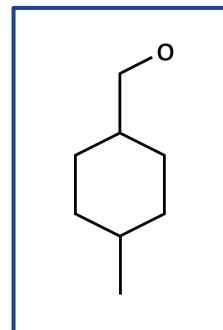


## SUMMARY

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**Background:** 4-Methylcyclohexanemethanol (MCHM) is a clear colorless oil that is produced as a mixture with other compounds and used to reduce impurities in mined coal. MCHM is often sold as a crude mixture, which can contain 68% to 89% MCHM with additional components. A significant spill in 2014 leaked a 75% mixture of MCHM into West Virginia's Elk River, upstream of the intake of an Elk River water treatment plant. Concerns about MCHM toxicity led to a federal advisory to limit the compound to 1 part per million (ppm) in drinking water and to nominate it to NTP for a toxicity evaluation. Studies were conducted in female mice to assess potential skin irritation and dermal hypersensitivity (i.e., itching with bumps or hives) from exposure to MCHM and crude MCHM.



**Methods:** MCHM (2%, 20%, and 100%) and crude MCHM (1%, 2%, 5%, 20%, 40%, and 100%) formulations were applied to the ears of groups of five female mice for 3 consecutive days. Control animals were treated with a neutral agent (acetone/olive oil), an agent that causes a strong allergic reaction (1-fluoro-2,4-dinitrobenzene), or an agent that causes a weak allergic reaction (isoeugenol). Because two mice administered 100% MCHM had to be euthanized on day 1 of the study due to toxicity, the highest dose for MCHM was lowered to 50% (100/50% group) for days 2 and 3. In addition, due to the toxic effects observed in mice administered 100% crude MCHM, the highest dose for that chemical was lowered to 80% (100/80% group) on days 2 and 3. A repeat study of crude MCHM at formulations of 1%, 5%, 25%, 50%, and 75% was performed on groups of 13 female mice to confirm the observed dermal response in the absence of toxic effects. The potential for skin irritation was assessed by measuring changes in ear thickness (swelling) following application of MCHM or crude MCHM. Dermal hypersensitivity was evaluated by collecting the lymph nodes near the ear of each mouse and measuring cell proliferation (the immune system response to the chemical exposure).

**Results:** All mice survived until the end of the studies except for the two that were euthanized on day 1 after administration of 100% MCHM. Eye squinting, lowered activity levels, and/or isolation from cage mates were observed in mice administered 100/50% MCHM, 100/80% crude MCHM, and 50% or 75% crude MCHM in the repeat study. Increased ear swelling occurred in the 20% and 100/50% MCHM groups and in the 75% crude MCHM group in the repeat study. Mice administered 5% crude MCHM or greater had increased lymph node cell proliferation.

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**Conclusions:** MCHM induced dermal irritation in female mice, as indicated by increases in ear swelling at concentrations of 20% and 100/50%. Crude MCHM was identified as a skin sensitizer because of the stimulation of the immune response in the mice lymph nodes.

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