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Hazardous Chemical Agents Regulations, 2021

Biological Monitoring

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Member of Technical Committee 7

DEPARTMENT OF EMPLOYMENT AND LABOUR

NO. R. 280 29 March 2021

OCCUPATIONAL HEALTH AND SAFETY ACT, 1993

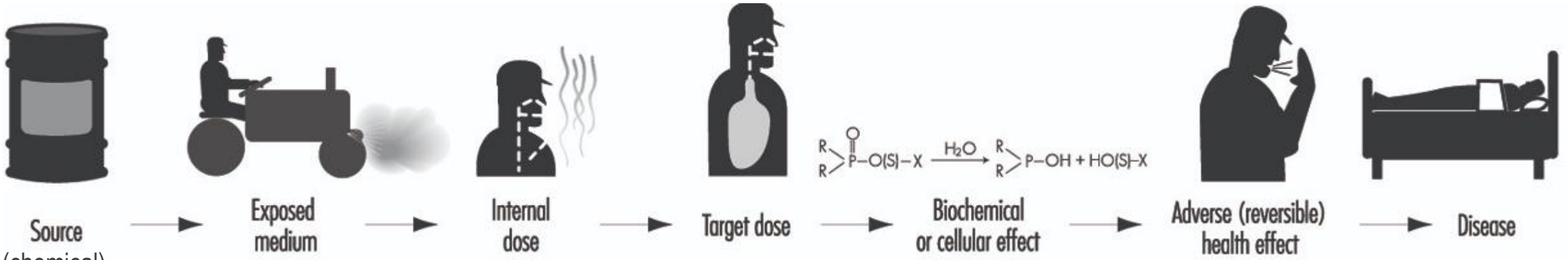
REGULATIONS FOR HAZARDOUS CHEMICAL AGENTS, 2021

Overview

- Brief Overview of Biological Monitoring (guidelines from the ILO)
- Where this guidance information is contained in Annexure 3
- Introduction to the new Biological Exposure Indices
- The link between the new OELs & the new BEIs
- Discussion

What is Biological Monitoring?

"The measurement and assessment of agents or their metabolites either in tissues, secreta, excreta, expired air or any combination of these to evaluate exposure and health risk compared to an appropriate reference"



INDUSTRIAL HYGIENE (AIR) MONITORING

BIOLOGICAL MONITORING

EXPOSURE MONITORING

BIOLOGICAL EFFECT MONITORING

HEALTH (MEDICAL) SURVEILLANCE

What do we measure when doing Biological Monitoring?

- Most often the amount of the chemical, or one or more of its metabolites, to which the worker is exposed, in blood or urine (rarely in milk, saliva, or fat)

Less often,

- the concentration of volatile organic compounds (solvents) in alveolar air
- the biologically effective dose of compounds which have formed adducts to DNA or other large molecules and which thus have a potential genotoxic effect.

Advantages of Biological Monitoring

- Includes absorption (uptake) of a substance via all routes, including the skin & GIT.
- Addresses the issue of uptake in circumstances that affect the degree of exposure, such as the physical effort required by the job, ventilation, or climate
- Provides a means to test the efficacy of PPE and work practices
- Includes exposure as a result of worker mobility in the working environment (eg roving jobs)
- Assesses exposure over an extended time period (eg the full work week, or longer)
- Addresses the quantity of a substance absorbed where individual factors that can influence the toxicokinetics of the chemical; for example, age, sex, genetic features, or functional state of the organs where the toxic substance undergoes biotransformation and elimination.
- overall exposure as a result of different sources of pollution, both occupational and non-occupational (also a disadvantage)

Practical Considerations in Biological Monitoring

Time of sampling

- Influenced by the metabolism of the agents to be measured
- To guide this, Table 4 in the HCA regs provides a recommendation (“end of shift”, “end of workweek”, etc.)

Interfering factors that affect the interpretation of the levels

- Physiological factors - diet, sex and age
- Personal habits - smoking and alcohol consumption
- Contamination during collection / processing (dust from clothing lands in the sample)
- Genetic factors affecting metabolism, as seen in various ethnic groups
- Impaired organ function (eg impaired kidney function and cadmium levels)
- Medications?
- Multiple exposures to toxic substances at work (they can interfere with each other’s biotransformation or excretion)

Some limitations of Biological Monitoring

- The list of substances which can be monitored biologically is still rather small.
- For acute exposure, biological monitoring supplies useful information only for exposure to substances that are rapidly metabolized, (e.g. aromatic solvents).
- Sometimes we don't know if the levels of a substance measured reflects current or cumulative exposure (e.g. urinary cadmium and mercury).
- Generally, biological indicators of internal dose allow assessment of the degree of exposure, but do not furnish data that will measure the actual amount present in the critical organ
- There is often little knowledge of possible interference in the metabolism of the substances being monitored by other substances to which the organism is simultaneously exposed in the working and general environment.
- There is *not always* sufficient knowledge on the relationships existing between the levels of exposure and the levels of the biological indicators on the one hand, and between the levels of the biological indicators and possible health effects on the other (external exposure – internal dose – adverse health effects).

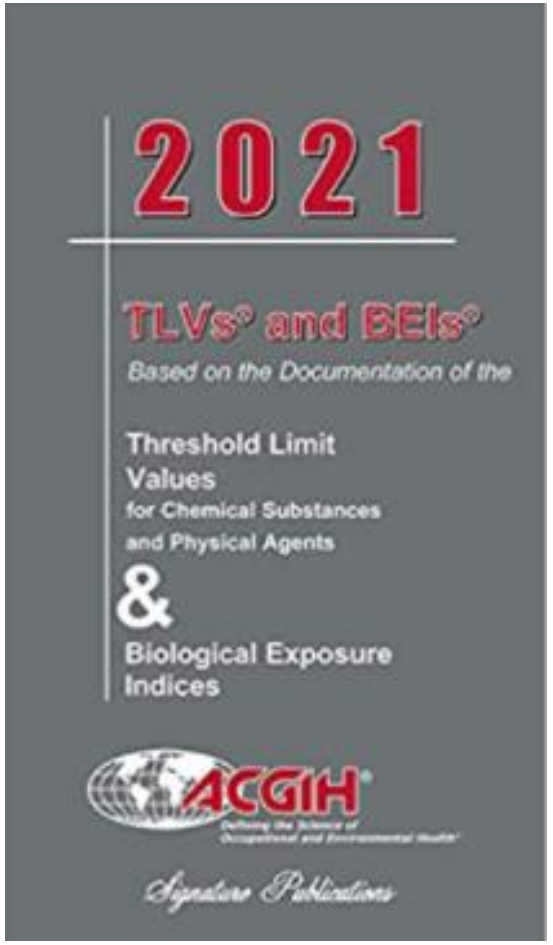
Aim of “Phase 1” HCA Regs regarding Biological Monitoring

- To update the Biological Exposure Index (“BEI”) values in alignment with the updated OELs (Table 4)
- To update the Guidance Note in Annexure 2

- NO CHANGES to the “Medical Surveillance” regulation (Reg 7)

New definition for Biological Exposure Indices

"BEI" or “Biological Exposure Index" is a value for assessing biological monitoring results, intended as a reference guideline for the likelihood of adverse health effects, and generally represents the level of determinants that are most likely to be observed in specimens collected from healthy employees who have been exposed to HCAs with inhalation exposure at the occupational exposure limit, as listed in Table 4 of Annexure 2 hereby, as revised from time to time and published in the Gazette;



Old definition (RHCS) for BEI: “is a reference value intended as a guideline for the evaluation of potential health hazards as listed in Table 3 of Annexure 1 hereby as revised from time to time and listed in the Government Gazette.”

OHSA definition for biological monitoring: “means a planned programme of periodic collection and analysis of body fluid, tissues, excreta or exhaled air in order to detect and quantify the exposure to or absorption of any substance or organism by persons.” (very similar to the ILO definition)

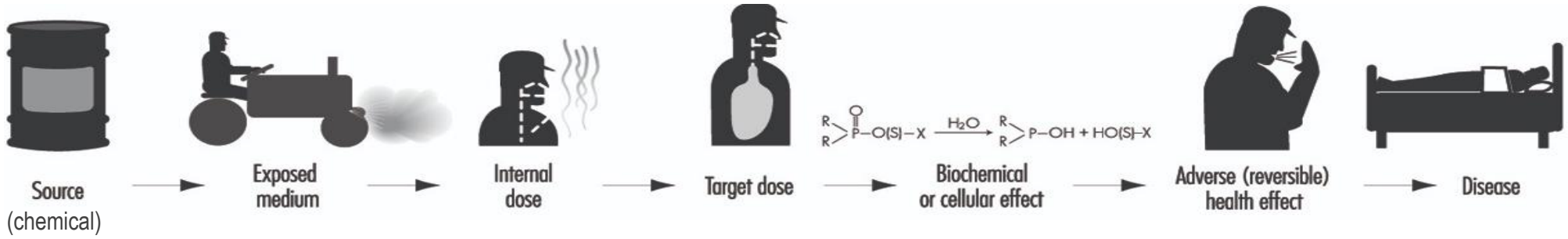
ANNEXURE 3

HAZARDOUS CHEMICAL AGENT GUIDELINES

Annexure 3: Medical Surveillance & Biological Monitoring

7. Biological monitoring is discussed in detail in paragraph 23. It is often incorrectly categorised as a type of medical surveillance. **Biological monitoring** provides an additional means to assess the exposure to an HCA by measuring metabolites of the HCA, or other similar markers of exposure. Therefore, it does not represent an adverse effect or an occupational disease – it only reflects exposure. A positive finding during biological monitoring does not necessarily mean that there has been a breach of the safety standard, but is a positive indication of employee exposure.

8. The distinction between early **biological effects** and **established disease** is not always clear, there tends to be a severity gradient in which one blends into the other. An occupational disease may be said to be present when the adverse biological effect progresses to clinically detectable organ damage requiring treatment or permanent impaired function. The categorisation of the condition is, therefore, sometimes at the discretion of the responsible medical practitioner. The distinction becomes important when considering a case for statutory reporting, as described in paragraphs 20, 21 and 22, where reporting of cases of established occupational disease is legally prescribed.



Annexure 3: Distinction between biological monitoring, biological exposure monitoring and biological effect monitoring

23. In these regulations, biological exposure monitoring and biological effect monitoring are subsets of the overarching term, biological monitoring.

24. **Biological exposure monitoring** is the measurement and assessment of chemicals or their metabolites (substances the body converts the chemical into, for purposes of elimination) in exposed workers. These measurements are made on samples of exhaled air, urine, blood or other biological materials, or any combination of these. Biological monitoring measurements reflect the total uptake of a chemical by an individual by all routes (inhalation, ingestion, through the skin or by a combination of these routes). Biological exposure monitoring, therefore, does not represent an adverse effect or an occupational disease – it only reflects exposure, but it is often incorrectly listed as a type of medical surveillance.

25. **Biological effect monitoring** is the measurement and assessment of early non-adverse reversible subclinical physiological effects caused by absorption of chemicals (i.e. prior to established clinical disease). It typically involves measuring biochemical responses. For example, measuring plasma and erythrocyte cholinesterase activity in workers exposed to organophosphate pesticides; or measuring increases in urinary protein following exposure to cadmium; or changes in functioning of enzymes.

26. Biological effect monitoring should be distinguished from medical testing for *established clinical disease*, which is also known as effect monitoring. For example, changes in blood cell counts following exposure to bone marrow toxins do not constitute biological effect monitoring.

Annexure 3: Objectives and uses of biological exposure monitoring

The main objective of biological monitoring is to provide a complementary technique to air monitoring when air sampling techniques alone may not give a reliable indication of exposure. Hence, it may be particularly useful in the following ways:

a) to detect and determine absorption via the skin or gastrointestinal system, in addition to that by inhalation;
b) to test the efficacy of personal protective equipment and monitor work practices;
c) to compliment air monitoring in circumstances when work practices are not normal, such as abnormally long or variable working hours or very strenuous work (high breathing rates = increased chemical intake);
d) to detect non-occupational exposures;
e) to assess total body burden;
f) to reconstruct past exposure in the absence of other exposure measurements for chemicals with long half-lives; and
g) to assess the effectiveness of medical removal procedures when indicated for certain chemicals (e.g. arsenic)

Annexure 3: Biological Exposure Indices

31. Biological exposure indices (BEIs) are reference values intended as guidelines for the evaluation of potential health hazards in the practice of industrial hygiene. BEIs must not be used as statutory reference values.

32. A BEI represents in theory the level of an HCA or metabolite most likely to be observed in a specimen collected from a healthy worker who has been exposed to an HCA to the same extent as a worker with inhalation exposure to an OEL-TWA. BEIs do not represent a sharp distinction between hazardous and non-hazardous exposures. For example, owing to biological variability, it is possible that an individual's measurements can exceed the BEI without incurring an increased health risk. Conversely, there may be some susceptible individuals who may be harmed at levels below the BEI.

33. If measurements in specimens obtained from a worker on different occasions persistently exceed the BEI, or if the majority of measurements in specimens obtained from a group of workers at the same workplace exceed the BEI, the cause of the excessive values must be investigated and proper action be taken to reduce the exposure.

34. BEIs apply to eight-hour exposures, five days a week. However, BEIs for differing work schedules may be extrapolated on toxicokinetic grounds. BEIs should not be applied, either directly or through a conversion factor, in the determination of safe levels for non-occupational exposure to air and water pollutants, or food contaminants. The BEIs are not intended for use as a measure of adverse effects or for diagnosis of occupational disease.

Table 4: the Biological Exposure Indices (“BEI”s)

Table 4: BIOLOGICAL EXPOSURE INDICES (BEIs) FOR HAZARDOUS CHEMICAL AGENTS

AGENT/DETERMINANT	CAS NUMBER	SAMPLE MATRIX	SAMPLING TIME	VALUE	UNIT	NOTATION
A						
Acetone	**67-64-1**					
Acetone		urine	End of shift	25	mg/L	Ns
Acetylcholinesterase inhibitors						
Cholinesterase activity in red cells		blood	Discretionary	70	% of baseline	Ns
Aniline	**62-53-3**					
p-Aminophenol		urine	End of shift	50	mg/L	B, Ns, Sq
Arsenic, elemental and soluble inorganic compounds (excluding gallium arsenide and arsine)	**7440-38-2**					
Inorganic arsenic plus methylated metabolites		urine	End of workweek	35	µg/L	B
B						
Benzene	**71-43-2**					
S-phenylmercapturic acid (SPMA)		urine	End of shift	25	µg/g creatinine	B
t,t-Muconic acid (ttMA)		urine	End of shift	500	µg/g creatinine	B
1,3-Butadiene	**106-99-0**					
1,2-Dihydroxy-4-(N-acetylcysteinyl)-butane		urine	End of shift	2,5	mg/L	B, Sq
Mixture of N-1-and N-2-(hydroxybutenyl)valine haemoglobin adducts		blood	Not critical	2,5	pmol/g	B, Sq
2-Butoxyethanol	**111-76-2**					
Butoxyacetic acid (BAA)		urine	End of shift	200	mg/g	B
C						
Cadmium and inorganic compounds	**7440-43-9**					
Cadmium		urine	Not critical	5	µg/g creatinine	B

B: “Background”
The determinant may be present in biological specimens collected from subjects who have not been occupationally exposed, at a concentration which could affect interpretation of the results. Such background concentrations are incorporated in the BEI value.

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p-Aminophenol		urine	End of shift	50	mg/L	B, Ns, Sq
Arsenic, elemental and soluble inorganic compounds (excluding gallium arsenide and arsine)	**7440-38-2**					
Inorganic arsenic plus methylated metabolites		urine	End of workweek	35	µg/L	B
B						
Benzene	**71-43-2**					
S-phenylmercapturic acid (SPMA)		urine	End of shift	25	µg/g creatinine	B
t,t-Muconic acid (ttMA)		urine	End of shift	500	µg/g creatinine	B
1,3-Butadiene	**106-99-0**					
1,2-Dihydroxy-4-(N-acetylcysteinyl)-butane		urine	End of shift	2,5	mg/L	B, Sq
Mixture of N-1-and N-2-(hydroxybutenyl)valine haemoglobin adducts		blood	Not critical	2,5	pmol/g Hb	Sq
2-Butoxyethanol	**111-76-2**					
Butoxyacetic acid (BAA)		urine	End of shift	200	mg/g creatinine	-
C						
Cadmium and inorganic compounds	**7440-43-9**					
Cadmium		urine	Not critical	5	µg/g creatinine	B

Ns: “Non-specific”
The determinant is non-specific, since it is also observed after exposure to other chemicals.

Table 4: the Biological Exposure Indices (“BEI”s)

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AGENT/DETERMINANT	CAS NUMBER	SAMPLE MATRIX	SAMPLING TIME	VALUE	UNIT	NOTATION
A						
Acetone	**67-64-1**					
Acetone		urine	End of shift	25	mg/L	Ns
Acetylcholinesterase inhibitors						
Cholinesterase activity in red cells		blood	Discretionary	70	% of baseline	Ns
Aniline	**62-53-3**					
p-Aminophenol		urine	End of shift	50	mg/L	B, Ns, Sq
Arsenic, elemental and soluble inorganic compounds (excluding gallium arsenide and arsine)	**7440-38-2**					
Inorganic arsenic plus methylated metabolites		urine	End of workweek	35	µg/L	B
B						
Benzene	**71-43-2**					
S-phenylmercapturic acid (SPMA)		urine	End of shift	25	µg/g creatinine	B
t,t-Muconic acid (ttMA)		urine	End of shift	500	µg/g creatinine	B
1,3-Butadiene	**106-99-0**					
1,2-Dihydroxy-4-(N-acetylcysteinyl)-butane		urine	End of shift	2,5	mg/L	B, Sq
Mixture of N-1-and N-2-(hydroxybutenyl)valine haemoglobin adducts		blood	Not critical	2,5	µg/g Hb	-
2-Butoxyethanol	**111-76-2**					
Butoxyacetic acid (BAA)		urine	End of shift	200	mg/g creatinine	-
C						
Cadmium and inorganic compounds	**7440-43-9**					
Cadmium		urine	Not critical	5	µg/g creatinine	B

Sq: “Semi-quantitative”
The biological determinant is an indicator of exposure to the chemical, but the quantitative interpretation of the measurement is not clear.

Table 4: the Biological Exposure Indices ("BEI"s)

ADOPTED BIOLOGICAL EXPOSURE DETERMINANTS			
Chemical [CAS No.] (*Documentation* date) *Determinant*	*Sampling Time*	*BEI®*	*Notation*
METHYL ETHYL KETONE [78-93-3] (2012) Methyl ethyl ketone in urine	End of shift	2 mg/L	Ns
METHYL ISOBUTYL KETONE [108-10-1] (2009) Methyl isobutyl ketone in urine	End of shift	1 mg/L	—
N-METHYL-2-PYRROLIDONE [872-50-4] (2006) 5-Hydroxy-N-methyl-2-pyrrolidone in urine	End of shift	100 mg/L	—
NAPHTHALE[illegible]91-20-3] (2012) 1-N[illegible]hol★ + 2-Naphthol★	End of shift	—	Nq, Ns
NITROBENZENE [98-95-3] (2013) Methemoglobin in blood	*See* Methemoglobin Inducers BEI®	—	—
‡ PARATHION [56-38-2] (1992) Total p-Nitrophenol in urine (Cholinesterase activity in red cells)	End of shift (Discretionary)	0.5 mg/g creatinine (70% of individual's baseline)	Ns (B, Ns, Sq)
PENTACHLOR[illegible]ENOL [87-86-5] (2013) Penta[illegible]phenol in urine★	Prior to last shift of workweek	—	Nq
PHENOL [108-95-2] (2005) Phenol in urine★	End of shift	250 mg/g creatinine	B, Ns

Nq: "Non-quantitative"
Biological monitoring should be considered for this compound based on the ACGIH review; however, a specific BEI could not be determined due to insufficient data.

Relationship between OEL, TLV and BEI (1)

Bear in mind that:

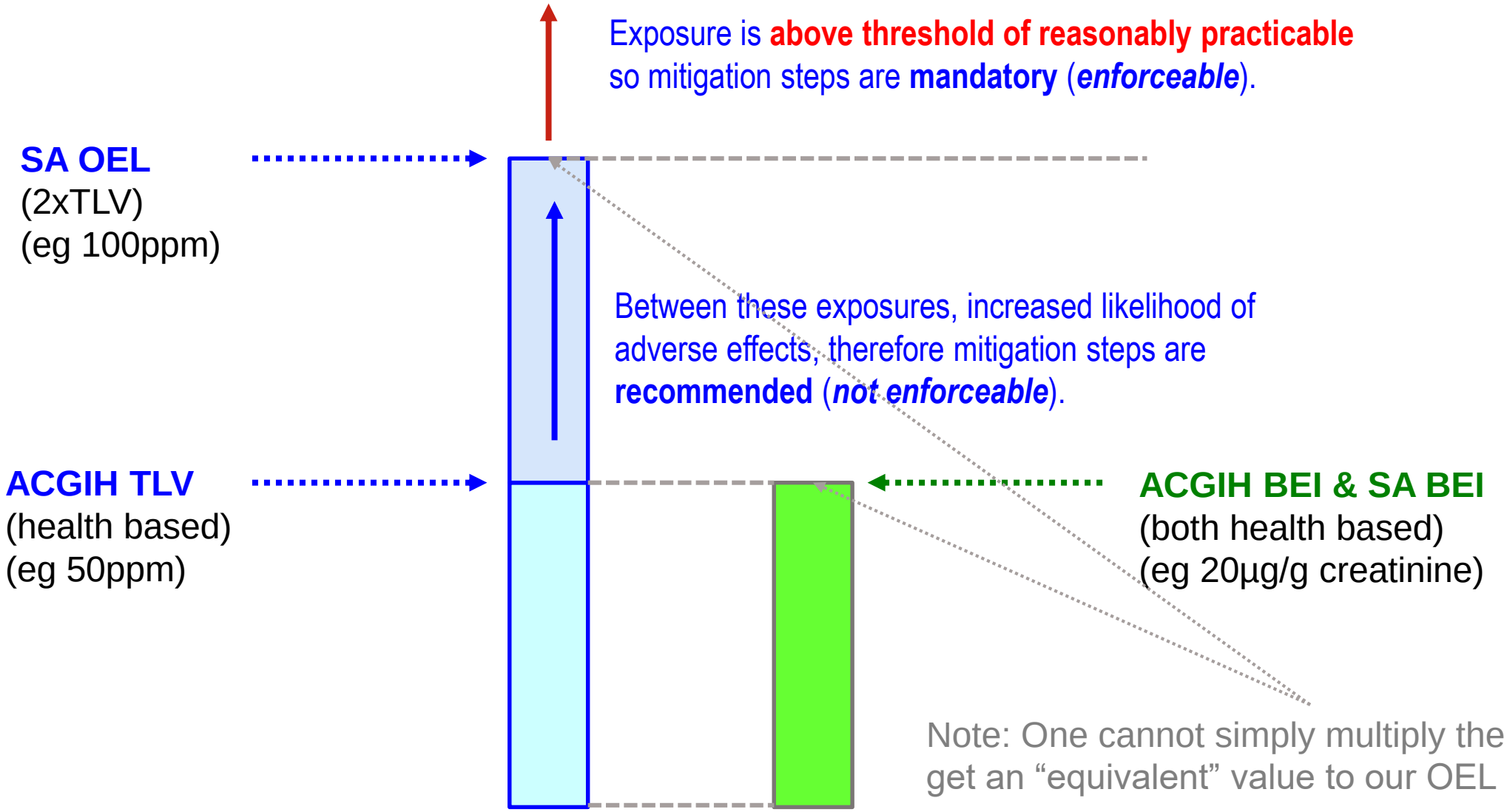
- A BEI usually represents a level of an agent that is most likely to be observed in a specimen collected from a healthy worker who has been exposed to the chemical to the same extent as a worker with an inhalation exposure to the ACGIH TLV (threshold limit value) time-weighted average (TWA). (There are some exceptions to this rule, such the BEI for lead)
- BEIs and ACGIH TLVs are both health based *non-enforceable* guideline values
- This means that when an employee's biomonitoring level reaches the BEI value, that employee's exposure has reached the level of the health-based (ACGIH) TLV, above which *adverse effects are increasingly likely to emerge*, and mitigation measures should start to be implemented.

Given the 2x relationship between the ACGIH TLV and the RHCA OEL:

- the RHCA can simply adopt the ACGIH BEIs, with all the documented research that has gone into their development, and
- an employee who is exposed at the level of the (non-enforceable) BEI can be considered to be at approximately 50% of the RHCA (enforceable) OEL.

Relationship between OEL, TLV and BEI (2)

Using a fictitious chemical with a new SA OEL of 100ppm and a new BEI of 20µg/g creatinine



Note: One cannot simply multiply the BEI by 2 to get an “equivalent” value to our OEL

Additional Reading

Health Surveillance Report (Biological Monitoring and Biological Effect Monitoring

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http://www.occhealth.co.za/?/viewArticle/1406

Thank you for your attention

Questions / Discussion