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"Involvement of metabolic reactive intermediate Cr (IV) in Chromium (VI) cytotoxic effects "

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### Abstract:

Addition of Cr VI (dichromate) to isolated rat hepatocytes results in rapid glutathione oxidation, reactive oxygen species (ROS) formation, lipid peroxidation, decreased mitochondrial membrane potential and lysosomal membrane rupture before hepatocyte lysis occurred. Cytotoxicity was prevented by ROS scavengers, antioxidants, and glutamine (ATP generator). Hepatocyte dichlorofluorescein oxidation to dichlorofluorescein (DCF) to determine ROS formation was inhibited by mannitol (a hydroxyl radical scavenger) or butylated hydroxyanisole and butylated hydroxytoluene (antioxidants). The Cr VI reductive mechanism required for toxicity is not known. Cytochrome P450 inhibitors, Particularly CYP 2E1 inhibitors, but not inhibitors of DT diaphorase or glutathione reductase also prevented cytotoxicity. This suggests that P450 reductase and/or reduced cytochrome P450 contributes to Cr VI reduction to Cr IV. Glutathione depleted hepatocytes were resistant to Cr (VI) toxicity and much less dichlorofluorescein oxidation occurred. Reduction of dichromate by glutathione or cysteine in vitro was also accompanied by oxygen uptake and was inhibited by Mn II (a Cr IV reductant). Cr VI induced cytotoxicity and ROS formation was also inhibited by Mn II, which suggests that, Cr IV and Cr IV GSH mediate "ROS" formation in isolated hepatocytes. In conclusion Cr VI cytotoxicity is associated with mitochondrial/lysosomal toxicity by the metabolic reactive intermediate Cr IV and "ROS".

### Keywords:

Chromium , Hepatocytes , Reactive intermediate

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