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Toxicological and toxicogenomic responses in male and female F344 rats following 28-days repeated dose sub-acute dietary exposure to 2-monochloro-1,3-propanediol (2-MCPD)

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Introduction: Monochloropropanediols (MCPDs) are a class of chemicals that are generated as a result of high temperature processing of vegetable oils and foods that contain such refined oils. The toxicology of 3-MCPD is well-understood and is classified as a 'possible human carcinogen' (IARC Group 2B); however, there is insufficient data to characterize the toxicity of 2-MCPD, a related compound.

Objective: This study was conducted to fill a regulatory data gap in identifying the mode of action of dietary 2-MCPD in tissues of F344 rats exposed for 28 days according to the Organization of Economic Cooperation and Development (OECD) test guideline-407 using both apical and toxicogenomic endpoints.

Methodology: Weanling male and female F344 rats (n=10 rats/group/sex) were fed *ad libitum* AIN-93G diets containing 2-MCPD to provide estimated daily doses of 25, 50, 100 or 200 mg/kg body weight (BW). Rats were killed 28 days (unless found moribund) after exposure and their tissues processed for endpoint analyses.

Findings: Within the first week of exposure, female rats in the 100 and 200 mg/kg BW dose groups of 2-MCPD became moribund and were euthanized. Male rats were spared from exposure to these high doses and these groups were excluded from the study. Non-cancerous lesions with minimal to moderate scores were observed specifically in the kidney and spleen (50 mg/kg BW in males), heart (50 mg/kg BW in females) and thyroid (25 and 50 mg/kg BW in males and 50 mg/kg BW in females). Weights of kidneys in both sexes were significantly higher in the 2-MCPD groups along with higher levels of creatine kinase and lower levels of blood urea nitrogen. Heart weights were significantly higher in the 50 mg/kg BW groups in both sexes. Additionally, we observed significantly lower ALT and AST in males at both 25 and 50 mg/kg BW 2-MCPD, together with lower levels of high-density lipoproteins and cholesterol at 50 mg/kg BW 2-MCPD in both sexes. Genomic data indicated that in treated kidneys, 2-MCPD significantly increased *Hmox1* and *Ptgs2* genes, both involved intrinsically in inflammation. Several pathways were targeted in the heart as a consequence of 2-MCPD exposure such as angiogenesis, metabolic regulation and cell migration. The liver tissue only showed limited changes in the battery of genes tested.

Conclusion: For 2-MCPD (a) at the lowest tested dose of 25 mg/kg BW, treatment-related changes were notable in the kidneys and thyroid, (b) sex-specific changes in certain biochemical and hematological parameters were apparent, (c) pathological changes were observed in the kidney, heart, and thyroid, and (d) a no-observed-effect level (NOEL) was not reached in this study. Genomic analysis of the three tissues identified differential expression of key genes in the kidney and heart of animals treated with 2-MCPD.

Significance: This detailed sub-acute dietary exposure study provides toxicology and toxicogenomic data to support the hazard characterization of food-borne 2-MCPD for regulatory purposes; however, the lack of a NOEL provides impetus to further study 2-MCPD exposure.

Biography

Jayadev Raju completed his MSc and PhD in Life Sciences from Jawaharlal Nehru University, New Delhi, India. He received his Post-doctoral training and research expertise in Nutrition and Cancer at the University of Manitoba, Winnipeg Canada; the American Health Foundation Cancer Centre, Valhalla, New York, USA; the German Cancer Research Centre in Heidelberg, Germany; and University of Waterloo, Waterloo, Ontario, Canada. He is currently a Research Scientist in the Federal Food Regulatory Setting (Bureau of Chemical Safety, Health Canada). He provides toxicological research expertise related to carcinogenesis and co-carcinogenesis of foods and food constituents, including those that are classified as additives, contaminants, process-induced compounds and packaging material-migrating chemicals. The main goal of his research is to provide hazard characterization of food-borne chemicals, using both conventional OECD testing guidelines and models of diseases (specifically cancer), for supporting regulatory chemical risk management processes. He is also interested in the biology of precancerous lesions of the colon and their use as a surrogate biomarker in evaluating foods and drugs. He is a recipient of the V E Henderson Award (Society of Toxicology of Canada; 2010) and the International ToxScholar Outreach Award (Society of Toxicology, USA; 2016).

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