NATIONAL CANCER INSTITUTE FactSheet

Benzene Causes Lowered Blood Cell Counts in Workers Exposed at Low Levels

Key Points

- White blood cell counts were decreased in shoe manufacturing workers exposed to low levels of benzene in China.
- It has been previously established that benzene lowers blood cell counts and causes leukemia at high levels of occupational exposure.
- Researchers conducted multiple workplace air samples and measured benzene and other chemicals over the course of one year or more, during different seasons, so as to accurately estimate workers' exposures over time.
- This study shows that there are changes in white blood cell counts in workers exposed to at or below 1 ppm benzene. More research is needed to understand what these changes mean, and what other kinds of biologic changes are occurring in the bone marrow where blood cells are formed.
- It is important to determine if results can be independently confirmed. It is also important to examine long-term health effects in workers exposed to low levels of benzene, such as increased occurrence of serious diseases of the blood system, including leukemia, and other blood system diseases.

OVERVIEW

A new study found that white blood cell counts were lowered in workers exposed to less than 1 ppm of the chemical benzene (part benzene per million parts air). Additionally, the study examined inherited differences in genes that are involved in the metabolism of benzene in the body. People with certain genetic traits were especially susceptible to the toxic effects of benzene on blood cells. The study, "Hematotoxicity in Workers Exposed to Low Levels of Benzene," reports results from a study of 250 Chinese workers exposed to benzene through the air in their workplace and compares blood cell counts to 140 non-exposed workers.

This study was performed by a team of investigators from the National Cancer Institute (NCI), University of California, Berkeley, the Chinese Center for Disease Control and Prevention

(Chinese CDC), University of North Carolina at Chapel Hill, and the New York Blood Center and was published in the December 3, 2004, issue of *Science**.

BACKGROUND

1. What is benzene?

Benzene is a clear, colorless and flammable liquid with a sweet odor. At room temperature, liquid benzene evaporates easily into the air and can dissolve in water. Benzene is present in crude oil and gasoline and is an important industrial chemical which is used in industry as a solvent, or to make other chemicals and products such as dyes, detergents, nylon, and plastics.

2. Where is benzene found?

Benzene is present at very low levels in air and water in our environment, coming mainly from petroleum and combustion. Benzene makes up about 1 percent of every gallon of gasoline in the United States and it is released as a by-product of fuel combustion. Benzene is also produced in the burning of tobacco. The once widespread use of benzene as a solvent in paints, adhesives, and paint removers has decreased in recent years.

3. How might people be exposed to benzene?

People can be exposed to benzene by smoking, breathing second-hand smoke, pumping gasoline, driving, and from air pollution. Elevated levels of benzene can occur in the air around gas stations, areas of high car traffic, and industrial plants that either produce or use it.

4. Can people get cancer from being exposed to benzene?

The International Agency for Research on Cancer (IARC), after examining many scientific studies, concluded that benzene does cause cancer in humans. Occupational studies of workers exposed to high levels of benzene have shown that benzene causes leukemia, a cancer of the bone marrow (where blood cells are made).

5. Is benzene regulated by the U.S. government?

Yes. The U.S. Environmental Protection Agency (EPA), charged with protecting human health and the environment, regulates benzene in the air and water, as well as emissions by industry. Levels of benzene in the air vary. The EPA has passed laws to limit the use and release of benzene to keep these levels as low as possible. Regulations set by the Occupational Safety & Health Administration (OSHA) limit workplace exposure to a maximum of one part benzene per million parts air (ppm), averaged over an eight-hour workday.

NEW RESEARCH ON BENZENE EXPOSURE

6. What past research is this new study based on?

NCI researchers in its Division of Cancer Epidemiology and Genetics have been studying industrial workers in China since the mid-1980s. The project, which is a collaboration with the Chinese CDC, grew out of a Chinese national health survey which found that it was common for industrial workers to be exposed to benzene at work.

The NCI-funded studies included 75,000 workers exposed to benzene and 35,000 unexposed workers in over 700 factories in 12 cities in China. These studies collected information on the workers' exposures, work histories, and what types of diseases they developed. The results of these studies suggested that benzene exposure is associated with a spectrum of blood and related disorders. Risks for these conditions were elevated at average benzene exposure levels of less than 10 ppm.

Also, in the mid-1980s, Dr. Martyn Smith's lab at U.C. Berkeley demonstrated that benzene could be turned into toxic substances by the enzyme myeloperoxidase (MPO), which was later shown to be important in making some people more sensitive to effects of benzene exposure. At around the same time, Dr. Stephen Rappaport, then at U.C., Berkeley, now at University of North Carolina at Chapel Hill, began to develop methods for measuring the amount of benzene bound to proteins and the levels of benzene and its metabolites in urine.

In the early 1990s, Smith's lab and Rappaport's lab began to collaborate with NCI and Chinese CDC epidemiologists and industrial hygienists. In 1992, this interdisciplinary team carried out a study of 44 workers exposed to benzene and 44 controls (workers not exposed to benzene) in Shanghai. That study found evidence of lowered blood cell counts among workers exposed to under 31 ppm benzene, with an average exposure of about 14 ppm.

7. Why was this new study done?

Previous research carried out by this investigative team and by other scientists (see http://monographs.iarc.fr/ENG/Monographs/vol29/volume29.pdf) has shown that benzene causes leukemia and lowers blood cell counts in people who are exposed to high levels of benzene at work. The study investigators wanted to find out if benzene affects blood cell counts even at low levels of exposure, at or below 1 ppm.

8. How was this study done?

This new study looked at 250 workers who make shoes and 140 controls (workers not exposed to benzene) in China. Researchers measured levels of benzene exposure in the air and in urine collected from workers. To accurately estimate the workers' exposures over time, benzene air levels were repeatedly monitored over the course of a year or more.

9. What is the main finding of this study?

White blood cell counts were decreased in Chinese shoe manufacturing workers exposed to benzene at levels lower than 1 ppm compared to unexposed controls.

10. Do people's genetics have an effect on how they react to benzene exposure?

Past studies showed that people with certain inherited traits might be more sensitive to benzene exposure. This new study looked at genetic traits in three genes that influence the way that benzene is processed when it gets into the body. When exposed to benzene, workers with two of these genetic traits tended to have lower white blood cell counts than workers without, so that benzene did have a stronger effect on workers with certain inherited differences in these genes. In particular, the study found that people with the more common version of the MPO gene were more susceptible to the effects of benzene on white blood cell counts.

11. What still needs to be done?

This study found changes in white blood cell counts in workers exposed at or below 1 ppm benzene. More research is needed to confirm these findings; to understand what these changes mean with regard to future disease risk; to identify if other biologic changes are occurring in the bone marrow where blood cells are formed; and to determine if cancer is caused by exposure to low levels of benzene.

RESOURCES

Related Scientific Articles:

Eastmond DA, Smith MT, Ruzo LO, Ross D. Metabolic activation of phenol by human myeloperoxidase and horseradish peroxidase. *Molecular Pharmacology*. 1986; 30:674–9.

Hayes, RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Travis LB, Li CY, Rothman N, Hoover RN, and Linet MS. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine—National Cancer Institute Benzene Study Group. *Journal of the National Cancer Institute*. 1997; 89:1065–1071.

Rappaport SM, Waidyanatha S, Qu Q, Shore R, Jin X, Cohen B, Chen LC, Melikian AA, Li G, Yin S, Yan H, Xu B, Mu R, Li Y, Zhang X, Li K. Protein adducts of benzene oxide and 1, 4–benzoquinone as measures of human benzene metabolism. *Cancer Research*. 2002; 62: 1330–7.

Rothman, N., Li, G.L., Dosemeci, M., Bechtold, W.E., Marti, G.E., Wang, Y.Z., Linet, M., Xi, L.Q., Lu, W., Smith, M.T., Titenko-Holland, N., Zhang, L.P., Blot, W., Yin, S.N., and Hayes, R.B. Hematotoxicity among Chinese workers heavily exposed to benzene. *American Journal of Industrial Medicine* 1996; 29:236–246.

Rothman, N., Smith, M.T., Hayes, R.B., Traver, R.D., Hoener, B., Campleman, S., Li, G.L., Dosemeci, M., Linet, M., Zhang, L., Xi, L., Wacholder, S., Lu, W., Meyer, K.B., Titenko-Holland, N., Stewart, J.T., Yin, S., and Ross, D. Benzene poisoning, a risk factor for hematological malignancy, is associated with the NQO1 609C →T mutation and rapid fractional excretion of chlorzoxazone. *Cancer Research* 1997; 57:2839–2842.

Smith MT, Yager JW, Steinmetz KL, Eastmond DA. Peroxidase-dependent metabolism of benzene's phenolic metabolites and its potential role in benzene toxicity and carcinogenicity. *Environmental Health Perspectives* 1989; 82:23–9.

Waidyanatha S, Rothman N, Fustinoni S, Smith MT, Hayes RB, Bechtold W, Dosemeci M, Guilan L, Yin S, Rappaport SM. Urinary benzene as a biomarker of exposure among occupationally exposed and unexposed subjects. *Carcinogenesis* 2001; 22:279–86.

Web Resources on Benzene:

10th Report on Carcinogens: Benzene section, National Toxicology Program: http://ehp.niehs.nih.gov/roc/tenth/profiles/s019benz.pdf

EPA toxicity reviews: www.epa.gov/iris/toxreviews/0276-tr.pdf

Safety and Health Topics: Benzene, U.S. Department of Labor, Occupational Safety & Health Administration: http://www.osha.gov/SLTC/benzene/index.html

Volume 29: Some Industrial Chemicals and Dyestuffs. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer (IARC): http://monographs.iarc.fr/ENG/Monographs/vol29/volume29.pdf.

ToxFAQs for Benzene, Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC): http://www.atsdr.cdc.gov/tfacts3.html

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* Lan Q, Zhang L, et al. Hematotoxicity in workers exposed to low levels of benzene. *Science*, December 3, 2004, Vol. 306, pp 1774–1776. This research was supported by NIH grants RO1ES06721, P42ES04705, P30ES01896, P42ES05948, and P30ES10126.

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Related NCI materials and Web pages:

- Cancer Causes and Risk Factors Home Page (http://www.cancer.gov/cancertopics/prevention-genetics-causes/causes)
- Understanding Cancer Series: Cancer and the Environment (http://www.cancer.gov/cancertopics/understandingcancer/environment)

For more help, contact:

NCI's Cancer Information Service
Telephone (toll-free): 1–800–4–CANCER (1–800–422–6237)
TTY (toll-free): 1–800–332–8615
LiveHelp® online chat: https://cissecure.nci.nih.gov/livehelp/welcome.asp

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