Letter to the Editor**Vinyl Institute Comments on Cicalese et al.:
“An Ecological Study of the Association
between Air Pollution and Hepatocellular
Carcinoma Incidence in Texas”**

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Dear Editor

Cicalese et al. [1] improperly draw conclusions regarding suggested cause and effect from the associations described by the data in their study. The authors derive effects from estimates of ambient vinyl chloride monomer (VCM) that describe only associations based on inconsistent data. A link between VCM and liver cancer cannot be demonstrated nor assumed from the data in the study.

The authors used 4 sets of National Air Toxics Assessment (NATA) data for the chemicals obtained from the years 1996, 1999, 2002, and 2005 but fail to explain its limitations for ground level concentrations (see <https://www.epa.gov/national-air-toxics-assessment/nata-limitations>). Those data were compared with hepatocellular carcinoma (HCC) rates from 2 time frames: 2000–2013 and 2006–2013. The latency period for angiosarcoma of the liver (ASL) and HCC is much longer than the 7- to 13-year duration used in the study (36–48 years) [2]. The time between measurement and observation periods for HCC is far too short. The authors do not support their time frames and latency rationales. Similarly, there is no information on the age of the population, residency period, or histological examinations of the livers to demonstrate typical changes of the liver caused by VCM. The authors neglected to match HCC rates with NATA Texas counties reporting VCM emissions from point sources, numbering 17 in 2002 and only 12 in 2005, which could skew the statistical analysis. No explanation is provided why their hypothesis would not apply to Washington, DC, listed as having the highest HCC rate (see Altekruse et al. [3], Table 4, liver cancer mortality rate per 100,000 people, 2006–2010).

The authors note that the results are inconsistent. Table 1 [1] indicates, for example, that VCM was found to have a statistically significant association with HCC using model 1 for data years 2002 and 2005 but not for data years 1996 and 1999. Model 2 indicated that VCM was associated with HCC for all 4 data years. Inconsistencies between models were also evident for arsenic, benzene, and butadiene.

The authors note that the highest NATA value for VCM was $0.01 \mu\text{g}/\text{m}^3$, and the screening threshold for VCM is $1.2 \mu\text{g}/\text{m}^3$. The United States Environmental Protection Agency (US EPA)'s carcinogenic inhalation unit risk estimate for VCM is $8.8 \times 10^{-6} (\mu\text{g}/\text{m}^3)^{-1}$ for lifetime exposure. The highest NATA concentration found in the study yields an insignificant lifetime risk of approximately 10^{-7} , one in 10 million. The no significant risk level (NSRL) adopted by California's Proposition 65 is 3 μg per day. Based on the EPA and Proposition 65 default daily inhalation rate of 20 m^3 per day, the ambient concentration that does not exceed the NSRL is $3 \mu\text{g}/\text{day} \div 20 \text{m}^3/\text{day} = 0.15 \mu\text{g}/\text{m}^3$. No available risk assessment suggests that an ambient level of VCM of $0.01 \mu\text{g}/\text{m}^3$ presents a risk of harm based on exposures over an average lifetime. In humans, the level

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of exposure to VCM must be >7,531 ppm-years to develop ASL [4]¹. Available information suggests that exposure to VCM must be 10-fold higher to develop HCC, far exceeding actual exposures. The evidence of risk of HCC from VCM exposure is based on a few and overlapping data [4–6]^{2,3}.

The authors provide limited qualifying statements regarding “the first analysis” and some inconsistencies in their data but did not take those restrictions into account when drawing conclusions. Rather than concluding that associations observed suggested possible links between volatile airborne contaminants and HCC, they instead dropped any qualification when singling out VCM exposure and HCC. Strangely, the associations in the logistic regression for VCM were strongest for the shortest latency period, which is inconsistent with established epidemiology [2]. Nor do the authors account for the most likely cause of increased occurrence – hepatitis C or B virus infection [7]⁴.

The authors knew the limitations of the study but then ignored those limitations when making conclusions. There were many inconsistencies in the regression analyses performed on the different chemical species. Specifically, some associations for each chemical species were significant with one regression method but not the second method. The authors did not explain why the 2 regression methods should not be consistent and provided no rationale for using gamma-regression without exploring other nonlinear approaches. A subsequent article by Cicalese et al. [8] does not include VCM among air pollutants associated with primary liver cancer in Texas.

Because of the inconsistent results and the inherent limited nature of associations derived from statistical relationships, it is inappropriate to attribute a significant association to VCM exposure and HCC incidence, and there is certainly no attributable cause and effect relationship.

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¹ The “role of inhalation exposure VC and HCC risk remains unclear” [4].

² “Apart from the known risk of ASL, workers exposed to vinyl chloride may experience an increased risk of hepatocellular carcinoma and soft-tissue sarcoma; however, these results may have been influenced by the underdiagnosis of true ASL” [5].

³ “The maximal overlap between these two analyses was four cases, since only four hepatocellular carcinomas from Italy were included in the multicentric cohort” [6].

⁴ “Most HCC is thought to be associated with either chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. In the United States, more than 3 million people are chronically infected with HCV” [7].