Biological Exposure Index (BEI) review

ARSENIC AND SOLUBLE COMPOUNDS AS As (ARSENIC CAS NO: 7440-38-2)

March 2020

New Zealand Government

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers changes to the Biological Exposure Indices (**BEI**) for arsenic and soluble compounds, as **As**.

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 arsenic, which is currently set at BEI of 35**µg/L** as the sum of inorganic arsenic and its methylated metabolites 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 are 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 proposing to adopt a **WES-TWA** for airborne arsenic and soluble compounds of 0.001**mg** arsenic/m^3, as As [**inhalable fraction**].

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

Arsenic in urine can be analysed in New Zealand and Australia.

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: As, AsIII, AsIII, AsV, AsV, As3+, As3+, As5+, As5+.

2.0 Exposure standards

IN THIS SECTION:

The WorkSafe BEI for arsenic was lowered in 2018.

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

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe New Zealand (2018)	35µg/L (urine)
ACGIH® (2001)	35µg/L (urine) with the exception of arsine and gallium arsenide
DFG (2018)	15µg/L (urine) [corresponds to an airborne concentration of 0.001**mg/m³**] (except arsine)
ECHA (2017)	10µg/L (urine)

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

2.1 ACGIH®

The ACGIH® 2001 review of arsenic and soluble inorganic compounds recommended a BEI of 35µg/L in urine (excluding gallium arsenide and arsine). They state that:

- the BEI for arsenic is based on a large database relating occupational arsenic exposure to urinary excretion of arsenic metabolites and urinary excretion to cancer risk
- the urine BEI intends to correspond with the background rate of lung cancer observed at the **TLV-TWA** of 0.01mg/m³
- most studies have a linear relationship between inhalation exposure and urinary excretion of arsenic
- the mean urinary excretion of arsenic, at the TLV-TWA of 0.01mg/m³ from reviewed studies, was 36µg/L ± 14 standard deviation
- a key study by Enterline and colleagues (1987) provided the basis for the BEI relationship between lung cancer and arsenic concentration in urine. A urinary concentration of 35µg As/L corresponded with a standardized mortality ratio [**SMR**] of 106 (an SMR of 100 denotes a baseline or background level of lung cancer, implying no additional risk from arsenic exposure)
- a urinary concentration of 35µg As/L seems to be a reasonable BEI (measurement of inorganic arsenic and its two major organic metabolites expressed as arsenic) since it relates well to both exposure at the TLV-TWA and to the cancer health endpoint on which the TLV-TWA is based.

2.2 DFG

In its 2018 addendum to *Arsine and inorganic arsenic compounds (with the exception of arsine)*, the DFG correlates an airborne concentration of 0.001mg/m³ (the proposed WorkSafe WES-TWA) to a level of 15µg/L for the sum of As (+III), As (+V), monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) in urine.

The DFG state in their review that:

"The regression lines from the study by Apostoli *et al*. (1999) can be used to derive a relationship between arsenic concentrations in the air and concentrations of arsenic species in urine. From the relevant regression equations, the following relationships between inhalation exposure to arsenic and urinary concentrations of arsenic species can be obtained (see Table 4).

"These data from Apostoli *et al*. (1999) on the correlation between arsenic in the air and the sum of urinary arsenic species can be used for the evaluation of an EKA correlation. The correlation thus determined agrees well with the EKA for arsenic trioxide as derived from the studies by Smith *et al*. (1977), Enterline *et al*. (1987), Yamauchi *et al*. (1989) and Offergelt *et al*. (1992), and in which also the renal arsenic elimination is given as sum of the concentrations of As (+III), As (+V), monomethylarsonic acid and dimethylarsinic acid. The study by Jakubowski *et al*. (1998) also supports this correlation.

"On the basis of these data, the following EKA correlation is derived for arsenic and inorganic arsenic compounds including arsenic trioxide:

AIR	URINE
Arsenic and inorganic arsenic compounds (with the exception of arsine) µg/m³	Σ As (+III), As (+V), monomethylarsonic acid and dimethylarsinic acid µg/L
1	15
5	30
10	50
50	90
100	130

Interpretation of data

"When interpreting the data for internal arsenic exposure, the eating habits of those examined must be taken into account, particularly regarding previous fish or sea-food consumption, as this produces a marked increase in the content of organic arsenic compounds, also including dimethylarsinic acid, and thus also the total arsenic content. In addition, regional differences must also be considered, as the presence of natural arsenic in the drinking water can vary greatly, and is accordingly able to affect the results of the study. Finally, age, sex, smoking habits and alcohol consumption have been identified as possible factors influencing the arsenic concentration in biological material (see Heinrich-Ramm *et al*. 2001; Leese *et al*. 2014 for example).

"All threshold values in biological material, particularly also the **BAR** and the EKA correlations, relate to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3.0g/l. In addition to this, the Commission considers it useful, for further improving the validity of the analyses, to select a narrower target range of 0.5–2.5g/l for urine samples. As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated volunteers is recommended (see BAT Documentation 2010, translated)." (References cited in DFG, 2018).

2.3 ECHA

The European Chemicals Agency [ECHA] opinion on arsenic acid and its inorganic salts recommended an acceptable biological guidance value [**BGV**] of 10µg As/L in urine (post-shift sample at end of a working week) as combined As3+, As5+, and MMA and DMA. This was based on the data from France showing **95th percentile** of 8.9µg/L in adults after controlling for seafood consumption, and from Belgium showing 90th percentile of 10.7µg/L in 20–40 year old mothers.

Their rationale states:

> "At European level, a value representing the background exposure to inorganic arsenic in the general population could be used as a basis for setting a BGV. Since dietary sources, especially seafood may have a significant impact on total MMA and DMA levels, speciation of arsenic species and separate determination of As3+ and As5+ would be the preferred method for assessing occupational exposure. However, due to the limited database no BGV for As3+ and As5+ can be currently set." (ECHA, 2017).

Therefore, ECHA reviewed reference values for inorganic arsenic in urine of the general population from Germany, the UK, France and Belgium:

- Germany (DFG) – see section 2.2 for the correlation of urinary arsenic to airborne arsenic levels.
- UK – the UK Health and Safety Laboratory (Leese *et al*, 2014) determined that the 95th percentile for combined inorganic arsenic species, MMA + DMA among 95 volunteers was 15.1µg/L.
- France – the data were obtained by the French National Nutrition and Health Study (ENNS), which was carried out between 2006 and 2007. The study showed a 95th percentile for inorganic arsenic + MMA + DMA, of 8.9µg/L in adults (n=5,217) after controlling for seafood consumption.
- Belgium – 90th percentile of 10.7µg/L in 20-40 year old mothers.

As the data from France and Belgium controlled for seafood consumption, ECHA preferred that data (over others) in the setting of the BGV of 10µg As/L for the sum of inorganic arsenic + MMA + DMA.

3.0
Discussion

Based on the aforementioned documentation, informed by the conclusions of the ACGIH®, DFG and ECHA reviews, and considering WorkSafe's proposal to reduce the WES-TWA for arsenic and soluble compounds, WorkSafe considers its current BEI of 35µg/L (urine) for arsenic and soluble compounds, as As, to be inadequate to manage health risks from possible workplace exposure. Data used to inform this view includes:

- "Epidemiological studies of populations occupationally exposed to arsenic consistently demonstrate an excess lung cancer risk (see Section 7.7.1). In addition, epidemiological studies in the general population also show that the oral exposure to arsenic via drinking water increases the risk of skin and urinary bladder cancer (see Section 7.7.1)." (ECHA, 2017).
- As it is currently not possible to identify a threshold for the carcinogenicity of arsenic acid and its salts, a value representing the background exposure to inorganic arsenic in the general population (such as the 95th percentile) could be used as a basis for setting a BEI. (ECHA, 2017).
- French data on arsenic levels in the general population showed a 95th percentile of 8.9µg/L in adults after controlling for seafood consumption, and from Belgium showed a 90th percentile of 10.7µg/L in 20–40 year old mothers. (ECHA, 2017).
- Based on regression lines from a study by Apostoli *et al*. (1999), the DFG stated that an airborne concentration of 0.001mg/m^3 (that is, the proposed WES-TWA) correlates with 15µg/L as the sum or AsIII, AsV, MMA and DMA in urine. (DFG, 2018).
- Based on the relationship between arsenic concentration in urine and airborne exposure Enterline *et al* (1987), an airborne concentration of 0.001mg/m^3 (that is, the proposed WES-TWA) equates to a BEI of 13µg/L (urine). (ACGIH®, 2001).

Considering the above information, and the proposed WorkSafe WES of 0.001mg/m^3, there is merit for setting a BEI at either 10 or 15µg/L. The ECHA recommended a BGV of 10µg As/L based on data from France and Belgium, which they considered preferable data as it controlled for seafood consumption.

4.0
Recommendations

WorkSafe considers its BEI of 35µg/L (urine) for arsenic and soluble compounds, as As, to be inadequate to manage health risks from possible workplace exposure, based on current knowledge.

It is proposed that WorkSafe adopt a BEI of 10µg As/L for the sum of inorganic arsenic compounds and its metabolites (MMA and DMA) in urine. (Note: prohibit fish consumption during 48 hours before sampling.)

Noting that the proposed **WES** and BEI values may not eliminate all risk, due to the uncertainty as to the carcinogenic threshold for arsenic 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

TERM	MEANING
95%CI	95% Confidence Interval.
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.
As	Arsenic.
BAR	*Biologische Arbeitsstoff-Referenzwerte*. Describes the background level of a substance which is present concurrently at a particular time in a reference population of persons of working age who are not occupationally exposed to this substance. 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. Occupational exposure can be assessed by comparing biomonitoring values in occupationally exposed persons with the BAR. A DFG term.
BEI	Biological Exposure Index.
BGV	Biological Guidance 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.
DMA	Dimethylarsinic Acid.
ECHA	The European Chemicals Agency (an agency of the European Union).
EKA	Exposure equivalents for carcinogenic substances. The 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.
Inhalable fraction	Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly <100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009b). (*cf.* Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter)
µg	Microgram or one millionth of a gram.
µg/L	Microgram or one millionth of a gram per litre.
mg	Milligram or one thousandth of a gram.
mg/m³	Milligrams of substance per cubic metre of air.
MMA	Monomethylarsonic Acid.
OEL	Occupational Exposure Limit (equivalent to a WES).
SMR	Standardised mortality ratio.
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.
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). *Arsenic and Soluble Inorganic Compounds 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.

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Notes

Published: March 2020

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WSNZ_3679_MAR 2020

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