consisting of five blocks. To date, four of the five blocks have been completed with over 1200 rats treated and 1000 litters examined. F-344 rats were gavaged on gestation days (GD) 6-15 with TCE (0, 10.1, 32, 101, and 320 mg/kg/d), DEHP (0, 24.7, 78, 247, and 780 mg/kg/d), and HEPT (0, 0.25, 0.8, 2.5, and 8.0 mg/kg/d) in corn oil. The dams were allowed to deliver and their pups were weighed and examined on days 1 and 6. Implants were counted to determine prenatal loss. Linear and logistic regression models were used to analyze continuous and proportional endpoints, respectively. Preliminary data analysis after four replicates revealed TCE and DEHP main effects and synergism for reduced maternal weight gain during GD 6-8; however, DEHP and HEPT were antagonistic. Full-litter resorptions were associated with main effects and a two-way synergism of DEHP and HEPT. Eye defects were associated with TCE and DEHP main effects. Decreased pup weights were associated with a main effect of each agent and DEHP antagonisms with the other two agents. Postnatal loss was associated with a HEPT main effect and a TCE-DEHP-HEPT three-way synergism. Results will be discussed in terms of study design and implications for risk assessment.

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YASUDA, M., N. Inoue* and T. J. SATO*, Department of Anatomy, Hiroshima University School of Medicine, Hiroshima, Japan. Exencephalic mouse fetuses are resistant to cleft palate induction by retinoic acid, cortisone, and 6-aminonicotinamide.

Previously we reported that exencephalic mouse fetuses were resistant to the cleft palate inducing action of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In order to test whether this resistance is specific to TCDD or not, we examined the effect of exencephaly on the cleft palate induction by retinoic acid (RA), cortisone acetate (CA), and 6-aminonicotinamide (6AN).

Pregnant Jcl:ICR mice were pre-treated with $CdCl_2$ at 6 mg/kg intraperitoneally on gestational day (GD) 7 (VP=GD 0) for induction of exencephaly in embryos. Then the dams were treated with RA at 160 mg/kg orally on GD 10 or 12, with CA at 100 mg/kg intramuscularly on GD 11 and 12, or with 6AN at 15 or 30 mg/kg intraperitoneally on GD 13. Their fetuses were examined for malformations on GD 18.

The obtained results are tabulated below: The values are shown in %. EX=exencephalic fetuses, non-EX=fetuses without exencephaly, CP=fetuses with cleft palate.

Treatment	dead/total	EX/live	CP/EX	CP/non-EX
RA (GD 10)	42	29	0	94
RA (GD 12)	52	59	0	100
CA	40	76	0	50
6AN (total)	46	30	0	100

The above results clearly indicate that exencephalic fetuses are resistant to cleft palate induction by various chemicals. (Supported by Grant in Aid for Scientific Research on Priority Areas #03202133 from the Ministry of Education, Science and Culture, Japan.)

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NELSON, B.K., D.L. CONOVER, D.M. WERREN, R.M. EDWARDS, and P.B. SHAW. Division of Biomedical and Behavioral Science, National Institute for Occupational Safety and Health, Cincinnati, Ohio. Evidence for synergistic teratogenicity of radiofrequency (RF) radiation and 2-methoxyethanol (2ME) in rats: external malformations.

Previous research suggests synergism between RF radiation exposure and 2ME administration in pregnant rats (Nelson et al. Teratology 43: 621-634, 1991). Concurrent administration of RF radiation, sufficient to maintain rectal temperatures at 42°C for 30 minutes, and 150 mg/kg 2ME on gestation day 13 was found to increase significantly the incidence and severity of external malformations in rat offspring. The present study is designed to replicate and extend those observations by investigating the dose-effect relationships. Five durations of RF exposure (sham, 0, 10, 20 and 30 min) at 42°C and five levels of 2ME (0, 75, 100, 125, and 150 mg/kg, p.o.) were administered to groups of six Sprague-Dawley rats on gestation day 9 or 13. Dams were sacrificed on day 20, and fetuses were removed serially, blotted dry, weighed, and examined for external malformations. Approximately one half of the fetuses were preserved in ethanol and the other half in Bouin's solution for later examination for skeletal or visceral malformations. Consistent with our previous observations, an enhancement of the incidence and severity of external malformations was dependent on the duration of RF radiation and dose of 2ME.

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GAVIN, C.,* B. KATES,* and P.M. RODIER, Department of Obstetrics and Gynecology, University of Rochester, Rochester, NY. Acute exposure to ethanol *in utero* reduces the number of luteinizing hormone releasing hormone cells in rat brain.

Several reports have concluded that rodents exposed to ethanol *in utero* exhibit late onset of sexual maturity. Such an effect could arise from ethanol injury to the gonads, the gonadotrophs of the pituitary, or the hypothalamic neurons which regulate pituitary function. The present study was designed to test whether acute ethanol exposure during neurogenesis of the LHRH cells could reduce their number. These cells are formed on day 12-13 of rat gestation (day of mating = day 1). Dams were exposed to 5.8 g/kg of ethanol by IP injection (divided into

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TERATOLOGY SOCIETY ABSTRACTS

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BRENT, R.L., Departments of Pediatrics, Anatomy, and Radiology, Jefferson Medical College, Philadelphia, PA, and Division of Developmental Biology, A.I. duPont Institute, Wilmington, DE. The impact of radiation research on the understanding of teratology principles.

Studies dealing with the effects of various forms of radiation on the developing mammalian embryo have assisted us in understanding many aspects of developmental biology and teratology and have had impact on the social, regulatory, legal and political aspects of teratology as well. The following concepts were discovered or amplified from radiation embryology studies: the "all-or-none" period of embryonic development, the repairability of the embryo, the sensitive period for the induction of mental retardation, the threshold concept for teratogenesis, the importance of stage sensitivity, and the realization that there were serious mid and late gestational effects from some embryotoxins. Even the controversial field of transplacental carcinogenesis was a component of early studies. The animal research has even more significance, because it agrees so well with the studies of children who were exposed in utero. This agreement has permitted counselors to provide more accurate teratologic counseling to pregnant women. Because there are misconceptions about environmental risks to the embryo and, in particular, about radiation risks, this information has been extremely helpful in providing competent and compassionate counseling, which has resulted in the prevention of thousands of unnecessary abortions of wanted pregnancies. These misconceptions about radiation risks are reflected in regulatory actions, courtroom testimony and political decisions. Examples of these activities will be given. Experience with human and animal pregnancy radiation exposures has given us a historical view of teratology which should assist us in understanding the mechanisms of teratogenesis and provide research approaches that may lead to the prevention of human malformations.

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Barr, M. Jr. and A.B. Sedman*, Department of Pediatrics, University of Michigan, Ann Arbor, Michigan. ACE inhibitor fetopathy: an update.

In the last decade, the angiotensin converting enzyme (ACE) inhibitors have gained widespread acceptance in the management of virtually all forms of hypertension. As early as 1980, there were reports of extraordinary fetal loss rates in experimental animals. In 1981, the first adverse outcome in a captopril-exposed human pregnancy was reported, followed by other cases implicating both captopril and enalapril as fetotoxins. Warnings were sounded by 1985 against the use of ACE inhibitors in human gestation. ACE inhibitor fetopathy is characterized by renal tubular dysplasia, anuria-oligohydramnios, pulmonary hypoplasia, growth restriction, and hypocalvaria. We have observed cases of fetopathy associated with exposure to captopril, enalapril and lisinopril. We (Barr & Cohen '91; Martin et al. '92) postulate that the fetopathy is not specific to these drugs but is due to fetal hypotension. However, these drugs are particularly effective in producing fetal hypotension. Although the true frequency of adverse effects has yet to be determined, because of the severely debilitating and lethal nature of the fetal damage when it occurs, it is recommended that ACE inhibitors not be used in women of child-bearing potential and certainly not in the 2nd & 3rd trimesters of gestation. As recently as 3 years ago, product information on these agents in the PDR was vague and unhelpful. In light of our cases and others recently reported (Rosa et al. '89; Cunniff et al. '90), the FDA has now directed that all ACE inhibitors be classified as Pregnancy Category D (formerly C) and has recommended that product information include a boxed warning about fetal effects and that a "Dear Doctor" letter be sent by the manufacturers.

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JONES, K.L., JOHNSON*, K.A., CHAMBERS*, C.C., Department of Pediatrics, Division of Dysmorphology and Teratology, University of California San Diego, La Jolla, California. Pregnancy Outcome in Women Treated with Phenobarbital Monotherapy.