West Virginia Chemical Spill: Prenatal Developmental Toxicity Evaluation December 2014 NTP Update

Synopsis

The National Toxicology Program (NTP)[1] is conducting studies in which 4-methylcyclohexanemethanol (MCHM), the primary chemical involved in the Elk River spill, is being given to pregnant rats to study the effects on prenatal development of their offspring. This evaluation will occur in two parts. The first is a small study to identify a range of doses of the chemical to use in the main study, and this is then followed by the main prenatal toxicity study. For the first study, MCHM was administered orally to pregnant female rats at doses of 0, 150, 300, 600, and 900 mg/kg body weight/day[2]. The dams (mothers) and offspring were evaluated for a number of endpoints to estimate doses for use in the main study that would result in minimal maternal toxicity and yet provide an adequate challenge to reveal specific effects on the offspring, should they occur. Maternal toxicity was observed in the first study in dams receiving MCHM doses of 600 mg/kg/day or higher. Offspring of dams receiving lower doses showed decreased fetal weight. No other effects on the development of the offspring were observed. The main prenatal toxicity study is underway and results will be reported in subsequent updates.

Background

The chemical 4-methylcyclohexanemethanol (MCHM), used to clean coal, was among the chemicals leaked from storage containers into the Elk River in West Virginia, resulting in potential exposure to residents of the area. One concern for acute exposures is the effect on the developing embryo and fetus. Pregnant women in the Charleston area were potentially exposed to MCHM, for which toxicity data during pregnancy are lacking. Therefore, NTP is conducting a prenatal developmental toxicity study in rodents to evaluate effects of MCHM on embryo and fetal development. This study will evaluate potential effects to the dam (mother) and the developing embryo and fetus after exposure to MCHM during pregnancy.

Range-Finding Prenatal Developmental Toxicity Study

To ensure that the dams receive sufficient doses of MCHM in the prenatal toxicity study, a range-finding study was conducted. This study identified the dose that would be expected to result in minimal maternal toxicity. MCHM was mixed in corn oil vehicle and dose levels of 0 (controls), 150, 300, 600, and 900 mg/kg/day of MCHM were administered via oral gavage to pregnant female Harlan Sprague Dawley rats (n=10 per group) from gestational day (GD) 6 to GD 20. A number of endpoints were evaluated in dams and offspring.[3]

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[1] NTP is a federal, interagency program whose goal is to safeguard the public by identifying substances in the environment that may affect human health. NTP is headquartered at the National Institute of Environmental Health Sciences, which is part of the National Institutes of Health. For more information about NTP and its programs, visit http://ntp.niehs.nih.gov/

[2] The drinking water advisory level set by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry for MCHM is 1 part per million (ppm). For comparison to the doses used in these animal studies, a 70 kg (154 lbs) adult drinking 2 liters of water per day containing 1 ppm MCHM would be exposed to a dose of 0.028 mg/kg/day.

[3] Endpoints evaluated in maternal animals were survival, clinical observations, body weights, food consumption, gravid uterus weight, and postmortem observations on GD 21 (gross visceral examination, corpora lutea, implants, and embryo/fetal mortality). Endpoints evaluated in offspring were fetal sex, weight, external abnormalities, and placental appearance.

Because dams given the top dose of 900 mg/kg/day showed overt clinical signs of toxicity, that group was terminated early. Three dams in the 600 mg/kg/day group were also terminated early for the same reason. The remaining animals in the 600 mg/kg/day group showed decreased fetal weight and increased numbers of dead fetuses and resorptions (post-implantation pregnancy loss). The 300 mg/kg/day group showed decreased fetal weight, and the 150 mg/kg/day group showed slight fetal weight changes. No dose groups showed any increase in gross external fetal malformations.

The results from this range-finding study indicate that the increased post-implantation pregnancy loss occurred at doses that induced significant maternal toxicity. Such significant maternal toxicity from chemical exposure often results in embryo-fetal toxicity, and effects on the fetus in these situations are usually considered non-specific, and secondary to maternal toxicity. Maternal toxicity in this study occurred at generally similar doses as reported in a 28-day toxicity study by the Eastman Kodak Company,[4] which was the basis for the drinking water advisory level of 1 part per million set by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry.

Main Prenatal Developmental Toxicity Study

The objective of the main prenatal toxicity study is to evaluate potential maternal and embryo-fetal toxicity over an optimal dose range. The data from the range-finding study provided preliminary information on maternal and prenatal developmental toxicity for MCHM and guided the design of the main prenatal toxicity study; doses of 0, 50, 100, 200, and 400 mg/kg/day (in corn oil vehicle) will be administered to Harlan Sprague Dawley rats (n=20 per group) via oral gavage. The top dose of 400 mg/kg/day is expected to induce minimal maternal toxicity. Fetuses will be examined in more detail than in the first study. In addition to the endpoints listed above, they will also be evaluated for skeletal and visceral abnormalities. Additional maternal examinations will include histopathology evaluation of the kidneys, clinical chemistry, and hematology. Collectively, these data will provide more complete information regarding MCHM effects on the dam and developing embryo and fetus.

Next Steps

The main prenatal developmental toxicity study is underway and findings will be reported in subsequent updates.

[4] http://www.eastman.com/Literature_Center/Misc/Pure_Distilled_MCHM-28-day_Oral_Feeding_Study.pdf