DEBORAH POPE, CONNOR TYREE, CHRISTOPHER RACINE, DIANNE K. ANESTIS, and GARY O. RANKIN, Department of Pharmacology, Physiology, and Toxicology, Marshall University, Huntington, WV, 25755. **In vitro nephrotoxicity induced by 2,4,5- and 2,4,6-trichloronitrobenzenes.**

Chloronitrobenzenes are key chemical intermediates used in the manufacture of dyes, agricultural agents and industrial compounds. Although some data exists on the toxicity of mono- and dichloronitrobenzenes, there is a paucity of data on the toxicity profile of trichloronitrobenzenes (TCNBs). One of the target organs for mono- and dichloronitrobenzenes is the kidney. The purpose of this study was to examine the in vitro nephrotoxic potential of two TCNBs, 2,4,5-trichloronitrobenzene (2,4,5-TCNB) and 2,4,6- trichloronitrobenzene (2,4,6-TCNB), using freshly isolated rat renal cortical cells (IRCC), and to study potential mechanisms of bioactivation and toxicity. Briefly, IRCC were obtained from male Fischer 344 rats using a collagenase perfusion technique and incubated (~4 million cells/ml, 3 ml) with a TCNB (0.5 or 1.0 mM) or vehicle (dimethyl sulfoxide) for up to 90 min. In some experiments, cells were pretreated with an antioxidant (ascorbate, alpha-tocopherol, glutathione, N-acetyl-L-cysteine) or metabolizing enzyme inhibitor prior to a TCNB or vehicle treatment. Cytotoxicity was determined by measuring lactate dehydrogenase release. 2,4,6-TCNB induced cytotoxicity as early as 60 min and at 0.5 mM, while 2,4,5-TCNB did not induce cytotoxicity until 90 min at 1.0 mM. Antioxidant pretreatments were effective in reducing the toxicity induced by both TCNBS but were more effective against 2,4,5-TCNB. Cyclooxygenase inhibition reduced 2,4,6-TCNB, but not 2,4,5-TCNB, cytotoxicity, while inhibition of cytochrome P450, flavin monooxygenase and peroxidase activity were not protective. These results suggest 2,4,6-TCNB is more nephrotoxic than 2,4,5-TCNB and that free radicals contribute to TCNB nephrotoxicity in vitro.

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