Biological Exposure Index (BEI) review

BENZENE
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New Zealand Government

WORKSAFE
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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers changes to the Biological Exposure Indices (**BEI**) for benzene.

Biological monitoring is an assessment of overall systemic exposure to chemicals by measurement of the chemicals, their metabolites, or conjugates in blood, urine or breath.

The review considers BEIs from other jurisdictions/organisations around the world and includes a recommendation to change the WorkSafe BEI for benzene, which is currently set at BEI of 25**µg/g** creatinine of S-phenylmercapturic acid (**S-PMA**) in urine, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Edition (WorkSafe, 2019).

It is noted that only the BEIs which have a documented rationale for why they have been set at that level have been considered for this review. The BEIs considered are from the:

- American Conference of Governmental Industrial Hygienists (**ACGIH**®)
- Deutsche Forschungsgemeinschaft (**DFG**) of Germany, and
- European Chemicals Agency (**ECHA**).

It should be noted that WorkSafe is also proposing to:

1. Adopt a **WES-TWA** for airborne benzene of 0.05**ppm**.

Discussion on benzene exposures in New Zealand and its health effects are described in the WorkSafe Workplace Exposure Standards review of benzene (2020) included in this consultation period.

S-PMA in urine can be analysed in New Zealand and Australia.

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: benzol; coal naphtha; cyclohexatriene; phenyl hydride.

2.0 Exposure standards

IN THIS SECTION:

2.1 ACGIH®

2.2 DFG

2.3 ECHA

The WorkSafe BEI for benzene was introduced in 2018.

Table 1 below shows the current WorkSafe, ACGIH®, DFG and ECHA BEI values for benzene.

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe New Zealand (2019)	25µg/g creatinine S-PMA in urine
ACGIH® (2001)	25µg/g creatinine S-PMA in urine 500µg/g creatinine t-t-muconic acid (**t,t-MA**) in urine
DFG (2019)	**EKA**: 3µg/g creatinine S-PMA in urine [corresponds to an airborne concentration of 0.06ppm] **BAR**: 0.3µg/g creatinine S-PMA in urine 150µg/g creatinine t,t-MA in urine 0.3µg/L benzene in urine
ECHA (2018a,b)	2µg/g creatinine S-PMA in urine 0.7**µg/L** benzene in urine

TABLE 1:
BEI values adopted by WorkSafe, ACGIH®, DFG and ECHA

2.1 ACGIH®

The ACGIH® 2001 review of benzene recommended a BEI® of 25µg/g creatinine S-PMA in urine and 500µg/g creatinine t-t-muconic acid in urine. They state that:

- The BEIs® for benzene are based on the **TLV-TWA** of 0.5ppm.
- Van Sittert et al (1993) validated S-PMA as a biomarker in 12 separate studies. They found an 8-hour exposure at 1ppm benzene corresponded to 46µg S-PMA/g creatinine (95% confidence interval: 41–50µg S-PMA/g creatinine).
- Boogard and Van Sittert (1995) found a similar result, where 1ppm led to a calculated average concentration of 47µg S-PMA/g creatinine.
- Ghittori et al (1995) calculated the average S-PMA concentration in urine samples was 45µg/g creatinine (90% confidence interval: 20–95µg/g creatinine).
- Based on the study of Ghittori et al (1995), an airborne benzene exposure at the TLV-TWA of 0.5ppm corresponds to a S-PMA excretion of about 25µg/g creatinine.
- Sufficient data from 11 field studies were used to support a BEI® for t,t-MA in urine. Based on regression calculations, the range was 208 to 4,900µg/g creatinine t-t-MA in urine, which correlated with 0.5ppm benzene in air.
- The ACGIH® recommended a value of 500µg/g creatinine t,t-MA in urine as a BEI®.

(References cited in ACGIH®, 2001)

2.2 DFG

In its 2019 *Addendum to Benzene*, the DFG correlated levels of benzene and its metabolites in urine to workplace air concentrations (**EKA correlations**). A level of 3µg/g creatinine S-PMA in urine to an airborne concentration of 0.06ppm (for non-smokers only). Accordingly, a level of 5µg/g creatinine S-PMA in urine corresponds to an airborne concentration of 0.15ppm (see Table 2) (DFG, 2019).

The DFG has also recommended a Biological Reference Value [BAR] of 0.3µg/g creatinine S-PMA in urine for benzene. The BAR represents the upper reference concentration of a biomarker in the general adult population without occupational exposure to the agent. The BAR are based on the 95th percentile without regarding effects on health. It must be taken into account that the reference level of the background exposure can be influenced by such factors as age, sex, social status, residential environment, life style and geographical region.

For carcinogens and substances for which no Maximum Workplace Concentration [**MAK**] value can be derived, they are not given Biological Tolerance Values [**BAT**] because it is not possible at present to specify safe levels. Therefore, DFG investigates the relationship between the concentration of the carcinogen in the workplace air and that of the substance or its metabolites in biological material to derive exposure equivalents for carcinogenic substances (EKA).

As the BAR is based on the general population (non-occupationally exposed), this proposal prefers the EKA as there is a correlation between occupational airborne exposure levels and biological exposure levels.

AIR		URINE		
Benzene		Urine S-Phenyl-mercapturic acid	t,t-Muconic acid	Benzene in urine
mL/m³ ppm	mg/m³	µg/g creatinine	µg/g creatinine	µg/L
0.03	0.1	1.5*	–	0.5*
0.06	0.2	3*	–	0.8*
0.15	0.5	5	–	1.5
0.3	1.0	12	300	2.75
0.6	2.0	25	500	5.0
1.0	3.3	45	750	7.5
2.0	6.5	90	1200	12.5

TABLE 2: Correlations between external and internal exposure

The DFG state in their review that:

> "So far, the EKA correlations for SPMA and t,t-MA have been derived from studies by van Sittert et al. (1993) and Ducos et al. (1992) for a range of 0.3–6mL benzene/m³ in air, and in consideration of a general background of 1**mg/L** for t,t-MA (Lehnert and Greim 1996). As most national and international threshold values for airborne benzene concentrations are in the range of up to 1**mL/m³**, it seems appropriate to adapt EKA correlations to this low-concentration range." (DFG, 2019).
>
> "For the parameter SPMA, the results of Manini et al. (2008), Carrieri et al. (2010), Angelini et al. (2011) and Mansi et al. (2012) were thus used to establish a correlation in the range of 0.03–0.06mL benzene/m³ air and the corresponding urinary SPMA concentration." (DFG, 2019).

* For non-smokers.

> "On the basis of this data, the following correlation can be established:
> - SPMA [µg/g crea] = 13.215 • airborne benzene [**mg/m³**] + 0.3225" (DFG, 2019).

Therefore, at the proposed WES-TWA of 0.05ppm, the corresponding BEI would be approximately 2µg/g creatinine S-PMA in urine. Sampling should be performed at the end of exposure or at the end of the shift.

2.3 ECHA

The European Chemicals Agency [ECHA] opinion on benzene recommended a biological limit value [**BLV**] of 2µg S-PMA/g creatinine and 0.7µg benzene/L urine (sampling at end of exposure or end of working shift). This was based on the correlation between airborne benzene and S-PMA and benzene in urine, as published by DFG 2017 (approved by the Working Group in 2017).

Their rationale states:

- "...benzene as such, S-phenylmercapturic acid, and t,t-muconic acid can be reliably measured in urine. However, for low exposure to benzene (<1ppm), benzene and S-phenylmercapturic acid in urine seem to be the most reliable biomarkers." (ECHA, 2018a).
- "Using SPMA as a biomarker at low concentrations has the benefit, compared to benzene, that there are no problems with respect to contamination or loss of material due to volatility. Also some authors found SPMA to be a more sensitive parameter than benzene in urine (Lovreglio et al 2017)." (ECHA, 2018b).
- "Urinary trans, trans-Muconic acid (ttMA) is not recommended anymore for benzene biomonitoring because it is not sensitive enough at low exposure levels." (ECHA, 2018a).
- "S-phenylmercapturic acid (SPMA) in urine is a suitable biomonitoring parameter for which sensitive analytical methods are available. However, for reliable results that can be correlated with benzene exposure in the air, acidification of the urine sample is required and a detection with appropriate chromatographic methods like **LC/MS/MS**. The reference value is 0.5µg SPMA/g creatinine. A concentration of 2µg SPMA/g creatinine corresponds to about 0.05ppm benzene in the air (0.16mg/m³)." (ECHA, 2018b).

3.0
Discussion

Based on the aforementioned documentation, informed by the conclusions of the ACGIH®, DFG and ECHA reviews, WorkSafe considers its current BEI of 25µg/g creatinine S-PMA in urine inadequate to manage health risks from workplace exposure:

- A mode-of-action-based threshold for chromosomal damage (aneugenicity and clastogenicity) in workers can, in the view of **RAC**, be used to establish an **OEL** for carcinogenicity. The limit so derived [0.05 ppm benzene], will avoid exposures that induce chromosomal damage in workers, is considered to have no significant residual cancer risk and will also avoid other adverse effects (ECHA 2018a).
- S-PMA is preferred over benzene in urine as a biomarker, because at low concentrations there are no problems with respect to contamination or loss of material due to volatility, and it is a more sensitive parameter than benzene in urine (ECHA, 2018b).
- Urinary t,t-MA is not recommended anymore for benzene biomonitoring because it is not sensitive enough at low exposure levels (ECHA, 2018a).
- Therefore, the DFG (2019) EKA correlations between airborne benzene and S-PMA were used to derive the BEI for benzene.

4.0
Recommendations

WorkSafe considers its BEI for benzene of 25µg/g creatinine S-PMA in urine, to be inadequate to manage health risks from workplace exposure, based on current knowledge.

It is proposed that WorkSafe:

1. Adopt the recommendation by ECHA for assessing exposure to benzene;
2. As such, adopt a BEI of 2µg/g creatinine S-PMA in urine [measured at the end of exposure or at the end of the shift].

Noting that the proposed **WES** and BEI values may not eliminate all risk, due to the uncertainty as to the carcinogenic threshold for benzene and the potential for non-occupational exposures.

Therefore, workplace exposures should be minimised so far as is reasonably practicable.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

Appendix 2: References

Appendix 1: Glossary

TERM	MEANING
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
BAT	Biologische Arbeitsstoff-Toleranzwerte [Biological Tolerance Value], a DFG term.
BEI	Biological Exposure Index.
BLV	Biological Limit Value.
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
ECHA	The European Chemicals Agency (an agency of the European Union).
EKA correlations	Exposure equivalents for carcinogenic substances. The DFG Commission investigates for carcinogenic substances the relationships between the concentration of the carcinogen in the workplace air and that of the substance or its metabolites in biological material ("Expositionsäquivalente für krebserzeugende Arbeitsstoffe", EKA: exposure equivalents for carcinogenic substances). From these relationships, the body burden which results from uptake of the substance exclusively by inhalation may be determined. A DFG term.
LC/MS/MS or LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry.
µg/g	Microgram or one millionth of a gram per gram of the matrix.
µg/L	Microgram or one millionth of a gram per litre.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
mg/L or mg/l	Milligrams of a substance per litre.
mg/m³	Milligrams of substance per cubic metre of air.
ml/m³ or mL/m³	Millilitres of substance per cubic metre of air; equivalent to ppm.
OEL	Occupational Exposure Limit (equivalent to a WES).
ppm	Parts of vapour or gas per million parts of air.
RAC	Committee for Risk Assessment, European Chemicals Agency.
SPMA/S-PMA	S-Phenylmercapturic acid.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-TWA	TLV® – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
t,t-MA	t-t-Muconic acid.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.

Appendix 2: References

American Conference of Governmental Industrial Hygienists (ACGIH®). (2001). *Benzene BEI*. Chemical Substances (7th Ed.) Cincinnati, Ohio: ACGIH®. From ACGIH®, *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 7th Edition. Copyright 2001. Reprinted with permission.

Deutsche Forschungsgemeinschaft (DFG, German Research Foundation). (2019). *Addendum to Benzene*. The MAK Collection for Occupational Health and Safety, Vol.: 4 No. 1; pp 200-232. https://onlinelibrary.wiley.com/doi/pdf/10.1002/3527600418.bb7143e2319

European Chemicals Agency (ECHA).)2018a). ECHA/RAC/O-000000-1412-86-187/F: *Committee for Risk Assessment RAC Opinion on scientific evaluation of occupational exposure limits for Benzene*. Helsinki. https://echa.europa.eu/documents/10162/13641/benzene_opinion_en.pdf/4fec9aac-9ed5-2aae-7b70-5226705358c7

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WorkSafe New Zealand. (2019). *Workplace Exposure Standards and Biological Exposure Indices* (11th Ed.) November 2019. worksafe.govt.nz/topic-and-industry/work-related-health/monitoring/exposure-standards-and-biological-exposure-indices

Notes

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