From:	Bruce Jarnot <jarnotb@api.org>
Sent:	Thursday, December 2, 2004 6:04 PM (GMT)
To:	Benz TF (E-mail) <benztf@listserve.api.org>; benzconsort-tc@listserve.api.org
Cc:	Richard Irons (E-mail) <richard.irons@uchsc.edu>; Otto Wong (E-mail) <OttoWong@aol.com>; Rob Schnatter (E-mail) <a.r.schnatter@exxonmobil.com>; Tom Armstrong (E-mail) <thomas.w.armstrong@exxonmobil.com>; Jerry Rice (E-mail) <Jmricewas@aol.com>; Andrew Jaques (E-mail) <Andrew_Jaques@americanchemistry.com>
Subject:	BHRC-TC / BzTF... "Workers exposed to low levels of benzene" in Dec 03 Science
Attach:	Page 1 Hematotoxicity in Workers Exposed to Low Levels of Benzene.pdf

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API Benzene Task Force, BHRC Technical Committee & colleagues -

Patsy Clegg (Shell) noted an interesting article appearing in the December 3rd issue of SCIENCE magazine. A pdf copy of the first page is attached:

Hematotoxicity in workers exposed to low levels of benzene
Qing Lan (NCI/NIH) *et al*., SCIENCE 306(5702), p.1774-1776.

Summary: We compared 250 benzene-exposed shoe workers with 140 unexposed age- and sex-matched controls who worked in three clothes-manufacturing factories in the same region near Tianjin, China. Subjects were young (mean T SD: 29.9 T 8.4 years), about two-thirds were female (table S1), and shoe workers had been employed an average of 6.1 T 2.9 years. For each subject, individual benzene and toluene exposure was monitored repeatedly up to 16 months before phlebotomy, and post-shift urine samples were collected from each subject (8, 9). Subjects were categorized into four groups by mean benzene levels measured during the month before phlebotomy controls, G1 ppm, 1 to G10 ppm, and Q10 ppm (Table 1), and more than 100 of the exposed workers had exposures below 1 ppm. All types of white blood cells (WBCs)…

With best regards - Bruce.

Hematotoxicity in Workers Exposed to Low Levels of Benzene

Qing Lan,[1]* Luoping Zhang,[2]* Guilan Li,[3] Roel Vermeulen,[1] Rona S. Weinberg,[4] Mustafa Dosemeci,[1] Stephen M. Rappaport,[5] Min Shen,[1] Blanche P. Alter,[1] Yongji Wu,[6] William Kopp,[7] Suramya Waidyanatha,[5] Charles Rabkin,[1] Weihong Guo,[2] Stephen Chanock,[1,8] Richard B. Hayes,[1] Martha Linet,[1] Sungkyoon Kim,[5] Songnian Yin,[3] Nathaniel Rothman,[1]† Martyn T. Smith[2]†‡

Benzene is known to have toxic effects on the blood and bone marrow, but its impact at levels below the U.S. occupational standard of 1 part per million (ppm) remains uncertain. In a study of 250 workers exposed to benzene, white blood cell and platelet counts were significantly lower than in 140 controls, even for exposure below 1 ppm in air. Progenitor cell colony formation significantly declined with increasing benzene exposure and was more sensitive to the effects of benzene than was the number of mature blood cells. Two genetic variants in key metabolizing enzymes, myeloperoxidase and NAD(P)H:quinone oxidoreductase, influenced susceptibility to benzene hematotoxicity. Thus, hematotoxicity from exposure to benzene occurred at air levels of 1 ppm or less and may be particularly evident among genetically susceptible subpopulations.

Benzene causes toxicity to the hematopoietic system (hematotoxicity) and leukemia (*1*). Exposure to benzene occurs worldwide to workers in the oil, shipping, automobile repair, shoe manufacture, and other industries and to the general public from cigarette smoke, gasoline, and automobile emissions (*2*). In addition to ongoing concern about health effects at or below the current U.S. occupational standard of 1 ppm, high environmental exposures in cities (*3*) have led to regulatory consideration of the risks posed by benzene as an air pollutant.

Limitations in previous occupational studies evaluating hematotoxicity at low levels of benzene exposure led us to perform a large cross-sectional study with detailed exposure assessment that measured lymphocyte subsets and colony formation from progenitor cells in addition to the standard blood-count analyses reported in most previous investigations. Because benzene is thought to lower blood cell counts via metabolite effects on hematopoietic progenitor cells (*4*), we also evaluated the influence of genetic variants in cytochrome P4502E1 (CYP2E1) and myeloperoxidase (MPO), which metabolize benzene to toxic quinones and free radicals (*5*), and NAD(P)H:quinone oxidoreductase (NQO1), which protects against this toxicity (*6*, *7*).

We compared 250 benzene-exposed shoe workers with 140 unexposed age- and sex-matched controls who worked in three clothes-manufacturing factories in the same region near Tianjin, China. Subjects were young (mean ± SD: 29.9 ± 8.4 years), about two-thirds were female (table S1), and shoe workers had been employed an average of 6.1 ± 2.9 years. For each subject, individual benzene and toluene exposure was monitored repeatedly up to 16 months before phlebotomy, and postshift urine samples were collected from each subject (*8*, *9*). Subjects were categorized into four groups by mean benzene levels measured during the month before phlebotomy [controls, <1 ppm, 1 to <10 ppm, and ≥10 ppm (Table 1)], and more than 100 of the exposed workers had exposures below 1 ppm.

All types of white blood cells (WBCs) measured in the Complete Blood Count and platelets (*9*) were significantly decreased in workers exposed to <1 ppm benzene compared to controls (Table 1). Lymphocyte subset analysis showed significantly decreased $CD4^+$–T cells, $CD4^+/CD8^+$ ratio, and B cells. Hemoglobin concentrations were decreased only among workers exposed to ≥10 ppm. Tests for a linear trend using benzene air level as a continuous variable were significant for platelets and all WBC measures except monocytes and $CD8^+$–T cells (Table 1). Adjustment for a range of potential confounders had a negligible effect on the strength of the associations (*9*).

We then restricted the linear-trend analyses to workers exposed to <10 ppm benzene, excluding controls and higher exposed workers, and found that inverse associations remained for total WBCs (P = 0.013), granulocytes (P = 0.02), lymphocytes

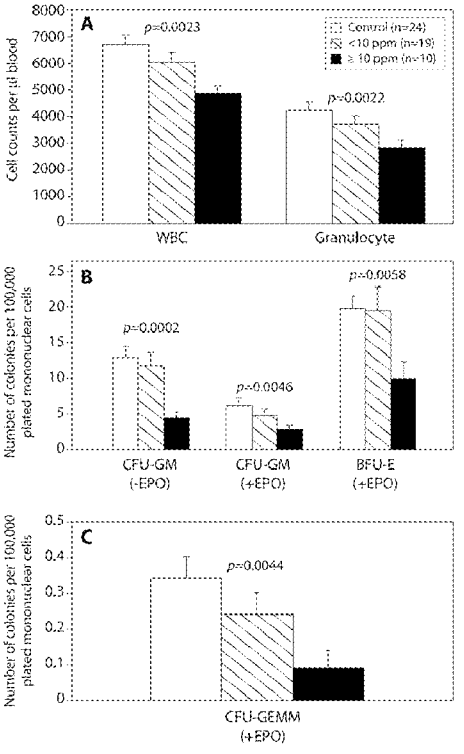

Fig. 1. Effect of benzene exposure on (**A**) white blood cell (WBC) and granulocyte counts; (**B**) colonies from the colony-forming unit–granulocyte-macrophage (CFU-GM) and burst-forming unit–erythroid (BFU-E); and (**C**) colonies from the colony-forming unit–granulocyte, erythroid, macrophage, megakaryocyte (CFU-GEMM). Erythropoietin (EPO) was added to half of the cultures (*9*). Trends with benzene were tested by linear regression (WBC, granulocytes), negative binomial regression (CFU-GM, BFU-E), and unconditional logistic regression [CFU-GEMM, categorizing subjects into 0 or more than 0 colonies (92%, 74%, and 40% of subjects had >0 colonies among controls, <10 ppm, and ≥10 ppm, respectively)]. Models were adjusted for age and sex, and additionally for smoking, alcohol, recent infections, and body mass index (BMI) if significant (*9*). Strong, inverse trends between benzene and all cell types were present (P_{trend} shown). There was a greater proportional decrease in colonies in workers exposed to ≥10 ppm versus controls for CFU-GM, BFU-E, and CFU-GEMM compared to the decline in WBCs (P < 0.011, 0.048, and 0.0078, respectively) and for CFU-GM and -GEMM compared to the decline in granulocytes (P = 0.026 and 0.0094, respectively) (*9*).

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services (DHHS), Bethesda, MD 20892, USA. [2]School of Public Health, University of California, Berkeley, CA 94720, USA. [3]Chinese Center for Disease Control and Prevention, Beijing, China. [4]New York Blood Center, Clinical Services, White Plains, NY 10605, USA. [5]School of Public Health, University of North Carolina, Chapel Hill, NC 27599, USA. [6]Peking Union Medical College, Beijing, China. [7]SAIC-Frederick, Inc., Frederick, MD 21702, USA. [8]Center for Cancer Research, NCI, NIH, DHHS, Bethesda, MD 20892, USA.

*These authors contributed equally to this work.
†These authors co-supervised this work.
‡To whom correspondence should be addressed. E-mail: martynts@berkeley.edu