

Emerging Science for Environmental Health Decisions

Mixtures and Cumulative Risk Assessment: New Approaches Using the Latest Science and Thinking about Pathways

Reading List for More Information

Session 1

Teuschler Linda K. Deciding which chemical mixtures risk assessment methods work best for what mixtures. *Toxicology and Applied Pharmacology* Vol 223(2) pp. 139-147. 1 September 2007. <http://www.sciencedirect.com/science/article/pii/S0041008X06002626>

Choudhry, H, Teuschler, LK, et al. Supplementary guidance for conducting health risk assessment of chemical mixtures. Office of Research and Development: EPA/630/R-00/002. August 2000. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533#Download>

U.S. DHHS, ATSDR's Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures. 2004. <http://www.atsdr.cdc.gov/interactionprofiles/ipga.html>

U.S. DHHS, ATSDR's Interaction Profiles for Toxic Substances. 2008. <http://www.atsdr.cdc.gov/interactionprofiles/index.asp>

U.S. DHHS, ATSDR's Guidance for the Preparation of an Interaction Profile. February 2001 http://www.atsdr.cdc.gov/interactionprofiles/interaction_profile_guidance.pdf

California EPA's Cumulative Impacts and Precautionary Approaches. <http://oehha.ca.gov/ej/index.html>

*National Academy of Science's National Research Council's Report on Phthalates and Cumulative Risk Assessment. Research Brief. Committee on the Health Risks of Phthalates (2008). http://dels.nas.edu/dels/rpt_briefs/phthalates_final.pdf

*National Academy of Science's National Research Council's Report on Science and Decisions Advancing Risk Assessment. Research Brief. http://dels.nas.edu/dels/rpt_briefs/IRA_brief_final.pdf

NIOSH Mixed Exposures Team Research Agenda. 2004. <http://www.cdc.gov/niosh/docs/2005-106/>

NoMiracle (Novel Methods for Integrated Risk Assessment of Cumulative Stressors in Europe) <http://nomiracle.jrc.ec.europa.eu/default.aspx>

U.S. EPA's Office of Science Policy Cumulative Risk Assessment Program <http://www.epa.gov/osa/spc/2cumrisk.htm>

U.S. EPA's Framework for Cumulative Risk Assessment May 2003 http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36941

Emerging Science for Environmental Health Decisions

U.S. EPA's Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document.

<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=190187>

U.S. EPA's Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures 2000. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533>

U.S. EPA's Information on Assessing Pesticide Cumulative Risk (Office of Pesticide Programs) Online. <http://www.epa.gov/pesticides/cumulative/>

<http://www.epa.gov/oppsrrd1/cumulative/>

<http://www.who.int/ipcs/methods/harmonization/areas/aggregate/en/index.html>

Session 2

Patel CJ, Bhattacharya J, Butte AJ. An Environment-Wide Association Study (EWAS) on Type 2 Diabetes Mellitus. PLoS ONE Vol 5(5) May 2010

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0010746>

Rappaport, Stephen M and Smith, Martyn T. Environmental and Disease Risks. Science 33 (6003) pp.460-461. 22 October 2010

<http://www.sciencemag.org/content/330/6003/460.full?sid=7c8beef-2302-4603-aba8-a32f3397fc99>

<http://www.ewg.org/sites/humantoxome/>

Ovacik MA, Sen B, Euling SY, Gaido KW, Ierapetritou MG, Androulakis IP, 2010. Pathway modeling of microarray data: A case study of pathway activity changes in the testis following in utero exposure to dibutyl phthalate (DBP). Toxicology and Applied Pharmacology. Available online 2010 Sep 17.

Makris SL, Euling SY, Gray LE Jr, Benson R, Foster PM, 2010. Use of genomic data in risk assessment case study: I. Evaluation of the dibutyl phthalate male reproductive development toxicity data set. Toxicology and Applied Pharmacology. Available online 2010 Sep 16.

Euling SY, White LD, Kim AS, Sen B, Keshava C, Keshava N, Wilson V, Ovacik AM, Hester S, Ierapetritou MG, Androulakis IP, Gaido KW, 2011. The use of genomic data in risk assessment case study: II. Evaluation of the dibutyl phthalate toxicogenomic dataset. Toxicology and Applied Pharmacology, Special Issue: Toxicogenomics in Risk Assessment. Available online 2011 Jun 30.

Chiu WA, Euling SY, Scott CS, Subramaniam RP, 2010. Approaches to advancing quantitative human health risk assessment of environmental chemicals in the post-genomic era. Toxicology and Applied Pharmacology. Available online 29 March 2010.

Emerging Science for Environmental Health Decisions

Mortensen H, Euling SY, 2011. Integrating mechanistic and polymorphism data to characterize human genetic susceptibility for environmental chemical risk assessment in the 21st century. *Toxicology and Applied Pharmacology*, Special Issue: Toxicogenomics in Risk Assessment. Available online 2011 Feb 1.

Euling SY, White LD, Kim AS, Sen B, Keshava C, Keshava N, Wilson V, Ovacik AM, Hester S, Ierapetritou MG, Androulakis IP, Gaido KW, in press . The use of genomic data in risk assessment case study: II. Evaluation of the dibutyl phthalate toxicogenomic dataset. *Toxicology and Applied Pharmacology*, Special Issue: Toxicogenomics in Risk Assessment. Anticipated online publication July 2011.

Daston GP, Naciff JM. Gene expression changes related to growth and differentiation in the fetal and juvenile reproductive system of the female rat: evaluation of microarray results. *Reprod Toxicol*. 2005 Jan-Feb;19(3):381-94. Review.

Daston GP. Genomics and developmental risk assessment. *Birth Defects Res A Clin Mol Teratol*. 2007 Jan;79(1):1-7.

Liu K, Lehmann KP, Sar M, Young SS, Gaido KW. Gene expression profiling following in utero exposure to phthalate esters reveals new gene targets in the etiology of testicular dysgenesis. *Biol Reprod*. 2005 Jul;73 (1):180-92. Epub 2005 Feb 23.

Plummer S, Sharpe RM, Hallmark N, Mahood IK, Elcombe C. Time-dependent and compartment-specific effects of in utero exposure to Di(n-butyl) phthalate on gene/protein expression in the fetal rat testis as revealed by transcription profiling and laser capture microdissection. *Toxicol Sci*. 2007 Jun;97(2):520-32. Epub 2007 Mar 22.

Gohlke JM, Thomas R, Zhang Y, Rosenstein MC, Davis AP, Murphy C, Becker KG, Mattingly CJ, Portier CJ. Genetic and environmental pathways to complex diseases. *BMC Systems Biology* 3(46). May 2009. <http://www.biomedcentral.com/content/pdf/1752-0509-3-46.pdf>

Thomas R, Gohlke JM, Stopper GF, Parham FM, Portier CJ. Choosing the right path: enhancement of biologically relevant sets of genes or proteins using pathway structure. *Genome Biology* Vol 10. 24 April 2009. <http://genomebiology.com/2009/10/4/R44>

Judson RS, Houck, KA, Kavlock, RJ, Knudsen TB, et al. *In Vitro* Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project. *Environmental Health Perspective* Vol 118(4) April 2010 http://ehp03.niehs.nih.gov/article_fetchArticle.action?articleURI=info%3Adoi%2F10.1289%2Fehp.0901392

Judson RS, Kavlock RJ, Woodrow Setzer R, et al. Estimating Toxicity-Related Biological Pathway Altering Doses for High-Throughput Chemical Risk Assessment. *Chemical Research in Toxicology*. 2011; Vol 24(4) pp. 451-462 <http://pubs.acs.org/doi/full/10.1021/tx100428e>

Emerging Science for Environmental Health Decisions

Knudsen TB, Houck KA, Sipes NS, et al. Activity profiles of 309 ToxCast™ chemicals evaluated across 292 biochemical targets. *Toxicology* Vol 282(1-2) pp. 1-15. March 2011. <http://www.sciencedirect.com/science/article/pii/S0300483X11000047>

Session 3

BE Expert Workshop and BE Concept Papers

Hays, S.M., R. Becker, H.-W. Leung, L.L. Aylward, and D.W. Pyatt. 2007. Biomonitoring equivalents: A screening approach for interpreting biomonitoring results from a public health risk

perspective. *Reg Toxicol Pharmacol.* 47(1):96-109. doi:10.1016/j.yrtph.2006.08.004

Hays, S.M., L.L. Aylward, and J.S. Lakind. 2008. Introduction to the Biomonitoring Equivalents Pilot Project: Development of guidelines for the derivation and communication of Biomonitoring Equivalents. *Reg. Toxicol. Pharmacol.* 51:S1-S2. doi:10.1016/j.yrtph.2008.02.007

Hays SM, Aylward LL, LaKind JS, Bartels MJ, Barton HA, Boogaard PJ, Brunk C, DiZio S, Dourson M, Goldstein DA, Kilpatrick ME, Krewski D, Krishnan, K, Lipscomb J, Nordberg M, Okino M, Tan Y-M, Viau C, Yager JW. 2008. Guidelines for the derivation of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop. *Reg. Toxicol. Pharmacol.* 51:S4-S15. doi:10.1016/j.yrtph.2008.05.004

LaKind, J.S., L.L. Aylward, C. Brunk, S. DiZio, M. Dourson, D.A. Goldstein, M.E. Kilpatrick, D. Krewski, M.J. Bartels, H.A. Barton, P.J. Boogaard, J. Lipscomb, K. Krishnan, M. Nordberg, M. Okino, Y.-M. Tan, C. Viau, J.W. Yager, and S.M. Hays. 2008. Guidelines for the communication of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop. *Reg. Toxicol. Pharmacol.* 51:S16-S26. doi:10.1016/j.yrtph.2008.05.007

BE Collaboration with German Human Biomonitoring Commission

Angerer, J., L.L. Aylward, S.M. Hays, B. Heinzow, M. Wilhelm. In press. Human biomonitoring assessment values: Approaches and data requirements. *Int. J. Hyg. Environ. Health*

BE Derivation, Interpretation, and Application Manuscripts

Aylward, L.L., S.M. Hays. In press. Biomonitoring-based risk assessment for hexabromocyclododecane (HBCD). *Int. J. Hyg. Environ. Health*

Aylward, L.L., Krishnan, K., Kirman, C.R., Nong, A., Hays, S.M. In press. Biomonitoring Equivalents for deltamethrin. *Reg. Toxicol. Pharmacol.*

Hays, S.M., Aylward, L.L., Kirman, C.R., Krishnan, K., Nong, A. In press. Biomonitoring Equivalents for diisononyl phthalate (DINP). *Reg. Toxicol. Pharmacol.*

Kirman, C.R., Aylward, L.L., Hays, S.M., Krishnan, K., Nong, A. In press. Biomonitoring Equivalents for DDT/DDE. *Reg. Toxicol. Pharmacol.*

Krishnan, K., Adamou, T., Aylward, L.L., Hays, S.M., Kirman, C.R., Nong, A. In press. Biomonitoring Equivalents for 2,2',4,4',5-pentabromodiphenylether (PBDE-99). *Reg. Toxicol.*

Emerging Science for Environmental Health Decisions

Pharmacol. July 1, 2011

Boogaard, P.J., S.M. Hays, L.L. Aylward. 2011. Human biomonitoring as a pragmatic tool for health risk management of chemicals - Examples under the EU REACH programme. *Reg. Toxicol. Pharmacol.* 59(1):125-32 <http://dx.doi.org/10.1016/j.yrtph.2010.09.015>

Aylward, L.L., S.M. Hays, M. Gagné, A. Nong, K. Krishnan. 2010. Biomonitoring Equivalents for hexachlorobenzene. *Reg. Toxicol. Pharmacol.* 58(1): 25-32 doi:10.1016/j.yrtph.2010.06.003

Hays, S.M., L.L. Aylward, M. Gagné, A. Nong, K. Krishnan. 2010. Biomonitoring Equivalents for inorganic arsenic. *Reg. Toxicol. Pharmacol.* 58(1):1-9. doi:10.1016/j.yrtph.2010.06.002

Krishnan, K., M. Gagné, A. Nong, L.L. Aylward, S.M. Hays. 2010. Biomonitoring Equivalents for triclosan. *Reg. Toxicol. Pharmacol.* 58(1):10-17 doi:10.1016/j.yrtph.2010.06.004

Krishnan, K., M. Gagné, A. Nong, L.L. Aylward, S.M. Hays. 2010. Biomonitoring Equivalents for bisphenol A (BPA). *Reg. Toxicol. Pharmacol.* 58(1):18-24 doi:10.1016/j.yrtph.2010.06.005

Aylward, L.L., C.R. Kirman, B.C. Blount, S.M. Hays. 2010. Chemical-specific screening criteria for interpretation of biomonitoring data for volatile organic compounds (VOCs) - Application of steady-state PBPK model solutions. *Reg. Toxicol. Pharmacol.* 58(1):33-44. <http://dx.doi.org/10.1016/j.yrtph.2010.05.011>

Aylward, L.L., M.K. Morgan, T.E. Arbuckle, D.B. Barr, C.J. Burns, B.H. Alexander, S.M. Hays. 2010. Biomonitoring data for 2,4-dichlorophenoxyacetic acid in the US and Canada: Interpretation in a public health risk assessment context using Biomonitoring Equivalents. *Environ. Health Perspect.* 118:117-181. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2831914/?tool=pubmed>

LaKind, J.S., D.Q. Naiman, S.M. Hays, L.L. Aylward, B.C. Blount. 2009. Public health interpretation of trihalomethane blood levels in the United States: NHANES 1999-2004. *J. Exp. Sci. Environ. Epidemiol.* 19(4):435-441. <http://www.nature.com/jes/journal/v20/n3/full/jes200935a.html>

Hays, S.M., L.L. Aylward, M. Gagné, K. Krishnan. 2009. Derivation of Biomonitoring Equivalents for cyfluthrin. *Regul. Toxicol. Pharmacol.* 55(3):268-75. doi:10.1016/j.yrtph.2009.09.002

Aylward, L.L., S.M. Hays, M. Gagné, K. Krishnan. 2009. Derivation of Biomonitoring Equivalents for di(2-ethylhexyl)phthalate (CAS No. 117-81-7). *Regul. Toxicol. Pharmacol.* 55(3):249-58. doi:10.1016/j.yrtph.2009.09.001

Emerging Science for Environmental Health Decisions

Aylward, L.L., S.M. Hays, M. Gagné, K. Krishnan. 2009. Derivation of Biomonitoring Equivalents for di-n-butyl phthalate (DBP), benzylbutyl phthalate (BzBP), and diethyl phthalate (DEP). *Regul. Toxicol. Pharmacol.* 55(3):259-267. doi:10.1016/j.yrtph.2009.09.003
July 1, 2011

Hays, S.M. and L.L. Aylward. 2009. Using biomonitoring equivalents to interpret human biomonitoring data in a public health risk context. *J. Appl. Toxicol.* 29(4):275-288.
<http://www3.interscience.wiley.com/journal/121588561/abstract?CRETRY=1&SRETRY=0>

LaKind, J.S., S.M. Hays, L.L. Aylward, and D.Q. Naiman. 2009. Perspective on serum dioxin levels in the United States: An evaluation of the NHANES data. *J. Exp. Sci. Environ. Epidemiol.* 19:435-441. <http://www.nature.com/jes/journal/v19/n4/full/jes200863a.html>

Aylward, L.L., J.S. LaKind, and S.M. Hays. 2008. Derivation of Biomonitoring Equivalent (BE) values for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds: A screening tool for interpretation of biomonitoring data in a risk assessment context. *J. Toxicol. Environ. Health Pt. A.* 71(22):1499-1508.
<http://www.informaworld.com/smpp/content~db=all?content=10.1080/15287390802361755>

LaKind, J.S., L. Barraj, N. Tran, and L.L. Aylward. 2008. Environmental chemicals in people: Challenges in interpreting biomonitoring information. *J. Environ. Health.* 70(9):61-64.
http://www.biomonitoringequivalents.net/LaKind_et_al_JEH_May_2008_Guest_Commentary.pdf

Hays, S.M., and L.L. Aylward. 2008. Biomonitoring equivalents (BE) dossier for acrylamide (AA) (CAS No. 79-06-1). *Reg. Toxicol. Pharmacol.* 51:S57-S67.
doi:10.1016/j.yrtph.2008.05.010

Hays, S.M., M. Nordberg, J.W. Yager, and L.L. Aylward. 2008. Biomonitoring equivalents (BE) dossier for cadmium (Cd) (CAS No. 7440-43-9). *Reg. Toxicol. Pharmacol.* 51:S49-S56.
doi:10.1016/j.yrtph.2008.05.008

Aylward, L.L., J.S. LaKind, and S.M. Hays. 2008. Biomonitoring equivalents (BE) dossier for trihalomethanes. *Reg. Toxicol. Pharmacol.* 51:S68-S77. doi:10.1016/j.yrtph.2008.05.005

Aylward, L.L., and S.M. Hays. 2008. Biomonitoring equivalents (BE) dossier for 2,4-dichlorophenoxyacetic acid (2,4-D) (CAS No. 94-75-7). *Reg. Toxicol. Pharmacol.* 51:S37-S48.
doi:10.1016/j.yrtph.2008.05.006

Aylward, L.L., H.A. Barton, and S.M. Hays. 2008. Biomonitoring equivalents (BE) dossier for toluene (CAS No. 108-88-3). *Reg. Toxicol. Pharmacol.* 51:S27-S36.
doi:10.1016/j.yrtph.2008.05.009

Emerging Science for Environmental Health Decisions

Hotchkiss, AK, Park-Saldutti LG, Gray, Jr. LE, et al. A Mixture of the “Antiandrogens” Linuron and Butyl Benzyl Phthalate Alters Sexual Differentiation of the Male Rat in a Cumulative Fashion. *Biology of Reproduction* Vol. 71(6), pp. 1852-1861. 1 December 2004
<http://www.bioreprod.org/content/71/6/1852.full.pdf+html>

Hannas BR, Lambright CS, Gray, Jr. LE, et al. Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following *in utero* exposure to diethylhexyl phthalate, diisobutyl phthalate, diisooheptyl phthalate and diisononyl phthalate. *Toxicological Sciences* 1 June 2011
<http://toxsci.oxfordjournals.org/content/early/2011/06/01/toxsci.kfr146.abstract>

Hotchkiss ak, Rider CV, Furr J, et al. In utero exposure to an AR antagonist plus an inhibitor of fetal testosterone synthesis induces cumulative effects on F1 male rats. *Reproductive Toxicology* Vol. 30(2), pp. 261-270. 30 September 2010.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951612/>

Rider CV, Furr JR, Wilson VS, and Gray, Jr. LE. Cumulative effects of in utero administration of mixtures of reproductive toxicants that disrupt common target tissues via diverse mechanisms of toxicity. *International Journal of Andrology*. Vol. 33(2), pp. 443-462. April 2010.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874988/>

Blystone CR, Lambright CS, Gray, Jr. LE, et al. Cumulative and Antagonist Effects of a Mixture of the Antiandrogens Vinclozolin and Iprodione in the Pubertal Male Rat. *Toxicological Sciences* Vol. 111(1), pp. 179-188. 29 June 2009
<http://toxsci.oxfordjournals.org/content/111/1/179.full.pdf+html>

Rider CV, Wilson VS, Gray, Jr. LE, et al. Cumulative effects of in utero administration of mixtures of “antiandrogens” on male rat reproductive development. *Toxicologic Pathology* Vol. 37(1), pp. 100-113. January 2009. <http://tpx.sagepub.com/content/37/1/100.full>

Howdeshell KL, Rider CV, Wilson VS, Gray, Jr. LE. Mechanisms of action of phthalate esters, individually and in combination, to induce abnormal reproductive development in male laboratory rats. *Environmental Research* Vol. 108(2), pp. 168-176. October 2008
<http://www.sciencedirect.com/science/article/pii/S0013935108001886>

Howdeshell KL, Rider CV, Wilson VS, Gray, Jr. LE, et al. A Mixture of Five Phthalate Esters Inhibits Fetal Testicular Testosterone Production in the Sprague-Dawley Rat in a Cumulative, Dose-Additive Manner. *Toxicological Sciences* Vol. 105(1), pp. 153-165 (2008).
<http://toxsci.oxfordjournals.org/content/105/1/153.full>

Session 5

Fisher J, Lumpkin M, Boyd, Mahle D, Bruckner JV, El-Masri HA. PBPK modeling of the metabolic interactions of carbon tetrachloride and tetrachloroethylene in B6C3F1 mice. *Environmental Toxicology and Pharmacology* Vol16 pp. 93-105

Emerging Science for Environmental Health Decisions

McLanahan ED, Andersen ME, Campbell, Jr. JL, Fisher, JW. Competitive inhibition of thyroidal uptake of dietary iodide by perchlorate does not describe perturbations in rat serum total T₄ and TSH. Environmental Health Perspective Vol 117(5) May 2009.

<http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info%3Adoi%2F10.1289%2Fehp.0800111>

Session 6

Putzrath R and Ginevan ME. Meta-Analysis: Methods for Combining Data to Improve Quantitative Risk Assessment. Regulatory Toxicology and Pharmacology Vol. 14(2), pp. 178-188. October 1991

<http://www.ncbi.nlm.nih.gov/pubmed/1792352>

Putzrath Resha M. Estimating Relative Potency for Receptor-Mediated Toxicity: Reevaluating the Toxicity Equivalence Factor (TEF) Model. Regulatory Toxicology and Pharmacology Vol. 25(1), pp. 68-78. February 1997

<http://www.ncbi.nlm.nih.gov/pubmed/9056502>

Putzrath, Resha M. Reducing Uncertainty of Risk Estimates for Mixtures of Chemicals within Regulatory Constraints. Regulatory Toxicology and Pharmacology Vol. 31 (1), pp. 44-52. February 2000

<http://www.sciencedirect.com/science/article/pii/S027323009991365X>

Haddad S, Charest-Tardif G, Krishnan K. Physiologically based modeling of the maximal effect of metabolic interactions on the kinetics of components of complex chemical mixtures. Journal of Toxicology and Environmental Health, Part A Vol. 6, pp. 209-223. 2000

<http://www.tandfonline.com/doi/abs/10.1080/00984100050131350#preview>

Silkworth JB, Lipinkas T, Stoner CR. Immunosuppressive potential of several polycyclic aromatic hydrocarbons (PAHs) found at a Superfund site: new model used to evaluate additive interactions between benzo[*a*]pyrene and TCDD. Toxicology Vol. 105(2-3), pp. 375-386 December 1995.

<http://www.sciencedirect.com/science/article/pii/0300483X95032358>

Krishnan K, Haddad S, Béliveau M, Tardif R. Physiological Modeling and Extrapolation of Pharmacokinetic Interactions from Binary to More Complex Chemical Mixtures. Environmental Health Perspectives Vol. 110(6), pp. 989-994 December 2002.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1241283/>

Groten JP, Butler W, Feron VJ, et al. An Analysis of the Possibility for Health Implications of Joint Actions and Interactions between Food Additives. Regulatory Toxicology and Pharmacology. Vol. 31(1), pp.77-91. February 2000

<http://www.sciencedirect.com/science/article/pii/S0273230099913569>