those produced by the individual compounds. Hence, mixtures of DCA and TCA may result in modulation of the hepatotoxic/hepatocarcinogenic outcomes of the individual compounds. (Supported by NIH/NIEHS grant # R15ES013706-01A2)

## PS 1018a Cumulative Toxicity of an Environmentally Relevant Mixture of Nine Regulated Disinfection By-Products in a Multigenerational Rat Reproductive Bioassay

J. Simmons, M. G. Narotsky, G. Klinefelter, J. M. Goldman, A. B. DeAngelo, D. S. Best, A. McDonald, L. F. Strader, A. S. Murr, J. S. Suarez, M. H. George and S. Hunter. *NHEERL/ORD, U.S. EPA, RTP, NC.*

Disinfection of water has advanced public health by decreasing waterborne disease. Dsinfectants react with organic materials in the water to form complex mixtures of disinfection by-products (DBPs). While a large unknown fraction remains, >600 DBPs have been identified. Most prevalent in chlorinated water are trihalomethanes (THMs) and haloacetic acids (HAAs); 4 THMs (chloroform, bromodichloromethane, chlorodibromomethane, bromoform) and 5 HAAs (chloroacetic, dichloroacetic, trichloroacetic, bromoacetic, dibromoacetic acid) are regulated by EPA as a group at 80 μg/L and 60 μg/L, respectively. This is the first multigenerational reproductive toxicity bioassay in animals with a drinking water mixture of the regulated THMs and HAAs. At realistic proportions, a mixture was prepared at 0, 500×, 1000×, and 2000× of EPA's maximum contaminant levels (MCLs). Timed-pregnant Sprague-Dawley rats (P0 generation) were exposed from gestation day 0 until weaning of the F1 offspring. Weanlings continued in their treatment groups, were examined for reproductive endpoints and bred to produce F2 litters. Pre- and postnatal survival was unaffected. F1 pup weights were unaffected at birth but reduced at 2000× on postnatal day (PND) 6 and at ≥1000× on PND 21. Males at 2000× had a small but significantly increased incidence of retained nipples and effects on sperm motility. Onset of puberty showed dose-related delays at 1000× and 2000×. F1 estrous cycles, breeding, and fertility were unaffected and F2 litters showed no effects on pup weight, or prenatal or neonatal survival. Histologically, P0 dams had nephropathy and adrenal cortical pathology at 2000×. In sum, while puberty was delayed at DBP concentrations ≥1000× and males at 2000× had retained nipples and altered sperm motility, exposure at these concentrations to an environmentally realistic mixture of 9 regulated DBPs did not affect F1 animals' ability to reproduce. (This abstract does not reflect EPA policy.)

## PS 1018b Toxicity Testing of Water, Air, and Soil near Mountaintop Removal Mining Sites in the Southern Coalfields of West Virginia Using *In Vitro* Methods—What the Data Can Tell Us

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As a result of published epidemiological studies indicating health impacts in mountaintop removal coal mining (MTR) areas of southern West Virginia (WV), the USGS conducted a survey of air, water and soil in the impacted area and at WV State Parks which served as control sites with no MTR. The analytes measured were organics, metals, and in vitro toxicity, collected over 2 years. Toxicity testing included three assays which measured 24 hr toxicity, 1 week clonal outgrowth and anchorage-independent growth effects of water and soil sample extracts on human cells. A case study was then conducted on samples collected from Artie, WV in close proximity to active mountaintop removal mining. Private wells, surface waters, soil, fruit/vegetable matter were sampled. Grab sampling was conducted during one week periods over the first year of the survey over all seasons at locations in several counties and at two State Parks outside the active mining area. Year two sampling concentrated on Artie, WV during spring and summer. From the sampling in year one, 2 of 22 samples (March), 3 of 21 (May), 4 of 18 (December) showed significant toxicity to human cells, while from the Artie, WV sampling in year two toxicity was seen in 16 of 19 (August) but 0 of 23 (December) samples. Ground whole apples from a site sampled in August also showed significant toxicity. This variation could be due to episodes of mining activity, seasonal differences in temperature, or water abundance and movement through the aquifer. The air, water and soil organics, metals, and fine particulates showed important differences between mined and non-mined locations. We will discuss how the latter relate to the toxicity results, potential overall importance and context within recent literature findings regarding the possible health effects of mountaintop mining removal.

## PS 1018c Assessment of *In Vivo* Toxicological Interactions from Criteria Air Pollutant Mixtures

L. Datko-Williams[1], B. Young[1], A. Wilkie[1], M. Madden[1], J. Dubois[1], L. W. Stanek[2], D. Johns[3] and E. Oesterling Owens[1]. *[1]NCEA, US EPA, RTP, NC, [2]NERL, US EPA, RTP, NC and [3]NIOSH, US CDC, Morgantown, WV.*

The US EPA sets National Ambient Air Quality Standards for criteria air pollutants, recognizing that air pollution in the environment exists as a complex mixture. Potential interactions between mixture components within biological systems are not well characterized. We reviewed past literature investigating the effects of mixtures of criteria air pollutants, starting with mixtures containing $NO_X$ (nitrogen oxides), and evaluated the presence of *in vivo* toxicological interactions. All endpoints and $NO_X$-containing mixtures were considered, however, most studies evaluated respiratory effects of $NO_X$+$O_3$ (ozone). Studies were classified into two categories: complete or incomplete response data. Complete data included the number of observations, mean response, and variance for each treatment group in the study. Studies lacking single pollutant exposures or complete response data were reviewed qualitatively. Of the 13 animal studies and 7 human studies in the qualitative analysis, 6 animal studies and 0 human studies suggested there may be interactions, though no pattern of response among the endpoints or exposures was apparent. Studies with complete data were analyzed quantitatively, and the response to the mixture was compared statistically to the sum of the responses to individual pollutants; the absence of a difference was defined as additive ($H_0$: combined effects = sum of individual effects, p=0.05). Of the studies in the quantitative analysis, all animal studies (n=17) had at least one non-additive endpoint, while the majority of endpoints evaluated in human studies (n=9) were additive. Among the studies that deviated from additivity, no pattern of response emerged in endpoints or exposure conditions. Thus, this analysis suggests that deviations from additivity exist in criteria air pollutant mixtures; however, many of the studies did not demonstrate interactions other than additivity.
The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the U.S. EPA.

## PS 1018d Mixture Effects at Human Relevant Exposure Levels?

A. Vinggaard[1], N. Hadrup[1], M. Pedersen[2], K. Skov[2], L. O. Bertelsen[1], H. Frandsen[2], K. G. Kongsbak[1], J. Boberg[1] and U. Hass[1]. *[1]Div. Toxicology & Risk Assessment, Technical University of Denmark, Søborg, Denmark and [2]Division of Food Chemistry, Technical University of Denmark, Søborg, Denmark.*

Mixtures of endocrine active chemicals usually act additively irrespective of the applied model system and the complexity of the endpoint measured. Most studies performed so far have tested doses ≥ NOAEL for individual chemicals. But what happens when we test mixtures of EDC's at doses close to human relevant exposure levels? We had the hypothesis that a low dose mixture of environmental chemicals and active food ingredients would not affect toxicity induced by perfluornonanoic acid (PFNA). PFNA was given at 13, 250 or 5000 μg/kg/day to male rats with or without a cocktail containing 14 chemicals including phthalates, bisphenol A, parabens, UV filters, pesticides, and the CYP3A4 inhibitors bergamottin (from grape fruit) and glabridin (from liquorice) at human relevant exposure levels (totally 2.5 mg/kg/day'). The lowest PFNA dose corresponded to an internal dose of ~6-fold total human PFC exposure. We did histology, hormone analysis, metabolomics in plasma and gene expression analysis in liver, testis and fat tissue. PFNA induced steatosis at the highest dose. At the low dose PFNA+Cocktail pronounced increases of androgen levels (dehydroepiandrosterone, androstenedione & testosterone) were evident. Gene expression analysis in low dose PFNA+Cocktail treated animals showed that CYP19 mRNA was affected in testis and fatty tissues. At higher PFNA doses several steroidogenic enzymes were down-regulated. Overall, we suggest that low dose PFNA+Cocktail affect the kinetics of androgens causing increased androgen levels. In addition the Cocktail protected against PFNA-induced increases in corticosterone levels via an effect on11β-HSD. The observations are effects at the molecular level that may be considered as biomarkers of direct adverse effects. This is to our knowledge a first indication that mixture effects appear in rats at doses close to human relevant exposure levels.

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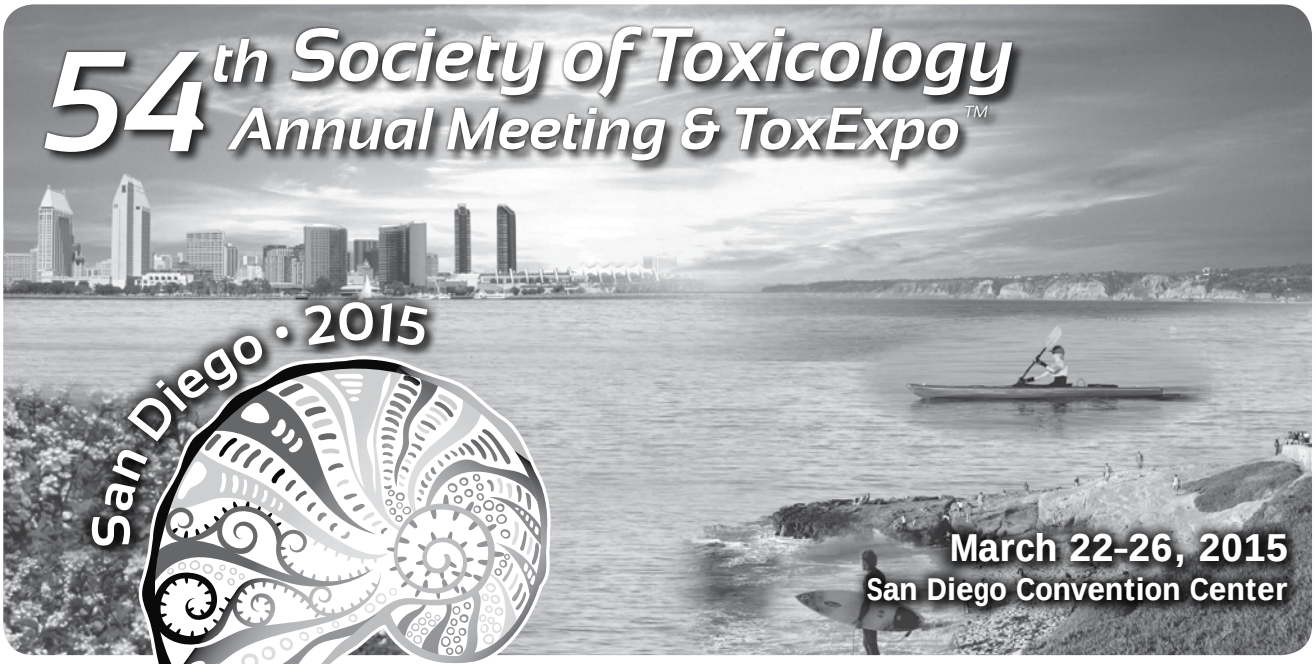


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# Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 53rd Annual Meeting of the Society of Toxicology, held at the Phoenix Convention Center, March 23–27, 2014.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 627.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 655.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence.

NOTE: Abstract numbers including a lower-case letter were programmed during second submission phase.

*Scientific Session Types:*

- EC Education-Career Development Sessions
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