was associated with 18 of 52 birth defects examined (OR range 2.7–62.3). We observed the strongest associations for sacral agenesis and both PGD1 (OR=74.0, 95%CI=34.1–160.0) and PGD2 (62.3, 26.6–146.3). We observed high ORs (OR≥10) for PGD1 and longitudinal limb deficiency (13.5, 6.9–26.6), heterotaxy (13.2, 5.7–30.3), and truncus arteriosus (crude OR=11.9, 2.3–40.0). We observed high ORs for PGD2 and holoprosencephaly (14.0, 5.8–34.0), heterotaxy (11.6, 5.5–24.8), truncus arteriosus (20.3, 8.9–46.3), conoventricular septal defects (22.7, 7.9–65.3), atrioventricular septal defects (12.2, 5.8–25.9) and single ventricle defects (29.8, 13.8–64.6). PGD1 and PGD2 were each strongly associated with birth defects across multiple body systems consistent with previous findings for pregestational diabetes overall. We observed potential differences in the associations with specific birth defects by type of diabetes; however, overall results were similar for PGD1 and PGD2 for most birth defects examined. Since PGD1 and PGD2 are relatively rare occurrences, more studies separately evaluating both types of pregestational diabetes could help inform future research.

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SCHRAW JM[1], BENJAMIN RH[2], SCOTT DA[3], MCLEAN SD[4], NORTHRUP H[5], LANGLOIS PH[6], CANFIELD MA[6], SCHEUERLE AE[7], SCHAAF OO[1], RAY, JW[8], CHEN H[9], SWARTZ MD[10], AGOPIAN AJ[11], LUPO PJ[12]. [1]Baylor College of Medicine, Houston, TX, United States, [2]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States, [3]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, United States, [4]Baylor College of Medicine, San Antonio, TX, United States, [5]University of Texas Health Science Center at Houston, Houston, TX, United States, [6]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, United States, [7]Department of Pediatrics, Division of Genetics and Metabolism, University of Texas Southwestern Medical Center, Dallas, TX, United States, [8]University of Texas Medical Branch, Galveston, TX, United States, [9]Center for Precision Health, UTHealth School of Public Health and UTHealth School of Biomedical Informatic, Houston, TX, Unites States, [10]Department of Biostatistics and Data Science, UTHealth School of Public Health, Houston, TX, Unites States, [11]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX United States, [12]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX, United States.

Co-Occurring Birth Defects in Children with Nonsyndromic Microtia

It has been reported that >30% of infants with apparently nonsyndromic microtia have co-occurring birth defects. We analyzed data from the Texas Birth Defects Registry (TBDR) in order to identify multiple birth defect patterns involving microtia, which may be indicative of undiagnosed or unrecognized multiple malformation syndromes. We excluded cases with known chromosomal or genetic syndromes. Using the Co-Occurring Defects Analysis (CODA) software platform, we calculated adjusted observed-to-expected (O:E) ratios for two- through five-way birth defect combinations involving microtia, diagnosed in Texas infants born 1999–2014. We focused our reporting on combinations diagnosed in ≥3 cases and with O:E ratios >1 (O:E ratios >1 indicate combinations that co-occur more often than expected by chance). We included N=427 children with microtia and co-occurring defect (35% of all microtia cases). Combinations with the largest O:E ratios involved co-occurring ear defects (anotia, hearing impairment), orofacial clefts, microcephalus, hydrocephalus, microphthalmia, heart defects (e.g., septal defects, pulmonary artery anomalies, and transposition of great vessels), and musculoskeletal anomalies (e.g., anomalies of the spine or ribs/sternum). Combinations with the largest O:E ratios included 1) microtia, hydrocephalus, ventricular septal defect, spinal anomalies, and rib/sternum anomalies (N=3, O:E=246); and 2) microtia, microphthalmia, atrial septal defect, and anomalies of the aorta (N=3, O:E=77). We also observed nonrandom co-occurrence with pulmonary artery anomalies and anomalies of the larynx, trachea, and bronchus (N=3, O:E=40); this was the only combination involving the latter anomaly. We identified numerous multiple birth defect patterns involving microtia with evidence of nonrandom co-occurrence. Some may represent undiagnosed cases of known conditions such as oculo-auriculo-veterbral spectrum (OAVS). Others may represent suspected rare associations (e.g., microtia with pulmonary artery and laryngeal anomalies, described previously in a case report). Population-based birth defects registries are useful for identifying offspring possibly affected by chromosomal or genetic syndromes, and can play a role in the characterization of previously undescribed, rare multiple malformation syndromes.

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SHUMATE CJ[1], RUSSELL K[2], NAVARRO SANCHEZ ML[3], LE M[1], CANFIELD MA[4]. [1]Texas Department of State Health Services, Austin, TX, United States, [2]Maternal and Child Health Epidemiology, Texas Department of State Health Services, Austin, TX, United States, [3]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States, [4]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, United States. The Association between the Occurrence of Gastroschisis and Maternal Chlamydia Infection among Cases in the Texas Birth Defects Registry, 2013–2017

Chlamydia trachomatis (CT) is a sexually transmitted infection with a high burden among reproductive aged women. Little is known about the effects of maternal CT infection on the occurrence of birth defects. In this study we describe CT positivity among mothers of infants diagnosed with a birth defect in Texas by linking data from the Texas Birth Defects Registry (TBDR) and CT data from the Texas STD program at the Department of State Health and Human Services, 2013–2017; and, estimate the association of maternal CT infection with gastroschisis. Isolated cases in the TBDR (N=48,615) were linked to positive maternal CT test results. Positivity estimates were calculated and stratified by maternal age group. CT positivity was calculated as the percentage of TBDR cases with a link to mother's positive CT (CT+) test divided by total TBDR cases, and 95% confidence intervals (CIs) were calculated using the exact binomial method. A logistic regression model with gastroschisis as the dependent variable (Yes vs. No) was constructed to estimate the association between CT infection and gastroschisis. CT positivity across defects was high, and significantly higher for gastroschisis 23.4% (20.1%–27.0%) vs. any other defect 10.4% (10.1%–10.7%). For gastroschisis, CT positivity was lowest in the >29 age group and highest in the 10–19 age group, 9.8% (3.3%–21.4%) and 30.3% (23.8%–37.4%). For any other defect, CT positivity was lowest in the >29 age group and highest in the 10–19 age group, 2.7% (2.5%–3.0%) and 27.1% (25.7%–28.5%). Significant differences were observed when comparing the overall CT positivity among mothers of infants with gastroschisis vs. any other defect: 13 percentage points higher than for all other birth defects. Positivity varied by maternal age group; and, significant differences for mothers aged 25–29 and >29, $p<0.0001$. Univariate analysis found a statistically significant increased odds for gastroschisis compared to any other defect [2.63; 95% CI: 2.17–3.18] that remained significant after controlling for maternal age, race/ethnicity, and BMI [1.53; 95% CI: 1.20–1.96]. To our knowledge, this is the first linkage between a birth defects registry and state-level CT testing data. Infections were high among mothers of TBDR cases, and highest among mothers of infants with gastroschisis. The high CT+ among infants with gastroschisis, and the association between maternal CT infection and the occurrence of gastroschisis merits further study.

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ADRIEN N[1], YAZDY M[2], NESTORIDI E[2], CARMICHAEL SL[3], ORTA OR[4]. [1]Department of Epidemiology, Boston University School of Public Health, Boston, MA, United States, [2]Massachusetts Center for Birth Defects Research and Prevent, Department of Public Health, Boston, MA, United States, [3]Department of Pediatrics and Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, United States, [4]Boston University School of Public Health, Department of Epidemiology, Boston, MA, United States. Maternal Vitamin D Status and Risk of Select Birth Defects in the National Birth Defects Prevention Study (1997–2011)

Vitamin D deficiency is associated with both maternal and fetal adverse events. However, its role in the etiology of birth defects remains unclear. We examined the association between maternal vitamin D status and birth defects in offspring. We used data from the National Birth Defects Prevention Study, a population-based case-control study conducted across ten centers in the United States from 1997 through 2011. Cases were offspring with any qualifying major birth defect and without a known genetic syndrome. Maternal dietary vitamin D, measured in international units per day (IU/d), was determined from food frequency questionnaires and evaluated using tertiles, based on the distribution in controls. We used data from the National Oceanic and Atmospheric Administration Weather Service to assign UV indices based on location and estimated date of conception, then dichotomized maternal UV light exposure into low or high base on definitions from the Environmental Protection Agency (EPA). Finally, we categorized seasons of conception as summer/fall or winter/spring. Unconditional logistic regression models were employed to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI). Lower dietary vitamin D intake (<65.21 IU/d vs >107.55 IU/d) was associated with increased odds of anencephaly (aOR = 1.28, 95% CI: 1.01–1.63), hypospadias (aOR = 1.21, 95% CI: 1.04–1.40), diaphragmatic hernia (aOR = 1.42, 95% CI: 1.13–1.79) and gastroschisis (aOR = 1.27, 95% CI: 1.07–1.52), after adjusting for study center, age, conception year, race/ethnicity, education, prepregnancy body mass index, periconceptional smoking and alcohol consumption, periconceptional multivitamin or prenatal vitamin use, and caloric intake. These findings for dietary vitamin D were consistent across strata based on UV exposure and season of conception. We did not observe evidence of an independent association for UV exposure or season of conception and odds of birth defects. This is the first study to use prepregnancy diet, UV exposure and season of conception to investigate associations between maternal vitamin D status and birth defects in offspring. Our findings suggest that prepregnancy lower dietary intake of vitamin D may be associated with increased risk of anencephaly, hypospadias, diaphragmatic hernia and gastroschisis. Further investigations are warranted to evaluate the effects of other nutrients and appropriate thresholds and sources of vitamin D using serum levels.

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BLACKBURN J[1], CHAPUR VF[2], STEPHENS JA[3], ZHAO J[3], SHEPLER A[4], PIERSON CR[5], OTERO JJ[6]. [1]The Ohio State University, Columbus, OH, United States, [2]Instituto de Ecoregiones Andinas (INECOA)/Consejo Nacional de investigaciones científicas y técnicas, San Salvador de Jujuy, Argentina, [3]The Ohio State University, Center for Biostatistics, Columbus, OH, United States, [4]Franklin County Forensic Science Center, City of Columbus, Ohio, Columbus, OH, United States, Nationwide Children's Hospital, Department of Pathology and Laboratory Medicine, Columbus, OH, United States, [6]The Ohio State University, Department of Pathology, Division of Neuropathology, Columbus, OH, United States.

Unique Clusters of Sudden Unexpected Infant Death (SUID) Decedents Revealed Through Machine Learning Epidemiological Analyses

Sudden unexpected infant death (SUID) rates have substantially declined due to public health prevention efforts as well as mechanistic research over the past thirty years. Following an extensive medicolegal investigation, the decedent under the age of one is assigned as the cause of death: sudden infant death syndrome (SIDS), accidental suffocation and strangulation, or other ill-defined or unspecified cause of mortality. However, the extent to which these diseases manifest with an underlying neuropathological mechanism is highly controversial due to the heterogeneity of findings. In addition, substantial disparities are present when comparing SUID rates amongst distinct racial groups in the United States (US). The intersection of an underlying unknown biological abnormality and health disparities in the role of SUID is not well understood. Cluster analysis within heterogenous diseases has been highly instructive in neuropathology by identifying unique patient subtypes and we utilized similar approaches in our work. Using maternal and infantile characteristics, we sought to identify unique groups of SUID decedents indicating distinct risk factors and neurodevelopmental causes. Using the US Period Linked Birth/Infant Mortality Files from 1990–2017 (excluding 1992–1994), we performed unsupervised machine learning dimensionality reduction techniques. Following identification of unique groups, we analyzed SUID rates in these clusters at the state level. We were able to identify three groups of SIDS decedents, each with a unique mean age at death when adjusting for length of gestation and performed similar analyses with the remaining SUID causes. We found that the implementation of clinical guidelines had a distinct impact in decreasing the SUID rate in the unique clusters country and statewide, however not all are experiencing as rapid reduction. The unexpected death of a previously seemingly healthy infant places a hard emotional burden on families. Through identifying unique risk factors and developmental timepoints of distinct SUID clusters, our findings can assist with public health infant mortality prevention policies and aid basic mechanistic research.

Platform Session 3

Chairpersons: William Slikker Jr., National Center for Toxicological Research, US FDA and Bevin Blake, National Institute of Environmental Health Sciences

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CHANG X[1], KLEINSTREUER NC[2], CASEY WM[3], ALLEN DG[4], CEGER P[4], BELL S[4], MANSOURI K[2], PALMER J[5], DONLEY OO[5], LUMEN A[6], LEE UJD[7]. [1]Integrated Laboratory Systems, LLC, Morrisville, NC, United States, [2]NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, NC, United States, [3]NIH/NIEHS/DNTP, Research Triangle Park, NC, United States, [4]Integrated Laboratory Systems, LLC, Morrisville, NC, United States, [5]Stemina Biomarker Discovery Inc., Madison, WI, United States, [6]US FDA/NCTR, Jefferson, AR, United States, [7]Albert Einstein College of Medicine, Bronx, NY, United States. *In Vitro* to *In Vivo* Extrapolation for Developmental Toxicity Potency of Valproic Acid Analogues

The devTOX quickPredict assay (devTOXqP) is a human-induced pluripotent stem cell biomarker-based assay developed as an alternative to animal tests to screen for developmental toxicity potential. The developmental toxicity potential (dTP) concentration from the devTOXqP assay indicates a chemical's developmental toxicity potency. Previous work showed that the potency ranking of dTP concentrations for valproic acid and its analogues was consistent with *in vivo* developmental toxicity. In this study, we applied *in vitro* to *in vivo* extrapolation (IVIVE) to address whether the devTOXqP dTP concentrations could quantitatively predict the *in vivo* developmental toxicity lowest effect levels for these chemicals. We evaluated the impact of *in vitro* kinetics, pharmacokinetic (PK) parameters, and different PK models on IVIVE outcomes. To evaluate the effect of *in vitro* kinetics, an equilibrium distribution model was applied to devTOXqP assay to translate nominal concentrations to free and cellular concentrations, which were used subsequently in IVIVE analyses. A one-compartment PK model including population variability, standard physiologically based pharmacokinetic (PBPK) models, and pregnancy-specific PBPK models were used for reverse dosimetry. The equivalent administered doses (EADs) that would result in maternal or fetal blood concentrations equivalent to *in vitro* activity concentrations were estimated by IVIVE. These EADs were compared to lowest effect levels in rat developmental toxicity studies and/or human therapeutic doses, and to EADs from a recent OECD case study publication derived using different sets of *in vitro* data. We also explored a chemical read-across approach incorporating structural similarity information in data interpretation. Our preliminary results showed close agreement between EADs and *in vivo* rat lowest effect levels, indicating that the devTOXqP assay can quantitatively predict the developmental toxicity potential of chemicals at relevant concentrations. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.

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ROY MA, GRIDLEY CK, LI S, PARK Y, TIMME-LARAGY AR. University of Massachusetts Amherst, Amherst, MA, United States. Does Nrf2 Play a Role in the Developmental Toxicity of the Sulfate Metabolite of 3,3′-dichlorobiphenyl (PCB-11)?

The environmental pollutant 3,3′-dichlorobiphenyl (PCB-11) is a byproduct of pigment manufacturing and detected in both environmental and human samples, including in pregnant women. Our previous research in zebrafish (*Danio rerio*) shows that 20 uM exposures to PCB-11 or its metabolite 4-PCB-11-Sulfate between 1–4 days post fertilization (dpf) suppresses hepatic Cyp1a enzyme activity, and that chronic 0.2 uM exposures to 4-PCB-11-Sulfate between 1–15 dpf increase hepatic lipids. This research explored whether oxidative stress contributes to PCB-11 embryotoxicity via the master-regulator of the adaptive response to oxidative stress, Nuclear factor erythroid-2 (Nrf2), as well as whether Nrf2 plays a role in 4-PCB-11-Sulfate mediated metabolic endpoints. Transgenic embryos expressing GFP in pancreatic β-cells Tg(ins:GFP) crossed with homozygous wildtype (W) or mutant (M) nrf2a(fh318/fh318) embryos were exposed from 1–4 dpf to either 0.2–20 uM PCB-11, 4-PCB-11-Sulfate, or a DMSO control, and at 4 dpf morphology and hepatic Cyp1a enzyme activity were captured *in vivo*. In a separate experiment, Nrf2a W and Nrf2a M embryos were exposed from 1–15 dpf to 0.2 uM 4-PCB-11-Sulfate or DMSO, and at 15 dpf subsets of larvae were imaged for morphology and primary pancreatic islet area, and were also collected for fatty acid profiling and RNA sequencing. Consistent with previous results, at 4 dpf significant reductions in Cyp1a enzyme activity were observed for embryos exposed to PCB-11 or 4-PCB-11-Sulfate, but no genotype differences were observed. In 15 day experiments, 80–85% survivability was observed for fish exposed to 4-PCB-11-Sulfate, significantly more than the 65–73% survival for fish exposed to DMSO. At 15 dpf, fish exposed to 4-PCB-11-Sulfate had primary pancreatic islets 10% larger than fish exposed to DMSO. Nrf2a M fish regardless of exposure were significantly smaller than Nrf2a W fish, and Nrf2a M fish exposed to 4-PCB-11-Sulfate had significant decreases in the Omega-3 fatty acid DHA. RNA sequencing revealed 308 differentially expressed genes, driven mostly through genotype, and confirmed through pathway analysis. Further research would be beneficial to understand the importance of Nrf2a throughout the lifecourse, especially in the context of environmental chemicals.

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PIERRO JD[1], BAKER NC[2], RICHARD AM[1], KLEINSTREUER NC[3], KNUDSEN TB[1]. [1]US EPA, Research Triangle Park, NC, United States, [2]Leidos, Research Triangle Park, NC, United States, [3]NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, NC, United States. A Data-Driven Model Analysis of Retinoid Signaling in Skeletal Dysmorphogenesis and Potential Adverse Outcome Pathways

Homeotic transformations and malformations of the fetal skeleton can occur as locally-regulated all-trans retinoic acid (ATRA) gradients. Such gradients determine skeletal patterning morphogenesis and can be disrupted by diverse genetic or environmental factors. Adverse Outcome Pathway (AOP) frameworks for ATRA metabolism, signaling, and, homeostasis allow for the development of scalable computational models to support new approach methodologies (NAMs) to improve predictive toxicology without animal experimentation. Here, a data-driven model was constructed to identify chemicals associated with both ATRA pathway bioactivity and prenatal skeletal defects. We identified altered skeletal phenotypes in prenatal developmental toxicity studies in ToxRefDB and/or ToxCast high-throughput screening (HTS) and identified 375 chemicals associated with the alterations. Defects were organized into four skeletal phenotype groupings: cranial, postcranial axial, appendicular, and other nonspecified skeletal defects. For each chemical, the distribution of phenotype(s) was scored as a normalized fraction for inclusion in ToxPi k-means clustering. The clustering identified trends in skeletal defects due to shared structural characteristics among chemicals. Chemotypes were examined to identify structural similarities between chemicals with ATRA bioactivity and skeletal defects. In order to build a multivariate statistical model, HTS results from >8,070 chemicals in ToxCast/Tox21 across 13 *in vitro* assays, representing key nodes in the retinoid signaling system were evaluated and compared to candidate reference chemicals for *in vitro* testing. Over 40 chemicals were identified for constructing data-driven models to link this *in vitro* data with adverse skeletal outcomes for computational modeling. These preliminary findings will guide the development of dynamic modeling and AOPs for mechanistic validation to strengthen evidence for causality. This abstract does not represent the official views of EPA or any government agency.

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ERWIN NJ[1], LIU J[2], KAPRON CM[3]. [1]Environmental and Life Sciences, Peterborough, ON, Canada, [2]Shandong University, School of Medicine, Jinan, China, [3]Trent University, Peterborough, ON, Canada. The Effects of Low Dose Cadmium on Mouse Embryo Vascular Development *In Vitro*

Cadmium is a toxic, nonessential metal known to cause a variety of detrimental effects in adults and to be teratogenic in experimental animals. It has harmful effects on the renal and skeletal systems, and also on blood vessels. Cadmium has a concentration-dependent effect on tumour angiogenesis, where high concentrations of cadmium are largely inhibitory in action or apoptotic, but lower concentrations have either a stimulatory or an inhibitory effect. The aim of this study was to investigate the effects of a continuous low-level exposure to cadmium on the development of fetal mouse vascular tissue, in an *ex vivo* explant model of angiogenesis (Song et al., 2015. *Nature Protocol* 10:1459). Fetal metatarsal bones from CD-1 mice at Day 17 of gestation were dissected and plated onto gelatin-coated 24-well plates. Beginning on day 3, cultures were exposed to 0.125 μM cadmium chloride. The culture media was refreshed every other day for continuous cadmium exposure for an additional seven days. Following this period, the samples were fixed and stained via immunofluorescence with PECAM-1 antibody, which allows for visualization of the endothelial cells that have migrated from the perichondrium to form vessels. Analysis was carried out using ImageJ software with a vessel analysis plugin. Continuous cadmium exposure to 0.125 μM had a proangiogenic effect on the developing vasculature, as indicated by an increase in the number of sprouted vessels relative to the controls (one-sample t-test, $p=0.0184$, $n=10$), as well as by an increase in the area covered by vascular outgrowth (one-sample t-test, $p=0.0366$, $n=10$). In contrast, higher concentrations of cadmium attenuated the overall growth of the cultures. These results point out the importance of further research into the potential effects of low-level cadmium exposure on embryonic development.

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SPARKS NRL[1], WILLIAMS D[2], ZUR NIEDEN NI[1]. [1]University of California, Riverside, Riverside, CA, United States, [2]Department of Molecular, Cell, and Systems Biology, College of Natural and Agricultural Sciences, Riverside, CA, United States. Transcriptome Analysis Reveals Toxicant-Induced miRNA Signatures Associated with Aberrant Human Embryonic Stem Cell Osteoblast Differentiation

Birth defects that affect skeletal tissues are a major public health concern causing a life-long impact on the individual and their families. Insults from environmental chemicals can disrupt the dynamic genetic regulatory processes that can affect tissues of the neural crest and/or mesoderm which would manifest skeletal disorders of the skull or short/long bones, respectively. Yet, the link between environmental exposure and molecular alterations that lead to a skeletal birth defect are least understood. Here, we aimed to identify microRNAs (miRNAs) that are associated with impaired skeletal development caused by toxicant exposure in an *in vitro* human embryonic stem cell (hESC) osteoblast differentiation model. Osteogenically differentiating hESCs were exposed to test chemicals categorized by their toxic effects on the neural crest cells, mesoderm cells, and general cytotoxicity, and known for *in vivo* skeletal defects. All tested chemicals inhibited hESC osteoblast differentiation. In addition, altered skeletal fate commitment determined by RUNX2 upregulation and downregulation of PAX7, SNAI2, TBX6, and CCN1. Global miRNA profiling provided evidence of toxicant-responsive miRNA profiles. Chemicals cyclopamine, cyclophosphamide, methotrexate, methoxyacetic acid, ogremorphin, triadimenol, valproic acid, and 5-flurouracil identified 202, 425, 404, 313, 518, 394, 354, and 259 differentially expressed (DE) miRNAs, respectively, after exposure. MiRNAs involved with ossification were significantly deregulated by each chemical. Global profiling revealed 10 downregulated and one upregulated miRNAs shared between all chemicals. Overlapping downregulated miRNAs include miR92b, miR145, miR520a, and miR526b and are reported to have a role in osteoblast differentiation. Gene ontology indicated that the 10 downregulated miRNAs are involved in skeletal system development, neural crest developmental/differentiation, mesoderm development, and epithelial to mesenchymal transition processes. Further, associated with key signaling pathways such as canonical WNT, BMP, TGF-beta, mTOR, and p53. Disruption of these necessary processes interferes with osteogenic development. We have demonstrated the relationship between changes in miRNA expression following toxicant exposure and potential as a toxicologic endpoint. These dynamic toxicant-induced changes in miRNA signatures reflect crucial roles of miRNAs during skeletal development and can serve as a biomarker for skeletal defects.

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JAMALPOOR A, HARTVELT S, ZWETSLOOT T, GHOUSSAIN N, OSTERLUND T, HENDRIKS G. Toxys B.V., Leiden, Netherlands. ReproTracker: A Human Stem Cell-Based Biomarker Assay for *In Vitro* Assessment of Developmental Toxicity

Testing for developmental toxicity according to the current OECD guidelines requires large numbers of animals, making these tests very resource intensive and time-consuming, as well as raising ethical concerns. Over the past years, several alternative *in vitro* assays have been developed, but these often suffer from low predictability and lack of mechanistic information. Here, we present ReproTracker, a human-induced pluripotent stem cell (hiPSC)-based biomarker assay that follows the differentiation during early embryonic development. The hiPSCs were directed to differentiate into three germ layer-specific cell types, hepatocytes, cardiomyocytes, and neural rosettes. The differentiation processes were followed by morphological profiling and expression patterns of the cell-specific biomarkers. In this system, a decrease in the expression of the biomarker genes and morphology disruption of the differentiated cells following compound treatment indicated teratogenicity. The assay was validated with over 40 well-known *in vivo* teratogens and 20 nonteratogenic compounds at noncytotoxic concentrations. In ReproTracker, *in vivo* teratogenic compounds markedly disrupted morphology and decreased the expression pattern of the biomarker genes in at least one of the three cell types. Nonteratogenic chemicals generally had no effect on the morphology of the differentiated cells, nor on the expression of the biomarker genes. Compared to the *in vivo* classification, the assay achieved high accuracy (80%), sensitivity (77%), and specificity (84%).In conclusion, ReproTracker is a state-of-the-art *in vitro* assay that is able to identify the teratogenic potential of new chemicals and drugs with high accuracy and provide a signal as to the likely outcome of *in vivo* test systems. The assay can best serve as an early phase teratogen screening platform, or as a late phase verification for animal testing outcomes.

Platform Session 4

Chairpersons: Barbara F. Hales, McGill University and Madhumita Basu, Nationwide Children's Hospital

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MCHATTIE TJ, ISKANDARANI L[1], ROBAIRE B[1,2], HALES BF[1]. [1]Department of Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada, [2]Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada. Effects of Bisphenol A and Bisphenol AF on the Murine Limb Bud Transcriptome

Bisphenol A (BPA) and Bisphenol AF (BPAF) are bisphenol chemicals that are commonly used in consumer goods containing polycarbonate plastics, epoxy resins, and polyvinyl chloride plastics. Previously, we have shown that exposure to these chemicals is detrimental to endochondral ossification in murine limb bud cultures; adverse effects were observed at BPA concentrations ≥10 μM and BPAF ≥1 μM. The goal of this study was to elucidate the effects of BPA and BPAF on gene expression in these limbs. Gestation day 13 murine forelimbs were cultured in the presence of vehicle (DMSO), BPA (10 μM or 50 μM) or BPAF (1 μM or 5 μM) for 3, 24, or 48 hours. Total RNA was isolated and paired-end sequencing was done. The total number of differentially expressed genes (adjusted p-value<0.05 and fold change>1.5) increased with time and dosage, with the greatest effects seen in limbs exposed to the highest concentrations (50 μM BPA; 5 μM BPAF) for the longest time (48 hours); BPA exposure differentially regulated 639 genes (493 down, 146 up) whereas BPAF affected 554 genes (438 down, 116 up). While the genes that were differentially expressed after BPA and BPAF treatment for 3, 24, or 48 hours overlapped extensively (35%, 61%, and 65%), each bisphenol also induced chemical-specific alterations in gene expression. Affected pathways were analyzed using IPA software. Both bisphenol-treated groups exhibited a downregulation of Rho GDI signalling genes. Exposure to BPA (10 μM or 50 μM) resulted in upregulation of key genes involved in cholesterol biosynthesis, possibly through the action of upstream regulator SREBF2. Exposure to BPAF (5 μM) induced an upregulation of genes involved in the P53 signalling pathway. Together, these data show that BPA and BPAF have both similar and distinctive effects on the mouse limb bud transcriptome. Shared effects on cholesterol biosynthesis and Rho GDI may relate to their impact on endochondral ossification, whereas the effects of BPAF on P53 signalling may contribute to its enhanced toxicity. Acknowledgments: Supported by a Canadian Institutes of Health Research (CIHR) Team Grant: "Endocrine disrupting chemicals: Towards responsible replacements."

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HOOTNICK D[1], DESESSO JM[2]. [1]SUNY Upstate Medical University, Syracuse, NY, United States, [2]Exponent and Georgetown University School of Medicine, Alexandria, VA, United States. A New Entity: Vascular-Induced Skeletal Dystrophisms of the Lower Limb

Classifications of the congenitally shortened limbs (CSL) with fibular deficiency have traditionally been based on plain radiography, relatively neglecting the accompanying radiolucent soft tissues. Detailed embryologic examination of CSL reveals that such fibulae are not absent, but only radiolucent. The newly described syndrome of proximal femoral, fibular and midline metatarsal long bone deficiencies has introduced embryonic vascular dysgenesis as the most frequent cause of such dysmorphic limbs. Maldevelopment of lower limb vessels during gestational weeks 6–7 leads to inadequate vascularization of the cartilaginous scaffolds at three metabolically active locations, which later appear as sites of congenital skeletal long bone deficiencies. More distally, failure of a descending branch of the dorsalis pedis artery to join with the lateral plantar artery beneath the second and third metatarsals may lead to midline metatarsal absences or maldevelopment. Embryonic vascular dysgenesis may affect not only development of the skeletal anlagen and the longitudinal growth of affected long bones, but also latitudinal expansion of the distal femoral and proximal and distal tibial epiphyses through failure of anastomosis between forming arteries and also failure of vessels to sprout in a timely fashion. The normal progression of vascular patterning, termed "transitioning," when disordered, can result in valgus angular deformities at the knee and ankle. Arteriography of CSL reveals failed embryonic axial (sciatic) artery transitioning to the usual posterior tibial, anterior tibial and peroneal arteries. Additionally, eccentric, proximal nutrient invasion of the tibia by the profunda popliteal portion of the axial artery instead of the normal posterior tibial artery contribution, contributes to subsequent anteromedial bowing of the tibia. Thus, all major features of the CSL with fibular deficiency (including proximal femoral focal deficiency (PFFD), fibula deficiency, bent tibia, midline metatarsal reductions and valgus angular deformities of the knee and ankle in CSL) can be more comprehensively understood in dystrophic vascular rather than dysmorphic radiologic terms.

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CHEN S-Y[1], LU L[1], YUAN F[1], LIU J[1], WILKEY DW[2], MERCHANT ML[2]. [1]Department of Pharmacology and Toxicology, University of Louisville Health Science Center, Louisville, KY, United States, [6]Department of Medcine, University of Louisville Health Science Center, Louisville, KY, United States. Alteration of the Expression of Proteins Associated with Radical Glial Scaffold Development in Ethanol-Exposed Forebrain Organoids Derived from Human Embryonic Stem Cells

During early cortical development, radial glial cells (RGCs) are not only the source of the newborn neurons but also serve as the supportive scaffold to guide neuronal migration. Recent studies have shown that the abnormality in the polarity and morphologies of radial glial cells can significantly influence neuronal migration leading to cortical dysplasia. Cytoskeletons such as microtubules and intermediate filaments are major components of the radial glial scaffold. In the current study, we aim to determine whether ethanol exposure can disrupt the radial glial scaffold by altering the expression of the proteins associated with the development of radial glial scaffold in human forebrain organoids derived from human embryonic stem cells. These organoids exhibited well-organized neural progenitor cell layers and neuronal layers, resembling the architecture of the developing human cerebral cortex. Proteomic analysis of differentially expressed protein was conducted in control and ethanol-exposed day 28 human forebrain organoids that contain abundant apical radial glial cells in the ventricular zone. We found that exposure of human forebrain organoids to ethanol for 24 hours resulted in the upregulation of the cytoskeleton-associated proteins DNAH5, PALLD, KIF1C, ACTR10, MFAP2, and ARPC1B. Ethanol exposure also downregulated the cytoskeleton-associated proteins TUBA1B, TUBA1A, CAPZA1, ACTR3, TBCA, TPPP3, MACF1, and TBCC. These proteins are involved in the formation and functions of the cytoskeleton that is important for the formation and maintenance of radial glial scaffold. These data suggest that ethanol exposure might disrupt radial glial scaffold development and result in abnormal neuronal migration contributing to ethanol-induced abnormalities in cortical development. Supported by NIH grants AA021434, AA028435, and AA024337 (S-Y.C).

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RAPPOLEE DA[1], ABDULHASAN M[1], RUDEN X[1], YOU Y[1], HARRIS S[2], RUDEN D[1], AWONUGA A[1], ALVERO A[1], PUSCHECK [01]. [1]Wayne State University, Detroit, MI, United States, [2]University of Michigan, Ann Arbor, MI, United States. Using Live Imaging and FUCCI ESC to Provide QC for a DevTox HTS and to Define Stressful Doses of PFOA and DEP

Fluorescence-ubiquitinated cell cycle indicator (FUCCI) ESCs grow over time as indicated by time-lapse data from a live imager that generated an S-shaped curve for accumulation of cells during normal stemness (NS) culture with leukemia-inhibitory factor (LIF). Since it was hypothesized that ESC were heterogeneous in the cell cycle, it was expected that green fluorescence, cells in S-G2-Mphase of the cell cycle, would increase in an S-shaped curve parallel to the accumulation curve. Unexpectedly, it was observed that the fraction of FUCCI ESC in green decrease over time to a nadir at ~24hr after the previous feeding and then rapidly enter S-G2-Mphase of cell cycle to create a green peak after media change. The fed/unfed fold increase in green ESCs ranged from 4.8 on day 1 to 6.8 on day 2 during NS culture. We tested whether doses of perfluoro-octanoic acid (PFOA) would suppress the magnitude of the green fluorescent fed peak and found that doses of 1, 10 and 100nM had no effect, but at 1uM there was a significant suppression of the peak to 3FC (LOAEL dose). The LOAEL dose for PFOA to suppress increase in FUCCI green indicator compared with zero dose NS culture was 1uM, whereas the LOAEL dose of PFOA to suppress increase in confluence was 10uM. In this analysis, Diethyl phthalate (DEP) had a LOAEL dose at 1nM where the green peak/nadir was suppressed from 4.8FC NS zero dose to 3.3FC at 1nM, but no significant decrease at doses from 10nM to 100uM. Hypothetically, more frequent media change should increase growth rate by preventing longer cell cycle and decrease the amplitude of fold increase in green cells in S-G2-Mphase after media change. The second outcome occurred as fold change in green increase after 12hr feeding was less than for 24hr feeding. But growth was not increased, perhaps due to confounding variables. Live imaging was used to provide daily QC analysis of inter-well and inter-plate variability and has led to 1/3rd decrease in variation. The data presented here suggest that FUCCI ESC can be used to predict the instantaneous suppression of future growth in a predictive model of developmental toxicity for environmental toxicants.

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FOSTER E, CLOUGH K, CURRAN CP. Northern Kentucky University, Highland Heights, KY, United States. Aryl Hydrocarbon Receptor Mediated Disruption of Dopaminergic and Serotonergic Signaling in the Hippocampus and Prefrontal Cortex of Mice Exposed to Benzo[a]pyrene during Development

Traffic-related air pollution (TRAP) consists of particulates, gases, and polycyclic aromatic hydrocarbons (PAHs). Recent studies have found that aryl hydrocarbon receptor (AhR) agonists, including PAHs, have neurotoxic effects, especially during early brain development. Exposure to benzo[a]pyrene (BaP), a model PAH, has been linked to deficits in learning and memory and changes in dopaminergic pathways in animal studies. Our study aims to determine the effects of genetic variation on BaP developmental neurotoxicity. We use mice with genetic differences in the AhR and Cyp1a2, an enzyme regulated by the AhR, to model human genetic variation. Pregnant dams were treated with 10mg/kg/day BaP in corn oil-soaked cereal or the corn oil vehicle from gestational day 10 to postnatal day 25. One male and one female per litter were randomly selected for behavioral testing. Following behavioral testing at postnatal day 120, striatum, hippocampus, prefrontal cortex, and hypothalamus were collected. Dopamine, serotonin and their metabolites were measured using High-Performance Liquid Chromatography with Electrochemical Detection. While there were significant differences in neurotransmitter levels in the striatum, the most compelling results come from the hippocampus and prefrontal cortex with multiple significant gene x treatment interactions. In the hippocampus, differences were observed in all genotypes of BaP-treated mice, but the greatest significant differences were in low-affinity AhrdCyp1a2(-/-) mice. BaP-treated low-affinity knockouts had significantly decreased dopamine levels ($P < 0.01$) and significantly increased dopamine turnover rates ($P < 0.05$) compared to corn oil controls. In the prefrontal cortex, BaP-treated high-affinity AhrbCyp1a2(-/-) mice had significantly increased dopamine turnover rates and low-affinity AhrdCyp1a2(-/-) mice had significantly decreased dopamine turnover rates compared to corn oil controls ($P < 0.01$). Serotonin signaling was also affected, with BaP-treated wild type AhrbCyp1a2(+/+) mice having increased serotonin levels, while high-affinity knockouts had significantly decreased levels compared to corn oil controls ($P < 0.05$). Our Cyp1a2 knockouts seem to be the most susceptible to changes in neurotransmitter levels following developmental BaP exposure but were differentially affected depending on the AhR allele present. Identifying genetic susceptibilities could potentially lead to targeted interventions.

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VARSHAVSKY J[1], ROBINSON JF[1], ZHOU Y[1], PUCKETT K[1], BUARPUNG S[1], ABURAJAB R[1], GAW S[1], SEN O[2], CRISPO SMITH S[3], FRANKENFIELD J[3], PARK J-S[3], FISHER S[1], WOODRUFF T[1]. [1]University of California, San Francisco, San Francisco, CA, United States, [2]The University of Tennessee Health Science Center, Memphis, TN, United States, [3]Department of Toxic Substances Control, Berkeley, CA, United States. Exposure to Flame Retardants and Surfactants *In Utero* and Biomarkers of Human Placental Development and Disease

While human health risks remain unresolved, epidemiological and toxicological studies suggest that classes of environmental chemicals (e.g., per- and polyfluoroalkyl substances [PFASs], polybrominated diphenyl ethers [PBDEs], and organophosphate flame retardants [OPFRs]) cause developmental toxicity and contribute to pregnancy complications and related adverse maternal health outcomes. To study these relationships in the context of human pregnancy, biomarkers may be utilized as proxies of exposure, development, and disease progression. In this study, we evaluated chemical levels of PFASs (n=12; serum), PBDEs (n=19; serum and placenta), and OPFR metabolites (n=4; urine) in 132 healthy pregnant women during midgestation. In a subset of placental samples (n=62), we examined immunoreactivity of proteins with critical roles in placental development–Integrin Alpha 1 (ITGA1), Cadherin 5 (CDH5), and Matrix Metalloproteinase 1 (MMP1)–*in uterine*-invading placental cytotrophoblasts (CTBs). We also assessed placental morphological indicators of stress (fibrinoid deposition, leukocyte infiltration) and development (CTB endovascular remodeling), as well as maternal blood pressure and lipid levels. To examine associations between environmental chemical levels and placental biomarkers, we employed censored Kendall's tau correlation and maximum likelihood regression. Perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47), 2,2′,4,4′,5-pentabromodiphenyl ether (BDE-99), diphenyl phosphate (DPP), and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) were widely detected in all biomatrices (>99% above detection limits). BDE-47 (geometric mean [GM] = 0.19 [95% CI: 0.17–0.20] ng/mL in serum and 0.10 [95% CI: 0.09–0.11] ng/g in placenta), PFOS (2.8 [95% CI: 2.6–3.1] ng/mL), and BDCIPP (3.6 [95% CI: 2.2–3.1] ng/mL) were the most prevalent compounds of the three major chemical classes. We observed inverse associations between select PFASs, PBDEs, or OPFRs and immunoreactivity of ITGA1 or CDH5 *in uterine*-invading CTBs. Associations were also observed with indicators of placental stress, maternal blood pressure, and lipid levels. These results signal a relationship between maternal/fetal environmental chemical levels and biomarkers of placental developmental and disease during a vulnerable period in pregnancy that precedes common pregnancy complications associated with impaired placentation.

Innovator Award Finalists Platform Session 5

Chairperson: Kembra L. Howdeshell, National Institute of Environmental Health Sciences

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CHEN H[1], ROBINSON JF[1], JIGMEDDAGVA U[1], WILLIAMS KE[1], HUNTER CL[2], YAN CD[1], IYER NS[1]. [1]University of California, San Francisco, San Francisco, CA, United States, [2]SCIEX, San Francisco, CA, United States. Transcriptomic and Proteomic Profiling of Alternative Flame Retardant Exposures in Human Embryonic Stem Cell Neural Derivatives

Over the past decade, polybrominated diphenyl ethers (PBDEs) have been phased out of the marketplace due to their environmental persistence and ability to cause human developmental neurotoxicity (DNT). Brominated and nonbrominated alternative flame retardants (AFRs) have replaced these compounds in consumer products. Emerging studies suggest that many of these AFRs are widely detected in humans (e.g., pregnant women) and their health effects remain unresolved. Previously, we demonstrated human embryonic stem cell (hESC)-derived neural progenitor cells (NPCs) to be sensitive to PBDE-induced DNT. Here, we extended these analyses and determined if AFRs alter NPC function and induce DNT via similar mechanisms as BDE-47. First, we screened a panel of 12 relevant AFRs on cell death and proliferation/viability at 24h. The majority of AFRs-induced cell death and reduced proliferation/viability in a concentration and compound-specific manner (ANOVA; $p<0.05$). Select AFRs (e.g., isopropylated phenyl phosphate (IPP), 2-ethylhexyl diphenyl phosphate (EHDP) and Firemaster 550 (F550)) were found to be as toxic as BDE-47, a common PBDE congener and suspected human neurotoxicant. In subsequent assessments, we performed transcriptomic (RNA sequencing) and proteomic (mass spectrometry) profiling of IPP, EHDP, F550, and BDE-47 (3 or 10 μM) exposed NPCs to identify mechanisms underlying DNT. In general, all four FRs altered mRNA and protein expression in a concentration-dependent manner. These signature changes were unique by compound and between transcriptomic and proteomic readouts. Sixty genes were identified to be commonly dysregulated (e.g., TRIB3, PAX6, and HMOX1) and only one protein (i.e., tyrosine-protein kinase BAZ1B) was altered by all four FRs. On a pathway level, FRs commonly altered genes associated with neurogenesis, adhesion, cell morphogenesis; and proteins linked with cerebral cortex development, cell migration, and lipid transport. Our results suggest that AFRs induce DNT via unique mechanisms as compared to BDE-47, however, specific molecules and associated pathways related to neural cell function and development may serve as common targets.

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PITSAVA G[1], PANKRATZ N[2], LANE J[2], YANG W[3], RIGLER S[4], SHAW GM[5], MILLS JL[1]. [1]NICHD, NIH, Bethesda, MD, United States, [2]Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, MN, United States, [3]Department of Pediatrics, Stanford University School of Medicine, Standford, CA, United States, [4]Department of Neonatology, Naval Medical Center Portsmouth, Portsmouth, VA, United States, [5]Standford University School of Medicine, Standford, CA, United States. Exome Sequencing Findings in 115 Children with Annular Pancreas

Annular pancreas (AP) is a congenital defect in which the pancreas completely encircles the duodenum. Three main pathogenesis theories have been posited: 1) abnormal migration and rotation of the ventral bud, 2) persistence of ectopic pancreatic tissue, and 3) inappropriate fusion of ventral and dorsal buds before rotation. The few reported familial cases suggest a genetic contribution. We conducted whole exome sequencing in newborn bloodspots of 115 infants identified from the population-based California Birth Defects Monitoring Program (1984–2014) to have AP. Data were processed using BWA-MEM for alignment, GATK for quality recalibration, indel realignment, GATK HaplotypeCaller for genotyping, SNPPEff for functional annotation, and ANNOVAR for frequency annotation. Loss of function and missense variants were prioritized if they were defined as rare (minor allele frequency <0.005) in public databases (e.g., gnomAD). Of the 115 with AP sequenced, 91 passed our sample quality filters (FREEMIX<0.05) and 78 harbored at least one variant passing our variant thresholds. Seven children had a single heterozygous missense variant in IQGAP1 (none were recurrent), five of them with CADD scores >20 (top 1% of deleterious variants in the genome); seven other infants had a single heterozygous missense variant in NRCAM (none were recurrent), five of them with CADD scores >20. All IQGAP1 and NRCAM variants were present in public databases. We looked at genes previously associated with AP risk and found two rare missense variants in PDX1 and FOXF1 (one heterozygous missense variant in each gene). IQGAP1 is crucial in actin organization and regulates cell motility. It is also highly expressed in pancreatic tissue; when mutated it results in decreased cell dynamics and thus causes decreased motility which could possibly alter the ventral bud to not migrate normally. Notably, high IQGAP1 activity is associated with cancer metastasis. NRCAM is also involved in cell migration. Signaling from its intracellular domain to the actin cytoskeleton influences directional cell migration. To our knowledge, this is the first study reporting a possible association for IQGAP1 and NRCAM with AP. Our findings of two genes involved in migration in 12% of our population supports the hypothesis that AP is related to abnormal cell migration. However, confirmation of our findings is needed.

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LUPO PJ[1], ARCHER NP[2], MARENGO LK[2], HOYT AT[2], DRUMMOND-BORG M[2], FREEDENBERG D[2], LANGLOIS PH[3], CANFIELD MA[3]. [1]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX, United States, [2]Texas Department of State Health Services, Austin, TX, United States, [3]Birth Defects Epidemiology and Surveillance, Texas Department of State Health Services, Austin, TX, United States. Newborn Screening Analytes and Structural Birth Defects: Evaluating Novel Associations using a Phenotypic Spectrum Analysis

Newborn screening (NBS) is an important public health program that tests for the presence of health disorders using a heel stick blood sample collected soon after birth. There is evidence that NBS analytes are also associated with conditions not included in traditional screening programs, including some birth defects. However, there have been no large-scale efforts to evaluate associations between NBS analytes and a range of birth defects. Therefore, we conducted a phenotypic spectrum analysis to evaluate associations between NBS analytes and birth defects evaluated in the Texas Birth Defects Registry (TBDR). Information on children with birth defects included as part of the National Birth Defects Prevention Network (N=39) was obtained from the TBDR for the period 2007–2009. Controls were infants without birth defects. Study subjects were linked to their NBS laboratory records, including values for 36 analytes. Logistic regression models were used to evaluate analyte-birth defect associations. A Bonferroni correction was used to account for the number of comparisons (significant associations noted at p<3.56x10–5). A total of 20,741 cases and 7,439 controls were included in the assessment. Among the 1,404 associations evaluated (39 birth defects by 36 analytes), there were 512 (36%) significant findings after correcting for multiple comparisons. Analytes most consistently associated with birth defects included tyrosine (N=31) and thyroxine (N=29). Birth defects most commonly associated with a range of analytes included gastroschisis (N=31), several cardiovascular defects (e.g., transposition of the great vessels, N=29), and spina bifida (N=24). When restricting to isolated birth defects, there were fewer significant associations (N=95), although consistent patterns with spina bifida and gastroschisis remained. For instance, 30 of 36 analytes were associated with isolated gastroschisis, with decreasing levels of tyrosine being the strongest observed association (adjusted odds ratio=0.23, p=2.56x10–55). In our study, there were several statistically significant associations between NBS analytes and birth defects. While these associations must be replicated and more fully explored, our findings could point to undiscovered syndromes, especially analyte associations among children with multiple congenital anomalies. Additionally, analyte-isolated birth defect associations could inform new etiologic studies for these conditions.

Society for Birth Defects Research and Prevention

POSTER ABSTRACTS

(Presenter designated by underlined author.)

Poster Session 1

P1

HAN A[1], LEE S[2]. [1]Myunggok Research Center, Konyang University, Daejeon, Republic of Korea, [2]Department of Obstetrics and Gynecology, Konyang University College of Medicine, Daejeon, Republic of Korea. Maternal and Fetal Safety of Intravenous Immunoglobulin in Women with Reproductive Failure

Problem: Intravenous immunoglobulin G (IVIG) is an emerging regimen for women with reproductive failures (RF) during- or prepregnancy who have aberrant cellular immune reactions. Studies investigating the teratogenicity of IVIG is limited. Herein, we evaluated the fetal teratogenicity of IVIG and IVIG-related obstetric complications. Method of study: Women who used IVIG during pregnancy due to RF with cellular immune aberrances were enrolled from four medical centers in Korea. The pregnancy outcomes were collected. Results: A total of 370 RF women who used IVIG during their pregnancy were enrolled. Most of the patients started the IVIG therapy before 12 weeks of gestation and 229 women continued IVIG treatment beyond 12 weeks of gestation. The mean age of the subjects was 34.8 years and the mean total dosage of IVIG was 125.3 g. A total of 307 women had livebirths and six of them were twins. Of 301 singleton livebirths, obstetric complications were developed as follows: preterm births (12%), gestational diabetes (7%), preeclampsia (4%), placental abruption (1.3%), placenta previa (4.3%), and placenta accrete (1.7%). Total six cases (1.99%) had major fetal anomalies in livebirths. The incidence of birth defects is similar to those of the general population in Korea and the previous report in infertile women. No IVIG-related viral contamination was noted. Conclusion: IVIG use during pregnancy did not increase obstetric complications and fetal teratogenicity. This study can be evidence of maternal and fetal safety of IVIG administration during pregnancy.

P2

DAZA M[1], VALENCIA D[2], MULKEY SB[3], MERCADO MM[4], MOORE CA[2]. [1]Vysnova Partners, Bogotá, Colombia, [2]Centers for Disease Control and Prevention, Atlanta, GA, United States, [3]Children's National Hospital, Washington, DC, United States, [4]Instituto Nacional de Salud, Bogotá, Colombia. Congenital Infections in Twin Pregnancies: A Narrative Review

Fetal outcomes resulting from congenital infections are influenced by factors like genetic backgrounds, type of infectious agent, timing of infection, placental defense mechanisms, and immune responses. Twin studies have been used to understand genes and environment contributions to outcomes resulting from adverse exposures. Congenital infections have been associated with concordant and discordant birth defects and developmental disabilities in twins; twin discordance could be more expected, but not exclusive to dizygotic (DZ) pregnancies. We reported the first occurrence of monozygotic (MZ) twins discordant for congenital Zika syndrome and sought to characterize outcomes of selected congenital infections in twin pregnancies. A narrative review was carried out in MEDLINE (PubMed) and SciELO retrieving English or Spanish publications at or before December 31, 2020. Zika virus (ZIKV), cytomegalovirus (CMV), toxoplasmosis, rubella, lymphocytic choriomeningitis virus (LCMV), syphilis, and varicella congenital infections were included. Data regarding number of twin pairs, placentation, zygosity, laboratory results and clinical outcomes were abstracted. Clinical discordance was determined when birth defects were reported in only one of the infants; laboratory discordance when evidence of infection was present in only one of the infants' samples. Reports of congenital infections occurring in twin pregnancies were found for all selected agents. Nineteen reports were reviewed. The distribution of twin pairs per agent was ZIKV (19 pairs), CMV (19), toxoplasmosis (16), rubella (2), LCMV (2), varicella (1) and syphilis (2). Information about zygosity and type of placentation was not always present. Discordant twin outcomes were reported for all selected agents; discordance in MZ twins was reported infrequently and only for toxoplasmosis, rubella, and ZIKV, possibly indicating a differential effect by infectious agent. DZ twin pregnancies had a higher frequency of discordant outcomes within all agents; thus, dichorionic placentation and fetal genetic backgrounds seem to be an important factor related to twin discordance, though separate placentas were not always predictive of compromise. This review provides insights into the potential role of zygosity and placentation on outcomes of congenital infections in twin pregnancies, a systematic review is needed to better understanding the the interaction of genetic and environmental factors on clinical outcomes.

P3

GOODMAN CV[1], HALL MK[1], GREEN R[1], HORNUNG R[2], MARTINEZ-MIER EA[3], LANPHEAR B[4], TILL C[5]. [1]Faculty of Health, York University, Toronto, ON, Canada, [2]Retired, Loveland, OH, United States, [3]Indiana University School of Dentistry, Indianapolis, IN, United States, [4]Faculty of Health Sciences, Simon Fraser University, Burnaby, BC, Canada, [5]York University, Toronto, Toronto, ON, Canada. Gestational Fluoride Exposure and Birth Outcomes: The MIREC Cohort

Exposure to high levels of fluoride in drinking water (i.e., >1.5 mg/L) has been associated with adverse pregnancy and birth outcomes. However, little is known about the effect of exposure to optimal levels of fluoride during pregnancy on birth outcomes. We examined the relationship between gestational fluoride exposure and birth outcomes in a Canadian birth cohort living in areas with and without water fluoridation. We estimated gestational fluoride exposure using specific gravity adjusted maternal urinary fluoride concentration (MUF; mg/L), averaged across all three trimesters, and water fluoride concentration (mg/L) collected from local water treatment plants. Data on birthweight (BW; grams), gestational age (GA; weeks), preterm birth (PTB), and small-for-gestational-age (SGA) were extracted from 1,466 mother-child dyads enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) study with available MUF (N = 1350) and water fluoride (N = 1082) concentrations. We examined associations between gestational fluoride exposure and birth outcomes using multiple linear regression (BW and GA) and logistic regression models (SGA and PTB) adjusted for maternal age, body mass index, parity, child sex, city of residence, and other relevant covariates. No significant associations between MUF and BW (B = 54.66, 95% CI: -14.11, 123.44); GA (B = 0.08, 95% CI: -0.13, 0.28); SGA (OR = 0.89, 95% CI: 0.43, 1.84); or PTB (OR = 0.97, 95% CI: 0.47, 2.00) were observed. Similarly, no significant associations were identified for water fluoride concentration and BW (B = 14.87, 95% CI: -97.66, 127.40); GA (B = 0.01, 95% CI: -0.32, 0.35), SGA (OR = 0.66, 95% CI: 0.24, 1.82); or PTB (OR = 1.38, 95% CI: 0.48, 3.94). No evidence of effect modification by child sex was detected. In this Canadian birth cohort, fluoride exposure during pregnancy was not associated with either adverse or optimal birth outcomes.

P4

SHEIKH I, CLUBB SK, MOONEY K. Charles River Laboratories, Edinburgh, United Kingdom. Validation Studies to Assess Toxicological Endpoints of Group Housed Pregnant Rabbits for Use in Reproductive Toxicology Studies

To improve animal welfare and enhance enrichment for future reproductive and developmental toxicology study designs, two in-house studies were conducted with the objective to evaluate paired housing of pregnant rabbits from Gestation Day (GD) 2 to 29. The first study was conducted as a preliminary evaluation of paired housing involving six pregnant rabbits. The success of this study led to the subsequent larger study conducted on 18 rabbits. On arrival, randomly selected paired presumed pregnant rabbits were housed into two standard cages (per cage: W= 743mm D=716mm H =55cm) linked together but open within to allow movement throughout the cages and option to distance from cage mate. Enrichments included: a supply of hay, fruit and vegetables and periods of exercise. Daily detailed examinations, body weight and food consumption recordings were performed. For the larger study, regular behavioral checks were performed throughout the day. On GD 29, rabbits on the smaller study were rehoused individually for evaluation of the littering phase up to Postnatal Day 30. Rabbits for the larger study were euthanized on GD 29 for evaluation of any adverse effects on pregnant rabbits and fetal development (external abnormalities, body weights, visceral/fixed head/skeletal examination). There were no adverse clinical observations or evidence of aggression at any stage of the study. Body weights were unaffected (minor fluctuations in weight gain), correlating with the food consumption recordings. Behavioral checks confirmed that paired animals remained calm, with a mixture of animals being together or in separate cages, throughout the day. In the first study, paired housing prior to littering did not impact the maternal care or preweaning developmental landmarks (hair growth, eye opening and pupil constriction) in the kits. Although one rabbit did not produce a litter and another rabbit had a total litter loss. The remaining four females raised their litters successfully. In the larger study, there were no effects on fetal weights or fetal findings when compared to controls on concurrent studies. There were no adversities from pair housing pregnant rabbits compared to single housed rabbits. There were no indications of aggressive behavior; animals appeared calm and showed freedom of movement between cages for distance when desired. Body weights and food consumption was unaffected. Fetal examinations and maternal performance indicated no adversities from paired housing.

P5

BLAKE BE[1], ARZUAGA X[2], DRUWE I[1]. [1]US EPA, Research Triangle Park, NC, United States, [2]US EPA, Washington, DC, United States. Implementation of the Key Characteristics of Male Reproductive Toxicants to Synthesize Mechanistic Eevidence: A Case Study of Benzo[a]pyrene

Mechanistic evidence plays a critical role in the hazard identification of reproductive toxicants and requires synthesis of complex data across studies that differ in experimental methods, models, and scope. The eight key characteristics (KCs) of male reproductive toxicants provide an approach for systematically identifying and organizing data across mechanistic studies of male reproductive toxicity. Here we demonstrate the utility of applying the eight KCs of male reproductive toxicants to identify, organize, and analyze the toxicological and mechanistic evidence for male reproductive effects induced by the chemical benzo[a]pyrene (B[a]P). A literature search was performed, and 2,172 studies were identified then screened using both SWIFT-Active Screener and DistillerSR, resulting in 64 *in vitro* and *in vivo* studies that met predefined inclusion criteria for full text review. Relevant study information was manually extracted and compiled into an evidence inventory which underwent quality control by a second reviewer. Mechanistic information in the literature inventory was organized using the eight KCs of male reproductive toxicants, which led to the development of a putative mode of action (MOA) for B[a]P for male reproductive effects by facilitating the identification of potential key events and key event relationships within the MOA. This MOA is informed by the mechanistic evidence across the literature inventory and illustrates where the KCs contribute to B[a]P-induced male reproductive effects at the molecular, cellular, organ, and organism levels. Given the importance of mechanistic evidence in establishing biological plausibility and human relevance of effects observed in experimental models, this work demonstrates the KCs approach is a systematic, efficient, and transparent qualitative method for identifying, organizing, and summarizing mechanistic data for male reproductive hazard identification that can be expanded to other toxicants of interest.

P6

NAVARRO SANCHEZ ML[1], AGOPIAN AJ[1], SWARTZ MD[2], CANFIELD MA[3], LANGLOIS PH[3]. [1]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States, [2]Department of Biostatistics and Data Science, UTHealth School of Public Health, Houston, TX, United States, [3]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, United States. Epidemiology of Nonsyndromic, Orofacial Clefts in Texas: Differences by Cleft Type and Presence of Additional Defects

The last descriptive epidemiology study of nonsyndromic cleft palate alone (CP) and cleft lip with or without cleft palate (CL±P) in Texas examined data from 896 infants born between 1995 and 1999. We sought to update this work. Our objective was to describe epidemiologic features of nonsyndromic CP and CL±P in Texas among 1999–2014 deliveries, examining differences in the characteristics of infants with CP and CL±P based on the presence/absence of additional defects. Our descriptive analyses used data from the Texas Birth Defects Registry (TBDR), a statewide active birth defect surveillance system for 1,815 cases with CP and 5,066 with CL±P, without a syndrome diagnosis. Poisson regression was used to calculate crude and adjusted prevalence ratios for each characteristic, separately for each cleft subphenotype. The prevalence of CL±P and CP in our study was estimated to be 8.3 and 3.0 per 10,000 live births, respectively. After adjusting for several characteristics, multiple factors were associated with CL±P, CP, or both, including infant sex and maternal race/ethnicity, age, smoking, and diabetes. In addition, there were several differences between infants with isolated versus nonisolated clefts. For example, maternal prepregnancy diabetes was strongly associated with an increased prevalence of CL±P (adjusted prevalence ratio [aPR] 8.23, 95% CI 5.77, 11.74) and CP (aPR 3.24, 95% CI 1.43, 7.36) when additional defects were present, but not among isolated cases. Findings from this study provide a contemporary description of the distribution of orofacial clefts in Texas and may contribute to increasing our understanding of the etiology of CP and CL±P.

P7

ALDAY A, SOLIS JC, MURIANA A, QUEVEDO C. BBD BioPhenix-BIOBIDE, Donostia, Spain. Validation of Zebrafish Embryotoxicity Test (ZET) as a Qualified Alternative Assay for Its Regulatory Use

The new ICH S5 (R3) guideline on reproductive toxicology that applies to all pharmaceuticals for which reproductive and/or developmental toxicity studies are appropriate, proposes the use of alternative testing assays as part of an integrated testing strategy to minimize the use of animals. The guide provides a Reference Compound List that contains 29 compounds that have been shown to induce specific malformation or embryo-fetal lethality plus three negative compounds that can be used to support the qualification of an alternative assay. Our research focused on the predictivity of the zebrafish developmental toxicity assay. Zebrafish embryo model is highly popular in toxicology and provides an ethically acceptable small-scale analysis system with the complexity of a complete organism. This model enables continuous developmental monitoring and has been widely used for the generation of relevant answers on mammalian developmental hazards. Our goal is to further validate this model for its regulatory use by testing the 32 compounds indicated in the new ICH S5 guideline. To determine the teratogenic risk of these chemicals, the presence of morphological alterations was analyzed at two different stages and a teratogenic index (TI) was established as the ratio between LC50/EC50. Developmental toxicity was well predicted for 23 of the 29 teratogenic compounds indicated in the guideline (Sensitivity = 79.3%). For compounds not properly identified, only results obtained for Cytarabine were conclusive. Although embryo morphology was not or barely affected after exposure to Phenytoin, Pomalidomide, Thalidomide, and Vismodegib, the limited solubility of these compounds in water restricted the concentrations that could be assayed. For Aspirin, the limitation was in this case due to the acidification of the exposure medium. At last, no toxicity was caused by Cetirizine, Saxagliptin, and Vildagliptin, the three negative compounds selected in the guide (Specificity = 100%). These promising results need to be further confirmed by increasing the number of replicates for reproducibility estimation. Moreover, bioanalysis for internal concentration determination in zebrafish embryos will be also evaluated to determine the ability of this assay to predict mammalian embryotoxic exposure.

P8

BETANCOURT D[1], SHUMATE CJ[1], CANFIELD MA[2], ETHEN MK[1], NAVARRO SANCHEZ ML[3].[1]Texas Department of State Health Services, Austin, TX, United States, [2]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, United States, [3]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States. Comparing Socio-Demographic Characteristics of Mothers Who Did and Did Not Participate in a Survey Related to the Prevention of Neural Tube Defects

Women who have had a pregnancy affected by a neural tube defect (NTD) have an increased risk of a subsequent NTD-affected pregnancy. The Texas Birth Defects Epidemiology and Surveillance Branch (Branch) mails information about high-dose folic acid supplementation for NTD recurrence prevention to women who have had a recent NTD-affected pregnancy. The Branch surveyed these women to evaluate the effectiveness of the NTD recurrence prevention mailing. The Branch identified 177 women who had been sent the mailing, whose child was believed to be still living based on a search of death certificates. These women were surveyed to assess their recall of the mailing and knowledge about NTD recurrence prevention. The Branch compared socio-demographic characteristics of survey participants and nonparticipants using data from the Texas Birth Defects Registry. To assess significant differences between the two groups, Tukey multiple comparison tests were performed, $p < 0.05$. In total, 71 of the 177 women completed the survey (70 biological mothers and 1 adoptive mother) and 106 women declined to participate or could not be reached. Among 70 respondents, 80% (56/70) recalled receiving the mailing, 57% (32/56) of whom provided accurate information about folic acid for prevention of NTDs, when asked what they remembered from the mailing. For 41% (26/64) of survey participants and 38% (33/88) of nonparticipants, the highest level of education obtained was a high school diploma or GED. For 58% (37/64) of participants and 59% (52/88), of nonparticipants Medicaid was the principal source of payment for their child's delivery. An equal percentage (14%) of participants and nonparticipants resided in a Texas county bordering Mexico at the time of delivery. The largest proportion for survey participants (24/70; 34%) were ages 25–29 at the time of their child's birth and the largest proportion of nonparticipants (31/103; 30%) were ages 30–34. Fifty-six percent of participants (39/70) and 59% of nonparticipants (61/104) were Hispanic. Sixty-six percent of participants (42/64) and 77% (68/88) of nonparticipants were born in the United States. None of these differences were statistically significant ($p < .05$). The similarities in sociodemographic characteristics between the survey participants and nonparticipants reinforce the findings of the survey, which demonstrated the value of the NTD mailing.

P9

KANCHERLA V[1], MOWLA S[1], RÄISÄNEN S[2], GISSLER M[3]. [1]Emory University, Atlanta, GA, United States, [2]Tampere University of Applied Sciences, Highland Heights, KY, United States, [3]THL Finnish Institute of Health and Welfare, Helsinki, Finland. Early Neonatal Mortality among Babies Born with Spina Bifida in Finland, 2000–2014

Early neonatal mortality among infants with spina bifida is a concern and varies geographically. Early neonatal mortality, its trends, and factors associated with it are not well understood in the Nordic region. We examined early neonatal mortality risk, temporal trends, and selected infant and maternal factors associated with early neonatal mortality among all spina bifida-affected live births in Finland. We linked multi-registry population-based data from the national registers in Finland for infants born with spina bifida from 2000–2014. Early neonatal mortality was defined as death in 0–6 days after birth. Early neonatal mortality risk and 95% confidence intervals (CI) was estimated using the Poisson approximation of binomial distribution. Poisson regression was used to examine temporal trend in early neonatal mortality from 2000 to 2014 for spina bifida cases and all births in Finland. Selected infant and maternal characteristics were compared between cases that experienced early neonatal mortality and cases that did not using Chi square or Fisher's Exact test (when cell sizes were less than five). Exact logistic regression was used to estimate unadjusted odds ratios (uORs) and 95% confidence intervals (CIs). A total of 181 babies were born alive with spina bifida in Finland during the study period; 61% had isolated spina bifida. Pooling all study years, 7.2% (95% CI=4.2%, 12.4%) of all live-born cases experienced early neonatal death. There was a significant increase in early neonatal mortality among spina bifida births over the study period (p <0.0001). Low gestational age (<37 weeks) (uOR=6.96; 95% CI=1.86, 29.01), cases occurring as a part of a syndrome (uOR=125.67; 95% CI=14.90, >999.999), and advanced maternal age at gestation (≥35 years) (uOR=5.33; 95% CI=1.21, 21.87) were positively associated with early neonatal mortality. Using national data from Finland, we found high early neonatal mortality with increasing trend over birth period spanning 15 years (2000–2014), and unadjusted positive associations with some infant and maternal factors. Future studies should pool data from Nordic countries to increase study size allowing multivariable analysis.

P10

MAXWELL JR[1], NOOR S[1], PAVLIK N[1], RODRIGUEZ D[2], ENRIQUEZ MARQUEZ L[2], DIDOMENICO J[1], BAKHIREVA L[2]. [1]University of New Mexico, Albuquerque, NM, United States, [2]University of New Mexico, College of Pharmacy, Albuquerque, NM, United States. Moderate Prenatal Alcohol Exposure Increases Toll-Like Receptors Activity Detectable in Umbilical Cord Blood at Birth

One in nine pregnant women report drinking during pregnancy. Prenatal alcohol exposure (PAE) increases the risk of infection in the newborn by altering development with resultant changes in immune function including cytokine expression. Toll-like receptors (TLRs) are expressed on multiple types of cells and play a vital role in modulation of the innate immune system and the release of inflammatory mediators. Therefore, we predicted that PAE would result in dysregulated cytokine expression following stimulation with TLR agonists, in umbilical cord blood samples. Cord blood samples were obtained from a subset of infants born to the prospective ENRICH-2 cohort study participants. This study includes two prenatal visits, a comprehensive assessment at birth/first month of life, and a six-month follow-up assessment. Pregnancy alcohol use was ascertained by four Timeline Follow-Back interviews and comprehensive ethanol biomarker panels. Women were grouped into PAE and Control (no exposure) groups. Peripheral blood mononuclear cells (PBMCs) were isolated from cord blood by Ficoll-isopaque density gradient centrifugation. Cells were plated and stimulated with lipopolysaccharide (LPS, TLR4 agonist), Pam3CSK4 (TLR2 agonist), CpG ODN (TLR9 agonist) and Poly I:C (TLR3 agonist). Electrochemiluminescence assay was performed to measure cytokines typically produced from innate immune cells- IFN-γ, IL-10, IL-12p70, IL-13, IL-1β, IL-2, IL-4, IL-6, IL-8 and TNF-α. The cytokine (protein) expressions were compared by Student's t-test. To date, samples from 14 infants were evaluated (Control=7, PAE=7). Alcohol use was moderate (AA/day[SD]=0.4[0.2]). No differences in maternal age or education were observed. Significant increases in IFN-γ, IL-10, IL-12p70, IL-13, IL-1β, IL-2, IL-4, IL-8 and TNF-α expression following stimulation with LPS were observed (p<0.05) when compared to baseline, with PAE having more significant increases. Additionally, significant increases were observed following stimulation with Pam3CSK4, CpG ODN and Poly I:C. Interestingly, PAE resulted in a more robust increase in expression (control p values: 0.01–0.07; PAE p values: 0.001–0.05) following stimulation with Pam3CSK4 compared to the control group. hese results support that even moderate PAE may alter the developing immune system, with alterations in cytokine expression that have the potential to impact lifelong immune function. This study is funded by NIAAA grant 2R01AA021771 (PI: Bakhireva).

P11

CHAMBERS T[1], KEYZER M[1], BENJAMIN RH[2], SHUMATE CJ[3], LE M[3], CANFIELD MA[4], LEWIS RA[1], HUFNAGEL RB[5]. AGOPIAN OO[2], BROOKS BP[5], MITCHELL LE[6], LUPO PJ[7]. [1]Baylor College of Medicine, Houston, TX, United States, [2]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States, [3]Texas Department of State Health Services, Austin, TX, United States, [4]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, United States, [5]National Eye Institute, Bethesda, MD, United States, [6]University of Texas School of Public Health, Houston, TX, Unites States, [7]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX, Unites States. Epidemiology of Coloboma: Prevalence and Patterns in Texas, 1999–2014

Coloboma is a rare birth defect that can affect several parts of the eye, including the iris, retina, choroid, or optic nerve. Children with coloboma can experience reduced vision or increased risk of amblyopia development. As little is known about the epidemiology of this condition, our goal was to leverage data from a large population-based birth defects surveillance system to both determine the overall prevalence of coloboma as well as evaluate differences by demographic and clinical characteristics. Information on children with coloboma born during the period 1999–2014 was obtained from the Texas Birth Defects Registry (TBDR) while information on all live births in Texas from the same period was obtained from the Texas Center for Health Statistics. Crude and adjusted prevalence ratios (PRs) were estimated for the association between demographic characteristics and nonsyndromic coloboma. Overall, there were 1,635 children born with coloboma for the period 1999–2014, which resulted in a prevalence of 3.5 per 10,000 live births. Among those children, 934 did not have an identified syndrome, which resulted in a prevalence of nonsyndromic coloboma of 2.0 per 10,000 live births. There were some differences in the prevalence of nonsyndromic coloboma by demographic and clinical factors. For example, the prevalence of coloboma appeared to increase over time (PR=2.09, 95% confidence interval [CI]: 1.75–2.50 for 2010–2014 and PR=1.46, 95% CI: 1.22–1.76 for 2004–2009 compared to 1999–2003). Coloboma was less frequent in females compared to males (PR=0.86, 95% CI: 0.76–0.98). Additionally, the prevalence of coloboma was higher among the offspring of mothers who had diabetes (PR=1.51, 95% CI: 1.14–2.01) or a multiple pregnancy (PR=1.60, 95% CI: 1.17–2.19). Alternatively, the prevalence of coloboma was lower among mothers residing along the Texas-Mexico border (PR = 0.43, 95% CI: 0.34–0.56). When evaluating associations among infants with isolated coloboma (N=292), patterns remained largely the same. Overall, our prevalence estimates in a large and diverse population were consistent with other reports. While differences in prevalence could point to variability in diagnostic practices or access to care, our findings could point to novel factors associated with coloboma, a relatively understudied birth defect.

P12

CHIANG C[1], ZURLINDEN T[2], KAPRAUN D[2], CARLSON LM[2], TRGOVCICH J[3], SILVA R[3], CHRISTENSEN K[2], SCHLOSSER P[2], LEHMANN 02. [1]US EPA, Morrisville, NC, United States, [2]US EPA, Durham, NC, United States, [3]ICF International, Durham, NC, United States. Identifying Congener-Specific Half-Lives of Polychlorinated Biphenyls: A Mapping Review of the Literature

Polychlorinated biphenyls (PCBs) are halogenated persistent organic pollutants with 209 unique congeners with varying pharmacokinetic properties. This variability combined with multi-generational human exposure to mixtures of PCB congeners presents unique challenges to pharmacokinetic modeling efforts and risk assessment. In addition, the toxicokinetics of PCB exposure *in utero* and during early development via breast milk remains a large source of uncertainty in PCB risk assessment. To support modeling efforts, we conducted a scoping review to identify literature containing half-life information for PCBs in humans and laboratory animal species (e.g., nonhuman primates, rats, mice, and dogs), extracted all half-life data, and identified data gaps. Our literature search was designed to identify studies that reported elimination information for individual PCB congeners by searching PubMed (National Library of Medicine), Web of Science (Thomson Reuters), and Toxline (National Library of Medicine). A population, exposure, comparators, and outcomes (PECO) statement was developed to guide title, abstract, and subsequent full text screening of search results. A Keyword Analysis Tool (KAT) was used in conjunction with text analytics to identify studies potentially containing PCB half-life or elimination data. A total of 103 studies were identified that reported half-life data for at least one PCB congener in any matrix in any species. Some common matrices used in these studies include whole blood, whole body, adipose tissue, liver, serum, plasma, milk, feces, and urine. Within these studies, 86 PCB congeners had at least one half-life reported. Of these congeners, 55 had whole body half-lives reported in laboratory animal species. Although inter-study half-lives often had large variability, whole body congener half-lives tended to be longer with increasing halogenation of the congener. A total of 154 congeners have no reported half-lives data. The results of this scoping review could be useful to support future toxicokinetic modeling efforts to better characterize the toxicological consequences of human exposure to a mixture of PCBs. Furthermore, owing to the presence of congeners in breast milk and the multi-generational exposure to PCBs, this study provides the toxicokinetic information needed to assess exposure risk during gestation and early childhood. In addition, these data can support efforts to estimate or extrapolate half-lives of data-poor PCB congeners.

P13

FORESTIERI NE[1], LEE RC[2], AVERY M[2]. [1]NC Birth Defects Monitoring Program, Raleigh, NC, United States, [2]NC State Center for Health Statistics, Raleigh, NC, United States. Racial and Ethnic Disparities in Infant Mortality among Infants with Birth Defects in North Carolina, 2003–2017

Birth defects account for approximately 20% of infant deaths in North Carolina and in the United States. While mortality attributable to birth defects has declined over time along with declining overall infant mortality, racial/ethnic disparities have persisted. Several studies have examined infant mortality attributable to birth defects using linked birth and infant death records, but fewer have examined factors associated with infant deaths among comprehensive birth defects registry populations. This analysis describes racial/ethnic differences in first-year mortality among infants with birth defects in North Carolina. A retrospective cohort of 60,018 infants with birth defects liveborn from 2003–2017 was identified by the North Carolina Birth Defects Monitoring Program and matched to vital records. Infant mortality rates were calculated for the overall sample and for birth defects by organ system, and rate ratios (RRs) adjusted for maternal age, region of residence, maternal education, and birth defect classification group (isolated, multiple, or chromosomal/syndromic) were then computed to compare differences in mortality by maternal race/ethnicity. Overall mortality rates (per 1,000 live births) were lowest for non-Hispanic White infants (50.0), and highest for non-Hispanic Black (82.5), followed by Hispanic (70.4), and other infants (67.2). Compared to non-Hispanic White infants, non-Hispanic Black infants had significantly higher mortality in all defect categories except respiratory defects, with the largest disparity among those with orofacial clefts (RR 1.76, 95% confidence interval [CI] 1.27–2.45). Hispanic infants had higher mortality than non-Hispanic White infants among those with heart defects (RR 1.46, 95% CI 1.17–1.83), and infants with other races/ethnicities had higher mortality in several defect categories, with the largest relative risk among those with gastrointestinal defects (RR 1.73, 95% CI 1.17–2.56). In this large, population-based registry cohort, there were differences in infant mortality by maternal race/ethnicity for most birth defect groups examined. After adjustment for potential confounders, disparities remained, particularly for non-Hispanic Black and other (non-Hispanic, non-White) groups. Further investigation into factors such as access to quality care for infants with birth defects is needed to inform efforts to address mortality disparities.

P14

COOPER C. ORISE Fellow, Alexandria, VA, United States. Infant Exposure to Chemicals via Human Milk: Next 22 High Priority Chemicals Under Review at US EPA

Background: Breastfeeding provides many nutrients to infants, but studies have also found environmental chemicals present in human milk. Children are more vulnerable to these exposures than adults because they consume more in proportion to their body size. They also have a significantly less varied diet and may only be consuming human milk for sustenance. It is important to consider the ingestion of human milk as a route of exposure to chemicals. EPA is currently reviewing 22 chemicals under their Toxic Substances Control Act and a review of the chemicals that have been detected in human milk can help inform their risk assessment process. Objective: Compile the available human milk biomonitoring data for 22 chemicals that are currently under review at the EPA. Methods: Reviewed literature identified from PubMed literature searches. Chemicals of interest included dichlorobenzenes, chlorinated solvents, flame retardants, phthalates, and others. Specific search strings were used to identify studies that measured the specific chemical in human milk, or in some cases the metabolite. Titles and abstracts were manually screened and then data was thoroughly extracted from articles that met the criteria. Results: Half of the 22 chemicals reviewed had biomonitoring data available. The chemicals p-Dichlorobenzene, o-Dichlorobenzene, TBBPA, TCEP, TPP, HHCB, DBP, BBP, DEHP, DiBP, and DiNP have all been detected in human milk in varying concentrations. The flame retardants and phthalate metabolites have been detected the most, with medians ranging from 0.02–101 μg/L. Conclusion: This literature review demonstrates that human milk is an important exposure pathway to infants, for some of the chemicals currently under review at the EPA. This is an important route of exposure to consider when assessing childhood exposures in risk evaluations.

P15

PERRY C, FOSTER E, NIANG D, CLOUGH K, FORREST T, CURRAN CP. Northern Kentucky University, Highland Heights, KY, United States. Assessing Adult Motor Function in Three Genotypes of Mice Exposed to Benzo[a] Pyrene During Early Brain Development

Benzo[a]pyrene (BaP) is a carcinogenic polycyclic aromatic hydrocarbon commonly found in traffic-related air pollution, tobacco smoke, and grilled foods. BaP is linked to learning deficits and to neurodevelopmental delays in human and animal studies. We are using a mouse model to determine if genetic differences increase susceptibility to BaP exposure during early brain development. Mice lacking the CYP1A2 metabolic enzyme and wild type control mice were exposed to BaP from gestational day 10 (GD10) through weaning at postnatal day 25 (P25). A battery of motor function tests were performed when the mice reached young adulthood (P60). We used a pole climb test and rotarod to assess motor function and motor learning. In the pole climbing test, we found a significant main effect of genotype with AhrbCyp1a2(-/-) knockout mice having shorter latencies to turn ($P < 0.001$) and shorter latencies to descend the pole ($P < 0.01$). There was no effect of treatment. In the rotarod test, each day the mouse has three trials. We found a main effect of genotype on the first two days of testing ($P < 0.05$) There was no effect of treatment.

P16

HRUBEC TC[1], SEGUIN RP[2], XU L[3], CORTOPASSI GA[4], DATTA S[4], HANLON AL[5], LOZANO AJ[5], MCDONALD VA[6], HEALY OO[6], ANDERSON TC[6], MUSSE NM[6], WILLIAMS RT[6]. [1]E. Via College of Osteopathic Medicine, Blacksburg, VA, United States, [2]Department of Medicinal Chemistry, School of Pharmacy, Seattle, WA, United States, [3]Department of Medicinal Chemistry, School of Pharmacy, Albuquerque, NM, United States, [4]Department of Molecular Biosciences, School of Veterinary Medicine, Davis, CA, United States, [5]Center for Biostatistics and Health Data Science, Roanoke, VA, United States, [6]E. Via College of Osteopathic Medicine–Virginia, Blacksburg, VA, United States. Extent and Effects of Quaternary Ammonium Disinfectant Exposure in People

Individuals are extensively exposed to quaternary ammonium compounds (QACs). Two common QACs are benzalkonium chloride (BAC), and didecyl dimethyl ammonium chloride (DDAC). Both are commonly found in cleaners and disinfectants used in the home and medical settings. They are present in over half of the products approved for use against the Sars CoV 2 virus. Additionally, they are found in food and personal care products as preservatives. Despite their prevalence, little is known about the health effects associated with chronic low-level exposure. Studies have linked workplace exposure to asthma and contact dermatitis; however, other effects of low level chronic exposure have not been investigated. We previously demonstrated that BAC and DDAC cause neural tube birth defects, infertility, and altered neutrophil function in mice. In-vitro studies identified increased inflammation, decreased mitochondrial function, and decreased cholesterol synthesis with QAC exposure. Inflammation is associated with many common diseases, while mitochondria play a vital role in bioenergetics; cholesterol regulates membrane fluidity, cell function and cell signaling. If the animal and in-vitro studies translate to people, many basic physiological functions and disease processes could potentially be affected. This study tested whether BAC and DDAC could be detected in the blood of individuals, and if blood concentrations were associated with markers of inflammation, mitochondrial function, and altered cholesterol synthesis. Blood samples were collected from 40 volunteers and analyzed for the above markers. BAC and DDAC were detected in 80% of study participants. Exposed individuals demonstrated decreased mitochondrial function and increased inflammatory cytokines in a dose-dependent manner. Intermediates in the cholesterol synthesis pathway were altered, with significant differences between exposed and unexposed individuals. This was the first study to measure systemic QAC exposure in people and to correlate blood QAC concentrations with health related measurements. The results clearly suggest the possibility for detrimental health effects with BAC and DDAC exposure and demonstrate the need for large-scale studies to investigate the role exposure may play in disease.

P17

VERA-COLON MKM, SOH R, SPARKS NRL, WALKER LM, ZUR NIEDEN NI. University of California, Riverside, Riverside, CA, United States. Exposure to Camel Snus *In Utero* Causes Skeletal Defects

Occurrence of smoking during pregnancy, either intentional or accidental, remains a global issue today. The US Department of Health and Human Services reports greater than 100,000 babies have died in the last 50 years due to complications from smoking throughout pregnancy. Often these statistics neglect to children born with birth defects related to *in utero* tobacco exposure despite surviving exposure. In the US, 10–12% of women still consume tobacco products during pregnancy, however, opt to alternatives to conventional cigarettes. These alternative products bear a "harm-reducing" label and are advertised as having lower tar and nicotine content, including noncombustible products such as Snus. Our prior *in vitro* work detected hypomineralization in human embryonic stem cells when differentiated toward bone-forming osteoblasts upon smokeless Snus tobacco extract exposure, suggesting that exposure *in utero* may still carry risk for other ailments, including bone health and development. Currently, the ramifications of *in vivo* Snus exposure towards embryonic skeletal development exposed to tobacco remain unclear. To assess the effects of maternal exposure to Camel Snus on the developing skeleton, pregnant dams were injected with Snus tobacco extracts at E6.5 and E8.5. Embryos were harvested on E17.5 to assess skeletal morphology. Embryos were stained with Alizarin Red S/Alican Blue to identify calcified bone and cartilage, respectively. Preliminary work suggested irregularities in the long bones, such as the forearms and femurs. Upon further analysis, lengths of forearms were shown to be shorter and wider in diameter compared to controls but showed no change in calcified bone lengths. However, femurs demonstrated an increase in the length of calcified bone in Snus-exposed embryos, while overall morphology of the long bone was unchanged. Other phenotypes in the forearm include irregular "cupping and fraying" in exposed embryos. Camel Blue exposure was also tested, however skeletal changes were more variable in comparison. These seemingly minor changes to bone formation can cause detrimental effects later in life, as commonly seen in epidemiological studies that show an increase of osteoporosis and other related bone diseases in patients born to smoking parents.

Poster Session 2

P18

ZHANG X[1], WEN H[1], CHEN LJ[2]. [1]Women's Hospital School of Medicine, Zhejiang University, Hangzhou, China, [2]Zhejiang University, Seattle, WA, United States. Differences in Prenatal Detection of Birth Defects between Singletons and Multiples: An Observational Study of More Than 1.9 Million Births in Zhejiang Province, Eastern China, During 2012–2018

Objectives: Multiples might face a higher risk of birth defects (BDs) than singletons. There are few studies on prenatal detection of multiples. We aimed to compare the differences in prenatal diagnose of BDs between singletons and multiples. Method: Data were obtained from BDs surveillance system in Zhejiang province from 2012 to 2018. It covers all the births (live births and fetal death ≥28 weeks) born in 90 hospitals located in 30 regions. Births with BDs were followed up within seven days after delivery. In the study, differences in prenatal detection between singletons and multiples were tested using chi-square test, and multivariate logistic regression models in consideration of confounders. The study included 25 BDs subtypes. BDs were diagnosed according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (Q00–Q99). Results: 30,325 out of 1,900,166 births were multiples during the study period, yielding an incidence of 1.60%. The total number of singletons and multiples with BDs were 49,872 and 3,324, respectively. 14.38% BDs in multiples were prenatally detected, which was significantly lower compared to singletons (32.00%, chi2 = 452.94, P<0.001). After adjusting for time, maternal age, and education, multiples with BDs had lower detection rates in total BDs (ORadj = 0.36, 95%CI: 0.32–0.40), congenital heart defects (OR adj = 0.32, 95%CI: 0.27–0.38), congenital hydrocephalus (OR adj = 0.24, 95%CI: 0.13–0.45), cleft lip with cleft palate (OR adj = 0.18, 95%CI: 0.11–0.30), congenital talipese quinovarus (OR adj = 0.50, 95%CI: 0.27–0.92), cleft lip without cleft palate (OR adj = 0.27, 95%CI: 0.14–0.50), limb reduction defects (OR = 0.33 adj, 95%CI: 0.16–0.68), congenital diaphragmatic hernia (OR = 0.18 adj, 95%CI: 0.06–0.58), trisomy 21 syndrome (OR adj = 0.09, 95%CI: 0.04–0.23), congenital malformation of urinary system (OR adj = 0.30, 95%CI: 0.19–0.47), other chromosomal malformations (OR adj = 0.22, 95%CI: 0.06–0.86) compared to singletons with BDs. Singletons were more easily detected before 28 gestational weeks (74.82% Vs 70.08%). 73.45% BDs were detected by ultrasound, 30.02% by clinical presentation, 4.86% by chromosomal testing. Conclusions: Singletons with BDs are easily to be detected prenatally and earlier than multiples, particularly in CHD, chromosomal malformations and body surface malformations. Ultrasound is the most frequently used method.

P19

DODGE PA[1], NADOLSKI K[1], KOPKAU H[1], FORRESTAL K[2], BAILEY B[1]. ZABLOCKI V[1]. [1]Central Michigan University College of Medicine, Mount Pleasant, MI, United States, [2]Central Michigan University, Mount Pleasant, MI, United States. The Impact of Timing of *In Utero* Marijuana Exposure on Fetal Growth

Background: Recent studies have found that marijuana use in pregnancy predicts growth deficits. While birthweight and head circumference appear to be most affected, additional studies are needed to better understand if timing of exposure plays a role and how early in development effects might be seen. Objective: The study goal was to examine whether timing of *in utero* marijuana exposure negatively impacts fetal growth and if these effects are global or specific to certain growth parameters. Methods: A search of electronic health records for a five-year period at a large academic obstetric practice identified patients for study inclusion. Eligible women completed an anatomy ultrasound between 18–24 weeks gestation, and had no self-reported alcohol, tobacco, or other biochemically verified drug use. The two primary study groups were 66 marijuana users identified through self-report or urine toxicology screens, and a randomly selected control group of 100 nonusers. Medical records were manually reviewed for background and medical information, and anatomy ultrasound results (estimated fetal weight, femur length, head circumference, biparietal diameter, abdominal circumference) were coded as percentiles for gestational age. Results: After controlling for significant background differences, regression results indicated significant (p<.05) growth deficits in head circumference and biparietal diameter on the second trimester ultrasound in those who used marijuana throughout pregnancy compared to nonsubstance users. While these same growth parameters were decreased for those with marijuana use only in the first trimester, after control for confounding the differences were not significant. Conclusions: Marijuana exposure throughout pregnancy predicted decreased head circumference and biparietal diameter at second trimester ultrasound, with nonsignificant trends for estimated fetal weight, femur length, and abdominal circumference that may be clinically meaningful. There were no statistically significant effects or sizable trends among those who used marijuana in the first trimester only. Due to limited information about the amount of marijuana used, it is possible that those who quit early in pregnancy were lighter users than those who continued to use throughout pregnancy. Future studies should focus on amount of marijuana use to determine whether timing of marijuana or amount of marijuana consumed is most associated with fetal growth parameters.

P20

HANNA V, CARDONA A. Columbia University, New York, NY, United States. Quality of Life in Adult Patients with Congenital Heart Defects

Congenital heart defects (CHDs) can result in decreased quality of life in adulthood. Assessing quality of life (QoL) in patients with CHDs is an important factor in determining outcomes after medical and surgical treatment. There is limited data that exists regarding health-related quality of life (HRQoL) in adults with CHDs. This systematic review assesses how CHDs affect QoL in adulthood. Methods involved utilizing PubMed and CINAHL databases to assess indicators affecting QoL. Two independent reviewers screened articles that were included in the study. Studies were included if they focused on QoL in adults following a cardiac procedure or if they assessed long term psychological impact of CHDs on QoL indicators. Results of this review indicate conflicting endpoints with regards to QoL in adults with CHDs. Some studies indicate no significant difference between those with CHDs compared with adults of the same age, sex, and general health status. Other studies indicate that adults with CHDs are more likely to report fair or poor general health compared to those adults without CHDs. Such results indicate that more research needs to be conducted to better understand the relationship between CHDs, childhood surgeries, and their impact on QoL in adulthood.

P21

KUMAR SN[1], BASTIA B[2], AGRAWAL U[3], BORGOHAIN D[4], RAISUDDIN S[5], JAIN AK[2]. [1]ICMR, National Institute of Pathology, New Delhi, India, [2]Environmental Toxicology, National Institute of Pathology, New Delhi, India, [3]Cancer Research, Imaging and Bio-banking Laboratory, ICMR- National Institute of Pathology, New Delhi, India, [4]Department of Obstetrics and Gynaecology, Assam Medical College and Hospital, Dibrugargh, India, [5]Department of Medical Elementology and Toxicology, Jamia Hamdard (Hamdard University), Delhi, India. The Effect of Smokeless Tobacco Consumption on Placental Development During Pregnancy

Background: Smokeless tobacco (SLT) consumption during pregnancy is a well-recognized health risk that causes placental damage. However, the effects of SLT consumption have not been evaluated in placenta from tea garden workers. This study was aimed to explore the effects of SLT consumption on placental structure, expression of hypoxia and oxidative DNA damage. Methods: Fifty-one placentas were collected at full-term normal delivery from SLT users and nonusers, who were involved in the plucking of tea leaves during pregnancy in tea plantation. Systematic homogeneous random sampling was used for the collection of samples and tissue sectioning. Placental tissues were processed for transmission electron microscopy study. Immunohistochemical analysis was also performed for the expression of Hypoxia-Inducible Factor (HIF)1-α and 8-Hydroxy-2′-Deoxyguanosine (8-OHdG) in placenta from both groups. Results: Ultrastructure of placental villi from smokeless tobacco-users were compared with that of nonusers. The villi from SLT user's placenta had abnormalities of the microvilli and endothelial cells, focal syncytial necrosis and degenerated cytoplasmic organelles in trophoblastic layer. Thickening of basement membrane in villous stroma was also observed. These gross alterations were accompanied by significant elevated placental hypoxia (HIF-1α) expression along with evidence of oxidative damage (8-OHdG) in SLT-user. Conclusions: SLT use might affect the placenta structure and may be responsible for increased hypoxia and oxidative DNA damage during pregnancy. The prevailing hypoxic conditions, oxidative DNA damage and morphological changes in placenta due to SLT use could result in reduced placental blood flow, ultimately leading to LBW babies.

P22

SILVA MH, Retired from a Career in Toxicology and Risk Assessment, Davis, CA, United States. A Comparison of Computational Toxicology Test Results with *In Vivo* and *In Vitro* Endpoints Related to Mode of Action and the Endocannabinoid System: A Case Study with Chlorpyrifos, Chlorpyrifos-oxon and Δ9Tetrahydrocannabinol

Currently, there is a lack of knowledge about the effects of co-exposures of cannabis, contaminated with pesticides such as chlorpyrifos (CPF) and the toxic metabolite CPF-oxon (CPFO). With the development of computational toxicology (CompTox) tools some of the roadblocks or deficiencies leading to difficulties in data interpretation can be resolved. Medicinal and recreational cannabis use has increased globally since 2010 to over 145 countries in 2016 and use has increased 60% (~ 200 million people) in 2019. CPF (organophosphate pesticide) used on cannabis crops is unregulated in the United States because cannabis is not a federally legal crop. CPF/CPFO residues, and Δ9Tetrahydrocannabinol (Δ9THC), the main component in cannabis, are each known to disrupt the endocannabinoid system (ECS) resulting in neurodevelopmental defects. While there is an abundance of data characterizing CPF/CPFO as AChE inhibitors, less has been done to characterize involvement with the ECS in relation to neurodevelopment perhaps due to mechanistic data gaps and deficiencies. This case study used computational toxicology tools with CPF/CPFO and Δ9THC to: 1) obtain active hit-calls for assays in the Toxicity Forecaster and Tox21 (ToxCast/Tox21) database of high throughput *in vitro* assays relevant to the mode of action (MOA) for each chemical; 2) use those assays in the Toxicology Priority Index (ToxPi) program to rank the chemicals based on modeled toxicity ranking. ToxPi ranking was compared to literature-based known toxicity ranking; 3) compare the established lowest observed effect levels (LOEL: mg/kg/day) for ECS-related *in vivo* endpoints to predicted human equivalent administered dose (EADHuman: mg/kg/day) by use of the Integrated Chemical Environment PBTK (i.v.) models. The downloaded ToxCast/Tox21 active hit-calls were compiled after screening for potential false positives based on cautionary flags. The selected *in vitro* ToxCast/Tox21 assays were associated with several critical targets in the CPF/CPFO and Δ9THC metabolic pathways, including neurological ECS-related receptors. ToxPi-predicted ranking was concordant with observed *in vivo* toxicity ranking (CPF>CPFO> Δ9THC). PBTK (i.v.) modeled EADHuman values were concordant with *in vivo* measured endpoints associated with the ECS for all three chemicals. The open access tools used in this case study, identified known mechanistic targets, and accurately predicted toxicity rank, and EADHuman values for three high risk chemicals.

P23

ZHOU Y, CRIDER K, YEUNG L, ROSE CE, BERRY RJ, MOORE CA. CDC, Atlanta, GA, United States. Periconceptional Folic Acid Use Prevents Both Rare and Common Neural Tube Defects

Maternal folic acid use has been shown to reduce the risk for neural tube defects (NTDs), which are major birth defects of the brain and spine. The objective of our study was to assess if the preventive effect of periconceptional exposure to folic acid varied by NTD type, baseline prevalence, and infant sex. We included participants of a population-based pregnancy-monitoring system, which collected information on every pregnancy outcome in selected locations in northern and southern regions of China between 1993 and 1996. All birth outcomes which could be confirmed as either having or not having an NTD were included in the analysis. Each woman's folic acid pill use was collected prospectively monthly. Women who took 400 micrograms of folic acid daily during the 42 days after last menstrual period (LMP) were considered folic acid pill users. Nonusers included women who never took folic acid pills, and who did not start taking folic acid until at least 60 days after LMP. We calculated birth prevalence by NTD type, pill use status, geographic region, and infant sex. We used logistic regression to study the factors that influenced the association between folic acid use and birth prevalence of NTDs. There were 626,042 births and 700 NTD cases in the study population. Among nonusers, the NTD baseline prevalence was 37 per 10,000 births in the north vs. 7.9 per 10,000 in the south. Folic acid use significantly reduced birth prevalence of NTDs in the north with odds ratio (OR) of 0.21 (95% CI: 0.11, 0.40). In the south, OR was 0.72 (95% CI: 0.49, 1.04). Among folic acid users, the magnitude of prevalence reduction was greatest for the rarest forms of NTDs in both geographic regions, i.e., craniorachischisis, iniencephaly and encephalomyelocele. Case counts for these NTD types dropped to zero among users, while they accounted for 26% and 16% of cases among nonusers in the north and south. For spina bifida, the prevalence among folic acid users decreased by 71% in the north and 53% in the south. For anencephaly and encephalocele, prevalence among users declined by 87% and 53% respectively in the north, while folic acid use did not reduce prevalence for these two NTDs in the south. The difference in prevalence between male and female infants were reduced among folic acid users in both geographic regions. In conclusion, folic acid use was most effective at preventing the rarest NTD types and had variable effects on reducing the risks of the more common NTD types.

P24

STANFIELD J[1], COREY A[2], MCCALLUM M[2], JAO NC[1], STROUD LR[1]. [1]Brown University, Providence, RI, United States, [2]The Miriam Hospital, Providence, RI, United States. Maternal Smoking During Pregnancy and Newborn Neurobehavior and Abstinence: A Review of the Literature

Maternal smoking during pregnancy (MSDP) remains the most widespread prenatal drug exposure worldwide. MSDP has been shown to increase fetal health risks and interfere with fetal development. Although newborns prenatally exposed to other substances (e.g., opiates, benzodiazepines) have been shown to have increased stress and withdrawal symptoms (e.g., restlessness, poor autonomic regulation, increased muscle tone), few studies have explored the effect of MSDP on newborn signs of abstinence. To address this gap, our aim was to conduct a systematic literature review to determine whether MSDP-exposed newborns demonstrate altered neurobehavior and symptoms of abstinence over the first postnatal month. We performed a comprehensive search for empirical research articles investigating the effects of MSDP on early newborn neurobehavior and signs of abstinence in PubMed and PsycINFO database searches. We considered only peer-reviewed, original studies published from 1980 to 2020. The early neonatal period is defined as birth to five days, and the late neonatal period is 10 to 35 days. Our search yielded 14 empirical articles published between 2003 and 2020 for final analysis. In the early neonatal period, MDSP was shown to have a medium to large effect on multiple behavioral outcomes, including excitability, hypertonicity, irritability, need for handling, arousal, muscle tone, reflexes, and alertness ($d \geq 0.5$). MSDP was also associated with signs of withdrawal (stress/abstinence) in four studies ($d \geq 0.5$). MSDP was shown to have a small effect on neonatal irritability, the peak of excitement, self-regulation, and lability of state ($d < 0.5$). In the late neonatal period, the majority of studies found MSDP to have a medium to large effect on neonatal self-regulation, attention, quality of movement, and abnormalities in reflexes ($d \geq 0.5$); and a small effect on motor maturity, lethargy, need for handling, and stress signs ($d < 0.5$). Our review of the literature revealed that MSDP has been associated with alterations in behavior suggestive of potential abstinence symptoms, with large effect sizes especially found for excitability, irritability, hypertonicity, attention, reflex abnormalities, and stress/abstinence signs. With the recent proliferation of novel smoking products and their increased use among reproductive-aged women, additional rigorous research needs to delineate the impact of MSDP (and other tobacco products) on newborn signs of abstinence.

P25

CHEN S-Y[1], YUAN F[1], LU L[2], LIU J[1]. [1]Department of Pharmacology and Toxicology, University of Louisville Health Science Center, Louisville, KY, United States, [2]Department of Pharmacology and Toxicology, University of Louisville Health Science Center, Tampere, Finland. Ethanol-Induced Reduction in the Activity of the Putative Enhancers of TFAP2A Contributes to the Repression of TFAP2A and Apoptosis in Ethanol-Exposed Human Neural Crest Cells

The transcription factor AP-2 alpha (TFAP2A) is a master regulator of neural crest development and plays a critical role in neural crest cell (NCC) induction, specification, survival, and differentiation. Studies have shown that around 30% of all human NC enhancer regions were bound by TFAP2A and that the mutations or loss of TFAP2A can cause abnormal neural crest-derived facial structures. This study aims to identify the enhancers associated with the expression of TFAP2A and determine the role of these enhancers in ethanol-induced repression of TFAP2A and apoptosis in human NCCs (hNCCs). Using ChIP-qPCR, we found that exposure to 50 mM ethanol for 24 hours resulted in a significant reduction in the activity of the putative enhancers of TFAP2A in hNCCs, as indicated by significantly reduced enrichment of H3K27ac at the putative enhancers of TFAP2A. Ethanol exposure also dramatically reduced the mRNA expression of TFAP2A in hNCCs. To functionally validate the role of selected enhancers in ethanol-induced dysregulation of TFAP2A, selected putative enhancers of TFAP2A were knocked down or activated by CRISPR interference (CRISPRi) or CRISPR activation (CRISPRa), respectively. We found that CRISPRi knockdown of selected putative enhancers of TFAP2A significantly exacerbated the ethanol-induced repression of TFAP2A and apoptosis in hNCCs. In contrast, CRISPRa activation of selected putative enhancers of TFAP2A diminished ethanol-induced repression of TFAP2A and apoptosis in hNCCs. These results demonstrate that ethanol-induced reduction in the activity of the putative enhancers of TFAP2A contributes to ethanol-induced dysregulation of TFAP2A and apoptosis in hNCCs. Supported by NIH grants AA021434, AA028435, and AA024337 (S-Y.C).

P26

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The Impact of *In Utero* Opioid Exposure on Newborn Outcomes: Results from a Matched Cohort Study

Much of the research on the impact of *in utero* opioid exposure has focused on Neonatal Opioid Withdrawal Syndrome (NOWS). However, mixed results from a handful of studies suggest a possible impact on fetal growth and newborn wellbeing, whether or not NOWS develops, with inconsistencies likely driven by how well studies address confounding including polydrug exposure. The current goal was to compare birth outcomes between newborns with prenatal opioid exposure and a control group 1:1 matched on background factors including other drug exposure. Participants were identified via manual review of electronic medical records of all deliveries over a five-year period within a regional health system with six delivery hospitals in two states. From the over 18,000 births, the most recent 300 with prenatal opioid exposure and complete data were included, along with 300 control newborns matched on year of delivery, birth hospital, maternal age, maternal race, maternal marital status, maternal medical insurance, pregnancy smoking and alcohol use, and infant gender. Additional data collected from both groups and statistically controlled for was biochemically verified marijuana and benzodiazepine use, maternal medical conditions/status, and additional demographics. Primary outcomes included pregnancy/delivery complications, newborn size, and newborn health status. Bivariate analyses showed that compared to controls, mothers of newborns with prenatal opioid exposure were more likely to become anemic and experience fetal growth restriction. Compared to controls, exposed newborns weighed less, had decreased length and head circumference, and had higher rates of respiratory distress, sepsis, and jaundice. No significant differences in c-section rates, gestational length, Apgar scores, or neonatal hypoglycemia were found. Adjusted regression analyses found that compared to control participants, those exposed had an average 150g decrease in birthweight, a two-fold increased risk for IUGR (OR=2.09), a nearly three-fold (OR=2.80) increased risk for jaundice, a more than seven-fold (OR=7.40) increased risk for respiratory distress, and a more than thirty-fold (OR=30.47) increased risk for sepsis. The results from this large-scale, well-controlled study suggest significant pregnancy and newborn impacts from pregnancy opioid use, and provide important information to inform clinical decisions to enhance health and wellbeing in pregnancy, during the neonatal period, and beyond.

P27

HALL MK[1], GREEN R[1], GOODMAN CV[1], FARMUS L[1], LANPHEAR B[2], MARTINEZ-MIER EA[3], HORNUNG R[4], AYOTTE P[5], TILL O[6]. [1]Faculty of Health, York University, Toronto, ON, Canada, [2]Faculty of Health Sciences, Simon Fraser University, Burnaby, BC, Canada, [3]Indiana University School of Dentistry, Indianapolis, IN, United States, [4]Retired, Loveland, OH, United States, [5]Québec National Institute of Public Health, Québec City, QC, Canada, [6]York University, Toronto, Toronto, ON, Canada.

Fluoride Exposure and Hypothyroidism in a Canadian Pregnancy Cohort

Fluoride exposure has been associated with thyroid dysfunction, but little is known about the risk of hypothyroidism among pregnant women exposed to fluoride. We investigated the association between fluoride exposure and hypothyroidism in Canadian pregnant women enrolled in the Maternal-Infant Research on Environmental Chemicals cohort study. Using a case-control design, we compared pregnant women who reported a diagnosis of clinical hypothyroidism or reported taking medication to treat hypothyroidism (n=64) against nonhypothyroid controls. We measured fluoride concentration in drinking water (n=1260) and in urine averaged across three trimesters and standardized for specific gravity (n=1436). We also estimated prenatal fluoride intake based on self-reported beverage consumption (water, coffee, tea) (n=1116). We assessed the association between fluoride exposure and hypothyroid status using logistic regression models adjusted for maternal age, prepregnancy body mass index, level of education, race, and city of residence. The median ± SD water fluoride concentration and fluoride intake level was 0.52 ± 0.26 mg/L and 0.61 ± 0.54 mg/day; the median urinary fluoride concentration was 0.50 ± 0.39 mg/L. A 0.5 mg/L increase in water fluoride concentration was associated with a 2.05 (95%CI: 1.15, 3.66) increased odds of having hypothyroidism. Similarly, a 0.5 mg increase in fluoride intake per day was associated with a 1.46 (95%CI: 1.08, 1.97) increased odds of having hypothyroidism. In contrast, we observed no significant association between urinary fluoride concentration and hypothyroidism (OR for 0.5 mg/L increase=0.97; 95%CI: 0.67, 1.40). Higher exposure to fluoride from drinking water was most strongly associated with higher risk of hypothyroidism in pregnant women, suggesting that chronic fluoride exposure may be more strongly associated with hypothyroidism than contemporaneous measures, such as urinary fluoride.

P28

NAVARRO SANCHEZ ML[1], SHUMATE CJ[2], BETANCOURT D[2], CANFIELD MA[3]. [1]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States, [2]Texas Department of State Health Services, Austin, TX, United States, [3]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, United States. Predictors of Medicaid Case Management among Infants in the Texas Birth Defects Registry, 2010–2015

In Texas, Medicaid covers health care services for two out of every five children and for 57% of those with special needs. Members with complex conditions, including birth defects, are eligible to receive case management. Our objective was to explore patterns and potential disparities in receipt of case management among infants with birth defects in Texas. Cases in the Texas Birth Defects Registry (TDBR) born 2010–2015 were linked to Medicaid claims for the same period (N=66800). Infants receiving case management were identified based on relevant claim procedure codes (CPT), and frequency distributions were computed across a spectrum of birth defects. Logistic regression was used to evaluate the association between receiving case management (yes vs. no) and a specific birth defect diagnosis, as well as socio-demographic characteristics. Infants with defects other than the one of interest were used as referent group. Unadjusted (UOR) and adjusted odds ratios (AOR) with 95% confidence intervals were calculated. About 5.6% of infants in the linked TDBR-Medicaid dataset received case management. Infants with chromosomal defects had the highest receipt of case management (37.9%), followed by those with a syndrome (14.2%), and compared to 2.2% with an isolated defect. In multivariable analysis, several defects were associated with higher odds of receiving case management, e.g., spina bifida without anencephaly (AOR 13.86, 95% CI 11.40–16.85), cleft palate with cleft lip (AOR 11.91, 95% CI 10.13–14.00), encephalocele (AOR 4.04, 95% CI 2.55–6.42), and Trisomy 21 (AOR 6.36, 95% CI 5.38–7.52). Infants with heart defects were less likely to receive case management, e.g., Tetralogy of Fallot (AOR 0.68, 95% CI 0.48–0.96), ventricular septal defect (AOR 0.74, 95% CI 0.66–0.84), and atrial septal defect (AOR 0.87, 95% CI 0.79, 0.96). There were also significant differences in receipt of services by public health region, maternal age, and education. In summary, we identified predictors of receipt of Medicaid case management among infants with birth defects in Texas. As expected, infants most likely to receive services tend to have defects with high severity, low mortality, and a potential for early developmental delays. Lower receipt of case management by infants with heart defects, as well as variation between regions, present opportunities for future research. Results may be used by public health programs to improve delivery of case management to infants with birth defects.

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POSOBIEC L[1], KOPP C[2], MURZYN S[1], OLITAN T[3], RENDEMONTI J[1], FRENCH J[4], TAMBORINI E[5], CAMPEY J[6], LONGO M[5], DANBERRY T[1], VAILLENCOURT M[7], SPRIGDEN D[6], NOWLAND W[8], DAOUD M[9], QUALLS C[10], HARRIS SB[11]. [1]GSK, Collegeville, PA, United States, [2]CRL Ashland, Ashland, OH, United States, [3]BMS, New Brunswick, NJ, United States, [4]Syngenta, Berkshire, United Kingdom, [5]Accelera, Nerviano, Italy, [6]Covance, Harrogate, United Kingdom, [7]CRL, Laval, QC, Canada, [8]Pfizer, New Haven, CT, United States, [9]CRL, Hertogenbosch, Netherlands, [10]Covance, Greenfield, IN, United States, [11]Stephen B. Harris Group, San Diego, CA, United States. Skeletal Ossification Terminology and Criteria Harmonization

In order to determine the current terminology being used for fetal skeletal evaluation, and to ensure consistency by clarifying criteria for range-of-normal, a committee of assessors for the Royal Society of Biology's International Register of Fetal Morphologists (IRFM) surveyed 55 laboratories. These laboratories, from North America and Europe, routinely conduct fetal examinations. IRFM assessors have extensive experience performing fetal examinations and training others. The comprehensive listing of recommended terminology in Makris et al., 2009, a commonly used fetal examination reference document has been adopted as the glossary for the SEND initiative (which seeks to harmonize data provided to regulatory agencies) was used to design the survey. The survey focused on the examination of Gestation Day (GD) 21 Sprague-Dawley rat fetuses stained with Alizarin Red S. Based on the 20 replies to the survey, the committee's collective knowledge as Fetal Morphologists and other published literature, recommendations will be provided for both terminology and criteria when final. Preliminary results presented here will include anonymized results by survey participants and summarization of terminology recommendations. Criteria recommendations will be presented separately. These recommendations will complement Makris, 2009 and assist in intra- and interlaboratory harmonization of fetal skeleton observations for regulatory submissions, including SEND.

P30

KANCHERLA V[1], MA C[2], PURKEY N[3], HINTZ SR[3], LEE HC[3], GRANT G[3], CARMICHAEL SL[4]. [1]Emory University, Atlanta, GA, United States, [2]Stanford University, Stanford, CA, United States, [3]Stanford University School of Medicine, Stanford, CA, United States, [4]Department of Pediatrics and Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, United States. Factors Associated with Distance to Hospital for First Surgical Repair among Infants with Myelomeningocele in California

Myelomeningocele is a serious birth defect requiring early surgical intervention. Selected infant and maternal factors are known to be associated with the distance to care for receiving timely surgery. We examined factors associated with distance to care for first surgical repair among infants with myelomeningocele in California. A total of 677 eligible cases with complete geocoded data were identified for birth years 2006–2012 using data from the California Perinatal Quality Care Collaborative linked to hospital and vital records. The median distance from home to birth hospital among eligible infants was nine miles, and from birth hospital to repair hospital was 15 miles. We used these median values to dichotomize distances. Our analysis was limited to infants who lived close to the birth hospital, creating two study groups to examine transfer distance patterns: 'lived close and had a short transfer' (i.e., lived <9 miles from birth hospital and travelled <15 miles from birth hospital to repair hospital) (n=92), and 'lived close and had a long transfer' (i.e., lived <9 miles from birth hospital and travelled ≥15 miles from birth hospital to repair hospital) (n=96). Log-binomial regression was used to estimate crude and adjusted risk ratios (cRRs and aRRs, respectively) and 95% confidence intervals (CIs). Selected maternal, infant, and birth hospital characteristics were compared between the two study groups. We found that low birthweight (aRR=1.44; 95% CI=1.04, 1.99) and preterm birth (aRR=1.41; 95% CI=1.01, 1.97) were positively associated, whereas initiating prenatal care early in the first trimester was inversely associated (aRR=0.64; 95% CI=0.46, 0.89) with transferring a long distance (≥15 miles) from birth hospital to repair hospital. Contrary to similar studies from other US states, we found no associations between selected infant health (having co-occurring multiple birth defects or hydrocephalus), level of care at birth hospital (Levels I–IV) or maternal characteristics (age, race/ethnicity, education, insurance, and poverty) and having to travel a long distance from birth hospital to repair hospital for infants with myelomeningocele. There were no significant disparities in the distance to access surgical care between birth and repair hospitals by maternal race/ethnic or socio-economic indicators in our study group. Distance-based barriers to care should be considered and optimized when planning deliveries of at-risk infants.

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PENARD L[1], FLENET T[2], EYNARD C[2], BOUILLON C[2], BORY C[3], BAUDET S[3], MARSDEN E[3]. [1]Charles River, Saint Germain Nuelles, France, [2]Etisense, Lyon, France, [3]Charles River, Saint Germain-Nuelles, France. Implementation of Cardiorespiratory Monitoring in the Juvenile Minipig Using a Noninvasive Jacketed Telemetry System

Successful feasibility trials were previously conducted to monitor cardiorespiratory functions in the juvenile minipig using a noninvasive jacketed system, DECRO® from ETISENSE. Further development has now been completed using baclofen, known to decrease respiratory rate. In Phase 1, one litter of seven Göttingen Minipigs was allocated to two groups, one untreated and one given baclofen orally. Piglets were fitted with the adjustable DECRO® jacket on the day before recording. Three biosignals [electrocardiogram, respiration by inductance plethysmography (RIP bands) and activity by accelerometry] were recorded simultaneously for up to 20h post dose, once weekly from one to four weeks of age. In Phase 2, with four additional untreated piglets, modifications to the jacket and recording system were tested. The tolerability range of baclofen was very restricted for neonatal piglets. An initial dose of 6 mg/kg, selected based on adult minipig data, induced labored breathing and decreases in activity, heart rate (HR) and respiratory rate (RR), leading to premature euthanasia. At doses of 2 to 4 mg/kg, either similar but reversible clinical signs were noted with no clear changes in HR or RR, or there were no findings at all. Although jackets remained in place for most piglets aged one week, the embedded RIP bands only remained operational for approximately half of the band from two weeks of age. In addition, the jacket-induced axillary skin lesions but with no impact on general health and growth. Based on these findings, the robustness and comfort of the jacket were improved for the second phase. At one week of age, there was a clear correlation between high activity levels and elevated HR and RR values. On average, animals spent 20% of the time resting (activity level <50 mG). Overall, 90% of the ECG signals were of good quality, with well-defined waveforms and low noise. At two weeks of age, RR (90–135 breaths/min) and HR (181–252 beats/min) values and PR (62–70 ms) and QT (154–184 ms) intervals were comparable with results from restrained animals in previous studies (snapshot ECG and visual assessment of respiratory rate). Over the first four weeks of life, RR and HR values decreased with age. Although baclofen-related RR and HR effects were not detected at the doses tested, noninvasive recording and analysis of quality electrocardiographic, respiratory and activity signals were achieved in the fast-growing Göttingen Minipig from the first week of life using the DECRO® system.

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Abstract withdrawn

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CLOUGH K, FOSTER E, PERRY C, MULLAGURU J, HONAKER A, TOWELL A, CURRAN CP. Northern Kentucky University, Highland Heights, KY, United States. Adult Learning and Memory in Three Genotypes of Mice Exposed to Benzo[a] Pyrene During Early Brain Development

Benzo[a]pyrene (BaP) is a carcinogenic polycyclic aromatic hydrocarbon commonly found in traffic-related air pollution, tobacco smoke, and grilled foods. BaP is linked to learning deficits and to neurodevelopmental delays in human and animal studies. We are using a mouse model to determine if genetic differences increase susceptibility to BaP exposure during early brain development. Mice with variations in the aryl hydrocarbon receptor, lacking the CYP1A2 metabolic enzyme and wild type control mice were exposed to 10mg/kg/day BaP from gestational day 10 (GD10) through weaning at postnatal day 25 (P25). One male and one female per litter were randomly selected for neurobehavioral testing. A battery of cognitive and motor function tests were performed when the mice reached early adulthood (P60). We used Novel Object Recognition and Morris Water Maze to assess hippocampal dependent nonspatial and spatial learning and memory. There was a significant main effect of treatment with BaP-exposed mice spending less time exploring the novel object ($P < 0.05$). We found impairments in BaP-exposed AhrbCyp1a2(-/-) mice in the first phase of the Hidden Platform tests (Acquisition) with significantly longer path lengths on Days 2, 3 and 5 ($P < 0.05$). We also found impaired reference memory in BaP-exposed mice in two of the three Probe trials ($P < 0.05$).

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RYCHLIK KA[1], KASHIWAGI C[2], LIAO J[2], TRAN V[2], MATHUR A[2], ILLINGWORTH E[2], SANCHEZ S[2], KLEENSANG A[2], MAERTENS O[2], SILLÉ, FCM[2]. [1]The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, United States, [2]Johns Hopkins University, Baltimore, MD, United States.

Preconception and Prenatal Arsenic Exposure and Gene Expression Alterations in Liver, Placenta, Heart, and Lung

An estimated 140 million people worldwide are exposed to arsenic at levels above the WHO standard of 10 ppb in drinking water. Prenatal exposure to arsenic is linked to myriad negative health outcomes including increased risk of infectious disease in the first year of life, increased risk of multiple cancers, and increased risk of metabolic disease. However, there is little data comparing specific gene expression alterations in different organs affected by arsenic following preconception and prenatal exposure. Therefore, we chose to investigate the effects of preconception and prenatal arsenic exposure on gene expression in the liver, placenta, heart, and lung of gestation day (GD) 18 C57Bl/6 mouse fetuses. Mice were exposed to either 0 or 100 ppb sodium (meta) arsenite in drinking water from two weeks prior to mating until tissue collection at GD18. RNA isolated from the organs of interest was analyzed using an Agilent 44K expression microarray followed by data cleanup and analysis using RStudio. Significantly altered mRNAs were queried in the String Database to create interaction networks and identify significantly enriched biological pathways. For the liver, placenta, heart, and lung, 251, 165, 158, and 41 genes, respectively, were significantly altered in treated compared to controls. We are validating these findings in a few select genes using RT-PCR. Six of the ten most significantly enriched biological processes (based on gene ontology) in the heart were immune-related. Interestingly, three of the most significantly enriched biological processes in the liver were related to heart valve morphogenesis and formation. As we continue to probe the depth of data obtained with our microarray, we will relate existing data to our gene expression findings to continue to provide new insight into early alterations that play a role in outcomes due to preconception and prenatal arsenic exposure. Importantly, results from the current study could result in the pursuit of early intervention strategies to reduce the long-term impact of early life arsenic exposure.

Poster Session 3

P35

HANNA V. Rutgers University, Piscataway, NJ, United States. Health Concerns in Turner Syndrome Patients

Turner Syndrome (TS) is a genetic disorder in which there is a partial or total absence of one X chromosome. This was a cross-sectional study which aimed to characterize the self-reported survey data from the Turner Syndrome Foundation (TSF) Patient Registry in order to ascertain commonly reported health concerns among TS patients who self-report TS and parents of children who report TS from July 1, 2015 until May 1, 2017. Univariate analysis of health concerns separately assessed women with TS and parents of children with TS. Bivariate analysis of survey response fields and association measurements were used to refine the final model, stratified by sample and assessed using Chi-square, Fisher's exact test, and T-tests for continuous data. Logistic regression was used for multivariate analysis. Data were analyzed separately for those women reporting and for parents who completed surveys because there could have been overlap. Two uniquely reported health concerns by parents of children with TS were physician awareness (2%, 95% CI: 1.45, 3.49) and bullying (<1%, 95% CI: 0.07, 1.05). Among women with TS, those who reported health concerns ($\bar{x}$ =9.96 years, SD=9.17) had a lower mean age at diagnosis compared to those who did not ($\bar{x}$ =11.61 years, SD=11) ($p< 0.001$). A large proportion of US women (75%) reported health concerns compared to non-US women (48%) ($p< 0.001$) and women with health coverage (85%) were more likely to report health concerns compared to the uninsured (81%) ($p< 0.001$). According to parents, mean age at diagnosis was higher ($\bar{x}$ =13.18 years, SD=12.02) among those who reported health concerns compared to those who did not ($\bar{x}$ =11.08 years, SD=9.04) ($p< 0.001$). No other variables were significantly associated with the outcome. Cramer's V was used to assess correlations between independent variables to determine which variables would be included in the regression model. Multivariate logistic regression analysis of potential predictors on the outcome of reporting health concerns (yes vs. no) of women with TS showed age at diagnosis was negatively associated with the outcome (OR = 0.840, p = 0.0343) and early interventions was positively associated with the outcome (OR = 52.62, p = 0.0088). More education regarding TS is essential to the public, parents and patients, and medical professionals, as this can improve early diagnosis and interventions, as well as improve quality of life.

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ELSOM T, CLUBB SK. Charles River Laboratories, Edinburgh, United Kingdom. Developmental Toxicity Study in the Dog

Beagle dogs from Marshalls UK were mated on site to allow treatment of females on a developmental study to commence treatment on Gestation Day (GD) 1, GD 0 being the day of mating. Treatment by once daily subcutaneous injection of either a vehicle or test article continued for the entire organogenesis period i.e., until GD 35. The females underwent terminal procedures on GD 56, with full fetal evaluations including external, visceral and skeletal examinations. Females showing signs of coming into season were paired with a viable male from day seven after the first sign of estrous, for up to two hours per day or until a tie was observed (assigned GD 0). Males were reintroduced to the female each day until the female was no longer in season or three ties had been observed. One male was used with up to three females by re-pairing males with different females after a minimum seven-day rest period. The first tie was considered to be GD 0. An ultrasound scan was performed to confirm pregnancy, from around GD 32. "Mother and puppy" diet was used for the females. Females were moved from multiple housing to individual housing in a double pen with a dog bed from GD 49. The necropsy procedure was very similar to that used in rabbit developmental toxicity studies with exceptions noted for the volume of pentobarbitone used and fetal identification methods. For fetal evaluations the standard classification of live and dead fetuses was modified because the maternal overdose tended to kill the fetuses. A single transverse cut was made through the skull and brain to aid fixation and for evaluation of the brain *in situ*. Fetal morphologists also used slightly modified procedures for rabbit fetuses with one primary exception for the alizarin stain volume. After 83 confirmed mating's, 70 litters were produced on GD 56. The control groups showed mean body weight gains of 1 to 4% from GD 1–35 and 23 to 26% from GD 1–56. Pre- and post-implantation loss was 5 to 10%. Mean values from these control groups ranged from 6.5 to 6.7 for litter size and 192 to 198g for fetal weight (sexes combined). Differences from fetal evaluations in rabbits were noted in skeletal head and body findings. This project generated morphology control data from 160 fetuses.

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CARLSON LM[1], HUBBARD H[2], SHIRKE A[3], ANGRISH MM[4], LIN C[2], VETTER N[2], THAYER K[4]. [1]US EPA, Durham, NC, United States, [2]ICF International, Durham, NC, United States, [3]US EPA Office of Research and Development, Center for Public Health and Environmental Assessment, Washington, DC, United States, [4]US EPA Office of Research and Development, Center for Public Health and Environmental Assessment, Research Triangle Park, NC, United States, [7]US EPA Office of Research and Development, Center for Public Health and Environmental Assessment, Research Triangle Park, NC, United States. Systematic Evidence Mapping to Support an Evaluation of ~430 PFAS Chemicals

Thousands of distinct per- and polyfluoroalkyl substances (PFAS) are used in consumer products and industrial processes, leading to widespread environmental contamination, human exposures, and concern for public health effects. This scoping review identifies and catalogs human and mammalian studies that have investigated the potential for exposures to ~430 PFAS chemicals to result in adverse health effects. A search strategy and Populations, Exposures, Comparators, and Outcomes (PECO) statement was developed for screening, tagging, and inventory of literature into a systematic evidence map of PFAS human health effects. A total of 11,614 records were identified from comprehensive database searches. Topic clustering facilitated prioritization of 6,785 studies for title/abstracting screening using machine learning. After full text screening 159 records were considered PECO relevant or supplemental material. In addition, a gray literature search identified an additional 26 included studies after full text screening. Overall, 137 mammalian studies and 48 human studies were identified as PECO relevant. All full text included studies were organized by health effect category (cardiovascular, dermal, developmental, endocrine, gastrointestinal, hematologic, hepatic, immune, metabolic, musculoskeletal, nervous system, ocular, reproductive, respiratory, renal, etc.) exposure information, and species. Relevant study details (e.g., PFAS measured/administered, endpoints examined, exposure duration, etc.) were extracted into literature inventories to assess database characteristics, trends, and data gaps. Human evidence (available for 7 PFAS) mostly assessed the reproductive, endocrine, and developmental systems. Animal evidence (available for 34 PFAS) commonly investigated effects in cardiovascular, hematologic, hepatic, renal, immune, and developmental systems. Many of the ~430 PFAS were data poor. The results from this systematic evidence map will be combined with a prior analysis of a separate set of 150 PFAS as a resource to help the regulatory and research communities address the public health and environmental challenges raised by this large and complex group of chemicals.

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DESESSO JM[1], HARRIS SB[2], SCIALLI AR[3], WILLIAMS AL[4]. [1]Exponent and Georgetown University School of Medicine, Alexandria, VA, United States, [2]Stephen B. Harris Group, San Diego, CA, United States, [3]Scialli Consulting LLC, Washington, DC, United States, [4]Exponent, Alexandria, VA, United States. Systematic Assessment of QUATs for the Potential to Elicit Developmental and Reproductive Effects

Quaternary ammonium compounds (QUATs) are commonly found in cleaning products, disinfectants, hand sanitizers, and other personal care products. They have been in use for >50 years and are considered safe when used according to directions. Recent papers allege reduced fertility and neural tube defects in rodents after low levels of exposure. To address whether QUATs interfere with mammalian reproductive and developmental processes, a methodical assessment of the available data was conducted. A systematic literature search found 789 potential articles. Review of titles and abstracts reduced the total to eight relevant studies (including two dissertation chapters prepared as manuscripts for journal submission); six unpublished, guideline-compliant developmental and reproductive toxicity (DART) studies of the QUATs ADBAC & DDAC were added to these. Using the ToxRTool to evaluate all 14 studies for data quality, four studies were considered reliable without restriction; two studies were scored as reliable with restriction due to the numbers of rabbits per group being too few according to current guidance. No test article-related developmental or reproductive endpoints were reported to be adversely affected in any of these studies. We note that a slight increase in dead fetuses and reduced fetal weights were reported at the highest DDAC dose tested in rabbits; however, the findings were without dose-response, within the expected historical range, not statistically significant, and occurred in the presence of significant maternal toxicity. Thus, these findings were not considered treatment-related. The remaining eight studies were scored as not reliable by the ToxRTool. Issues affecting the data quality of these studies included failure to fully describe methods and/or parameters assessed; use of nonstandard test methods; reporting of atypical endpoints; assessment of endpoints at inappropriate times; and unquantified (and in some cases, unverified) exposures. While several of the unreliable studies implied adverse effects associated after very low levels of QUATs exposure, these results were inconsistent with the studies that tested much higher doses and were judged to be reliable (without or with restrictions). Thus, the current weight of evidence indicates no adverse developmental and reproductive effects associated with normal QUATs exposures. This effort was sponsored by the Household & Commercial Products Association.

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PAPADOPOULOS EA[1], HOWLEY MM[1], FISHER SC[1], VAN ZUTPHEN AR[1], WERLER MM[2], ROMITTI PA[3], BROWNE ML[1]. [1]New York State Department of Health, Albany, NY, United States, [2]Boston University, Boston, MA, United States, [3]University of Iowa, Iowa City, IA, United States. Antifungal Medication Use in Pregnancy and the Risk of Major Birth Defects in the National Birth Defects Prevention Study, 1997–2011

Fungal infections, especially vulvovaginal candidiasis (VVC), are common among women of reproductive age, with the prevalence of VVC in pregnancy ranging from 10–39%. Recent studies suggest positive associations between birth defects and specific oral antifungals. We estimated associations between first trimester antifungal medication use and 55 major birth defects in the National Birth Defects Prevention Study (NBDPS), a ten-state, population-based, case-control study in the United States (1997–2011). Trained interviewers collected self-reported information on pregnancy history, medication use (including antifungal use), demographics, and behaviors via a computer-assisted telephone questionnaire. Case infants with an NBDPS-eligible birth defect were ascertained from birth defect surveillance programs, with clinical data reviewed and classified by clinical geneticists. Control infants were live births without major birth defects randomly selected from birth records or hospital discharge lists. We calculated adjusted odds ratios (AORs) and 95% confidence intervals (CI) for birth defects with ≥5 exposed case infants using logistic regression with Firth's penalized likelihood, adjusting for maternal age at delivery, race/ethnicity, prepregnancy diabetes, and study center. In our preliminary analysis of 30,994 case and 11,426 control infants, mothers of 393 (1.3%) case and 123 (1.1%) control infants reported first trimester antifungal use. Of 34 birth defects with ≥5 exposed case infants, AORs were ≥1.5 for 19 birth defects. The strongest associations were observed for two heart defects: double-outlet right ventricle with transposition of the great arteries (AOR: 3.0; 95% CI: 1.2–7.1) and pulmonary atresia (2.4; 1.1–5.4), and for three central nervous system defects: encephalocele (4.9; 2.5–9.6), Dandy-Walker malformation (3.6; 1.6–8.1), and anophthalmia/microphthalmia (2.6; 1.1–6.1). We also observed statistically significant associations between antifungal use and two other birth defects: cleft lip with or without cleft palate (1.6; 1.1–2.2) and diaphragmatic hernia (2.0; 1.2, 2.4). Of the 12 remaining birth defects with ≥5 exposed case infants, most estimates were modest, and all 95% CIs included 1.0. We found positive associations between first trimester antifungal use and several birth defects. We are planning further analyses of antifungal use by route of administration, medication class, and individual medication, where sample size allows.

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CHENG A[1], YAN W[2]. [1]University of Toronto, Toronto, ON, Canada, [2]University of Guelph, Toronto, ON, Canada. DNA Double-Strand Breaks in Fetal Brains from Oxoguanine Glycosylase 1 (Ogg1) Knockout Mice Exposed *In Utero* to Physiological or Ethanol-enhanced Levels of Reactive Oxygen Species (ROS)

Oxidative DNA damage has been implicated in the mechanism of Fetal Alcohol Spectrum Disorders (FASD). Alcohol (ethanol, EtOH) increases embryonic formation of reactive oxygen species (ROS) which oxidatively damage the DNA nucleobase guanine, producing the 8 oxoguanine (8-oxoG) lesion, which is repaired by the base excision repair enzyme oxoguanine glycosylase 1 (OGG1). We previously reported that postnatal learning and memory deficits were enhanced in EtOH-exposed Ogg1 -/- knockout (KO) progeny compared to wild-type (+/+) littermates, implicating 8-oxoG as a developmentally pathogenic molecular lesion. Herein, we assessed the level of ROS-mediated DNA double-strand breaks (DSBs) determined by single cell gel electrophoresis (comet assay) in fetal brains exposed *in utero* to saline vehicle or EtOH as a potential mechanism of neurodevelopmental deficits in FASD. Male and female Ogg1 +/+, +/- and -/- mice of the same genotype were mated, and pregnant dams were treated intraperitoneally (ip) on gestational day (GD) 17 with saline vehicle or EtOH (2, 3 or 4 g/kg). Six hours post-treatment, dams were sacrificed, fetuses were extracted, and fetal brains were collected. The fetal brains were homogenized, and DSBs were quantified using the comet assay. In Ogg1 +/+ progeny, DNA DSBs increased with an increasing dose of EtOH (saline vs. 2 g/kg [p=0.0212], saline vs. 3 g/kg [p=0.0037], saline vs. 4 g/kg [p=0.0006]; 2 g/kg vs. 4 g/kg [p=0.0190]). In saline-exposed Ogg1 +/- and -/- brains, DSBs were increased compared to saline-exposed Ogg1 +/+ brains (p=0.0323 and p=0.0439, respectively). This suggests that with the loss of only one Ogg1 allele, physiological levels of ROS may be pathogenic, relevant to developmental disorders in the absence of drug exposure, possibly including some components of autism. The increase in DSBs in the brains of Ogg1 +/+ progeny exposed *in utero* to EtOH compared to saline-exposed Ogg1 +/+ brains is consistent with other measures of oxidative DNA damage implicating enhanced 8-oxoG formation in the developmental toxicity of EtOH. These results suggest that both physiological and drug-enhanced levels of ROS formation may be developmentally pathogenic in progeny with even partially compromised OGG1 activity. (Support: CIHR, University of Toronto Faculty of Pharmacy and CPO.)

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LAVU A[1], VACCARO C[2], SHOUMAN W[2], ALESSI-SEVERINI S[2], ELTONSY S[2]. [1]College of Pharmacy, University of Manitoba, Winnipeg, MB, Canada, [2]College of Pharmacy, Rady Faculty of Health Sciences, Winnipeg, MB, Canada. A Systematic Review of Antiepileptic Drug Exposure during Pregnancy and Neonatal Birthweight Outcomes and Interim Meta-Analysis

The prevalence of epilepsy in pregnant women is estimated at 0.3–1%. Antiepileptic drug (AED) exposure in-utero has shown to be associated with various neonatal outcomes including adverse birthweight outcomes. The study objective is to systematically summarize and meta-analyse the published evidence on AED exposure during pregnancy and neonatal growth outcomes. Including Small for Gestational Age (SGA), Low Birthweight (LBW), Birthweight (BW) as primary, and birth length, head circumference, and cephalization index as secondary outcomes. We searched for human studies in English and French from inception to October 2020. MEDLINE, EMBASE, Cochrane Library, Scopus, CINAHL, IPA, and Global Health databases were searched. All study designs were included except case reports, case series, and reviews. We used random-effects and fixed-effects models for meta-analysis based on the heterogeneity level (I2). We screened 15,720 identified studies, 4,279 were excluded after deduplication, 11,381 articles were excluded after title, abstract, and full-text review, and a total of 60 studies were finally included in the analysis. We identified 21 studies on SGA, including only seven studies with available data to conduct SGA meta-analysis. Three studies examined the class effect of AEDs, comparing women exposed to AEDs to women unexposed to any AED, showing a significant increased risk: pooled RR=1.37 (95% CI; 1.29, 1.46, I2 =17%). Six studies compared exposed vs unexposed women; however, only among women with epilepsy. The meta-analysis showed an increased risk of SGA but did not reach statistical significance; pooled RR 1.30 (95% CI; 0.98, 1.73, I2= 66%). Since both groups had diagnosed epilepsy, the results showed a potential impact that could be attributed to AED alone and not the combined effect of the disease (i.e., epilepsy) and AEDs. The preliminary sensitivity analysis showed comparable results. This review demonstrates that women taking AED during pregnancy have a significant increased risk of SGA when compared to unexposed women. Additional studies are needed to examine the separate impact of AEDs accounting for confounding by indication. Further, the review will report additional birthweight/growth outcomes in infants exposed to AED *in utero*.

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KRISCH M, HOOTNICK D, HORTON J. SUNY Upstate Medical University, Syracuse, NY, United States. Lateral Epiphyseal Reductions due to Vascular Dysgenesis are Hypothesized to Cause Congenital Valgus Deformities at the Knee and Ankle in Fibular Deficient Limbs

Reductions of the lateral (fibular) portions of the distal femoral and proximal and distal tibial epiphyses frequently present in congenitally shortened limbs (CSL) with fibular deficiency. Embryonic arterial dysgenesis, a feature of CSL, explains epiphyseal underdevelopment at the three anatomically distinct sites more plausibly than any prior mechanical hypotheses. The pathologic anatomy of the distal tibial epiphysis in CSL demonstrates that its anterior-medial portion remains preserved, despite arteriographically demonstrated absence of the peroneal, anterior and/or posterior tibial arteries. Where embryologically constant anterior periosteal contributions to the anterior medial portion of the distal tibial epiphysis are hypothesized to have persisted, the physis and bony epiphysis persist as well. Recent lineage tracing models demonstrated that mesenchymal chondro-osteoprogenitor cells migrate perpendicularly from Ranvier's groove, along the epiphyseal artery, to the resting zone of the growth plate. Here, they may originate clonal columns of growth plate chondrocytes, or undergo osteoblastic differentiation to establish the bony epiphysis. These findings suggest the importance of adequate embryologic vascularity to the latitudinal growth of the bony epiphysis as well as to the longitudinal growth of long bones as revealed in the syndrome of long bone deficiencies of the proximal femur, fibula, and midline metatarsals.

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RAPPOLEE DA[1], RUDEN X[1], ABDULHASAN M[1], HARRIS S[2], RUDEN D[1], PUSCHECK E[1]. [1]Wayne State University, Detroit, MI, United States, [2]University of Michigan, Ann Arbor, MI, United States. Using Live Imaging and FUCCI ESC to Distinguish G1 Cell Cycle Delays for General Stressors like PFAS and Phthalates or G2 Cell Cycle Delay for Mutagenic Stressors like Benzo(a) pyrene

Fluorescence ubiquitinated cell cycle indicator (FUCCI) ESCs are green in S-G2-M-phase of the cell cycle and not green in G1. It was previously established that infrequent media change is a form of general stress that de-lays cells in G1 phase of the cell cycle and after feeding there is a 5–7-fold increase in progression into S-G2-M-phase of the cell cycle occurs. This increased progression into cell cycle itself is suppressed by other general stressors such as phthalates (DEP) and PFAS (PFOA). Here we report that mutagenic stressors like ben-zo(a)pyrene (BaP) can also suppress cell cycle progression in S-G2-M-phase, but also suppress the ESC accumulation in G1 due to infrequent media change as cells are instead delayed in G2 to DNA adducts repair. BaP decreases FUCCI ESC growth (e.g., time-lapse confluence increase) at 10uM but increasing cell number at this dose, and increasing delay in G2, leads to a highly significant increase green G2 delayed cells throughout the 72hr culture period. Lesser doses of BaP do not have significant effects on decreased growth or G2 delay, but in previous reports in ESC, TSC and the blastocysts these stem cells are derived from, numerous outcomes, stress enzyme activation, apoptosis, implantation block of the blastocyst into the uterus, occur with IC50s that are slightly higher than those reported here for suppression of confluence or retention in G2. Previous reports of direness in ESCs, TSCs and blastocysts show that BaP and other stressors activate stress enzymes rapidly, with peaks within 15–60minutes and here 10uM BaP has increased G2 delay significantly by the first time-lapse measurement at 2hr. Thus, time lapse data here are consistent with mechanisms associated with G2 delays. The data suggests that the surprising accumulation of FUCCI ESC in nongreen G1 can be used in high throughput screens of many stressors, to define mutagenic stressors that block accumulation in G1 as well as previously reported block of increase in cell cycle progression from G1 by general stressors like media change.

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DAVIS SM, CODER PS, HUANG J. Charles River Laboratories, Ashland, OH, United States. Use of Fulvestrant as an Anti-Estrogenic Positive Control Substance in Uterotrophic Bioassays

OECD Document 150 recommends the Uterotrophic Bioassay in Rodents (OECD 440) and the OECD GD 71 on the procedure to test for anti-estrogenicity. This bioassay evaluates the ability of a chemical to elicit agonist or antagonist activities of natural estrogens. For agonists, 17α- ethynylestradiol is the preferred positive control substance used at Charles River Ashland. The test for estrogen antagonists is less common, and a specific positive control substance was not addressed in the TG, which also requires that laboratory proficiency be demonstrated. This study was designed to assess the feasibility of fulvestrant as a suitable anti-estrogenic control substance in the bioassay for estrogen antagonists. Ovariectomized young-adult female Sprague Dawley rats (Charles River) were randomly assigned to six groups (six rats each). Prior to initiation, vaginal lavages were performed to demonstrate the lack of estrous cyclicity in the females. Control Group 1 received corn oil vehicle and Positive Control Group 2 received the estrogenic control substance (17α-ethynylestradiol; 0.001 mg/kg/day); both via subcutaneous injection—Group 2 was expected to show an increase *in uterine* weight. Four groups (Groups 3–6) of six rats each received 17α-ethynylestradiol (0.001 mg/kg/day) in combination with the antiestrogenic control substance, fulvestrant via intramuscular injection, at doses of 0.5, 1.0, 1.5, and 2.0 mg/kg/day for three consecutive days. In these groups, fulvestrant was expected to mitigate the 17α-ethynylestradiol-dependent increase *in uterine* weight. In addition to standard endpoints, the uterus of each female was harvested ~24 hours following the last dose and unaltered (wet) and blotted (dry) uterine weights were recorded. In the 17α-ethynylestradiol positive control group, mean wet and blotted uterine weights were significantly higher than the vehicle control group, eliciting the anticipated estrogenic response. In Groups 3–6, mean wet and blotted uterine weights following co-administration of 17α-ethynylestradiol and fulvestrant were statistically significantly lower than estradiol alone. The most significant decrease was noted at a dose of 1.0 mg/kg/day fulvestrant co-administered 17α-ethynylestradiol (Group 4). In conclusion, while all doses of fulvestrant elicited anti-estrogenic effects, 1.0 mg/kg/day, with the most pronounced reductions, was selected as a suitable anti-estrogenic positive control substance for Uterotrophic Bioassays.

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GOMEZ-ACEVEDO H[1], NEMBHARD WN[1], MOORE CA[2], JENKINS MM[2], ALMLI LM[2], LOU X-Y[3], REEFHUIS J[2], SHAW GM[4], ROMITTI OO[5], WERLER MM[6], YAZDY MM[7], OLSHAN AF[8], KAY DM[9], FINNELL RH[10], FELDKAMP ML[11], BAMSHAD M[12], BRODY L[13], MULLIKIN J[13], PANGILINAN F[13], NICKERSON D[14], MCGOLDRICK DJ[14]. [1]University of Arkansas for Medical Sciences, Little Rock, AR, United States, [2]CDC, Atlanta, GA, United States, [3]University of Florida, Gainesville, FL, United States, [4]Standford University School of Medicine, Standford, CA, United States, [5]University of Iowa, Iowa City, IA, United States, [6]Boston University, Boston, MA, United States, [7]Massachusetts Center for Birth Defects Research and Prevention, Boston, MA, United States, [8]University of North Carolina, Chapel Hill, NC, Unites States, [9]New Your State Department of Health, Albany, NY, United States, [10]Baylor College of Medicine, Houston, TX, United States, [11]University of Utah School of Medicine, Salt Lake City, UT, United States, [12]University of Washington SOM, Seattle, WA, United States, [13]NHGRI NIH, Bethesda, MD, United States, [14]University of Washington Genome Sciences, Seattle, WA, United States. New Variants for Transverse Limb Deficiency Defects from Whole Exome Sequencing: The National Birth Defects Prevention Study.

Transverse limb deficiencies (TLDs) comprise a large group of genetically heterogeneous developmental conditions. It is likely that several molecular mechanisms during embryogenesis disrupt limb development. The National Birth Defects Prevention Study (NBDPS) is a multisite population-based case control study of genetic and nongenetic risk factors for birth defects. Participants provided buccal cell samples collected using cytobrushes. DNA was extracted at the CDC central laboratory using phenol chloroform or Gentra Puregene®. Exome sequencing was completed at the National Institutes of Health Intramural Sequencing Center, and the resulting data was reprocessed at the University of Washington Center for Mendelian Genomics. Using whole exome sequencing data from 149 triads (parents and infants) from NBDPS, we found 499 genes with *de novo* variants, and 263 genes with compound heterozygous variants that may be associated with TLDs. An integrative transcriptomic approach with avian and rodent limb development datasets was used to investigate potential genes in TLDs. We identified nine *de novo* variants: EDNRA (p.A272V), DAPK1 (p.A518P), TNC (p.G1385R, and p.S1361L), PHYHIPL (p.G152R), FL1 (p.L273fs), TENM4 (p.H284fs), SCAF11 (p.R922G), and RYR3 (p.R1240H); and six compound heterozygous variants: LTBP1 (p.N1005D, and PG1052S), TYRO3 (p.E4489K, and rs754256953), and RYR3 (p.Y2716C and pR3271H) not previously reported.

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RUYAK SL[1], MILLIGAN E[2], SOLOMON E[3], ALLEN A[2], MA X[4], WEINBURG J[5], ROBERTS M[4], RODRIGUEZ D[4], ENRIQUEZ MARQUEZ O[4], RAI R[4], STACY L[4], JACOBSON S[6], BAKHIREVA L[4]. [1]University of New Mexico, College of Nursing, Albuquerque, NM, United States, [2]University of New Mexico, Department of Neuroscience, Albuquerque, NM, United States, [3]University of New Mexico, Department of Neuroscience, Louisville, KY, United States, [4]University of New Mexico, College of Pharmacy, Albuquerque, NM, United States, [5]The University of British Columbia, Department of Cellular and Physiological Sciences, Vancouver, BC, Canada, [6]Wayne State University, Department of Psychiatry and Behavioral Neurosciences, Detroit, MI, United States. Psychosocial Stress During Pregnancy Affects Placental Programming of Hypothalamic Pituitary Adrenal Axis

Introduction: Prenatal alcohol exposure (PAE) and prenatal stress have been shown to alter placental glucocorticoid genes which may adversely affect fetal development and health outcomes across the lifespan. We examined associations among maternal alcohol use, prenatal psychosocial stress, and placental expression of hypothalamic pituitary adrenal (HPA) axis genes. Methods: ENRICH-2, a prospective cohort of maternal-infant dyads focusing on PAE includes four assessments: two prenatal visits (V1 and V2), birth-first month of life (V3), and six-months postpartum (V4). Women were classified into two groups, PAE and healthy control (HC), based on self-report measures and alcohol biomarker panels. Psychosocial stress was assessed as perceived stress (Perceived Stress Scale [PSS]), past/current traumatic life events (adverse childhood experiences [ACEs], PTSD Checklist for DSM-5 [PCL-5], anxiety/depressive symptoms (Edinburgh Postnatal Depression Scale [EPDS]; Generalized Anxiety Disorder-7 [GAD-7]). To date, 30 placentae (PAE = 10; HC = 20) underwent tissue processing to identify mRNA gene expression of 11-β hydroxysteroid dehydrogenases (11β-HSD1 and 11β-HSD2) and levels of glucocorticoid receptors—NR3C1-α, NR3C1-β. PAE and HC biomarkers were compared using t-tests and Mann-Whitney test. Associations between maternal stress and placental biomarkers were examined using Spearman correlation. Results: No PAE vs HC group differences were found for placental biomarkers. PSS scores at V2 (18.8 ± 5.6 vs 14.2 ± 5.6; $p = .04$) and PCL-5 scores (29.7 ± 17.4 vs 13.7 ± 15.5; $p = .01$) were significantly higher in PAE vs HC group. There was a significant negative correlation between NR3C1-α and PSS score at V1 and V2 ($r = -0.52$, $p = 0.02$; $r = -0.58$, $p = 0.01$, respectively) and maternal PCL-5 score ($r = -0.59$, $p < 0.001$). Inverse correlations between V2 PSS score and NR3C1-β ($r = -0.55$, $p = 0.01$), GAD-7 and NR3C1-β ($r = -0.51$, $p = 0.02$), and PCL-5 score and NR3C1-β ($r = -0.61$, $p = 0.00$) were also noted. Discussion: These preliminary results are consistent with previous findings that showed maternal psychosocial stress was associated with decreased NR3C1-α and

NR3C1-β gene expression. Given these associations were seen in the sample as a whole, future investigation will examine the stress/alcohol interaction. Additionally, the contribution of altered placental expression of HPA axis genes to early infant developmental outcomes warrants examination. NIH//NIAAA: R01AA021771.

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KALDHONE PR[1], HAN T[1], KRISHNAVENISIVAKUMAR K[1], PHANAVANH B[1], MOLAND C[1], FELTON R[1], LEE G[2], MELLON D[2], FISHER [02], HANIG, J[2], BEGER RD[1], INSELMAN AR[1]. [1]US FDA/NCTR, Jefferson, AR, United States, [2]US FDA/CDER, Silver Spring, MD, United States. Developmental Toxicity in CF-1 Mice after Gestational Opioid Exposure

The risks associated with opioid exposure during the first trimester of pregnancy are not fully understood. Limitations with previous epidemiological study designs, conflicting results from human and animal studies, and incomplete maternal toxicity data complicate risk assessment. To address the maternal toxicity data gap, CF-1 mice were treated subcutaneously with morphine [100 or 400 mg/kg] or methadone [10 or 30 mg/kg] on gestational day (GD) 8 of pregnancy (plug date = GD 0) and assessed for signs of hypoxia. The known human teratogen, valproic acid (VPA) [300 or 500 mg/kg], was used as a positive control compound. The CODA® high throughput noninvasive blood pressure system (Kent Scientific Corp.) was used to measure blood pressure following drug treatment (n=20/dose). Systolic, diastolic, mean blood pressure and heart rate were then measured. Systolic, diastolic and mean blood pressure along with heart rate in all treatment groups were lower than control values. The observed differences, while indicative of decreased perfusion, were not dose-dependent or significantly different from controls in a one-way ANOVA with Tukey's post hoc analysis. The Element POC (Heska) was used for blood gas measurements. Oxygenated blood samples, collected from the left ventricles, were assessed at 30 minutes and 2.5 hours post-dosing (n=10/dose/timepoint). Statistically significant differences at 30 minutes included: lower blood pH, increased partial pressure of carbon dioxide (pCO2), bicarbonate and total carbon dioxide (TCO2) levels. These changes were observed in both the low and high dose opioid treatment groups. At 2.5 hours post-dosing, the pH and pCO2 levels remained significantly different. While decreases in the partial pressure of oxygen (pO2) were anticipated, the only statistically significant decrease occurred in the methadone 30 mg/kg group. VPA did not affect clinical blood gas parameters in mice. Changes in blood gas measurements, combined with the blood pressure data, may suggest that opioid exposure induces maternal hypoxia in CF-1 mice. The data presented here will be combined with teratological assessments and maternal and fetal toxicokinetic data to provide a more comprehensive understanding of the risks related to opioid-exposure during early pregnancy.

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MARTIN-GIACALONE BA[1], SCOTT DA[2], MITCHELL LE[3], HUFNAGEL RB[4], BROOKS BP[4], LEWIS RA[1], AGOPIAN AJ[5], LUPO PJ[6]. [1]Baylor College of Medicine, Houston, TX, United States, [2]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, United States, [3]University of Texas School of Public Health, Houston, TX, United States, [4]National Eye Institute, Bethesda, MD, United States, [5]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States, [6]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX, United States.

Evaluating the Utility of Clinical Exome Sequencing for the Molecular Diagnosis of Nonisolated Microphthalmia, Anophthalmia, and Coloboma (MAC)

Microphthalmia, anophthalmia, and coloboma (MAC) are congenital eye defects, which can lead to severe visual impairment. Individuals with MAC are born with the reduced axial length of the eye, absence of the eye, or segmental defects in various eye tissues, respectively. These anomalies can occur unilaterally or bilaterally and can present either in isolation or in combination with other congenital anomalies (i.e., nonisolated MAC). Though several genes are known to be associated with MAC, the genetic architecture of MAC is not fully understood, which limits genetic testing and counseling strategies for patients and their families. Clinical exome sequencing (ES) has emerged as an efficient tool for reducing the diagnostic uncertainty for children with congenital anomalies. Therefore, we analyzed a database of >15,000 ES results from individuals recruited to Baylor Genetics and identified 202 individuals with nonisolated MAC. Using the 2015 American College of Medical Genetics/Association for Molecular Pathology standards, a clinical geneticist (DAS) categorized cases into definitive, probable, or provisional diagnoses. Overall, the diagnostic yield, defined as the proportion of definitive or probable diagnoses, was 27.7% (56/202, definitive, N=46; probable, N=10). We identified pathogenic variants in five recurrently altered, known MAC-related genes: KMT2D (N=4), PACS1 (N=3), CHD7 (N=3), RAB3GAP1 (N=2), and CREBBP (N=2). Specific findings that point to new genetic associations with MAC include single cases with *de novo* pathogenic variants in KAT6A or RAC1, compound heterozygous pathogenic variants in GNPTAB or HEXB, and heterozygous pathogenic variants in MAGEL2. Notably, mouse models of altered RAC1 also display MAC phenotypes. To our knowledge, this is the first report to suggest that these five genes contribute to nonisolated MAC. In one of the largest sequenced cohorts of MAC, our findings are consistent with previous assessments indicating that 14–70% of cases have an underlying molecular diagnosis. Differences across studies are likely due to cohort size, phenotypic heterogeneity, and gene inclusion criteria. Our study supports that ES is an efficient tool for determining a molecular diagnosis for nonisolated MAC. Future analyses will include evaluating diagnostic information on MAC patients to further define phenotypic subtypes. Our findings could inform genetic testing, medical management, and counseling strategies for these children.

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NAVARRO SANCHEZ ML[1], BENJAMIN RH[1], AGOPIAN AJ[1], LUDORF KL[1], CHEN H[2], CANFIELD MA[3], SWARTZ MD[4], SCHEUERLE AE[5]. SCOTT OO[6], STANGENES M[7], STALLINGS EB[8], SCARANO G[9], BERMEJO-SANCHEZ E[10], RISSMANN A[11], MUTCHINICK OM[12], LANDAU D[13], KURASAWA K[14], KIURU-KUHLEFELT S[15], KHOSHNOOD B[16], KÄLLÉN K[17], COCCHI G[18], LOPEZ CAMELO J[19], DE WALLE HEK[20], CSÁKY-SZUNYOGH M[21], BOTTO LD[22], AMAR E[23], LUPO PJ[24]. [1]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX, United States, [2]Center for Precision Health, UTHealth School of Public Health and UTHealth School of Biomedical Info, Houston, TX, United States, [3]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, United States, [4]Department of Biostatistics and Data Science, UTHealth School of Public Health, Houston, TX, United States, [5]Department of Pediatrics, Division of Genetics and Metabolism, University of Texas Southwestern Medical, Dallas, TX, United States, [6]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, Unites States, [7]Department of Health Registry Research and Development, Norwegian Institute of Public Health, Bergen, Norway, [8]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, United States, [9]U.O. di Genetica Medica, A.O.R.N., Bologna, Italy, [10]ECEMC, Research Unit on Congenital Anomalies (UIAC) Instituto de Investigación de Enfermedades Raras, Madrid, Spain, [11]Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke-University Magdeburg, Magdeburg, Germany, [12]Registro y Vigilancia Epidemiológica de Malformaciones Congénitas (RYVEMCE) Department of Genetics, Mexico, [13]Department of Obstetrics and Gynecology, Soroka University Medical Center, Be'er Sheva, Israel, [14]Department of Obstetrics and Gynecology, Yokohama City University, Yokahama, Japan, [15]Information Services Department, Health and Social Services Data and Information Management, Finni, Helsinki, Finland, [16]Université de Paris, CRESS, INSERM, INRA, Paris, France, [17]National Board of Health and Social Welfare, Stockholm, Sweden, [18]Neonatology Unit, Department of Pediatrics, University of Bologna, Bologna, Italy, [19]ECLAMC, Center for Medical Education and Clinical Research (CEMIC-CONICET), Buenos Aires, Argentina, [20]University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, Groningen, Netherlands, [21]Hungarian Congenital Abnormalities Registry and Rare Disease Centre, National Public Health CenterBudapest, Hungary, [22]International Center on Birth Defects (ICBD) of the International Clearinghouse for Birth Defects Su, Rome, Italy, [23]REMERA, Rhône-Alps registry of birth defects, Hospices Civils de Lyon, France, Lyon, France, [24]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX, United States. Patterns of Co-occurring Birth Defects among International Surveillance Systems

Patterns of birth defect co-occurrence can provide epidemiologic clues to underlying developmental mechanisms and perhaps identify new syndromes. We analyzed data from 12 international birth defect registries to determine which defect combinations occur together more often than we would expect if the defects were independent of each other. We obtained data from the International Clearinghouse for Birth Defects Surveillance and Research on multi-malformed cases (i.e., with two or more major birth defects) born 1994–2000 in Finland, France, Hungary, Israel, Italy, Japan, Mexico, Netherlands, Norway, South America, Spain, and the US. Because coding of defects differed between countries, we grouped defect codes into 86 broader categories. The analysis was limited to infants with two or more of these birth defect categories and without a known syndrome (n=5,277). We analyzed all two- to five-way combinations of these categories and calculated observed-to-expected ratios among the multi-malformed cases (OEmulti ratios). As few 4- and 5-way defect combinations were observed, we focused on 3-way combinations. OEmulti ratios ranged from 300.7 to 2.3, and the top five ranked combinations were: malrotation of gut, annular pancreas, septal heart defect (n=3, OEmulti = 300.7); spina bifida, microcephaly, congenital cataract (n=4, OEmulti = 179.7); renal agenesis and dysgenesis, other urinary tract malformations, sacrum anomalies (n=3, OEmulti = 163.3); anophthalmia/microphthalmia, severe eye anomalies, jaw malformations (n=3, OEmulti = 152.9); anorectal atresia/stenosis/fistula, indeterminate sex, urethra atresia/stenosis (n=6, OEmulti = 150.4). Many of the top results featured related or same-system defects and/or were suggestive of known associations (e.g., heterotaxy, CHARGE, VACTERL), or perhaps of certain maternal infections or teratogens. The analysis had important limitations. The tracking and coding of birth defects differed among countries, there was no consistent way to exclude all syndromic cases, and defect codes were not directly equivalent to well-known coding systems (e.g., ICD-9/10 or BPA). In summary, we examined birth defect co-occurrence patterns by combining data from international birth defect surveillance systems. We observed several combinations of birth defects that may warrant further evaluation. Future work may also involve collection and review of individual-level clinical information and additional clinical prioritization of top patterns.

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HONAKER A, PERRY C, CURRAN CP. Northern Kentucky University, Highland Heights, KY, United States. Measures of Anxiety in Mice Vary by Genotype, But Not Treatment Following Developmental Exposure to Benzo[a]pyrene

Benzo[a]pyrene (BaP) is a common polycyclic pollutant and known carcinogen found in grilled foods, tobacco smoke, and vehicle emissions. Its prevalence in the environment causes an increased risk of exposure to BaP for all organisms. For humans and animals alike, BaP has been linked to learning deficits as well as impaired or delayed neurological development. A mouse model was used to mimic the human genetic variation in the aryl hydrocarbon receptor and two metabolic enzymes regulated by the AHR: CYP1A1 and CYP1A2. Pregnant dams were treated from gestational day 10 to postnatal day 25 with 10/mg/day BaP in corn-oil soaked food or vehicle only. We assessed anxiety-like behavior using the Zero Maze and Marble Burying tests. We found no effect of treatment and no gene x treatment interaction; however, we found significant differences in both tests based on genotype. Cyp1a1(-/-) knockout mice buried significantly more marbles than all other genotypes ($P < 0.01$). In the Zero Maze, Cyp1a1(-/-) knockout mice spent significantly more time in the open ($P < 0.01$). Together, these results could suggest a hyperactive phenotype rather than anxiety-like behavior. We are assessing their open field locomotor activity to further explore this possibility.

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KRAMER EF[1], JONASSON AR[2], GRIPP KW[3], RASMUSSEN SA[1]. [1]Dept. of Pediatrics, University of Florida College of Medicine, Gainesville, FL, United States, [2]Dept. of Pediatrics, Div. of Genetics and Metabolism, University of Florida, Gainesville, FL, United States, [3]Div. of Medical Genetics, Nemours/A.I. DuPont Hospital for Children, Wilmington, DE United States. Noonan Syndrome with Multiple Lentigines and Pigmented Villonodular Synovitis in Multiple Generations: Insight into the Pathogenesis of a Benign Tumor

RASopathies are a clinically defined group of genetic conditions involving pathogenic variants in genes that encode for components of the RAS/MAPK pathway, a signaling pathway important for normal development and growth. Noonan syndrome with multiple lentigines (NSML) is a rare autosomal dominant RASopathy characterized by the phenotype of Noonan syndrome as well as multiple lentigines. This condition was previously known as LEOPARD syndrome to indicate the commonly described features including multiple lentigines, electrocardiogram abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, growth retardation, and deafness. Pigmented villonodular synovitis (PVNS) is a rare giant cell tumor characterized by benign proliferation in the synovial joint, synovial bursa, and/or tendon sheath. Reports suggest an association between Noonan syndrome and related conditions and giant cell lesions including lesions in the mandible and maxilla and PVNS. We report a family with NSML with PVNS in at least three generations. The proband is a 12-year-old female with typical phenotypic characteristics of NSML, including multiple lentigines on the face, trunk and extremities. She presented with PVNS in the left and right ankle at age 10 years. The proband's sister is a seven-year-old female with NSML, but no PVNS or giant cell lesions. The paternal family shows an extensive history of NSML, with PVNS seen in the paternal aunt, paternal uncle, paternal grandfather, and possibly the paternal great grandfather. In total, nine family members had features consistent with NSML, with four having PVNS. Genetic testing of the proband, her sister, and her father found a heterozygous pathogenic PTPN11 mutation c.1529 A>C (Gln510Arg), a variant previously seen in patients with NSML. Review of the literature identified no cases of NSML and PVNS, although cases of NSML with other giant cell lesions and of Noonan syndrome with PVNS have been reported. However, in none of these reports were cases with both conditions described in multiple generations. Further study into the RAS/MAPK pathway may provide insights into the pathogenesis of PVNS.

Author Index

Forty-Fifth Virtual Annual Meeting of the Developmental Neurotoxicology Society (DNTS)

Virtual | February 4–June 30, 2021

All time are in Eastern Time.

DNTS 2021 Program

Thursday, February 4, 2021

7:00 PM–8:30 PM **Member Social Hour**

Do You Know Your DNTS Colleagues ? It'll Be a (KA)HOOT

Thursday, February 25, 2021

7:00 PM–8:30 PM **Elsevier Distinguished Lecture**

Setting the Stage: How Diet and Neuroimmune Factors in Early Life Shape Cognitive Development
Teresa Reyes, University of Cincinnati, College of Medicine, Department of Pharmacology and Systems Physiology

Thursday, March 18, 2021

7:00 PM–8:30 PM **Mentoring Workshop**

Pathways to Science: Career Mentoring: Early/Mid and Tracks

Thursday, April 8, 2021

7:00 PM–8:30 PM **Neurodevelopmental Underpinnings and Consequences of Drug Exposures Symposium**

Developmental Drug Exposures: Cause and Effect
Gregg Stanwood, Florida State University

The Role of Stress Hormones in an Animal Model of Addiction-Like Behavior (Sign Tracking)
Beth Ann Rice, Slippery Rock University

Oxytocin, Stress, and Addictive Disorders: Clinical Implications
Amy McRae-Clark, Medical University of South Carolina

Developmental and Transgenerational Consequences of Nicotine Exposure
Pradeep Bhide, Florida State University

Tuesday, May 4, 2021

12:30 PM–2:30 PM **Developmental Neurotoxicity of Methylmercury**
(Joint Webinar with BDRP)

Methylmercury and Developmental Neurotoxicity: Historical Context and Current Exposure
Michael Garry, Exponent and University of Washington

Methylmercury Neurotoxicity: What Can We Learn from Worms?
Michael Aschner, Albert Einstein College of Medicine

Cognitive and Neurobehavioral Impacts of Prenatal and Early Life Methylmercury Exposure
Susan A. Korrick, Harvard Medical School and Harvard T.H. Chan School of Public Health

Updating the US EPA IRIS Assessment of Methylmercury
Deborah Segal, US Environmental Protection Agency

Thursday, May 20, 2021

7:05 PM–8:05 PM **Recent Developments in Neurobehavioral Teratology**

7:05 PM–7:20 PM **1** **Long-term Outcomes Following Prenatal GLP-1R Activation**
Devon Graham, Florida State University

7:20 PM–7:35 PM **2** **Assessing Adult Learning and Memory in Cyp1a1(+/+) Wild Type and Cyp1a1(-/-) Knockout Mice Exposed to Benzo[a] pyrene During Early Brain Development**
Katelyn Clough, Western Kentucky University

7:35 PM–7:50 PM **3** **Associations between Prenatal Phthalate Exposure and Neurobehavioral Outcomes in 4.5- and 7.5-Month-Old Infants**
Jenna L.N. Sprowles, Beckman Institute for Advanced Science and Technology, University of Illinois Urbana-Champaign

7:50 PM–8:05 PM **4** **Examining the Association between Maternal Prenatal Stress and Infant NonNutritive Suck**
Emily Zimmerman, Northeastern University

8:05 PM–8:30 PM **DNTS Member Poster Presentations**

1 **Cognitive and Functional Outcomes at Age 21 After Prenatal Cocaine/Polydrug Exposure and Foster/Adoptive Care**
Lynn T. Singer, June-Yung Kim, Sonia Minnes, Meeyoung O. Min, Gregory Powers

2 **Aryl Hydrocarbon Receptor Mediated Disruption of Dopaminergic and Serotonergic Signaling in the Hippocampus and Prefrontal Cortex of Mice Exposed to Benzo[a]pyrene during Development**
Emma Foster, Katelyn Clough, Lisa Massie, Christine Perdan Curran

3 **Glucagon-like Peptide-1 Receptor Expression in the Developing Mouse Brain**
Haley Madkour, Gregg Stanwood, Devon Graham

Thursday, June 10, 2021

3:00 PM–4:00 PM **DNTS Business Meeting—Virtual Event**

Friday, June 25, 2021

12:00 Noon–12:30 PM **Patricia Rodier Mid-Career Award for Research and Mentoring**

Manganese Overexposure during Development: Environmental and Genetic Effects
(Joint with BDRP)
(See page 729 for more information)

Monday, June 28, 2021

1:00 PM–3:00 PM **The Effects of Water Fluoridation on Neurodevelopment and Other Health Outcomes Symposium**
(Joint with BDRP)
(See page 731 for more information)

3:00 PM–5:30 PM **Neurobehavioral Research: Assessing Quality in Neurobehavioral Research**
(Joint with OTIS)

Essentials of Human Study Design
Julie Kable, Emory University School of Medicine
Maximizing Research Potential through Design
Claire Coles, Emory University School of Medicine
Practical Constraints of Research Design
Michele Levine, University of Pittsburgh School of Medicine
Interpreting Research through Case Studies
Diana Dow-Edwards, SUNY Downstate Health Sciences University

Wednesday, June 30, 2021

1:00 PM–3:00 PM **Molecular Mechanisms of Fetal Alcohol Spectrum Disorders (FASDs) in Humans and Animal Models Symposium**
(Joint with BDRP)
(See page 737 for more information)

OTIS
Organization of Teratology Information Specialists

Thirty-Third Virtual Annual Education Meeting for Organization of Teratology Information Specialists Members and MotherToBaby Affiliates

Virtual | June 22–July 1, 2021

All time are in Eastern Time.

OTIS 2021 Program

Monday, June 22, 2021

11:00 AM–11:45 AM	**Keynote Lecture** **Pregnancy and the Perils of Precaution: Toward a New Paradigm for the Ethics of Including Pregnant People in Vaccine Research and Deployment** (Joint with BDRP) *(See page 730 for more information)*
11:45 AM–12:30 PM	**BDRP and European Teratology Society Exchange Lecture** **Covid-19 in Pregnancy and Lactation: US & European Perspectives on Research & Public Health** (Joint with BDRP) *(See page 730 for more information)*
12:30 PM–1:00 PM	**Break**
1:00 PM–1:30 PM	**President's Welcome** *OTIS President, Sarah Obican, University of South Florida College of Medicine*
1:30 PM–2:30 PM	**Thomas H. Shepard Lecture** **From Down Syndrome to Congenital Zika Syndrome: A Review of My Career Thus Far** *Moderator: Sarah Obican, University of South Florida College of Medicine* *Speaker: Sonja Rasmussen, University of Florida*
2:30 PM–3:00 PM	**Break**

3:00 PM–5:00 PM **Neurobehavioral Research**

Assessing Quality in Neurobehavioral Research
(Joint with DNTS)
Moderator: Al Romeo, MotherToBaby Utah and Jennifer Willford, Slippery Rock University in Pennsylvania
Speakers: Claire Coles, Diana Dow-Edwards, Julie Kable, and Michelle Levine

Tuesday, June 29, 2021

11:00 AM–12:30 PM **OTIS Lunch Box Training**

Counselling Myths
Speakers: Jan Friedman, University of British Columbia and Tony Scialli, Reproductive Toxicology Center

1:00 PM–3:00 PM **Current Topics and Updates for Pregnancy Registries Workshop**
(Joint with BDRP)
(See page 736 for more information)

3:00 PM–3:15 PM **Break**

3:15 PM–4:00 PM **Gerald G. Briggs Research Symposium**

Gastroschisis: An Update on Embryology, Pathogenesis, and Environmental Risk Factors
Chairpersons: Lewis B. Holmes, MassGeneral Hospital for Children and Keele Elise Wurst, GlaxoSmithKline
Moderator: Robert Felix, University of California San Diego
Speakers: Marcia Feldkamp, Division of Medical Genetics, University of Utah and Russell Kirby, College of Public Health University of South Florida

4:30 PM–5:00 PM **Poster Session**

Wednesday, June 30, 2021

11:00 AM–12:00 Noon **Hot Topic Lecture**

Chairperson: Claire Coles, Emory University

Air Pollution, Climate Change and Weather Impacts on Pregnancy Outcomes
Speaker: Michelle Bell, Yale University

Covid 19 and Pregnancy
Speakers: Christina Chambers, University of California San Diego and Lorrie Harris-Sagaribay, Fullerton Genetics Center

1:30 PM–2:30 PM **OTIS Abstract Session**

Chairperson: Mara Gaudette, University of California San Diego

Presenting author is underlined.

1:30 PM–1:50 PM **1** **Self-Reported Medication Use among Pregnant and Breastfeeding Women during the COVID-19 Pandemic: A Cross-Sectional Study in Five European Countries**

Ceulemans M[1,2], Foulon V[1], Panchaud A[3,4],Winterfeld U[5], Pomar L[6], Lambelet V[6], Cleary B[7,8], O'Shaughnessy F[7,8], Passier A[2], Richardson JL[9], Nordeng H[10,11]. [1]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [2]Teratology Information Service, Pharmacovigilance Centre Lareb's Hertogenbosch, the Netherlands, [3]Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [4]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland, [5]Swiss Teratogen Information Service, Service de Pharmacologie Clinique, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [6]Materno-Fetal and Obstetrics Research Unit, Lausanne University, Hospital, Lausanne, Switzerland, [7]Irish Medicines in Pregnancy Service, Rotunda Hospital, Dublin, Ireland, [8]School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons Ireland, Dublin, Ireland, [9]UK Teratology Information Service, Newcastle upon Tyne Hospitals NHS Foundation Trust and Public Health England, Newcastle upon Tyne, United Kingdom, [10]Pharmacoepidemiology and Drug Safety Research Group, Department of Pharmacy, and PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway, [11]Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway

1:50 PM–2:10 PM **2** **New Data on the Transfer of untested Medications into Breast Milk**

Monfort A[1], Jutras M[1], Martin B[2], Boucoiran I[2], Leclair G[1], Ferreira E[1,2]. [1]Université de Montréal, Montréal, QC, Canada, [2]Centre Hospitalier Universitaire (CHU) Sainte-Justine, Montréal, QC, Canada

2:10 PM–2:30 PM **3** **Screening for Early Maternal Thyroidal Insufficiency (EMTI)—Is It Beneficial?**

Boroje IJ[1,2,3], Lamm SH[1,4]. [1]Center for Epidemiology and Maternal-Child Health (CEOH, LLC), Washington, DC, United States, [2]George Washington University, Washington, DC, United States, [3]Liberty University School of Behavioral Sciences, Lynchburg, VA, United States, [4]Georgetown University School of Medicine, Department of Pediatrics, Washington, DC, United States

Thursday, July 1, 2021

11:00 AM–12:30 PM **Transforming Women's Health Through Better Information on the Safety of Medications During Pregnancy and Lactation Symposium**

(Joint with OTIS)

(See page 738 for more information)

4:30 PM **OTIS Program Ends**

OTIS

PLATFORM ABSTRACTS

(Presenter designated by underlined author.)

1

CEULEMANS M[1,2], FOULON V[1], PANCHAUD A[3,4], WINTERFELD U[5], POMAR L[6], LAMBELET V[6], CLEARY B[7,8], O'SHAUGHNESSY F[7,8], PASSIER A[2], RICHARDSON JL[9], NORDENG H[10,11]. [1]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [2]Teratology Information Service, Pharmacovigilance Centre Lareb's Hertogenbosch, the Netherlands, [3]Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [4]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland, [5]Swiss Teratogen Information Service, Service de Pharmacologie Clinique, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [6]Materno-Fetal and Obstetrics Research Unit, Lausanne University Hospital, Lausanne, Switzerland, [7]Irish Medicines in Pregnancy Service, Rotunda Hospital, Dublin, Ireland, [8]School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons Ireland, Dublin, Ireland, [9]UK Teratology Information Service, Newcastle upon Tyne Hospitals NHS Foundation Trust and Public Health England, Newcastle upon Tyne, United Kingdom, [10]Pharmacoepidemiology and Drug Safety Research Group, Department of Pharmacy, and PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway, [11]Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway. Self-Reported Medication Use among Pregnant and Breastfeeding Women during the COVID-19 Pandemic: A Cross-Sectional Study in Five European Countries

Pregnant and breastfeeding women had disrupted access to healthcare services during the COVID-19 pandemic. To identify challenges and/or counseling opportunities related to perinatal medication use, we set-up a multinational study to investigate the prevalence and type of medications used by pregnant and breastfeeding women during the first pandemic wave. A cross-sectional study using an anonymous web survey promoted via social media was performed in Ireland (IE), Norway (NO), Switzerland (CH), the Netherlands (NL) and United Kingdom (UK) between 16 June and 14 July 2020. Pregnant women and women who breastfed in the last three months and who were older than 18 years could participate. Women were asked which 'medicinal products' they had used daily/occasionally in the last three months. Medications were classified according to the ATC system. Factors associated with perinatal medication use were estimated by multivariable logistic regression. In total, 8378 women participated in the survey (i.e., 3666 pregnant and 4712 breastfeeding women). Most responses were collected in Norway (34%) and the Netherlands (28%), followed by Switzerland (19%), Ireland (17%) and UK (2%). Overall, 59% of pregnant women (UK: 79%; IE: 67%; NL: 59%; NO: 56%; CH: 51%) and 56% of breastfeeding women (UK: 68%; IE: 61%; NO: 57%; NL: 55%; CH: 52%) reported having used at least one medication. Daily and occasional use was recorded by 34% and 42% of pregnant women and 29% and 44% of breastfeeding women. Most prevalent ATC categories during pregnancy were nervous system (30%), respiratory system (20%) and alimentary tract and metabolism (16%); during breastfeeding nervous system (37%), respiratory system (15%) and musculo-skeletal system (14%). While paracetamol (28%), antacids (10%), cetirizine (5%) and low dose aspirin (5%) were the most frequently used medications in pregnancy, breastfeeding women mainly used paracetamol (34%), ibuprofen (12%), hormonal contraceptives (5%) and cetirizine (5%). Having a chronic condition, country, maternal age, being tested for SARS-CoV-2, time since delivery and professional status were associated with perinatal medication use. Perinatal medication use was highly prevalent during the first pandemic wave, underlining the importance of maintaining counseling efforts on medication safety, even in times of societal crisis and disrupted healthcare services.

2

MONFORT A[1],JUTRAS M[1], MARTIN B[2], BOUCOIRAN I[2], LECLAIR G[1], FERREIRA E[1],[2].[1]Université de Montréal, Montréal, QC, Canada, [2]Centre Hospitalier Universitaire (CHU) Sainte-Justine, Montréal, QC, Canada. New Data on the Transfer of Untested Medication into Breast Milk

Breast milk is an essential nutrient source for newborns. The use of medication by mothers during lactation is frequent. Unfortunately, there is a lack of information on the excretion of several drugs into breast milk. Thus, health professionals and mothers often prefer to avoid breastfeeding, depriving the newborn from the benefits of breast milk. Centre IMAGe (CHU Sainte-Justine, Montréal, Qc, Canada), a teratology information centre, answers questions from health professionals about the use of drugs during pregnancy or breastfeeding. The pharmacists at IMAGe have identified 17 drugs, including aripiprazole, lacosamide and methotrexate, for which safety data during breastfeeding is scarce. The purpose of this project is to evaluate the transfer of these drugs in breast milk. Breastfeeding women treated with the selected medications are asked to provide eight samples of their milk at different times over a 24-hour period. Women must complete two questionnaires, one on their medical history and another on their infant's health in order to identify potential adverse effects linked to their exposure to the drug. Breast milk samples are analyzed by an LC-MS/MS method, developed and validated specifically for the study. The recruitment will continue during the next two years. This project was approved by the institutional ethics committee. From 01/2019 to 03/2021, 23 women were recruited, 17 answered the first questionnaire and 14 provided breast milk samples for vortioxetine, lacosamide, bisoprolol, letrozole, aripiprazole, clomiphene, methotrexate and melatonin. Average calculated relative infant doses (RID) were below 10% for most drugs except for aripiprazole (12.7%), lacosamide (29.9%) and letrozole (10.2%). Methotrexate concentrations were measured over a 72-hour period and showed a significant decrease during the first 24 hours in colostrum (142 to 31 µg/L) and mature breast milk (11.6 to 6.5 µg/L). The percentage of the pediatric dose could reach as much as 254% for lacosamide. No adverse effects were reported in breastfed infants. Our validated analysis method was used to quantify the breast milk concentration of eight drugs. These results on the excretion of drugs into breast milk and its effects on breastfed infants allow health professionals to make more individualized and data driven clinical recommendations.

3

BOROJE IJ[1,2,3], LAMM SH[1,4]. [1]Center for Epidemiology and Maternal-Child Health (CEOH, LLC), Washington, DC, United States, [2]George Washington University, Washington, DC, United States, [3]Liberty University School of Behavioral Sciences, Lynchburg, VA, United States, [4]Georgetown University School of Medicine, Department of Pediatrics, Washington, DC, United States. Screening for Early Maternal Thyroidal Insufficiency (EMTI)—Is It Beneficial?

Studies from 1990–2005 indicated that early maternal thyroidal insufficiency (EMTI) was a cause of neurodevelopmental deficits in offspring. Because of the uncertainty in knowing whether such was indeed beneficial, a study to assess that was carried out. The Controlled Antenatal Thyroid Screening (CATS) study was designed to test this by randomly, and with informed consent, testing the 12-week sera of half of the study women for TSH and T4 at 12-weeks and testing the other half post-partum. Thus, outcome could be assessed separately for those diagnosed with EMTI and treated with a set dose of L-thyroxine 150 ug/day and those diagnosed post-partum with EMTI and not treated. Neurodevelopmental studies were conducted at ages three and nine. Additionally, an NICHD study with screening at 8–20 weeks (mean 16-18) was conducted. At age three (CATS I), no difference in measures of IQ, the Child Behavior Check List, or the Brief P test of executive function were observed. At nine years of age (CATS II), there were no differences in IQ mean or in proportion with IQ<85 between those with treated-EMTI, those with untreated EMTI, and those without EMTI. Behavioral studies [child's emotional health difficulties (Strengths and Difficulties), ADHD (CBCL), and ASD screening (Social Communications)] were also conducted at age 9. A subset of children was found to show a greater frequency of abnormal results in the behavioral studies compared to each of the other groups. This subset consisted of those from treated pregnancies in which the response to treatment had led to excessively high T4 levels. The NICHD clinical trial of treatment of maternal subclinical hypothyroidism and of maternal hypothyroxinemia diagnosed, randomized, and placebo-controlled at 8–20 weeks (mean 16–18) gestation, which had adjusted dosages monthly, found no difference in cognitive and ADHD scores. Both studies revealed that screening and treatment for maternal thyroid function at 12 weeks and at 8-20 weeks did not lead to better neurodevelopment in the children. Further, excessive response to treatment, or overtreatment, did lead to lesser neurodevelopment outcomes. Thus, maternal thyroidal screening at 12–18 weeks gestation has not yielded significant benefit and may include adverse risk.

OTIS

POSTER ABSTRACTS

(Presenter designated by underlined author.)

1

CEULEMANS M, VAN GANSEWINKEL M, WESEL L, SILLIS L, FOULON V. Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Belgium. Preferences and Expectations of Potential Users towards the Role and Organization of a Future Teratology Information Service in Belgium: A Qualitative Study among Patients and Healthcare Professionals

Although discussions are ongoing, Belgium still has no Teratology Information Service (TIS). While the need for a Belgian TIS has clearly been demonstrated, there is no insight into the preferences and expectations of healthcare professionals (HCPs) and the public in Belgium towards the role and organization of the future TIS. As such evidence is pivotal to set-up a service that is fully adapted to the Belgian situation, we aimed to explore this in depth. A qualitative study using online semi-structured interviews with Dutch-speaking women and HCPs from different perinatal disciplines was performed in September–December 2020. The topic guides consisted of questions exploring individuals' experiences with information on perinatal medication use and their preferences towards information and counseling provided by a TIS. Data collection occurred until data saturation. A thematic analysis was performed in Nvivo. Ethical approval and informed consent from all interviewees was obtained. In total, 17 women and 18 HCPs participated, including obstetricians (N=3), pharmacists (N=4), general practitioners (N=2), midwives (N=3) and lactation consultants (N=6). Most women and HCPs reported having been confronted with inconsistent information or advice on perinatal medication use, possibly resulting in inappropriate patient care or unnecessary premature discontinuation of breastfeeding. Women also commonly struggled with complex medical terms in available sources and cited a lack of knowledge among HCPs on this topic. HCPs addressed a clear need for an up-to-date Belgian resource on perinatal medication use, which would be timesaving for professionals and beneficial to the quality of care. Overall, both women and HCPs assigned an important role to a future TIS, not only to provide evidence-based and easily accessible information through a user-friendly website, but also to offer individual counseling. Other roles HCPs attributed to a TIS included contributing to guideline development, educating HCPs and facilitating research. HCPs also attached great importance to keeping information up-to-date and to providing comprehensive documentation, including references and pharmacokinetic data. In conclusion, women and HCPs were generally very enthusiastic about a future Belgian TIS to which they assigned great value. Nevertheless, potential users also have high expectations in terms of expertise and quality of the provided service.

2

BLOMFIELD VILLARBA A, CASTANEDA M, ZELLNER J, ALVARADO S, KAO, K, CHAMBERS C, JONES K. University of California, San Diego, CA, United States. Addressing the Pregnancy Health Learning Needs of Migrant Women in the Southern California Border Region

Our project developed and implemented targeted marketing and outreach activities to improve knowledge and utilization of MotherToBaby information services among migrant women in the San Diego border region. We implemented brick-and-mortar advertising along public transit paths accessed by Mexican American women. From Aug 3–Sept 28, 2020, we posted a large Spanish-language billboard that directed users to a Spanish-language web page focusing on exposures of interest to migrant workers. The billboard generated 106 landing page visits. Compared to four-weeks prior, we experienced a 90% increase in Spanish-language chat and a 170% increase in chats from California. We also created visual communication tools for limited language proficient populations on three popular fact sheet topics: Nausea & Vomiting in Pregnancy, COVID-19 and Reproductive Hazards of the Workplace. Each had a QR code to take the user to the relevant Spanish-language fact sheet and included a URL to contact us. These were made available online, in print, and were distributed alongside existing resources to local organizations serving migrant populations. Staff provided outreach virtually to establish new and strengthen existing partnerships with organizations that serve migrant families. On Feb 28, 2021, we hosted a Zoom training that received 138 RSVPs and had 79 attendees. Registrants were subsequently emailed a link to the presentation and a landing page with resources including teratogen information in Spanish. The partnerships page received 161 online visits during the pilot project, and in the one-month post-training we added two new partners serving primarily Spanish-speaking women. Live chat increased 3.7% in the four weeks during and after the marketing of the event compared to the four weeks before. Finally, we used social media advertising to facilitate awareness of our program and promote potential partnerships among the network of migrant/Latinx advocacy groups. Website traffic increased 205% including a 100% increase to Spanish educational materials including fact sheets and blogs. The unique circumstances that migrant women face coupled with limited outreach capabilities during the COVID-19 pandemic proved challenging, but with a virtual and public presence we were able to adapt this pilot to enhance knowledge of MotherToBaby services among organizations serving migrant communities.

Society for Birth Defects Research and Prevention Code of Ethics

Preamble

The objective of the Society of Birth Defects Research and Prevention 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 the Society for Birth Defects Research and Prevention is to understand the cause and pathogenesis of structural and functional birth defects, developmental delays, perinatal death, and other disorders of developmental and reproductive origin in order to prevent their occurrence and improve diagnosis and treatment by promoting multi-disciplinary research and exchange of ideas; communicating information to health professionals, decision-makers, and the public; and providing education and training.

Code of Ethics

As a member of the Society for Birth Defects Research and Prevention, 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.**

Adherence to the Code of Ethics is a condition of membership in the Society of Birth Defects Research and Prevention.

Society for Birth Defects Research and Prevention Guidelines for Ethical Publication and Presentation of Scientific Information and Data

Members of the Society for Birth Defects Research and Prevention subscribe to the Code of Ethics adopted by the Society membership on June 8, 1990, and updated on February 8, 2021. 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 Society for Birth Defects Research and Prevention 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 the editors of both journals or upon request of an editor as in a review article.
2. Co-authors should have full knowledge of and agreement with the contents and conclusions of the paper and have made a substantial contribution to the work.
3. Manuscripts should reference published preliminary accounts or abstracts from the same work to permit association of preliminary and full reports of studies.
4. "Personal communication" citations or references (oral presentations) should have the approval of the cited individual.
5. The author must cite fairly the work of others. Appropriate citations are an important component of scholarship.
6. For all studies involving human subjects or tissues, the following conditions should be met:
    a. The principles in the Declaration of Helsinki must be followed.
    b. These studies must have received formal approval from the appropriate institutional review board, ethical review committee or equivalent, and such approval should be indicated in the manuscript.
    c. If there is significant risk or discomfort to subjects, the manuscript must indicate that informed consent was obtained.
    d. Photographs of patients' faces should be included only if there is scientific relevance, and written consent must have been obtained for the publication of such photographs.
7. For all studies involving the use of animals, the following conditions should be met:
    a. All research animals must have been obtained and used in compliance with federal, state, and local laws and institutional regulations.
    b. The Society recommends that animals be maintained in accordance with the guidelines of the NIH (Guide for the Care and Use of Laboratory Animals, 1996). Any veterinary accreditation should be noted in the manuscript.
    c. The author must have received permission from their institutional Animal Care and Use Committee, and the manuscript must indicate that such approval was received.

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

Responsibilities of Reviewers

1. Reviewers are obligated to make expert, critical, and unbiased scientific and literary appraisals of reports of research, or other publications as requested, in the fields of the reviewers' knowledge.
2. Reviews should be done in a timely manner to not impede release of information.
3. If the reviewer wishes to ask a colleague to review the paper, the colleague's name must first be identified, and permission obtained from the Editor. The person must be qualified in the opinion of the editorial staff of the journal.
4. A reviewer should not review a paper if:
    a. The reviewer does not feel it is in 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.
5. The reviewer's criticisms must be sufficiently detailed to justify the conclusion and should be referenced if necessary, to help the author.
6. The reviewer should assess whether the work of others is properly cited.
7. If the paper substantially resembles a published paper or another paper under review, this should be reported to the editor.
8. 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 Editor-In-Chief and Editors

1. The Editor-in-Chief and Editors manage and implement the policies of the journal and are responsible for the scientific and literary quality.

2. The Editor-In-Chief and Editors, to the best of their ability must assure that all authors receive confidential, expert, critical and unbiased reviews of their work in a timely fashion.

3. The Editor-in-Chief or Editors may not take part in the editorial management of the review of their own papers. They also should avoid conflict of interest in the review of papers closely related to their own work or organizational affiliation.

4. If an Editor becomes aware that the main substance or conclusion of a paper published in the journal may be erroneous, the Editor should communicate such to the Editor-in-Chief and the Publisher. They will investigate as necessary, communicate the findings with the original author, and work with the author and the publisher to 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 journal, he or she should consult with the Editor-in-Chief and the Publisher, with copy to the Chair of the Society's Publications Committee, concerning the appropriate course of action.

Responsibilities of the Publisher

1. As the owner of the journal, the Publisher holds immediate responsibility over ethical issues that arise which affect the journal. The publisher will work through its standard channels of investigation of alleged publication ethics violations and will consult with the Society's Publications Committee as appropriate.

2. If an alleged ethics violation occurs within the context of the journal and is brought directly to the Society and not the Editor-in-Chief or the Publisher, the Society should cede primary oversight of the investigation to the Publisher. However, if it is deemed crucial for the Society's best interests to initiate an investigation, a collaboration between the Publisher and the Society should be maintained.

Responsibilities of the Publications Committee

The Society for Birth Defects Research and Prevention Publications Committee, in consultation with the Publisher, will cooperate in any investigation of any breach of these policies and/or those of the Publisher, which follow generally the Committee on Publication Ethics (COPE) guidelines. They will make recommendations to Society for Birth Defects Research and Prevention Council, as appropriate, for actions which directly affect the Society, its members, and its good standing.

References

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

1. Wiley Publishing Best Practice Guidelines on Research Integrity and Publishing Ethics. https://authorservices.wiley.com/ethics-guidelines

2. *Birth Defects Research* Journal Author Guidelines. https://onlinelibrary.wiley.com/page/journal/24721727/homepage/forauthors.html

3. *Endocrinology* Journal Instructions to Authors. http://endo.endojournals.org

4. National Research Council. 1996. Guide for the care and use of laboratory animals. Washington DC: National Academy Press.

5. *Toxicological Sciences* Journal Instructions to Authors. https://academic.oup.com/toxsci

6. Society for Birth Defects Research and Prevention website. https://www.birthdefectsresearch.org

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