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NELSON, B.K., Division of Biomedical and Behavioral Science, NIOSH, Cincinnati, Ohio. Interaction of extraneous variables on developmental toxicity.

Interactions of various agents are important considerations in developmental toxicology. Several recent papers have reviewed such interactions, with a focus on multiple chemical exposures. The purpose of this paper is to discuss the potential confounding effects of multiple exposures on developmental toxicity--both in epidemiological evaluations and experimental studies. Not only must concurrent exposures to multiple chemicals be evaluated, but exposure influences may be separated in time. Personal habits and factors such as age, genetic makeup, diurnal variations, nutritional imbalances, and metabolic disturbances may alter an individual's response to a particular agent. In addition, both micro- and macro-environmental conditions such as altered ambient temperature, noise level, "stress," and proximity to atmospheric or dietary pollutant sources, may impinge on the adverse effects of target developmental toxicants. Leisure time as well as occupational exposures must be evaluated. Teratologists must be alert to the many extraneous variables which may interact to affect the developmental toxicity of individual agents.

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ANDREWS, J.E., J. SCHMID[1], H. NICHOLS, E.S. HUNTER, and G. KLINEFELTER, Reproductive Toxicology Division, [1]Research Support Division, NHEERL, USEPA, Research Triangle Park, North Carolina. Developmental toxicity of mixtures: The Water disinfection byproducts dichloro-, dibromo- and bromochloro-acetic acid in embryo culture.

The chlorination of drinking water results in production of numerous disinfection by-products (DBPs). One of the important classes of DBPs is the haloacetic acids. We have previously shown developmental toxicity of three haloacetic acids (HACs) dichloro- (DCA), dibromo-(DBA) and bromochloro- (BCA)acetic acid in whole rat embryo culture (WEC). Human exposure to these contaminants in drinking water would involve simultaneous exposure to all three HACs. This study explores the question of developmental toxicity interactions between these compounds. Gestational day (GD) 9.5 embryos were exposed to various concentrations of the three HACs (singly or in combination) for 48 hours and then evaluated for dysmorphology using the developmental score (DEVSC) as the parameter of comparison. Concentrations of individual compounds and mixtures were chosen (based on a dose addition model) and predicted to produce DEVSCs 10 and 20% lower than control levels. Evaluations were performed on all possible combinations of the three HACs. The DEVSCs for single compounds as well as all combinations indicated that the dose addition model adequately predicted the observed toxicity. There were marginal non significant interactions both at the two-HAC and three-HAC level. The HACs were dysmorphogenic and resulted in heart, prosencephalic, visceral arch, rotation, eye and somite defects. There was a striking absence of neural tube defects in the rat with the HACs. Following exposures to BCA and DCA, alone and in combination, there was a significant incidence of delayed embryonic caudal development with apparently normal development anterior to the 2nd visceral arch. This is a rare observation in our lab and suggests selective inhibition of segmentation and possibly gastrulation.

DISCLAIMER: The research described in this article has been reviewed by the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Agency nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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EULING[1], S., and C.A. KIMMEL[2]. [1]AAAS Fellow, [2]National Center for Environmental Assessment, USEPA, Washington, District of Columbia. Cumulative risk assessment for developmental toxic agents.

The Food Quality Protection Act mandates cumulative risk assessment for pesticides that work through a common mechanism of action. We reviewed the literature to determine whether information was available on the biological processes affected (mode of action) by developmental toxic agents and to determine how risks could be combined for two agents on that basis. Of interest is whether two chemicals that act via a common mode of action produce additive, synergistic, or inhibitory effects. Information was reviewed for 5 different classes of chemicals with substantial mechanistic data: glycol ethers, weak acids, teratogens that inhibit sonic hedgehog signaling, dioxins, and endocrine disruptors that act via estrogen or androgen receptors. After judging the relative availability of data on mode of action, human exposure and effects, pharmacokinetics, and dose-response in a reliable model system, we selected endocrine disruptors that bind to the estrogen or androgen receptors. Two chemicals within this class will be selected based upon a strong correlation between a chemical's *in vitro* binding potency and its *in vivo* assay potency. Potency data from a receptor binding-dependent reporter gene assay for the chemicals, singly and in combination, will be used to quantify the developmental effects. *In vivo* effects will need to be verified with the chemicals, singly and in combination. This example will aid in identifying data gaps for the receptor binding chemicals as well as data needs for establishing mechanisms of developmental toxicity for other chemical classes. Relying on data for one mechanism of action has limitations when combining risks, since chemicals may affect multiple or alternate mechanisms depending upon the route of exposure, dose level, and other factors. As new data on additional mechanisms become available, this information can be incorporated into risk assessment.

TERATOLOGY SOCIETY

PLATFORM SESSIONS
ABSTRACTS