TCE, Designated a Known Carcinogen, Now the Focus of Ongoing Research

By Caroline McNeil

Late last year, the International Agency for Research on Cancer (IARC) determined that trichloroethylene (TCE) was carcinogenic to humans, upgrading it from a probable to a known carcinogen.

The U.S. Environmental Protection Agency recently came to the same conclusion. Its evaluation of TCE in 2011 concluded for the first time that TCE was “carcinogenic to humans by all routes of exposure.”

And a third key organization, the National Institutes of Health National Toxicology Program, is evaluating whether TCE should be upgraded from its 2000 designation, reasonably expected to be a human carcinogen, to known human carcinogen.

Coming after decades of study, the three actions could seem a collective milestone for the field. But viewing them as part of a process far from over may be more realistic.

“They are important steps, but steps on a continuum,” said Aaron Blair, Ph.D., a scientist emeritus at the National Cancer Institute, who chaired the IARC committee on TCE. They represent decades of research that established strong links between occupational exposures and kidney cancer and possible links to non-Hodgkin lymphoma (NHL) and liver and other cancers. But much more is left to learn.

Some questions that remain, Blair said, include its links to other cancers, its effects at lower exposures, and the role of gene—environment interactions.

TCE, now used mainly as metal degreaser, was once common in the dry-cleaning industry. TCE use has declined over the past two decades in Europe and the U.S. and has stopped in cosmetics, drugs, food processing, and pesticides. Nonetheless, it is “ubiquitous in atmosphere, soil, ground, surface and drinking water, and food,” according to the National Toxicology Program’s concept paper for TCE, released last August as part of the evaluation process. And its use may be rising in developing countries, according to a 2013 United Nations Environment Programme report.

Other Cancers?

So far, studies have conclusively linked only kidney cancer to TCE via occupational exposures. Other studies have suggested that workplace exposures increase the risk of liver cancer and NHL and, to a lesser extent, cervical and other cancers. But results for these studies have been inconsistent.

One approach to gain more data on other cancers is to pool results of smaller studies. In the June 30 issue of JNCI (June 1 online), Johnni Hansen, Ph.D., of the Danish Cancer Society Research Center in Copenhagen, and colleagues established a pooled cohort—participants from earlier, smaller studies—that included more than 5,500 workers with documented exposure to TCE. After 154,778 person-years of follow-up, the authors found statistically significantly higher rates of liver and cervical cancer, but not of kidney cancer or NHL.

The strong association with liver and cervical cancers and the weaker finding for kidney cancer is the reverse of what many other studies found. Coming so soon after
the reclassifications of TCE as a known carcinogen, these findings raise the question of whether they would have influenced the conclusions of IARC and EPA.

NCI’s Mark Purdue, Ph.D., dismisses that possibility, pointing out that the number in the pooled cohorts who developed these cancers was low—just 16 people for cervical cancer and 30–40 for each of kidney and liver cancer and NHL. “Given these observations, it is unlikely that these findings from Hansen et al. would have changed the conclusion of the IARC panel,” he writes in an accompanying editorial.

Another recent study, appearing online in Occupational and Environmental Medicine at the end of May, found a positive association between TCE and NHL. In this updated meta-analysis, NCI authors led by Sara Karami, Ph.D., linked TCE exposure to NHL but not four other hematopoietic or lymphoid cancers.

The role of genetic polymorphisms, particularly in the metabolism of TCE, is another active area of research. Variants of the GST gene have been of interest for some time. In a large case-control study in central Europe, published in 2010 in Cancer Research, workers exposed to TCE who had at least one intact GSTT1 allele were at increased risk for kidney cancer, but subjects with two deleted alleles were not. The authors, led by Lee E. Moore, Ph.D., of NCI, note that about 80% of white people have the GSTT1 allele, making the finding potentially important for public health.

This study also found that variants of another gene involved in TCE metabolism, CCBL1, were statistically significantly associated with risk of kidney cancer. Two other genes involved in TCE metabolism, CYP2E1 and PPAR-α, have been associated with liver cancer, as has a TCE metabolite, trichloroacetate.

**Lower Exposures**

Other research tacks indicate that low levels of TCE exposure may be linked to NHL and other cancers. One NCI cross-sectional study led by Qing Lan, M.D., Ph.D., has collected data on early biomarkers of toxic effects in healthy workers exposed to various levels of TCE in Guangdong Province, China. With collaborators at the University of California, Berkeley, the researchers are evaluating chromosomal aberrations, cytokine levels, mRNA expression, and other markers gathered from exposed workers and unexposed control subjects.

Analyses of the data are now beginning to appear. One study, led by Luoping Zhang, Ph.D., at UC Berkeley, found reduced levels of immunoglobulins G and M in exposed workers. The difference between subjects and controls was highly statistically significant—even after researchers controlled for age, smoking, and alcohol consumption—and at all exposures, including 12 parts per million.

“I think this is a major point,” Zhang said. “The permissible [Occupational Safety and Health Administration] level is 100 ppm. So even at much lower exposures, we saw a difference.” The lower immunoglobulin levels support previous findings of lowered B-cell counts and other signs of immunosuppression in workers exposed to TCE.

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Published in Carcinogenesis online in December 2012, the article adds to the data linking TCE to higher rates of NHL, characterized by changes in the immune system. The authors write that “prospective studies, measuring serum immunoglobulin levels before the diagnosis of NHL... would be particularly informative.” NCI evaluated the possibility of carrying out a nested case-control study of TCE exposure in several existing prospective cohorts in the general population in China, but decided to forgo plans at this time due to a number of technical challenges, said Dr. Lan, senior author on the paper.

Another analysis of the Guangdong data has shown that factory workers exposed to TCE had elevated urinary levels of kidney injury molecule 1, a biomarker of kidney damage, compared with control subjects, even at low levels. In this study, Roel Vermeulen, Ph.D., of Utrecht University in The Netherlands, with Zhang and others, concluded that a link between TCE and kidney cancer was biologically plausible. The study was published online in Carcinogenesis in June 2012.

The possibility that lower TCE exposures are carcinogenic raises the question of whether contaminated drinking water or other environmental exposures could increase risk in the general population. One study at Camp Lejeune, a Marine Corps base in North Carolina where TCE and other chemicals contaminated the drinking water supply for 30 years, is looking at the incidence of childhood leukemia and NHL, as well as certain birth defects, in children whose mothers lived at the base during pregnancy.

The EPA is also conducting a mortality study to determine whether a link exists between all causes of death and exposure to contaminated drinking water at Camp Lejeune, as well as another study focusing on male breast cancer among exposed personnel at the base.