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Hepatic cytochrome P450 enzymes do not play a role in the nasal toxicity induced by the herbicide 2,6-dichlorobenzonitrile in mice

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The herbicide 2,6-dichlorobenzonitrile (DCBN) is one of the most potent toxic chemicals for the nasal tissues, especially the olfactory mucosa (OM). This toxicity of DCBN requires metabolic activation by cytochrome P450 (P450) enzymes. Previous *in vitro* studies indicated that P450 enzymes in the OM have much higher activities than those of the liver or other tissues in DCBN metabolism. In this study, we utilized a knockout mouse model, named liver-Cpr-null (LCN) mouse, to determine whether hepatic P450 enzymes play any role in DCBN toxicity. In LCN mouse, the gene encoding P450 reductase (Cpr) is specifically deleted in the liver, resulting in the ablation of liver P450 activities. We first compared DCBN toxicokinetics in the LCN and wild-type mice, to which DCBN was injected intraperitoneally at 50 mg/kg. We found that DCBN clearance was significantly decreased in the LCN mice, compared to the wild type littermate, as reflected in the following parameters: the area under plasma concentration-time curve ($626 \pm 187 \mu\text{g/ml}\cdot\text{h}$ vs. $120 \pm 14 \mu\text{g/ml}\cdot\text{h}$), clearance ($0.035 \pm 0.010 \text{ ml/min}$ vs. $0.18 \pm 0.02 \text{ ml/min}$) and the elimination half life ($69 \pm 13 \text{ h}$ vs. $9.0 \pm 1.6 \text{ h}$). Histopathological examination showed that the extent of DCBN-induced tissue damage to the OM did not differ between the two mouse strains, demonstrating that the loss of liver P450 activities in the LCN mice did not protect the animals against DCBN toxicity. Our findings indicate that hepatic P450-catalyzed DCBN metabolism is important for systemic elimination, but not for nasal toxicity, of DCBN.