Biological Exposure Indices (BEI)

REVIEW

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New Zealand Government

WORKSAFE NEW ZEALAND | MAHI HAUMARU AOTEAROA

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review looks at the Biological Exposure Indices (BEI) for 18 substances, or groups of substances.

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

The review includes recommendations to change a number or the current BEIs and to add new BEIs to the WorkSafe list of BEIs as published in the Special Guide *Workplace Exposure Standards and Biological Exposure Indices*, 9th Edition (WorkSafe, 2017).

This review considers BEIs from other jurisdictions/organisations around the world and their justification for setting those values. Note that only BEIs from other jurisdictions/organisations which have documented their rationale for setting the BEI have been considered for this review. This includes BEIs from the:

- American Conference of Governmental Industrial Hygienists (**ACGIH**®)
- European Scientific Committee on Occupational Exposure Limits (**SCOEL**)
- Deutsche Forschungsgemeinschaft (**DFG**) of Germany
- UK Health and Safety Executive (**HSE**).

All substances or their metabolites included in this review can be analysed in either New Zealand or Australia.

Terms that are **bold** (first occurrence only) are further defined in the Glossary.

2.0
Review of BEIs

IN THIS SECTION:

The BEIs have been reviewed for the following 18 substances or groups of substances, and a new WorkSafe BEI recommended.

2.1 Arsenic (elemental and soluble inorganic compounds)

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	100 µg arsenic/L of urine (sum of all metabolites)
ACGIH®	35 µg arsenic/L of urine (inorganic arsenic plus methylated metabolites)
DFG	50 µg arsenic/L of urine (arsenic plus methylated metabolites) (BLW)

TABLE 1: Arsenic (elemental and soluble inorganic compounds)

ACGIH®

In 2000, the ACGIH® revised its BEI® for arsenic from 50 µg/g creatinine to 35 µg/L arsenic in urine (ACGIH®, 2001a). They assigned it with a 'B' notation – this means arsenic may be present in biological samples from people not occupationally exposed (due to diet) and as a result could affect interpretation of the result.

Their BEI® is based on two complementary relationships:

1. the most likely value that would be observed at the ACGIH® **TLV-TWA** of 0.01 **mg/m³** (note WorkSafe's current **WES-TWA** is set at 0.05 mg/m³ but it has not been updated since its adoption in 1994 and is considered a priority for review) and
2. the observed relationship between exposure and lung cancer for urinary excretion of arsenic metabolites. A value of 35 µg/L is predicted at an observed standard mortality ratio (**SMR**) of approximately 100 (an SMR of about 100 denotes a baseline or background level of lung cancer).

The methodology recommended by the ACGIH® is the sum of inorganic arsenic and its methylated metabolites (monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA)) in urine, collected at the end of the work week. This provides an indication of inhalation exposure to elemental and soluble inorganic arsenic compounds. The BEI® does not apply to exposure to arsine gas, nor gallium arsenide.

DFG

In 2002, the DFG set a BLW of 50 µg arsenic/L urine (DFG, 2002). A BLW (Biologische Leit-Werte) is not the same as a BEI. It is the amount of arsenic or its metabolites which serves as an indicator for protective measures. BLWs are assigned for substances for which the available toxicological or occupational-medical data are insufficient for the establishment of a BEI value. This includes carcinogens such as arsenic and its inorganic compounds.

The DFG state:

- For the prevention of (non-carcinogenic) toxic effects of arsenic, irrespective of the carcinogenic potency of arsenic, exposure should remain below 50 µg arsenic/L urine.
- It is to be expected that arsenic-induced effects can develop at arsenic concentrations in urine in the range of 100 µg/L. Changes in the peripheral nerves of occupationally exposed persons were detected even at a mean arsenic concentration of 71 µg/L urine (Blom et al, 1985).
- The BLW value is compatible with the American (ACGIH®) BEI® value (35 µg arsenic/L urine, sampling at the end of the working week), as this refers to the collective median and does not represent an individual ceiling value.
- The method used is to measure inorganic arsenic and its methylated metabolites (MMA and DMA) in urine collected at the end of exposure, or end of shift after several previous shifts.
- Significant consumption of fish prior to testing can influence the result.
- The BLW is not relevant to arsine gas or salts of arsenic hydride.

WorkSafe

The WorkSafe BEI of 100 µg arsenic/L of urine (sum of all metabolites) has been unchanged since adoption in 1994.

WorkSafe does not consider its current BEI is acceptable to manage health risks. WorkSafe also does not consider the current method (sum of all metabolites) is as effective as the ACGIH® or DFG methods (inorganic arsenic and its methylated metabolites) as the organic arsenic compounds from dietary seafood will contribute to the 'sum of all metabolites'.

It is proposed that WorkSafe lowers the existing BEI for arsenic to 35 µg arsenic/L urine, measured as inorganic arsenic and its methylated metabolites.

The sample should be taken at the end of the work week, and diet should be considered in the sampling protocol.

2.2 Benzene

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	None
ACGIH®	25 µg S-phenylmercapturic acid (S-PMA) /g creatinine in urine 500 µg trans-trans-muconic acid (tt-MA) /g creatinine in urine
SCOEL	46 µg S-phenylmercapturic acid (S-PMA) /g creatinine in urine 28 µg benzene/L blood

TABLE 2: Benzene

ACGIH®

The ACGIH® BEI® for benzene is based on their TLV-TWA of 0.5 **ppm** which was derived from a review completed in 2001 (ACGIH®, 2001b). It has been assigned a notation of B (meaning it may be present in biological samples from people not occupationally exposed (due to exposure to vehicle emissions and from smoking) and this could affect interpretation of the result). Note WorkSafe's current WES-TWA is set at 1 ppm.

SCOEL

SCOEL adopted their biological limit values in 2006 based on:

- 46 µg S-phenylmercapturic acid/g creatinine in urine corresponds to air level of 1 ppm.
- 28 µg benzene/L blood corresponds to an air level of 1 ppm.
- The SCOEL 8-hour TWA for benzene is 1 ppm (set as a Binding Occupational Exposure Limit Values (**BOELV**) in 2004 under EU Directive 2004/37/EC). The Directive requires all EU states to set the value as the minimum standard (ie members states can set a lower WES (8-hour) than 1 ppm but no higher than 1 ppm). In 2006 SCOEL stated that human occupational exposures to benzene should be kept 'well below 1 ppm' (SCOEL, 2006).

WorkSafe

WorkSafe does not currently have a BEI for benzene.

It is proposed that WorkSafe adopts a new BEI for benzene of 25 µg/g creatinine in urine of S-phenylmercapturic acid (S-PMA).

The sample should be taken at the end of the work shift.

Although the proposed BEI is based on a lower WES-TWA (0.5 ppm) than WorkSafe's current WES (1 ppm), WorkSafe considers setting a lower BEI a prudent step to ensure workers' exposure to this carcinogen is reduced to a level below the WES.

2.3 Carbon disulphide

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	None
ACGIH®	0.5 mg 2-thioxothiazolidine-4-carboxylic acid (TTCA)/g creatinine in urine
SCOEL	1.5 mg TTCA/g creatinine
DFG	2 mg TTCA/g creatinine

TABLE 3:
Carbon disulphide

ACGIH®

ACGIH® completed a review of the BEI® for carbon disulphide in 2009 (ACGIH®, 2009). They assigned it a 'B' notation – this means TTCA may be present in biological samples from people not occupationally exposed (due to exposure to other substances that can be metabolised to carbon disulphide) and as a result this could affect interpretation of the result.

The ACGIH® BEI® is extrapolated from their 8-hour TLV-TWA (WES) of 1 ppm, which is based primarily on protecting workers from neurological endpoints, such as a reduction in conduction velocity in the motor and sensory nerves. They say all other organ systems including cardiovascular, reproductive, ophthalmologic and renal would also be protected at that WES value (and by implication, at that BEI® value).

SCOEL

SCOEL completed a review in 2008 (SCOEL, 2008). Their BEI is extrapolated from their recommended 8-hour TWA of 5 ppm. They report studies that show that an 8-hour TWA of 5 ppm corresponds to a mean biological value of ~1.0 to

1.6 mg TTCA/g creatinine, and that higher values may be indicative of excessive inhalation and/or dermal exposure.

SCOEL report the critical health effects in humans are neurotoxicity and cardiotoxicity. They reported various no observable adverse effects level (**NOAEL**) values for various health endpoints, but say that overall, the threshold/ NOAEL for the earliest non-clinical changes appear to be in the range of 3-10 ppm, and this leads to a recommendation of a TWA of 5 ppm. They report that this exposure concentration, which is based on the most subtle neurological and cardiovascular effects, is considered to be protective against the other reported effects, including those on reproductive function.

DFG

The DFG set a BEI value of 4 mg TTCA/g creatinine in 1998, and reviewed that value in 2008 in light of a reduction in their WES for carbon disulphide to 5 ppm (reduced from 10 ppm based on evidence that with several decades' exposure at the workplace, neurotoxic and cardiotoxic effects can occur in a concentration range below 10 ppm) (DFG, 2009). They reduced the BEI value to 2 mg TTCA/g creatinine.

WorkSafe

WorkSafe does not currently have a BEI for carbon disulphide.

It is proposed that WorkSafe adopts a new BEI for carbon disulphide of 0.5 mg TTCA/g creatinine in urine.

The sample should be taken at the end of the work shift.

Although the BEI is based on a lower WES-TWA (1 ppm) than WorkSafe's current WES (10 ppm), WorkSafe considers it a prudent step to set a lower BEI to ensure workers' exposure is reduced to a level below the WES.

WorkSafe intends to review the carbon disulphide WES-TWA in the near future.

2.4 Carbon monoxide

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	Carboxyhaemoglobin- 3.5% of haemoglobin (blood)
ACGIH®	Carboxyhaemoglobin- 3.5% of haemoglobin (blood), and/or 20 ppm in end-exhaled air
HSE (UK)	Carboxyhaemoglobin- 3.5% of haemoglobin (blood), and/or 30 ppm in end-exhaled air

TABLE 4:
Carbon monoxide

ACGIH®

The ACGIH® carboxyhaemoglobin BEI® of 3.5% corresponds to an 8-hour TLV-TWA of 25 ppm (the same as the WorkSafe WES-TWA) (ACGIH®, 2016). As carbon monoxide is eliminated unchanged by the lungs and there is an equilibrium between carbon monoxide in alveolar air and carboxyhaemoglobin, it is feasible to assess exposure based on exhaled breath. The ACGIH® report a study showing 20 ppm carbon monoxide in end-exhaled air corresponds to a carboxyhaemoglobin level of 3.5%. However this does not apply in emergency situations, although exposure can be roughly estimated using an equation provided in the ACGIH® documentation (not reproduced for the purpose of this discussion).

The end-exhaled air sample should be collected at the end of the work shift or during the highest exposure, and the value should only be used if exposure concentration during the shift is more or less constant. The ACGIH® note that samples collected more than 10 to 15 minutes after the end of exposure will be significantly lower than if collected immediately at the end of exposure.

Health and Safety Executive UK

The UK HSE has a biological monitoring guidance value (same as a BEI) of 30 ppm end-tidal breath carbon monoxide (HSE, 2001). This value is based on maintaining a carboxyhaemoglobin level of less than 5%. They report that exposure of a non-smoker to their UK 8-hour WES of 30 ppm carbon monoxide leads to an end of shift breath level of 30 ppm.

They report that a number of portable, direct reading carbon monoxide monitors for breath analysers are commercially available to take the measurement, which is collected at end of shift, or at end of exposure.

WorkSafe

WorkSafe considers that a BEI for end-exhaled air for carbon monoxide should be adopted in addition to the current BEI for carboxyhaemoglobin.

It is proposed that WorkSafe adopts a new BEI value of 20 ppm carbon monoxide in end-exhaled air, as this corresponds with the WorkSafe WES-TWA of 25 ppm (airborne exposure).

Sampling should be carried out using an appropriate breath analyser designed for this purpose.

2.5 Chromium VI (hexavalent chromium), water-soluble fume

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	30 µg total chromium/L of urine (end of shift at end of work week)
HSE (UK)	25 µg total chromium/L of urine (end of shift at end of work week) 10 µg/L total chromium in urine (increase during shift)

TABLE 5: Chromium VI (hexavalent chromium), water-soluble fume

ACGIH®

The ACGIH® BEI® for chromium (VI), water soluble fume, was set in 2004 and is based on total chromium in urine (ACGIH®, 2004). It is based in the observed correlation between the TLV-TWA of 0.05 mg/m^3 airborne soluble chromium (VI) compounds and urinary concentration. The basis of the ACGIH® TLV-TWA is *'to minimize the potential for respiratory tract irritation and cancer, dermatitis, and possible kidney damage'*.

On the basis of six studies, they also established a BEI® for the increase in urinary chromium during an 8-hour exposure of 10 µg/L.

WorkSafe

The WorkSafe BEI has been unchanged since adoption in 1994.

WorkSafe considers its current BEI and WES for hexavalent chromium are not protective enough of health. The WES-TWA is currently under review.

It is proposed that WorkSafe:

- lowers the existing BEI to 25 µg total chromium/L of urine. The sample should be taken at the end of the work shift, at the end of the work week.
- adopts a new BEI for the increase in urinary chromium during an 8-hour exposure of 10 µg/L.

WorkSafe considers setting a lower BEI a prudent step towards lowering workers' exposure to this carcinogen, to ensure workers exposure is reduced to a level below the WES. The WorkSafe hexavalent chromium WES-TWA is currently being reviewed.

2.6 Ethyl benzene

JURISDICTION OR ADVISORY BODY	BEI VALUE
ACGIH®	0.15 g/g creatinine (sum of mandelic and phenylglyoxylic acids in urine)
DFG	0.25 g/g creatinine (sum of mandelic and phenylglyoxylic acids in urine)

TABLE 6: Ethyl benzene

ACGIH®

The ACGIH® reviewed their BEI® for ethyl benzene in 2014 (ACGIH®, 2014a). They recommended the sum of mandelic and phenylglyoxylic acids in urine as the biological indicator of exposure. The BEI® corresponds, on average, to the level expected in a worker exposed to the ACGIH® ethyl benzene TLV-TWA of 20 ppm in the presence of xylene or other aromatic solvents. Their BEI® is based on field studies by Jang et al (2001) for workers exposed to various ethyl benzene concentrations.

They report that based on extrapolation, 20 ppm (the TLV-TWA) yields a predicted mandelic acid value of 0.15g/g creatinine. They also report a study by Korn et al (1992) which indicated a predicted concentration of 20 ppm would result in a mandelic acid concentration of 0.14 g/g creatinine (based on creatinine concentration of 0.14 g/L). In regards to phenylglyoxylic acid, they report that the study did not provide regression results but the mandelic acid/ phenylglyoxylic acid ratio was given as ranging from 0.6 to 11.

They state that exposure to ethyl benzene in combination with other aromatic solvents is common, and under most conditions the levels of these two ethyl benzene metabolites may be influenced significantly by competitive inhibition. The recommended BEI® takes this likely inhibition into account. In addition styrene is transformed to the same metabolites, thus results must be interpreted with caution and air measurements are recommended to confirm presence of ethyl benzene and absence of styrene.

The ACGIH® BEI® is aimed at preventing central nervous system depression, hearing loss and potential liver and kidney damage.

A urine specimen taken at the end of the shift is recommended.

DFG

The most recent DFG BEI was set in 2015 (DFG, 2015). They state that this value is based on correlation with the DFG airborne WES-TWA of 20 ppm and is based on the work of Korn et al (1992) (mentioned by ACGIH® above) who found that workers exposed to 12.6 ppm ethyl benzene produced a total average of 0.185 g/L of mandelic acid and phenylglyoxylic acid – assuming a creatinine

value of 1.2 g, this results in a value of 155 mg/L of the acids per gram creatinine. Based on the DFG WES-TWA, this correlates to a BEI of 0.25 g of mandelic acid plus phenylglyoxylic acid/g of creatinine.

DFG state that for interpretation of the mandelic acid and phenylglyoxylic acid metabolites, consideration must be given to the potential for styrene or phenyl glycol exposure. Thus simultaneous exposure to the substances will impact of the results.

They recommend samples are taken at the end of the work shift or end of exposure.

WorkSafe

WorkSafe does not have a BEI for ethyl benzene.

Although both the ACGIH® and the DFG have the same airborne WES value, they differ in their extrapolation of their WES value to a BEI®. It appears the ACGIH® BEI® is based on excretion data for mandelic acid, whereas the DFG value combines excretion data for both acids. WorkSafe considers the combination of both acids appropriate for setting a BEI.

It is proposed that WorkSafe adopts a new BEI for ethyl benzene of 0.25 g/g creatinine (sum of mandelic and phenylglyoxylic acids in urine).

The sample should be taken at the end of the work shift or end of exposure.

2.7 Fluorides

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	3 mg/L fluoride in urine (Prior to shift) 10 mg/L fluoride in urine (End of shift)
ACGIH®	2 mg/L fluoride in urine (Prior to shift) 3 mg/L fluoride in urine (End of shift)
SCOEL	8 mg/L fluoride in urine (End of shift)
DFG	4 mg/g fluoride in urine (end of exposure or end of shift)

TABLE 7: Fluorides

ACGIH®

The ACGIH® review of their BEI® for fluoride was completed in 2012 (ACGIH®, 2012). The ACGIH® BEIs® are based on prevention of skeletal fluorosis after exposure to the fluoride ion. Studies at the workplace were taken into account to recommend both BEIs®. They report:

- The methodology used is measuring of fluoride in urine to determine exposure to fluoride.
- Measurements in pre-shift samples are an indication of body burden and are significantly affected by environmental exposure. Therefore pre-shift samples represent long-term exposure to fluoride.
- Measurements in samples collected at the end of the shift are indicators of more recent exposure such as exposure during the previous work shift.
- Both sampling times should be considered for health preventative measures and in occupational hygiene.
- Both the pre and post-shift BEI® protects from skeletal fluorosis of stage II but may not protect from preclinical phases (stage O or I).
- The BEI® is not applicable to no-metal fluorides and organic fluoride-containing compounds.

- As dietary and environmental factors can vary fluoride body concentrations, repeated measurements are necessary.
- Biological levels of fluoride are indicators of the potential risk of systemic toxicity and cannot be used for the evaluation of irritative effects.

To establish the BEI® values the ACGIH® considered the following information:

- reports that the background levels in the general population of about 1 mg/L
- a study showing 3.4 mg/L in urine prior to shift was associated with skeletal fluorosis
- a study showing mean exposures between 0.3 and 7.5 mg/L prior to shift lead to an approximately 10-fold increase in bone density, a 2-fold increase in ossification, and a 3-4-fold increase in restricted joint movements compared to workers with levels between 0.25 and 1.8 mg/L
- a study showing mean exposures of 2 mg/L in pre shift samples were associated with mild increases in bone density and slight osteosclerosis that were not observed with mean concentrations of 1.6 mg/L
- a study showing mean concentrations of 2.9 mg/L excreted at the end of the shift were associated with mild increases in bone density and slight osteosclerosis
- a study showing mean concentrations of 5.2 mg/L excreted at the end of the shift were associated with increases in bone density and in some cases x-ray evidence of other osseous changes, mostly associated with disc lesions.

SCOEL

The SCOEL BEI was set in 1998 (SCOEL, 1998). It is based on fluoride ion in urine taken at the end of the shift. The value is based on a 1976 study indicating a urinary no-observable adverse effects level of 8 mg/L, and SCOEL consider the value would not be exceeded at an 8-hour TWA of 2.5 mg/m^3 of fluoride ion for mixtures of hydrogen fluoride and inorganic fluorides.

DFG

The DFG BEI was set in 2013 (DFG, 2013). It included the following considerations:

- The BEI for fluoride exposure must be oriented to the chronic fluoride effects such as fluorosis, osteosclerosis and osteoporosis.
- It has been taken into account that the maximum values of urinary fluoride excretion do not usually occur until 2–3 hours after the end of the shift. The urine samples should be collected after at least 3 days exposure.
- The DFG BEI value is established as a pair of values on the condition that internal exposures up to 7.0 mg fluoride/g creatinine in post-shift urine are only to be tolerated if after a pause in work of at least 16 hours and at the most 24 hours, the fluoride levels are a maximum of 4.0 mg fluoride/g creatinine in the next pre-shift urine sample.
- BEIs should be measured as fluoride anion (F^-) concentration.
- As a rule the additional pre-shift urine value should only then be determined if the post-shift urine value measured first is above 4.0 mg fluoride/g creatinine.
- As this BEI value documentation is oriented mainly to the chronic effects of the relevant occupational-medical internal fluoride exposure, a differentiation in the exposures due to hydrogen fluoride and fluoride can be dispensed with.
- The relating of the urinary excretion of fluoride to g-creatinine is necessary as a very large number of workplaces at which fluoride exposure occurs are high-temperature workplaces. According to the experience of the DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, at high-temperature workplaces with fluoride exposure the creatinine concentration is on average 1.9 g creatinine/L urine compared to an average

urinary excretion of 1.2 g creatinine/L urine. Neglecting the concentration of the urine at high-temperature workplaces would thus, with a large number of those exposed, lead to urine concentrations that seem too high if taken absolutely. For this reason standardisation with creatinine has been used for the BEI value of the fluorides.

- **NIOSH**, published a comprehensive evaluation of all the available studies on hydrogen fluoride and fluoride exposure in the industrial field. The tolerable internal and external fluoride exposures were compared in each case. The result of this evaluation was the statement that persons occupationally exposed to fluoride below a fluoride exposure of 2.5 mg F/m^3 air show a fluoride excretion in the post-shift urine of less than 7.0 mg/L. In the next pre-shift urine less than 4.0 mg/L urine was excreted. With this excretion rate no fluorosis or illnesses due to fluorine are to be observed (NIOSH, 1975; 1976). (Note the DFG WES-TWA for fluorides is 2.5 mg/m^3 thus this indicates the BEI is based on a correlation with the WES. The New Zealand WES-TWA is currently 2.5 mg/m^3).

WorkSafe

The WorkSafe BEI has been unchanged since adoption in 1994 of the then ACGIH® BEI®. Since that time the ACGIH® have reviewed and lowered their BEI® (see above). Based on the above BEI values, the most up to date is the ACGIH® BEI® and review.

Based on this information given in the ACGIH® review it is proposed that WorkSafe lowers the existing BEI to 2 mg/L F in urine (prior to shift), and 3 mg/L F in urine (end of shift) and note the following:

- The BEI is not applicable to no-metal fluorides and organic fluoride-containing compounds.
- As dietary and environmental factors can vary fluoride body concentrations, repeated measurements are necessary.
- Biological levels of fluoride are indicators of the potential risk of systemic toxicity and cannot be used for the evaluation of irritative effects.

2.8 Mercury (elemental)

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	50 µg in urine
ACGIH®	20 µg/g creatinine (prior to shift)
SCOEL	30 µg/g creatinine in urine
DFG	25 µg/g creatinine in urine

TABLE 8:
Mercury (elemental)

ACGIH®

The ACGIH® review of their mercury BEI® was completed in 2013 (ACGIH®, 2013b). They report:

- Mercury is toxic to both kidneys and nervous system with significant effects associated with urine concentrations above 35 µg/g creatinine. However, long term exposure to mercury leading to urinary mercury levels below 35 µg/g creatinine may be associated with memory deficits roughly equivalent to aging 10 years.

- Their BEI® is determined as a no-effect level. Because the significance of psychometric and renal biochemical changes observed below urinary concentrations of 20 µg/g creatinine are debatable, no safety factor is applied.
- Their BEI® applies only to exposures of elemental mercury.
- Urinary mercury is an indicator of average exposure during the past month rather than exposure at the time of urine collection. Throughout the day, the level of mercury in urine can vary.
- Occasional high levels of mercury in the urine should not be cause for immediate alarm and new samples should be taken.
- The long half-life of mercury means that sampling time is not critical but collection of urine in the morning prior to shift start is recommended to reduce possibility of contamination and effect of diurnal variation in excretion.
- Concentrations of mercury in urine reflect integrated long-term exposure, and the BEI® is meant as a reference value for samples collected after six months of occupational exposure.
- Measurement of mercury in blood is not recommended as the levels may be significantly affected by dietary exposures to organic mercury compounds.

SCOEL

The SCOEL review was completed in 2007 (SCOEL, 2007). They report:

- There are substantial data from human studies on the two toxic effects of principal concern (ie central nervous system (CNS) toxicity and kidney damage). Much of the information correlates the health state with biological monitoring rather than atmospheric monitoring of mercury exposure.
- There is common agreement in a number of studies that consistent CNS and kidney effects of adverse nature start to appear with urine mercury levels above 35 µg/g creatinine, which is viewed as the threshold for such effects.

> "However, recent meta-analytical data point to the possibility of beginning human neurobehavioral toxicity even below these limits, in a range of an excretion between 20 and 30 µg Hg/g creatinine. But the representativeness of the exposure data in most available studies is a possible critical issue. Taking into account the percentages of mean performances, the differences in effects between exposed and non-exposed subjects are comparable in their strength to steps in age norms of the tests between 5 and 20 years and correspond to about 5-7 percent of performance decrease. Assuming that higher working exposures in the past might be the reason for the effects measured in some studies, a critical level of 30 µg Hg/g creatinine can be recommended to avoid possible behavioural effects."

- Extrapolation from biological monitoring values to airborne exposure concentrations is subject to several qualifying conditions. Using the mean value for extrapolating from urinary mercury (µg/m^3) of 0.7, a value of 35 µg mercury/g creatinine is predicted to be equivalent to an airborne level of 25 µg/m^3. However, the ratio between levels of airborne exposures to mercury and levels in biological materials may vary with workplace conditions. This underlines that the biological monitoring of mercury exposures is superior to air monitoring, as it is more closely related to health effects.
- Acute exposure to mercury, for example through an accidental spill should be measured via blood testing.

DFG

The DFG BEI was set in 2005 as 30 µg/L of urine (equivalent to 25 µg mercury/g creatinine) (DFG, 2010a). DFG state the value is based on the expectation that clinically relevant neurotoxic or nephrotoxic effects would not occur with a maximum exposure at this level. In addition:

- DFG concluded that in a number of different studies, consistent changes in different mercury-relevant kidney parameters have been observed at mercury concentrations of 50 µg/L urine and above. No clear effects on kidney parameters were measured in workers found to have concentrations in urine of up to 35 or 42 µg mercury/L urine. In a 2003 study (El-Safty et al, 2003), nephrotoxic changes were found in non-smoking workers after more than 11 years of exposure, with concentrations in urine of 26 ± 19 µg mercury/L urine and in non-smoking workers after 10 years of exposure with levels of 31 ± 23 µg mercury/L urine, respectively. From the mean values and the standard deviations reported in this study, it can be deduced that the effects occur at concentrations corresponding to the 95th percentile of about 40 or 50 µg mercury/L urine. Thus, available data indicate that no relevant mercury-related nephrotoxic effects are to be expected at a concentration of 30 µg mercury/L urine when taking the 95th percentile into account.
- After publication of their 2006 decision on the mercury BEI they say:

> "Practical arguments were introduced into the discussion based on the fact that a large proportion of the industrial workplaces subject to mercury exposure involved working with heat. Under these conditions, creatinine is to be given precedence as reference. In this instance, for conversion from volume to creatinine reference, a factor of about 1.2 is obtained. Furthermore, in all the important published field studies used for evaluation in this context, creatinine was selected as reference. Thus, for mercury elimination in the urine, the use of creatinine values is now preferred. Taking the above factor as a basis, a BAT (BEI) value of 25 µg Hg/g creatinine is obtained."

WorkSafe

The WorkSafe BEI has been unchanged since adoption in 1994. WorkSafe considers its current BEI is not protective enough of health, and that it should be measured in urine as µg/g creatinine rather than as mercury µg/L in urine.

It is proposed that WorkSafe lowers the existing BEI for mercury in urine to 20 µg/g creatinine.

Samples should be taken prior to the work shift.

2.9 4,4-Methylene bis(2-chloroaniline) (also known as 2,2'-Dichloro-4,4' methylene dianiline, MOCA, MBOCA)

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	None
ACGIH®	Not quantitative – (biological monitoring should be considered but a specific BEI value could not be determined due to insufficient data)
SCOEL	Minimum detectable level
UK (HSE)	35 µg MBOCA/g creatinine

TABLE 9: 4,4-Methylene bis(2-chloroaniline) (also known as 2,2'-Dichloro-4,4' methylene dianiline, MOCA, MBOCA)

ACGIH®

The ACGIH® reviewed their BEI® for 4,4-methylene bis(2-chloroaniline) (MBOCA) in 2013 (ACGIH®, 2013a). They consider measurement of total MBOCA (after hydrolysis) in urine as 'an aid to exposure assessment'. They recommend that total MBOCA or MBOCA released after the hydrolysis of conjugates be used as an indicator of exposure. The ACGIH® did not set a numerical value as they could not justify one based on health outcome or airborne exposure. They say that the presence of MBOCA in urine above the detection limit for most methods cited (currently about 1 µg/L) is evidence of exposure to MBOCA but not necessarily an indication of a health risk or overexposure. They further state that since MBOCA is a suspected human carcinogen[1] it is especially prudent to monitor and control worker exposures to the lowest feasible levels.

SCOEL

A SCOEL review was completed in 2010 and an Annex in 2013 (SCOEL, 2013). They concluded that:

> "Since MOCA is a genotoxic carcinogen, no health based biological limit value can be recommended (SCOEL carcinogen group A). Since the general population is not exposed to MOCA, MOCA is not detected in the urine of occupationally non-exposed people. This means that urinary levels of occupationally non-exposed people stay below the detection limit of the method, which typically lay around 1–1.5 µg/L (3.7–5 nmol/L, ~ 0.37–0.5 µmol/mol creatinine) with commonly used analytical methods. Some methods reported to reach the detection limit of 0.1 µg/L. Thus, the Biological Guidance Value (BGV) for MOCA corresponds to the detection limit of the biomonitoring method.

They also say that:

> "In occupationally exposed populations, urinary MOCA levels (total MOCA in the urine) below 5 µmol/mol creatinine (~12 µg/g) can be reached using good working practises at the workplace. According to the risk assessment presented above, this corresponds to a cancer risk of 3–4 × 10-6 (ie 1 in 250,000 to 1 in 333,333). Urinary samples should be collected at the end of the work-shift."

SCOEL note that the UK HSE has recommended that worker's exposure to MOCA should be as low as reasonably practicable, located below their Biological Monitoring Guidance Value of 15 µmol MOCA/mol (35 µg/g)

[1] The substance is classified by the New Zealand Environmental Protection Authority as a confirmed human carcinogen.

creatinine. SCOEL report a study by Cocker et al (add year) which indicated that this value should be further reduced, as it would no longer act as an effective stimulus to reduce exposure.

The methodology used is measuring of total MOCA in urine (with alkaline hydrolysis) to determine exposure to MOCA. Sampling at end of shift is recommended.

HSE UK

The basis for the current HSE BEI of 35 µg/g is not available (HSE, 2001).

WorkSafe

WorkSafe does not have a BEI for MBOCA.

It is proposed that WorkSafe adopts a new BEI for total MBOCA in urine (after hydrolysis of conjugates) of the minimum detection limit of the analytical method.

The sample should be taken at the end of the work shift, and alkaline hydrolysis carried out on the sample.

WorkSafe considers this a prudent step to ensure workers' exposure to this carcinogen is identified, and steps can then be taken to minimise exposure so far as is reasonably practicable.

The WorkSafe WES-TWA is the same as that in the UK and from the ACGIH®.

2.10 4-4-Methylene diphenyl diisocyanate (MDI) (also known as (4-4-Methylene bisphenyl isocyanate (MDI))

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	None
ACGIH®	None
DFG	10 µg of 4,4-diaminodiohenylmethane/g creatinine (after hydrolysis) (end of shift, or end of exposure)

TABLE 10: 4,4-Methylene diphenyl diisocyanate (MDI) (also known as (4-4-Methylene bisphenyl isocyanate (MDI))

DFG

The DFG BEI for 4,4-methylene diphenyl diisocyanate (MDI) was set in 1997 and has remained unchanged since then (DFG, 1997). It included the following considerations:

- Comparatively little is known about the metabolism of MDI. At first, in analogy to the in vitro hydrolysis of the isocyanates, the reaction via carbaminic acid to the corresponding 4,4 diamino (methylene dianiline, MDA) catalysed by endogenous amines was postulated. The MDA excreted in the urine mainly in conjugated form (Henschler 1984; Henschler, 1992). MDA and its monoacetylation product, N-acetyl-MDA, can in addition be N-oxidized on one of the amino groups. This was concluded from the formation of sulfinic acid amides, which are produced from the reaction of the corresponding nitroso compound with the SH group of cysteine residues in glutathione, haemoglobin and human serum albumin (HSA).
- There is relatively good correlation of MDI in air with the urinary MDA excretion.
- Analysis of MDA and N-acetyl-MDA in urine is carried out after hydrolysis and enrichment.

- The time of sampling is important and should take place after the end of the shift, preferably at the end of the working week or shift period, and at the most 16 hours afterwards.

WorkSafe

WorkSafe does not have a BEI for MDI.

It is proposed that WorkSafe adopts a new BEI in urine for MDI of 10 µg of 4,4-diaminodiphenyl/g creatinine (after hydrolysis).

The sample should be taken at the end of the work shift, or end of exposure.

2.11 Methyl isobutyl ketone (MIBK)

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	2 mg MIBK/L in urine (end of shift)
ACGIH®	1 mg MIBK/L in urine (end of shift)
DFG	0.7 mg MIBK/L in urine (end of shift)

TABLE 11: Methyl isobutyl ketone (MIBK)

ACGIH®

The ACGIH® BEI® for methyl isobutyl ketone (MIBK) was set in 2010 (ACGIH®, 2010a). The BEI® is an indicator of recent exposure over the work day and corresponds to their TLV-TWA of 20 ppm. The TLV-TWA is based on protecting against human central nervous system symptoms, irritation, and gastro-intestinal symptoms.

The ACGIH® report that the determinant of MIBK in urine is specific to the exposure except when there is also exposure to methyl isobutyl carbinol (methyl amyl alcohol).

DFG

The DFG reviewed their BEI in 2014 (DFG, 2014). The value is based on their 8-hour WES for MIBK of 20 ppm. They consider there is good linear correlation between a concentration in air and urine results. They also consider that samples should be taken at the end of the shift.

Their WES value is based on avoiding the critical effects being irritation of the mucous membranes and central nervous system effects.

WorkSafe

WorkSafe considers its current BEI and WES for MIBK are not protective enough of health.

It is proposed that WorkSafe lowers the existing BEI to 0.7 mg MIBK/L in urine based on the most up to date review by the DFG.

The sample should be taken at the end of the work shift.

Although this proposed BEI is based on a lower WES-TWA (20 ppm) than the current WorkSafe WES (50 ppm), WorkSafe considers setting a lower BEI a prudent step towards lowering workers' exposure, to ensure workers' exposure is reduced to a level below the WES.

2.12 Pentachlorophenol (PCP)

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	1 mg/L total PCP in urine
ACGIH®	Non numeric BEI
DFG	None (see below)

TABLE 12: Pentachlorophenol (PCP)

ACGIH®

The ACGIH® completed a review of their pentachlorophenol (PCP) BEI® in 2014 (ACGIH®, 2014b).They removed their previous BEIs® of 2 mg/L total PCP in urine, and 5 mg/L free PCP in plasma, which were adopted in 1998. In removing the BEIs® they say that the published data are insufficient to allow correlation of airborne PCP levels or health effects, to levels of PCP in urine. Therefore a BEI® for PCP was not assigned, however an 'Nq' (nonquantitative) notation was assigned. They say that as the background level in the general US population is low and decreasing, urinary PCP levels above the background can be indicative of occupational exposure to PCP.

They report:

- The methodology to measure urinary PCP is robust.
- Analysis should include acid hydrolysis.
- The timing for sampling is prior to the shift and the end of the work week.
- Due to the half-life, several months of exposure are required for urine concentrations to reach steady state.
- Precautions must be taken to avoid contamination of the sample during collection due to contaminated clothing or skin.
- The BEI® for PCP in blood was removed due to insufficient data.

DFG

The DFG had a BEI value for PCP in urine but it was removed in 1992 (DFG, 2004). They consider that no BEI value can be evaluated from the relationship between airborne exposure and urinary levels. They report that although there is data comparing external and internal PCP levels, there is no data for urinary PCP at their (now removed*) WES level. They report that:

> "If one applies the biological values to the MAK value (which was 0.5 mg/m³) extreme PCP concentrations of approx. 8 mg/l blood or 3 mg/l urine result. It must also be taken into account that the absorption quotas differ with pentachlorophenol exposure on the one hand and its easily soluble phenolates on the other. In a study by the US EPA it was also determined that there is no correlation between the external and internal exposure. The biological values are known to take into account both inhalational as well as the oral and percutaneous uptake. The latter route of absorption is of importance in particular with an occupational exposure to pentachlorophenol."

* When PCP was classified as a Category 2 carcinogen (Substances that are considered to be carcinogenic for man because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can make a significant contributon to cancer risk), their WES and BEI were removed. In 2004 they set 'exposure equivalents' for PCP which compare air concentrations with urine levels. They report that: a value of 0.001 mg/m³ PCP in air is equivalent to 6 µg/L PCP in urine (extrapolated data); 0.05 mg/m³ PCP in air is equivalent to 300 µg/L urine, and 0.1 mg/m³ PCP in air is equivalent to 600 µg/L urine.

WorkSafe

Although PCP itself is no longer used in New Zealand, and its approval was revoked by the then New Zealand Environmental Risk Management Authority in 2008, there is the potential for exposure (eg during remediation or disposal activities).

Considering there is potential for exposure, and routes of exposure include oral and percutaneous uptake as well as airborne, WorkSafe considers it useful to maintain guidance on biological levels. As the BEI has not been reviewed since 1994 it is timely to review the value.

It is proposed that WorkSafe changes the existing BEI to a non-numeric BEI for PCP in urine (with acid hydrolysis). As such any level measured in the body (above analytical detection limits) indicates exposure has occurred and action should be taken to manage exposure.

Samples should be taken prior to the shift and the end of the work week.

The presence of PCP will indicate if exposure has occurred.

2.13 Phenol

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	250 mg phenol /g creatinine
ACGIH®	250 mg phenol /g creatinine
SCOEL	120 mg phenol/g creatinine
DFG	200 mg phenol /g creatinine (**BLW***)

TABLE 13: Phenol

ACGIH®

The ACGIH® review of phenol was completed in 2006 (ACGIH®, 2006). The BEI® is based on correlation between inhalation exposure at the TLV-TWA (5 ppm) and the expected levels (with hydrolysis) in urine specimens collected at the end of the shift. They report that there is no inhalation health effect expected at the exposure level predicted at the BEI® value. Their TLV-TWA is based on preventing systemic toxicity (cardiovascular, hepatic, renal and neurological effects), assuming that dermal contact with phenol or its solution is avoided.

They note that common household medicines and cleaning products can contain phenol and can result in urinary phenol measurements of up to 20 mg/g creatinine. They also note that phenol in urine can result from high exposure to benzene, and as such they give the BEI® an 'Ns' notation meaning it is non-specific to phenol exposure.

They recommend that analytical methods and hydrolysis must be selected carefully to avoid the interference of background levels and to assure that hydrolysis provides for measurement of total phenol.

SCOEL

The SCOEL review was completed in 2003 (SCOEL, 2003). The SCOEL 8-hour WES is set at 2 ppm and the BEI is based on correlation with this TWA. They report studies that show an 8-hour exposure to 2 ppm phenol corresponds to a urine concentration, measured at the end of the shift, of 120 mg phenol/g creatinine.

* ???

For context, SCOEL provide this summary on the setting of their WES:

> "The findings of repeated oral dosing studies in animals have been conflicting, so that the overall picture is confused. Some studies have indicated no effects in rats and mice receiving hundreds of **mg/kg**/day; others have reported adverse effects in mice receiving as little as 2 mg/kg/day. In the opinion of the SCOEL, the quality and reliability of the overall repeated oral exposure database is inadequate for use in the derivation of an OEL proposal. Hence, the SCOEL concluded that repeated daily exposure to 5 ppm phenol would probably produce no local or systemic toxicity in experimental animals. An uncertainty factor of 2 was applied to allow for the absence of human data. Taking into account the preferred value approach (the use only of decimals of 1, 2 or 5 for the WES value), an 8-hour TWA of 2 ppm is recommended. The genotoxic potential of phenol in vivo is weak and probably metabolism-dependent, so that at low concentrations no genotoxic potential is expected and a threshold mechanism can be assumed."

DFG

The DFG set their BLW value of 200 mg/L phenol in urine in 2003 (DFG, 2005a). It is the amount of phenol which serves as an indicator for protective measures. BLWs are assigned for substances for which the available toxicological or occupational-medical data are insufficient for the establishment of a BEI value. This includes carcinogens, and as phenol was classified as a Category 3 carcinogen by DFG, their 8-hour WES, and the BEI were withdrawn in 1998. A Category 3 carcinogen is defined as Substances for which *in vitro* or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories.

The DFG state:

- Damage to the kidneys is observed when the plasma creatinine levels increase to above 1 mg/decilitre and the proportion of free phenol detectable in urine exceeds 150 µg/g creatinine (Lewalter and Neumann, 1998). A value based on free phenol that could be used as a threshold value in biological material has not yet been adequately validated. A value of 150 µg free phenol/g creatinine is generally not exceeded by 95% of persons exposed to phenol with values up to 200 mg total phenol/g creatinine, corresponding to a value of 200 mg total phenol/L urine. In view of this, a BLW value has been set of 200 mg total phenol/L urine.
- Around 6% of central Europeans have a genetic polymorphism that makes it difficult for them to metabolize phenol. For these people, the determination of total phenol alone is not sufficient protection. In such cases, additional determination of free phenol is recommended. The BLW value for total phenol should therefore be regarded as provisional until there are sufficient data available to evaluate a threshold limit value for free phenol.
- Sampling should be carried out at the end of exposure or the end of the shift.

WorkSafe

The TLV-TWA value on which the ACGIH® established their phenol BEI is the same as the current WorkSafe WES. For this reason it would be reasonable to set the same BEI as the ACGIH®. The ACGIH® TLV-TWA is based on studies showing workers exposed at or below 5.2 ppm had experienced no ill effects (studies carried out in 1942 and 1989). However, SCOEL report that daily exposures of 5 ppm would probably produce no local or systemic toxicity in animals, but in

setting their WES consider an uncertainly factor of 2 should be applied as there is 'an absence of human data'.

It is proposed that WorkSafe lowers the existing BEI in urine to 120 mg phenol/g creatinine taken at the end of the shift and measuring total phenol in urine (with hydrolysis) based on the SCOEL approach of applying an uncertainty factor to the NOAEL (for animals) of 5 ppm.

The sample should be taken at the end of the work shift.

Although this proposed BEI is based on a lower WES-TWA (2 ppm) than the current WorkSafe WES (5 ppm), WorkSafe considers setting a lower BEI a prudent step towards lowering workers' exposure and to ensure workers' exposure is reduced to a level below the WES.

2.14 Tetrahydrofuran (THF)

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	None
ACGIH®	2 mg tetrahydrofuran/L urine
DFG	2 mg tetrahydrofuran/L urine

TABLE 14: Tetrahydrofuran (THF)

ACGIH®

The ACGIH® review of the BEI® for tetrahydrofuran (THF) was completed in 2008 and noted that THF is an A3 carcinogen (confirmed animal carcinogen with unknown relevance to humans) (ACGIH®, 2008a). Inhalation appears to be a significant route of absorption. A 'skin' notation has been assigned to THF, based on research indicating that THF is readily absorbed through the skin and biological monitoring should be considered when there is a risk of dermal absorption.

The ACGIH® report that while no metabolites suitable for exposure monitoring are known, the presence of the unchanged solvent in exhaled breath, blood and urine is a qualitative indicator of exposure to THF. Monitoring of THF in urine can be used for quantitative evaluation of recent exposure to THF and the test is specific. There is inadequate information to set a BEI® for THF in exhaled breath or blood.

The ACGIH® BEI® value is based on the level expected to appear in the urine when exposure is equivalent to an inhalation-only 8-hour TLV-TWA of 50 ppm. The **TLV®** is based on limiting upper respiratory tract irritation, neuropathy, liver cell proliferation, and central nervous system effects (anaesthesia and neuropharmacological effects). Note for comparison the current WorkSafe WES-TWA is 100 pm.

The methodology used is measuring of THF in urine to determine exposure to THF. Sampling is recommended to be carried out at the end of an exposure or shift (within one hour of the end of exposure).

DFG

The DFG BEI is based on their 8-hour WES of 50 ppm (DFG, 2005b). As this value was lowered in 1995 from 200 ppm to 50 ppm they also reviewed and updated the BEI. Using data from both a field study and lab study and the

resulting regression equation for airborne concentrations versus internal levels, they reassessed their BEI from a previous value to the current 2 mg THF/L urine.

They give the substance a 'skin' notation, and a Carcinogen category 4 rating *'considered to be carcinogenic for humans and for which a MAK value can be derived. A non-genotoxic mode of action is of prime importance and genotoxic effects play no or at most a minor part provided the MAK and BAT (WES and BEI) values are observed*'.

WorkSafe

WorkSafe does not have a BEI for tetrahydrofuran.

It is proposed that WorkSafe adopts a new BEI for tetrahydrofuran of 2 mg THF/L urine.

The sample should be taken at the end of the exposure or work shift (within one hour of the end of exposure).

Although this proposed BEI is based on a lower WES-TWA (50 ppm) than the current WorkSafe WES (100 ppm), WorkSafe considers setting a lower BEI a prudent step towards lowering workers' exposure and to ensure workers' exposure to this suspected human carcinogen (6.7B under HSNO classification) is minimised so far as is reasonably practicable.

2.15 Toluene diisocyanate-2,4- or 2,6- or mixture of isomers (TDI)

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	None
ACGIH®	5 µg/g creatinine measured as toluene diamine in urine (with acid hydrolysis)

TABLE 15: Toluene diisocyanate-2,4- or 2,6- or mixture of isomers (TDI)

ACGIH®

The ACGIH® reviewed the BEI® for toluene diisocyanate (TDI) in 2016 (ACGIH®, 2016). It is based on the levels of metabolites expected with an exposure to the equivalent of the TLV-TWA of 1 ppb (0.001 ppm) (equivalent to 0.007 mg/m^3). The determination of TDI in air concentration versus urinary toluene diamine levels was derived from studies carried out from 1993 to 2005. Estimated urinary toluene diamine levels at 1 ppb TDI were averaged across the studies.

The ACGIH® report that:

- 2,4- and 2,6-TDI rapidly react to their respective toluene diamines following adsorption, and the toluene diamines are excreted in the urine.
- It appears that creatinine normalisation improves correlation between airborne TDI and urinary toluene diamine levels, therefore creatinine correction is recommended.
- Due to short half-life, little or no accumulation of toluene diamine is expected during the work week so urine samples obtained at the end of any shift are appropriate.
- Hydrolysis is a critical step in toluene diamine analysis.

WorkSafe

WorkSafe does not have a BEI for TDI.

It is proposed that WorkSafe adopts a new BEI for TDI of 5 µg/g creatinine measured as toluene diamine in urine (with acid hydrolysis). Samples should be taken at the end of the work shift.

Although this proposed BEI is based on a lower WES-TWA (0.007 mg/m³) than the current WorkSafe WES (0.02 mg/m³), WorkSafe considers lowering the BEI a prudent step to ensure workers' exposure is reduced to a level below the WES.

WorkSafe intends to review the TDI WES-TWA in the near future.

2.16 Toluene

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	None
ACGIH®	0.03 mg/L (toluene in urine) 0.3 mg/g creatinine (*o*-cresol in urine) with hydrolysis
DFG	1.5 mg/L creatinine (*o*-cresol in urine)

TABLE 16: Toluene

ACGIH®

ACGIH® reviewed their BEIs® for toluene in 2010 (ACGIH®, 2010b). They are based on the concentration likely to be observed in individuals exposed by inhalation only, at the TLV-TWA of 20 ppm for toluene. The BEI® values were determined based on studies carried from 1979 and 2008. They report that:

- most studies suggest a value of 0.03 mg/L for urinary toluene
- with the exception of one study which showed a higher *o*-cresol value than other studies, field studies support a BEI® of 0.3 mg/g creatinine (*o*-cresol in urine).

They report:

- That unchanged toluene in urine is collected at the end of the shift. The measurement is an indicator of exposure over the workday, and is a sensitive indicator of exposure that can be used to assess exposure to toluene concentrations at or below 20 ppm.
- *O*-cresol is present in urine as a conjugate. The common methods for hydrolysis of urine is required otherwise measurements would only indicate free *o*-cresol.
- Non-occupational sources of exposure to *o*-cresol due to inhalation of tobacco smoke and other environmental factors create a potentially significant background problem. As such *o*-cresol concentrations above the BEI® must be confirmed using urinary toluene measurements to reduce false positives.
- Most field studies suggest a value of 0.03 mg/L for urinary toluene at a toluene concentration of 20 ppm (based on studies from 2000 to 2008).
- There are a limited number of laboratory studies on volunteers under controlled conditions for *o*-cresol in urine. All of these studies were done using toluene exposures at 100 ppm, so estimated *o*-cresol levels at 20 ppm were calculated from linear extrapolation of the data at 100 ppm.

DFG

The DFG BEI value was reviewed and updated in 2010 (DFG, 2010b). It is based on extrapolation from an airborne concentration of 50 ppm toluene (the DFG 8-hour WES value). The extrapolation is based on work by Angerer and Schaller (1994). According to this work, a concentration of 50 ppm produces between 1.1 and 2.4 mg *o*-cresol/L urine. Based on this, they set their BEI to 1.5 mg *o*-cresol/L urine.

They say:

- Samples are to be taken at the end of exposure or at the end of the work shift or for long-term exposure after several consecutive work shifts.
- The method used (hydrolysis) should ensure complete digestion of the excreted glucuronide of *o*-cresol, and that the previous American BEI® value (presumably they mean the ACGIH®) disregards if a full hydrolysis of the excreted glucuronide in urine has taken place.
- For the interpretation of the concentration of *o*-cresol in urine it is crucial to use the published analysis method for the determination of the concentration.
- The concentration of *o*-cresol in urine in the non-smoking general populous is more than a decimal power lower than the BEI value and can be neglected when interpreting the data.
- This differs for the case of smokers where the concentration of *o*-creosol in the urine of smokers is at a value of 0.2 mg/g creatinine (approx. 0.3 mg/L).
- The BEI value refers to normal concentrated urine with a creatinine range of 0.3 – 3 g/L. For improved accuracy of the analysis a more narrow range of 0.5 – 2.5 g/L is recommended. Urine samples with creatinine outside of the above ranges should be retaken with normally hydrated test subjects.

WorkSafe

WorkSafe does not have a BEI for toluene.

It is proposed that WorkSafe adopts new BEIs for toluene of 0.03 mg/L (urine) and 0.3 mg/g creatinine (*o*-cresol in urine) with hydrolysis.

Samples should be taken at the end of exposure or the end of the work shift.

2.17 Trichloroethylene (TCE)

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe	100 mg trichloroacetic acid/L urine
ACGIH®	15 mg trichloroacetic acid/L urine
DFG	None (see below)
SCOEL	20 mg trichloroacetic acid/L urine

TABLE 17:
Trichloroethylene (TCE)

ACGIH®

ACGIH® set their BEI® for trichloroethylene (TCE) in 2008 (ACGIH®, 2008b). TCE is extensively metabolised with the major metabolites being trichloroacetic acid (TCAA) and trichloroethanol (TCOH). The BEI® is extrapolated from the TLV-TWA of 10 ppm which should protect against the central nervous system effects of TCE as well as the potential for renal toxicity and cancer.

The ACGIH® report that:

- Measurement of the urinary concentration of TCAA or the blood measurement of TCOH without hydrolysis is recommended.
- Urine sampling is recommended to be carried out at the end of the shift, at the end of the week.
- Since TCAA and TCOH are also metabolites of other compounds (eg methyl chloroform) monitoring of TCE in end-exhaled air continues to be recommended as a confirmatory test.
- Neither TCAA or TCOH are along the causal pathway for renal effects, and are to be considered internal dose markers.
- Careful data interpretation is required due to a large number of factors that affect the biological concentration such as sampling time, ethnic differences, co-exposure with other solvents, certain medications and alcohol intake.
- Extrapolation of airborne concentration to urinary TCAA levels was based on studies carried out from 1970 to 1979 which showed a mean urinary TCAA level of 17 mg/L calculated for a 10 ppm exposure.

DFG

The DFG previously had a BEI however it was removed in 1997 when trichloroethylene was classified as a Category 1 Carcinogen (substances that cause cancer in man and can be assumed to contribute to cancer risk) (DFG, 2016).

In 2001 they set 'exposure equivalents' for trichloroethylene which compare air concentrations with trichloroacetic acid/L urine values. They report that a value of 10 ppm is equivalent to 20 mg trichloroacetic acid /L urine based on a 2010 study (Csanády GA, et. al. *Trichloroacetic acid in urine as biological exposure equivalent for low exposure concentrations of trichloroethene*. Arch Toxicol 84: 897–902).

DFG set a BAR value in 2010 of 0.07 mg trichloroacetic acid/L of urine. A BAR is a reference population of persons of working age who are not occupationally exposed to this substance.

SCOEL

SCOEL set their BEI in 2009 (SCOEL, 2009). They report:

- Biological monitoring of TCE is well established by measuring TCA concentrations in the urine after the shift.
- A concentration of 10 ppm TCE in air corresponds to 20 mg TCA/L urine. This is based on results from a 2003 study.
- As the SCOEL WES is 10 ppm, thus the recommended BEI is 20 mg TCA/L urine.

WorkSafe

WorkSafe reduced its WES-TWA for trichloroethylene to 10 ppm in 2017. Although the ACGIH® considers 10 ppm in air equivalent to 15 mg trichloroacetic acid/L urine, whereas SCOEL and DFG consider it equivalent to 20 mg trichloroacetic acid/L urine.

It is proposed that WorkSafe adopts the ACGIH® BEI and lowers the existing BEI to 15 mg trichloroacetic acid/L urine in line with the 2017 WorkSafe WES of 10 ppm.

WorkSafe considers this a prudent step to ensure workers' exposure to this confirmed human carcinogen is minimised so far as is reasonably practicable.

The sample should be taken at the end of the work shift, at the end of the work week.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a 501(c)(3) charitable scientific organization, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the *TLVs® and BEIs® book and Guide to Occupational Exposure Values*.
BEI	Biological Exposure Index.
BLW	Biologische Leit-Werte is a German biological guidance value and is the amount of a chemical substance or its metabolites which serves as an indicator for necessary protective measures. BLW values are derived for carcinogens and for substances without sufficient data.
BOELV	Binding occupational exposure limit value. The European Union requires all member states to set this value (or lower) as a BEI.
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.
HSE	The UK Health and Safety Executive.
Metabolite	The intermediates and products of metabolism of substances.
mg	Milligram or one thousandth of a gram.
mg/m³	Milligrams of substance per cubic metre of air.
mg/kg	Milligrams of substance per kilogram.
ml	Millilitre, or thousandth of a litre.
NIOSH	The National Institute for Occupational Safety and Health (NIOSH) is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. NIOSH is part of the Centers for Disease Control and Prevention (CDC) within the U.S. Department of Health and Human Services.
NOAEL	No observable adverse effects level.
ppm	Parts per million parts of air.
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
SMR	Standardized Mortality Ratio (SMR) is a ratio between the observed number of deaths in a study population and the number of deaths would be expected, based on the age- and sex-specific rates in a standard population and the age and sex distribution of the study population.
TLV®	Threshold Limit Value (see TLV-TWA below). An ACGIH® term.
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

ACGIH® (2001a). Arsenic and Soluble Inorganic Compounds. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2001. Reprinted with permission.

ACGIH® (2001b). Benzene. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2001. Reprinted with permission.

ACGIH® (2004). Chromium (VI), Water Soluble Fume. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2004. Reprinted with permission.

ACGIH® (2006a). Phenol. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2006. Reprinted with permission.

ACGIH® (2006b). Toluene diisocyanate-2,4- or 2,6- or mixture of isomers (TDI). Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2006. Reprinted with permission.

ACGIH® (2008a). Tetrahydrofuran. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2008. Reprinted with permission.

ACGIH® (2008b). Trichloroethylene. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2008. Reprinted with permission.

ACGIH® (2009). Carbon disulfide. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2009. Reprinted with permission.

ACGIH® (2010a). Methyl Isobutyl Ketone. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2010. Reprinted with permission.

ACGIH® (2010b). Toluene. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2010. Reprinted with permission.

ACGIH® (2012). Fluorides. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2012. Reprinted with permission.

ACGIH® (2013a). 4,4'-methylene Bis(2-Chloroaniline). Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2013. Reprinted with permission.

ACGIH® (2013b). Mercury, Elemental. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2013. Reprinted with permission.

ACGIH® (2014a). Ethyl Benzene. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2014. Reprinted with permission.

ACGIH® (2014b). Pentachlorophenol. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2014. Reprinted with permission.

ACGIH® (2016). Carbon Monoxide. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th Edition, ACGIH®, Cincinnati, Ohio. Copyright 2016. Reprinted with permission.

Angerer J, Schaller KH. Benzol und Alkylbenzole (BTX-Aromaten) (1994). In: Henschler D (Hrsg) Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Band 2: Analysen in biologischem Material, 11. Lieferung, VCH, Weinheim.

Csanády GA, et. al. (2010). Trichloroacetic acid in urine as biological exposure equivalent for low exposure concentrations of trichloroethene. Arch Toxicol 84: 897–902).

DFG (1997). The MAK Collection Part IV: BAT Value Documentations Vol 5. 4,4'-Methylene diphenyl diisocyanate (MDI) (inhalable fraction).

DFG (2002). The MAK Collection Part II: BAT Value Documentations Vol 4. Arsenic and inorganic arsenic compounds (with the exception of arsenic hydride and its salts).

DFG (2004). The MAK Collection Part IV: BAT Value Documentations Vol 5 Addendum Decklatt zu Pentachlorphenol.

DFG (2005a). The MAK Collection Part II: BAT Value Documentations Vol 4. Phenol, Addendum.

DFG (2005b). The MAK Collection Part II: BAT Value Documentations Vol 4. Tetrahydrofuran, Addendum.

DFG (2009). The MAK Collection Part IV: BAT Value Documentations Vol 5. Carbon disulphide, Addendum.

DFG (2010a). The MAK Collection Part IV: BAT Value Documentations Vol 5 Addendum to Mercury and Its Inorganic Compounds.

DFG (2010b). The MAK Collection Part IV: BAT Value Documentations Vol 5 Addendum zu Toluol.

DFG (2013). The MAK Collection Part II: BAT Value Documentations Vol 4. Addendum zu Fluorwasserstoff und anorganische Fluorverbindungen (Fluoride).

DFG (2014). Addendum to Hexone (methyl Isobutyl Ketone) The MAK Collection for Occupational Safety and Health Vol 2, No 2.

DFG (2015). The MAK Collection Part II: BAT Value Documentations Vol 4. Ethylbenzol, Addendum.

DFG (2016). The MAK Collection Part IV: BAT Value Documentations Vol 5 Addendum to Trichloroethylene.

HSE (2001). Biological monitoring Guidance Values – Guidance Sheet for Method for Monitoring Carbon Monoxide by Breath.

HSE (2001). Biological monitoring Guidance Values – Guidance Sheet for Methylene dianiline (MbOCA) in urine.

Jang J.Y., Droz P.O., Kim S. (2001). Biological monitoring of workers exposed to ethylbenzene and co-exposed to xylene. Int Arch Occup Environ Health Vol 74:31-37.

Korn M., Gfroner W., Herz R. et al. (1992). Stereometabolism of ethylbenzene in man: Gas chromatographic determination of urinary excreted mandelic acid enantiomers and phenylglyoxylic acid and their relations to the height of occupational exposure. Int Arch Occup Environ Health Vol 64: 75-78.

Maitre A., et al. (1996) Urinary hexane diamine as an indicator of occupational exposure to hexamethylene diisocyanate. Int Arch Occup Environ Health 69:65-98.

NIOSH (1975). Criteria for a recommended standard. Occupational Exposure to inorganic Fluorides. HEW Publication Nr. 76–103.

NIOSH (1976). Criteria for recommended standard Occupational Exposure to Hydrogen Fluorides. HEW Publication Nr. 76-143.

SCOEL (1998). Recommendation from the Scientific Committee on Occupational Exposure Limits for Fluorine, Hydrogen Fluoride and Inorganic Fluorides (not uranium hexafluoride). SCOEL/SUM/56.

SCOEL (2001). Recommendation from the SCOEL/SUM/83. Scientific Committee on Occupational Exposure Limits for Lead and its inorganic compounds.

SCOEL (2003). Recommendation from the Scientific Committee on Occupational Exposure Limits for Phenol. SCOEL/SUM/16.

SCOEL (2006). Recommendation from the Scientific Committee on Occupational Exposure Limits for Benzene SCOEL/SUM/140.

SCOEL (2007). Recommendation from the SCOEL/SUM/84. Scientific Committee on Occupational Exposure Limits for Elemental mercury and inorganic divalent mercury compounds.

SCOEL (2008). Recommendation from the Scientific Committee on Occupational Exposure Limits for Carbon Disulphide SCOEL/SUM/82.

SCOEL (2009). Recommendation from the Scientific Committee on Occupational Exposure Limits for trichloroethylene. SCOEL/SUM/142.

SCOEL (2013). Recommendation from the Scientific Committee on Occupational Exposure Limits for 4,4'-Methylene-bis(2-chloroaniline) [MOCA] SCOEL/SUM/174.

SCOEL (2014). Recommendation from the Scientific Committee on Occupational Exposure Limits List of Recommended Health-Based Biological Limit Values (BLVs) and Biological Guidance Values (BGVs).

WorkSafe (2017). Workplace Exposure Standards and Biological Exposure Indices, 9th Ed. worksafe.govt.nz/worksafe/information-guidance/all-guidance-items/workplace-exposure-standards-and-biological-exposure-indices

Notes

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PO Box 165, Wellington 6140, New Zealand

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WORKSAFE
NEW ZEALAND | MAHI HAUMARU AOTEAROA

Level 6, 86 Customhouse Quay
PO Box 165, Wellington 6140
0800 030 040 worksafe.govt.nz