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EVALUATING THE RISK TO WORKERS AND THE PUBLIC FROM STYRENE EXPOSURE

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Introduction

Styrene is used in the manufacture of a wide variety of products, including construction and packaging materials, tires and automotive parts, and household and office appliances. Annual production in the United States is approximately 10 billion pounds. Small quantities can be found in food and ambient air nearly everywhere. Larger exposures occur in the air inside some styrene-related manufacturing facilities. To evaluate the risk these exposures might pose to workers or the public, the Harvard Center for Risk Analysis (HCRA) convened a panel of scientists with expertise in epidemiology, toxicology, exposure assessment, and risk assessment in 1999.

The panel reviewed the extensive health literature on styrene and found that the epidemiological literature failed to demonstrate an association between styrene exposure and cancer. Data from laboratory animal experiments were ambiguous: styrene failed to cause cancer in rats at very high levels of exposure, but there was an association between styrene exposure and lung tumors in mice. Because the panel could not identify what makes mice more susceptible than rats to styrene-induced tumors, they could not rule out the possibility that styrene might also cause cancer in humans. Finally, the panel concluded that at occupational levels of exposure, styrene may have a subtle impact on color vision.

The Panel

In 1999, the Styrene Information and Research Center (SIRC) awarded HCRA a grant to convene a panel of independent experts to investigate styrene's potential health effects. The panel was chaired by Daniel Krewski, Director of the McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa. Other members of the panel were: Gary Carlson (School of Health Sciences at Purdue University), David Coggon (MRC Environmental Epidemiology Unit at the University of Southampton, UK), Elizabeth Delzell (Department of Epidemiology and International Health at the University of Alabama, Birmingham), Helmut Greim (GSF-

Institute of Toxicology, Neuerberg, Germany), Michele Medinsky, Richard Monson (Department of Epidemiology at the Harvard School of Public Health), Dennis Paustenbach (Exponent, Menlo Park, CA), Barbara Petersen (Novigen Sciences, Inc., Washington, DC), Stephen Rappaport (Department of Environmental Sciences and Engineering at the University of North Carolina, Chapel Hill), Lorenz Rhomberg (Gradient Corporation, Cambridge, MA), and P. Barry Ryan (Department of Environmental and Occupational Health, Rollins School of Public Health of Emory University). HCRA scientific staff included Gail Charnley (Health Risk Strategies, Washington, DC), Joshua Cohen, John Graham, and Kimberly Thompson.

HCRA selected the experts, compiled and disseminated the literature they studied, convened three meetings of the panel between October, 1999 and May, 2000, and wrote up the report of the panels findings. That report was published as a special issue of the Journal of Toxicology and Environmental Health in January, 2002. This issue of Risk in Perspective summarizes that work.

Findings

Exposure

Small amounts of styrene are present in air, food, water, consumer products, and waste materials. For the majority of the general public, inhalation is thought to be the most important route of exposure. Most airborne styrene exposure comes from industrial activities and motor vehicle exhaust, with typical ambient concentrations reaching around 1 part per billion (ppb). For smokers, the dominant source of inhaled styrene can be cigarettes, which can increase average exposures for these individuals to 6 ppb. The panel estimated that under a pessimistic set of conditions, individuals living near a large styrene manufacturing facility could be exposed to lifetime average ambient concentrations exceeding 200 ppb.

Dietary exposure can come from the naturally occurring styrene found in foods such as strawberries, beef, and spices. Federal regulations also permit low concentrations of styrene in food both as a direct additive and as an indirect additive due to migration from food packaging. Because of its rapid biodegradation, concentrations of styrene in drinking water are extremely low.

Occupational exposure to styrene has steadily declined over the years due to improved industrial hygiene and more stringent regulations, but it remains substantially higher than exposure to the general public. In the fiberglass-reinforced plastics segment of the styrene industry, where exposures are greatest, measurements indicate that airborne concentrations are now less than 20 parts per million (ppm). In other styrene industry segments, exposures are estimated to be 5 ppm or less.

The Consequences the Panel Considered

Cancer

The strongest evidence for styrene's potential to cause cancer via inhalation is its impact on the incidence of lung tumors in mice. In a recently published study, female mice exposed to between 20 and 160 ppm styrene, and male mice exposed to between 40 and 160 ppm styrene, had a lung tumor incidence statistically greater than the corresponding control group rates. In a very similar experiment conducted by the same

investigators, however, rats exposed to styrene concentrations as high as 1,000 ppm did not have an elevated incidence of tumors in the lung or at any other site.

Two studies have reported that rats exposed to inhaled styrene developed mammary tumors. However, the panel concluded that these reported associations are unlikely to be causal because:

- The dose-response relationship was not monotonically increasing in one of the studies that reported a positive finding.
- The control group mammary tumor incidence rate in the other positive study appeared to be depressed relative to past studies in the same lab.
- The two positive studies are inconsistent with a substantial number of other studies that have reported negative findings.

Administering large doses of the metabolic product styrene oxide to rats via stomach tubes has consistently resulted in cancer of the forestomach, but those findings are not considered to be relevant to humans because the most important route of exposure for humans is inhalation, and because metabolic detoxification of styrene oxide makes a substantial build-up of this metabolite in the stomach implausible.

Investigators have also conducted extensive studies of occupationally exposed populations to see if styrene might cause cancer in humans. Studies of workers in the reinforced plastics industry are thought to be the most informative because these workers are exposed to the highest level of styrene. While those studies did reveal an elevated incidence of respiratory tract cancer in general, and lung cancer in particular, for two reasons the panel concluded these associations were not caused by styrene exposure. First, the elevated incidence rates were limited to workers with only moderate levels of styrene exposure and did not appear to extend to the most heavily exposed workers. Second, workers with elevated lung cancer rates also had an elevated incidence of conditions thought to be associated with lifestyle factors (*e.g.*, cardiovascular disease).

Some studies have also shown that styrene workers have an elevated incidence of lymphatic and hematopoietic (LH) cancers. However, those studies are difficult to interpret because the number of such cancers is generally small and because of confounding by other industrial exposures that could cause cancer (*e.g.*, exposure to butadiene used in the production of styrene-butadiene rubber). Moreover, the data show no evidence of a monotonically increasing dose-response relationship. In particular, no elevation in LH cancers was observed among workers in the reinforced plastics industry where styrene exposures are highest.

The panel concluded that epidemiology studies to date do not provide clear evidence that styrene causes cancer. But they also noted that their statistical power is inadequate to rule out an elevation in cancer consistent with the magnitude of the risk implied by the mouse lung tumor data. That is, if the mouse lung tumor findings correctly characterize the amount by which styrene exposure increases the risk of cancer in humans, the effect may be too small to have shown up in even the best and largest epidemiology studies conducted to date.

Non-cancer:

Styrene exposures greater than 100 ppm have been shown to cause a variety of nervous system effects (e.g., nervous system depression, drowsiness, headaches, and disturbance of balance). However, at levels relevant to human exposure, the evidence of non-cancer effects is more limited. Some studies have reported that occupational styrene exposure can affect hearing. However, because those studies failed to control for exposure to noise, the panel did not find their results compelling. On the other hand, the panel did conclude that occupational exposure to styrene does have a subtle effect on color vision.

Other non-cancer effects that the panel considered included respiratory tract toxicity, immune system toxicity, reproductive toxicity, and developmental toxicity. While there is evidence in animals that styrene can cause these effects at sufficiently high levels of exposure, the panel could find no evidence that these effects occur in humans at relevant levels of exposure. Finally, the panel concluded that the current weight of the evidence does not suggest that styrene exhibits any hormonal activity.

Cancer Mode of Action

In order to better understand styrene's potential to cause cancer in humans, the panel reviewed evidence characterizing the molecular mechanisms by which it might act. First, the panel looked at whether styrene can directly damage DNA. If it can, then it can probably cause cancer in a wide range of species, including humans. Second, the panel investigated what it is about mice that makes them so much more susceptible than rats to the development of styrene-induced tumors. Even if styrene cannot cause cancer in a wide range of species, it might be able to cause cancer in humans if humans are more like mice than rats in terms of how our bodies process and eliminate styrene.

Regarding styrene's potential to cause genetic damage, the panel noted that although styrene does not appear to react with DNA, styrene oxide does bind to DNA molecules. The panel also concluded that styrene exposure increases the frequency of one type of chromosomal change (chromosomal aberrations). However, whether any of these changes can cause cancer is not clear. Styrene oxide causes mutations in isolated cells in a test tube, but the panel concluded that the evidence for styrene's mutagenicity in animals and humans is less definitive.

As to the susceptibility of mice to the development of lung tumors, the panel concluded that hyperplasia (organ enlargement due to rapid cell growth) plays a key role. In particular, it appears that styrene oxide injures mouse lung tissue. That damage in turn accelerates cell growth as the mouse lungs repair themselves, increasing the likelihood of DNA copying errors and mutations leading to cancer. While styrene exposure causes hyperplasia in mice, it does not do so in rats.

For two reasons, the panel was unable to definitively rule out the possibility that styrene might cause cancer in humans. First, even though hyperplasia is predominantly responsible for the development of lung tumors in mice, it is possible that genotoxicity might also contribute to these tumors, albeit to a much lesser extent. So even if hyperplasia does not occur in humans, it is still possible that styrene exposure could cause a low incidence of lung cancer (or other cancers) due to genotoxicity.

Second, it is not clear whether humans are susceptible to styrene-induced hyperplasia like mice, or resistant, like rats. Factors that contribute to the susceptibility of mice fall into two categories referred to as pharmacokinetics (the way in which the body distributes, metabolizes, and eliminates a substance) and pharmacodynamics (the extent to which the target tissue is sensitive to the active agent's effects). Some investigators have claimed that because of pharmacokinetic differences between mice and rats, rats exposed to styrene have much lower styrene oxide concentrations in their lungs than do mice, and humans might have even lower styrene oxide concentrations in their lungs than rats. So it would seem that if pharmacokinetic factors explain the difference in the susceptibility of mice and rats, they would also suggest humans are relatively immune to such tumors.

To test this hypothesis, the panel developed a physiologically based pharmacokinetic model to describe the toxicokinetics of styrene and styrene oxide in mice and rats. The panel model showed that the concentration of styrene oxide in the lungs of mice exposed to inhaled styrene is indeed higher than the corresponding concentrations in rats. However, the concentration of styrene oxide in the lungs of mice exposed to 40 ppm styrene (mice that did develop tumors) was lower than the corresponding concentration in rats exposed to 1,000 ppm styrene (rats that did not develop tumors). As a result, the panel concluded that pharmacodynamics must also play a role in the susceptibility of mice. Because it is not known whether humans share the pharmacodynamic characteristics of mice or rats, it is not clear whether humans would be susceptible to the development of styrene-induced cancer

After the panel completed its work, another group of investigators developed a more realistic pharmacokinetic model to describe how styrene is metabolized, distributed, and eliminated by mice, rats, and humans. That model indicates that the pharmacokinetic differences between rats and mice are larger than the panel model suggested, but the panel judged that the differences are still not large enough to explain the difference in susceptibility. Nor did the panel believe that the uncertainty in the newer model has been sufficiently addressed. In any case, however, even if humans are susceptible to the development of styrene-induced tumors, the new model indicates that they are likely to be substantially less susceptible than mice.

Risk Characterization

The panel concluded that evidence for styrene's carcinogenicity in humans is "suggestive," meaning that its carcinogenicity cannot be ruled out. To determine whether human exposure to styrene is high enough to warrant concern *if* styrene turns out to be carcinogenic, the panel estimated the "margin of exposure" (MOE) for several exposure scenarios. The MOE is the ratio of a "comparison exposure" to the level of actual exposure. The greater the MOE ratio, the less the potential concern. Depending on the nature of the health effect (its severity, whether it is reversible, *etc.*), MOE values above 100 may be considered satisfactory in an occupational setting. For the general public, MOE values above 1,000 may be considered satisfactory. The panel also computed MOE values for the non-cancer health effect that appears to occur at the lowest level of exposure, *i.e.*, subtle loss of color vision.

The comparison exposure is often taken to be the lowest exposure at which any adverse effect can be observed in a study. For cancer, the panel estimated the lowest dose in the mouse lung tumor experiment that could produce a statistically detectable elevation in the lung tumor incidence above background. When converted to its human equivalent, that dose corresponded to an atmospheric concentration of 2 to 20 ppm. For noncancer, the panel used the lowest exposure level at which color vision in workers was affected, which turned out to be 50 ppm.

Cancer MOE values for members of the general population were generally very large. The MOE for styrene in food ranged from 5,000 to 50,000. As shown in Table 1, the MOE values for general population ambient air exposure were also very large for the most part. The one exception is a pessimistic hypothetical scenario involving individuals living near a very large styrene manufacturing facility. Cancer MOE values for occupational settings ranged from 100 to 1,000 for workers not employed in the reinforced plastics segment of the styrene industry. For those workers, the MOE values ranged from 1 to 20.

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For the general population, noncancer MOE values were for the most part 1,000 or larger, depending on the specific exposure scenario. Once again, the hypothetical scenario involving individuals living in the vicinity of a large styrene plant yielded a much lower MOE value of 20. Occupational exposures in industry segments other than reinforced plastics ranged from 14 to 250. Within the reinforced plastics industry segment, the MOE value was 1.5.

Conclusion

The panel concluded that styrene's carcinogenicity in humans cannot be ruled out at this time. However, styrene exposure levels among the general population and among most workers are for the most part very low. In addition, even if styrene is carcinogenic in humans, pharmacokinetic considerations indicate that humans may be at less risk than mice. Noncancer effects at relevant levels of exposure are limited to subtle decrements in color vision, with only the most highly exposed workers likely to experience this impact.

Table 1
Non-Occupational Margins of Exposure

	Lifetime Average Exposure	Cancer MOE Corresponding to a Comparison Dose Producing an Estimated 10% Increase in Mouse Lung Tumor Incidence		
		Low-End Comparison Dose Value: 2 ppm	Most Likely Comparison Dose Value: 5 ppm	High-End Comparison Dose Value: 20 ppm
Typical ambient exposure	1 ppb	2,000	5,000	20,000
Exposure to styrene from lifetime smoking	6 ppb	400	800	3,000
Living 100 meters from a hypothetical 100,000 pound per year emission facility (high exposure scenario, 95th percentile individual)[e]	3 ppb	700	2,000	7,000
Living at the point of greatest exposure in the vicinity of a hypothetical 1 million pound per year emission facility (high exposure scenario, 95th percentile individual)[e]	220 ppb	10	20	100