



# Occupational cancer

## Workplace carcinogen: Benzene

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Cancer is one of the leading causes of death worldwide, with around 14 million new cases in 2012.<sup>1</sup> Cancer accounted for 8.8 million deaths in 2015.<sup>2</sup> Several risk factors play a role in the development of cancer, including:<sup>1,3</sup>

- Biological carcinogens: infections from viruses, bacteria or parasites
- Family history of cancer, age, sex and race
- Personal habits (smoking, drinking and diet)
- Physical/environmental carcinogens: ionising and ultraviolet radiation, air pollution
- Workplace carcinogens, such as chemicals (e.g. benzene) and metals (e.g. cadmium)

According to the World Health Organization (WHO),<sup>2</sup> 30-50% of cancers can be prevented by avoiding or minimising these risk factors. If an occupational carcinogen cannot be avoided, it is important to understand how the carcinogen increases the risk of cancer by altering cellular metabolism or damaging DNA directly in cells, in order to manage it. The main aim remains to prevent the cancer associated with the exposure. The International Agency for Research on Cancer (IARC) has classified benzene as a human carcinogen (Group 1), as it is associated with the development of acute myeloid leukaemia, non-Hodgkin's lymphoma and multiple myeloma.<sup>4</sup>

### SOURCES OF EXPOSURE

In the early 1900s, benzene was isolated from coal tar. Later in the 1900s, the first industrial scale isolation of benzene began. Leading up to World War II, benzene remained a by-product in the steel industry. Following this, as the demand for plastic increased, benzene was produced from petroleum and, today, most of the benzene comes from the petrochemical industry.<sup>5</sup> From an occupational health perspective, benzene was one of the earliest industrial chemicals to be implicated in the health of workers, as early as 1897.<sup>6</sup>

Benzene is commonly found in the environment – industrial processes and fire emissions are the main sources. Currently, with the exponential increase in motor vehicles globally, benzene, as an air pollutant in exhaust fumes, increases human exposure. Tobacco smoke is another source of benzene.<sup>7</sup>

The industries that produce benzene include petro-chemical manufacturing; petroleum refining; coke and coal chemical manufacturing; rubber tyre manufacturing; gasoline storage, shipment, and retail operations; plastics and rubber manufacturing; and shoe manufacturing. Other workers exposed to benzene include laboratory technicians, fire-fighters, and petrol station employees.<sup>7</sup>

### ABSORPTION AND METABOLISM

Absorption of benzene occurs mainly through skin contact and inhalation of vapours.<sup>8</sup> According to Susten et al.,<sup>9</sup> dermal absorption in the workplace could contribute to 20-40% of the total dose

absorbed. A fraction of absorbed benzene is excreted unchanged in urine (0.1%)<sup>10</sup> and exhaled air (10-50%),<sup>8</sup> the remaining fraction is metabolised (see Figure 1).

### BIOLOGICAL MONITORING

The measurement of total phenol in urine is recommended in the Occupational Health and Safety Act, 1993 (Act 85 of 1993) Regulations for Hazardous Chemical Substances. However, it stipulates a 'B' and 'C' notation, as follows:

- 'B' notation indicates that the determinant is usually present in a significant amount in biological specimens collected from subjects who have not been occupationally exposed. Such background levels are included in the Biological Exposure Index (BEI).
- 'C' notation indicates that the determinant is non-specific, since it is observed after exposure to some other chemicals. These non-specific tests are preferred because they are easy to use and usually offer a better correlation with exposure than specific tests. In such instances, a BEI for a specific, less quantitative biological determinant is recommended as a confirmatory test.

The measurement of total phenol was acceptable when the acceptable exposure amounted to 10 ppm.<sup>8</sup> Annex III of Directive 2004/37/EC (EU Parliament and Council Directive 2004) specifies a time-weighted average (TWA) limit value for occupational exposure to benzene of 1 ppm.<sup>12</sup> The background concentration of phenol in urine will prevent any reliable detection of a TWA lower than 5 ppm.<sup>13</sup> The tests now considered to assess benzene exposure reliably are benzene in blood; and S-phenylmercapturic acid (S-PMA), t,t-muconic acid (t,t-MA) and benzene in urine.<sup>8</sup> The measurement of benzene in urine may, however, be problematic due to the possibility of contamination of urine sample during collection.<sup>14</sup>

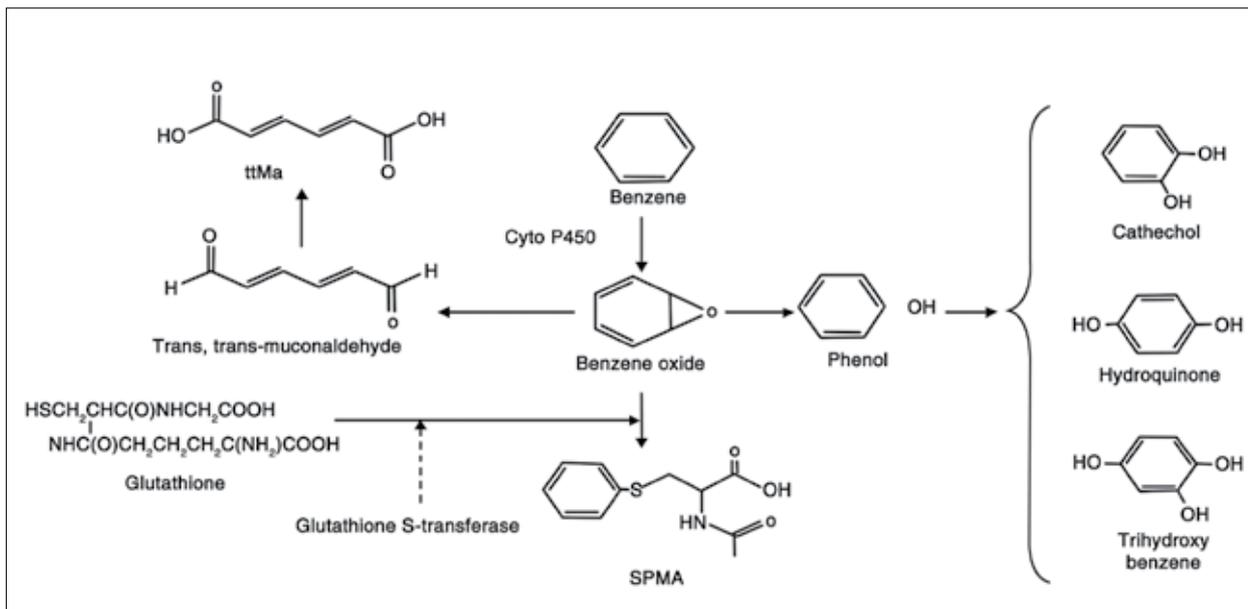
#### Benzene in blood

The half-life of benzene in blood is eight hours.<sup>15</sup> Therefore, blood sampling should be performed at the end of an exposure period to provide reliable results. As blood sampling requires invasive collection methods, this method is infrequently used.

#### S-phenylmercapturic acid

The half-life of S-PMA ranges from nine to thirteen hours.<sup>8</sup> As accumulation of S-PMA is not likely, S-PMA can be considered as a biomarker of recent exposure and does not reflect mid- or long-term exposure.<sup>12</sup> S-PMA in end-of-shift samples has been shown to be a reliable indicator of benzene exposure at 0.3 ppm<sup>8</sup>, but recent studies show that it can be a reliable marker at 0.1 ppm.<sup>12</sup>

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**Figure 1. Benzene metabolism<sup>11</sup>**

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#### *t,t*-muconic acid

The mean half-life of *t,t*-MA is five hours.<sup>8</sup> Human genetic factors can influence the levels of *t,t*-MA excreted in urine. Furthermore, in cases of occupational co-exposure to toluene, *t,t*-MA urinary levels are suppressed.<sup>12</sup> *t,t*-MA in end of shift samples has been shown to be a reliable indicator of benzene exposure for levels of benzene  $\geq 0.5$  ppm,<sup>8</sup> keeping in mind that dietary intake of sorbic acid may contribute to *t,t*-MA background levels.<sup>12</sup>

### BIOLOGICAL EFFECT MONITORING

Monitoring full blood counts at regular intervals can detect the haematological effects of chronic benzene exposure. The United States Occupational Safety and Health Administration (OSHA) recommends monthly counts and removal of workers with white blood cell counts  $< 4000/\text{mm}^3$  ( $4 \times 10^9/\text{L}$ ), or erythrocyte counts  $< 4\,000\,000/\text{mm}^3$  ( $4 \times 10^{12}/\text{L}$ ).<sup>16</sup>

### CONCLUSION

Benzene is a known occupational carcinogen but risk mitigation to eliminate or reduce exposure is not always possible. By measuring the appropriate metabolites for the exposure level (TWA), as well as monitoring full blood count levels at regular intervals, it is possible to minimise the risk of occupational cancer due to benzene exposure.

### REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr> (accessed 19 Mar 2018).
2. World Health Organization. Media Centre. Cancer. Fact sheet; February 2018. Available from: <http://www.who.int/mediacentre/factsheets/fs297/en/> (accessed 1 Mar 2018).
3. NIOSH Occupational cancer. Available from: <https://www.cancer.gov> (accessed 1 Mar 2018).

4. WHO International Agency for Research on Cancer Monograph Working Group A review of human carcinogens – Part F. Chemical agents and related occupations. The Lancet Oncology. 2009; 10 (12):1143–1144. Available from: [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(09\)70358-4/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(09)70358-4/fulltext) (accessed 19 Mar 2018).
5. New World Encyclopedia. Benzene. Available from: <http://www.newworldencyclopedia.org/entry/Benzene> (accessed 18 Mar 2018).
6. Snyder R. Leukemia and benzene. Int J Environ Res Public Health. 2012; 9(8):2875-2893.
7. Toxicological profile for benzene. US Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Georgia: Atlanta; 2007 Available from: <https://www.atsdr.cdc.gov/toxprofiles/tp3.pdf> (accessed 19 Mar 2018).
8. Lauwerys RP, Perrine Hoet P, Industrial Chemical Exposure. Guidelines for Biological monitoring. Third Edition Boca Raton, US: CRC Press; 2001. p 202-211.
9. Susten AS, Damers BL, Burg JR, Niemeier RW. Percutaneous penetration of benzene in hairless mice: an estimate of dermal absorption during tire-building operations. Am J Ind Med. 1985; 7:323-335.
10. Dor F, Dab W, Empereur-Bissonnet P, Zmirou D. Validity of biomarkers in environmental health studies: the case of PAHs and benzene. Crit Rev Toxicol. 1999; 29:129-168.
11. Lin L, Chen W, Chiung Y, Shih T, Liao P. Association between GST genetic polymorphism and dose-related production of urinary benzene metabolite markers, trans, trans-muconic acid and S-phenylmercapturic acid. Cancer Epidemiol Biomarkers Prev. 2008; 17(6):1460-1469.
12. European Chemicals Agency. Proposal by the European Chemical Agency (ECHA) in support of occupational exposure limit values for benzene in the workplace; 2017. Available from: <https://echa.europa.eu/documents/10162/214b2029-82fd-1656-1910-3e18d0906999> (accessed 1 Mar 2018).
13. Hotz P, Carbonnelle P, Haufroid V, Tschopp A, Buchet JP, Lauwerys R. Biological monitoring of vehicle mechanics and other workers exposed to low concentrations of benzene. Int Arch Occup Environ Health. 1997; 70:29-40.
14. Robinson SH, et al. The use of biomonitoring data in exposure and human health risk assessment: benzene case study. Crit Rev Toxicol. 2013; 43:119-153.
15. Brugnone F, Perbellini L, Maranelli G, Romeo L, Guglielmi G, Lombardini F. Reference values for blood benzene in the occupationally unexposed general population. Int Arch Occup Environ Health. 1992; 64:179-184.
16. International Programme on Chemical Safety. Benzene. Poisons Information Monograph 63. Geneva: WHO; 1999. Available from: <http://www.inchem.org/documents/pims/chemical/pim063.htm> (accessed 20 Mar 2018).