TOX IMPACT STATEMENT

Toxicant-Associated Liver Injury: Vinyl Chloride

Approved by SOT Council, May 2018

The Problem

The recognition of hemangiosarcoma in plastics workers in a Louisville, Kentucky, industrial area known as "Rubbertown" became one of the most important sentinel events in the history of occupational medicine and led to the worldwide recognition of vinyl chloride (VC) as a carcinogen. The initial report of VC-related liver toxicity occurred in 1974, when John L. Creech, MD, and Maurice N. Johnson, MD, described the occurrence of the unusual liver tumor, hemangiosarcoma, in three workers at a single B.F. Goodrich chemical plant in Rubbertown, where they also were employed. Although initial concerns regarding VC exposure related to hepatic hemangiosarcoma, hepatocellular carcinoma has become a more recent issue. Several new cases of hemangiosarcoma have appeared in Louisville's cohort of Rubbertown workers, which illustrates the importance of studying the mechanisms by which VC causes liver damage and its persistent effects. In addition to carcinogenesis, VC exposure has been shown to cause steatosis and toxicant-associated steatohepatitis (TASH) with fibrosis, necrosis, and cirrhosis. It is likely that VC-induced TASH has existed for decades in parallel with hepatic cancer, but was missed by prior investigators. Clearly, the exposure to and the impact of VC is an ongoing issue for toxicology and risk assessment.

Role of Toxicology

In humans, the hallmark of VC-induced liver injury is the paradoxical combination of normal liver enzymes and the presence of steatosis and necrotic cell death. However, the detailed mechanisms for VC-induced liver disease are largely unknown. Most VC studies have focused on liver cancer rather than non-malignant liver disease.

The direct hepatotoxicity of VC exposure has been established, but requires relatively high occupational exposure. Current safety restrictions lessen the risks of high exposures, but exposures to lower environmental concentrations, which are not overtly hepatotoxic, persist. In contrast, little is known about the potential impact of these exposure levels on hepatic health, especially in the context of the ever-increasing burden of underlying liver disease. Recent work has demonstrated that VC exposure below the US Occupational Safety and Health Administration limit exacerbated experimental liver disease caused by a high-fat diet, which models non-alcoholic fatty liver disease (NAFLD) in humans. This previously unidentified

interaction between VC and underlying fatty liver diseases raises the concern that the current knowledge base may underestimate risk.

Public Health Impact

Vinyl chloride is a volatile organic compound (VOC) used in industry to create the polymer polyvinyl chloride (PVC), and its production was recently estimated at 27 million metric tons annually. VC has been identified as a solvent degradation product at many US Environmental Protection Agency (US EPA) Superfund program sites. It is present in landfill leachates and in the groundwater near military installations, such as Camp Lejeune, North Carolina, and others, where it exists as a microbial metabolite of other VOCs, such as trichloroethylene and perchloroethylene. VOCs also are present in natural gas hydraulic fracturing fluids that leak into groundwater wells in close proximity to drilling operations. Another significant source of exposure is in the chemical industry. To date, tens of thousands of American chemical workers and up to one million people (military/civilian personnel and their families) at Camp Lejeune alone have been exposed to VC. VOCs also are found in significant concentrations in the ambient air surrounding manufacturing complexes.

However, the main environmental exposure risk stems from contaminated groundwater in areas surrounding production and Superfund sites. The fact that VOCs may be used in fracking procedures in the United States is also a concern for groundwater exposure. VC readily volatilizes in homes located above contaminated groundwater. VC can migrate through soil and foundations or volatilize from water sources, such as showers, to enter basements or living spaces where these vapors then recirculate.

Owing to its widespread presence in US EPA Superfund sites and its known potential human risk, VC is ranked fourth on the US Centers for Disease Control Agency for Toxic Substances and Disease Registry Hazardous Substance Priority List. However, until recently, investigators missed liver injury caused by VC or dismissed its importance because routine liver chemistries are normal during this disease. Therefore, even intense occupational surveillance programs as mandated by the Vinyl Chloride Standard (29 CFR 1910.1017) will not detect this disease. Review of the clinical literature demonstrates that hepatic steatosis with normal liver enzymes may actually be one of the most common forms of chemical hepatotoxicity.

References and Resources

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