# West Virginia Chemical Spill: Prenatal Developmental Toxicity Study
# June 2015 NTP Update

**Synopsis**
The National Toxicology Program (NTP)[1] evaluated the potential maternal and prenatal toxicity of MCHM, the primary chemical spilled into the West Virginia Elk River. This update is a follow-up to the December 2014 NTP Update,[2] which reported the results of a preliminary study used to design this more comprehensive main study. The main study evaluated the effects of MCHM on maternal health and embryo and fetal development in rats following oral administration of MCHM at doses of 50, 100, 200, and 400 mg/kg/day. NTP found that MCHM decreased fetal weight and induced malformations in fetuses in the highest dose group of 400 mg/kg/day. A small decrease in fetal weight was observed in the 200 mg/kg/day dose group, which is similar to the small decrease in fetal weight observed in the 150 mg/kg/day dose group of the preliminary study.

**Prenatal Developmental Toxicity Study**

***Background***
The prenatal developmental toxicity study in rats is frequently used to identify potential toxicity during embyro and fetal development. Pregnant rats are exposed to the chemical from gestation day 6 to gestation day 20, which covers the time period following implantation of the rat embryo in the uterine lining to the development of the rat fetus just prior to birth. During the exposure period, potential toxicity to the pregnant rat is assessed. Following the exposure period, maternal health and fetuses are evaluated (Table 1). This includes an examination of the fetus externally for potential adverse effects (changes in structure or appearance) on internal organs and the developing skeleton. Many fetuses (typically 200-300 per dose group) are examined in order to detect subtle or rare changes, which may include malformations or indications of delayed growth.

***MCHM Study***
MCHM was administered at dose levels of 0 (controls), 50, 100, 200, and 400 mg/kg/day (in corn oil vehicle) to pregnant Harlan Sprague Dawley rats via oral gavage from gestation day 6 to gestation day 20. Dams (mothers) and fetuses were evaluated for a number of endpoints to identify any potential effects of MCHM (Table 1).

At these dose levels, exposure to MCHM had no effect on maternal or fetal survival, and minimal effects were observed in maternal clinical pathology. The magnitude of these responses was small and not considered to adversely impact the health of the pregnant rat or the fetuses. Fetal weight was decreased significantly by 15 percent at 400 mg/kg/day, and a small decrease in fetal weight was observed in the 200 mg/kg/day dose group, which is consistent with the decrease in the 150 mg/kg/day dose group of the preliminary study.

There were also increases in specific malformations in the 400 mg/kg/day group. The malformations included extra ribs in the lumbar and cervical region of the fetus and decreased fusion of cartilage to the sternum. Although not considered a malformation, increases in unossified (non-mineralized bone) or

[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] http://ntp.niehs.nih.gov/ntp/research/areas/wvspill/ntp_wv_prenatal_dec2014_508.pdf

incomplete ossification (partially mineralized bone) of the sternebrae (bones of the sternum) and vertebrae were observed in fetuses in the 400 mg/kg/day dose group. These effects on ossification are consistent with the decreased fetal weight, indicating delayed fetal growth.

Taken together, these results show MCHM is a developmental toxicant in the absence of significant maternal toxicity and indicate that the developing fetus is more sensitive than the dam to MCHM exposure. The finding that MCHM is toxic to the developing rat fetus does not establish that it would cause similar effects in humans. Many factors determine whether toxicity in animal studies translate to similar effects in humans, such as the amount and duration of exposure, differences in how the human body handles the chemical compared to other species, and whether the biological basis for the effect is similar between different species and humans.

Table 1. Endpoints Evaluated in Rat Prenatal Developmental Toxicity Study

| **Maternal Endpoints Evaluated** | |
|---|---|
| **Endpoint** | **Evidence of an adverse effect** |
| Survival | Animal dies or becomes moribund (sick) |
| Clinical observations | Unusual behaviors exhibited |
| Weight | Decreased weight during pregnancy is observed |
| Gross observations | Lesions are observed during necropsy examination |
| Clinical pathology | Changes in circulating proteins or cells indicating organ or tissue toxicity |
| | |
| **Fetal Endpoints Evaluated** | |
| **Endpoint** | **Evidence of an adverse effect** |
| Survival | Presence of reabsorptions or dead fetuses within the uterus |
| Weight | Decrease in fetal weight |
| Placental exam | Changes in structure or appearance of the placenta |
| External exam | Changes in external structure or appearance of the placenta |
| Visceral exam | Changes in structure or appearance of internal organs |
| Skeletal exam | Changes in skeletal structure or appearance |

**Next Steps**

The studies to evaluate whether MCHM can cause prenatal developmental toxicity using the well accepted rat model are complete. NTP will consider the findings from these studies in any future, overall assessment of the spilled chemicals.