Exposure to Sub-Parts per Million Levels of Vinyl Chloride Can Increase the Risk of Developing Liver Injury

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Vinyl chloride is a manufactured substance that is used to make polyvinyl chloride (PVC) plastic products, such as pipes, wire coatings, packaging materials, and cigarette filters. Because vinyl chloride usually exists in a gaseous state, the most common way of taking vinyl chloride into the human body is inhalation. People who work at or near a facility that manufactures vinyl chloride and PVC products, hazardous waste sites, and landfills can therefore be exposed to vinyl chloride. Studies of humans and animals have indicated that exposure to high amounts of vinyl chloride increased risks of developing several types of cancer, including liver cancer, brain cancer, and lung cancer,[1,2] and as a consequence, vinyl chloride has been recognized as a carcinogen and ranked fourth on the Substance Priority List prepared by the Agency for Toxic Substances and Disease Registry.[3] Currently, the Occupational Safety and Health Administration (OSHA) regulates levels of vinyl chloride in the workplace to no greater than 1 ppm averaged over any 8-hour period. Although trace levels of vinyl chloride can be detected in various environmental matrices, such as drinking water, groundwater, and cigarette smoke,[4] the impact of chronic exposure to sub-ppm levels of vinyl chloride is still largely unknown.

Steatosis, inflammation, fibrosis, and necrosis, in addition to cancer, have been associated with exposure to high levels of vinyl chloride. In this issue of *Hepatology Communications*, Lang et al.[5] used a mouse model to investigate the effect of vinyl chloride at levels below the OSHA limit on the susceptibility to liver injury. Six-week-old mice were fed either a low-fat diet (LFD) or high-fat diet (HFD) for 12 weeks with and without inhalation of 0.85 ppm vinyl chloride for 6 hours per day, 5 days per week. The vinyl chloride exposure had a significant impact in the HFD-fed group, enhancing liver damage, neutrophil infiltration, apoptosis, oxidative stress, and endoplasmic reticulum stress, indicating that diet-induced obesity or the HFD itself sensitizes the liver for injury induced by sub-ppm levels of vinyl chloride. However, the most interesting observation in the study was that the sub-ppm levels of vinyl chloride dramatically dysregulated metabolic homeostasis and impaired mitochondrial function even in the LFD-fed mice. These findings indicate that exposure to sub-ppm levels of vinyl chloride can sensitize the liver to stressors and potentially lead to the onset of liver injury, including steatohepatitis, in both LFD- and HFD-fed animals. In fact, workers handling vinyl chloride have a greater risk of developing liver disease. Therefore, the risk of developing various types of liver disease in humans, such as nonalcoholic fatty liver disease, might be lowered by minimizing the potential exposure to even a sub-OSHA level of vinyl chloride.

In the liver, vinyl chloride is primarily metabolized to chloroethylene oxide by cytochrome P450 (CYP) 2E1.[6] The metabolite spontaneously undergoes rearrangement to chloroacetaldehyde or is metabolized to

Abbreviations: CYP, cytochrome P450; HFD, high-fat diet; LFD, low-fat diet; OSHA, Occupational Safety and Health Administration; PVC, polyvinyl chloride.

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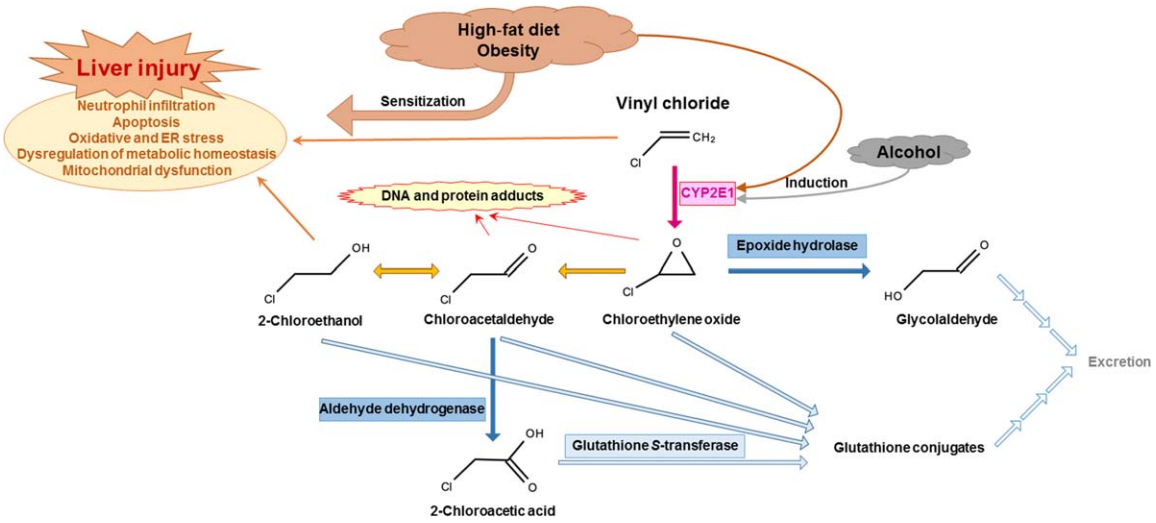

FIG. 1. Metabolic pathway of vinyl chloride and the impact on toxicity. Vinyl chloride is primarily metabolized to chloroethylene oxide by hepatic CYP2E1. The active metabolite undergoes rearrangement to chloroacetaldehyde or is metabolized to glycolaldehyde by epoxide hydrolase. Chloroacetaldehyde can be further converted to 2-chloroethanol or metabolized to 2-chloroacetic acid by aldehyde dehydrogenase. Glycolaldehyde as well as glutathione conjugates of chloroethylene oxide, chloroacetaldehyde, 2-chloroethanol, and 2-chloroacetic acid are inactive metabolites. Chloroethylene oxide and chloroacetaldehyde are the reactive intermediate metabolites, and their formation of DNA and protein adducts is closely related to the carcinogenic property of vinyl chloride. In addition to vinyl chloride, 2-chloroethanol is involved in the enhanced susceptibility to liver injury by dysregulating glucose metabolism and inducing mitochondrial damage. Diet-induced obesity or a high-fat diet can sensitize the liver for injury induced by sub-ppm levels of vinyl chloride. Alcohol and a high-fat diet also enhance susceptibility to liver injury by inducing CYP2E1. Abbreviation: ER, endoplasmic reticulum.

glycolaldehyde by epoxide hydrolase. Chloroacetaldehyde can be further converted to 2-chloroethanol or metabolized to 2-chloroacetic acid by aldehyde dehydrogenase.[7] Glycolaldehyde and 2-chloroacetic acid as well as glutathione conjugates of chloroethylene oxide, chloroacetaldehyde, and 2-chloroethanol are inactive metabolites and are immediately excreted from the body (Fig. 1). While chloroethylene oxide and chloroacetaldehyde are the reactive intermediate metabolites and their formation of DNA and protein adducts is closely related to the carcinogenic property of vinyl chloride,[8,9] 2-chloroethanol is involved in the enhanced susceptibility to liver injury by dysregulating glucose metabolism and inducing mitochondrial damage.[10] It is therefore reasonable to speculate that increased CYP2E1 activity and/or decreased activities of the vinyl chloride-detoxifying glutathione transferase, epoxide hydrolase, and aldehyde dehydrogenase increase the risk of developing vinyl chloride-associated liver injury. Alcohol and an HFD induce CYP2E1 activity, and genetic polymorphisms can result in dramatically reduced enzyme activity. Accordingly, individuals who consume alcohol and a diet high in fat or who possess genetic polymorphisms on glutathione S-transferase, epoxide hydrolase, or aldehyde dehydrogenase might have a higher risk of developing vinyl chloride-associated liver injury.

If the data presented in this issue of *Hepatology Communications*[5] is translatable to humans, the current OSHA regulations on vinyl chloride exposure should be modified. Additionally, concentrations of vinyl chloride in drinking water and groundwater in locations near vinyl chloride and PVC product-manufacturing facilities and hazardous waste sites should be properly monitored. Importantly, drinking water in contact with PVC pipes can contain vinyl chloride. Development of cigarette and tobacco filters that do not produce vinyl chloride might also become in high demand.

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