WES Review 2018

Non-threshold based genotoxic carcinogens

Accessory document to Recommending health-based workplace exposure standards and notations

Australian workplace exposure standards and advisory notations

Safe Work Australia (2018)

safe work australia

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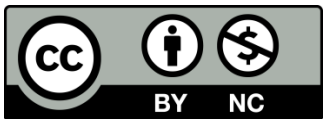

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Contents

Non-threshold based genotoxic carcinogens

This document outlines an approach to recommending workplace exposure standards for non-threshold based genotoxic carcinogens.

Occupational cancers

Approximately 1.5-3.6 million workers (23-40 per cent) in Australia are potentially exposed to occupational carcinogens[1], including hazardous chemicals (Carey et al., 2014; Fritschi, 2006). In 2006, it was estimated that approximately 14 per cent of cancer deaths in males and 2.2 per cent of cancer deaths in females were associated with occupational exposures. This means that, every year, about 5000 invasive cancers and about 34,000 non-melanoma skin cancers are associated with occupational exposures in Australia (Fritschi, 2006).

An occupational cause of cancer can be relatively easy to prove if the cancer is a rare type of cancer or the carcinogenic effect is so strong that the number of cancers in an occupation is clear. However, for many more common cancer types, a definitive determination of association with occupational exposure to a particular chemical is far more difficult, further complicated by the long latency period (sometimes decades) between exposure and when the carcinogenic effects become evident; there may be no early warning of adverse effects.

Cancer is a priority work-related disorder in the *Australian Work Health and Safety Strategy 2012-2022*, with the four main objectives of this Strategy being:

- reduced incidence of work-related death, injury and illness
- reduced exposure to hazards and risks
- improved hazard controls, and
- improved work health and safety infrastructure.

The extent to which Australian workers are protected against occupational carcinogens is facilitated by the rigour of enabling legislation and regulation, and its enforcement (Cancer Council Australia, 2016). Under the model Work Health and Safety (WHS) laws, persons who conduct a business or undertaking (PCBUs) have a responsibility to:

- eliminate health and safety risks so far as is reasonably practicable, and if this is not reasonably practicable, minimise those risks so far as is reasonably practicable (section 17 of the model WHS Act), and
- ensure, so far as is reasonably practicable, workers and other people are not exposed to health and safety risks arising from the business or undertaking (section 19 of the model WHS Act)

A hierarchy of risk control measures have been outlined in the Safe Work Australia document Guide to Managing Risks of Exposure to Carcinogens in the Workplace (SWA, 2016) (Figure 1). This hierarchy includes elimination and substitution. However, sometimes this is not possible and there needs to be a means of minimising the exposure of Australian workers to carcinogens in the workplace. Having up-to-date workplace exposure standards may assist with this (Fritschi, 2006).

Workplace exposure standards

Workplace exposure standards[2] represent airborne concentrations of chemicals that should not cause adverse effects or undue discomfort to nearly all workers. Under the model Work Health and Safety (WHS) laws, persons who conduct a business or undertaking (PCBUs) have a responsibility to ensure that no person at the workplace is exposed to a substance or mixture in an airborne concentration that exceeds the exposure standard for the substance or mixture (regulation 49 of the model WHS Regulations).

[1] The calculations do not take into account control measures, thus workers are 'potentially' exposed.

[2] Eight hour time-weighted average, short term exposure limit, peak limitation

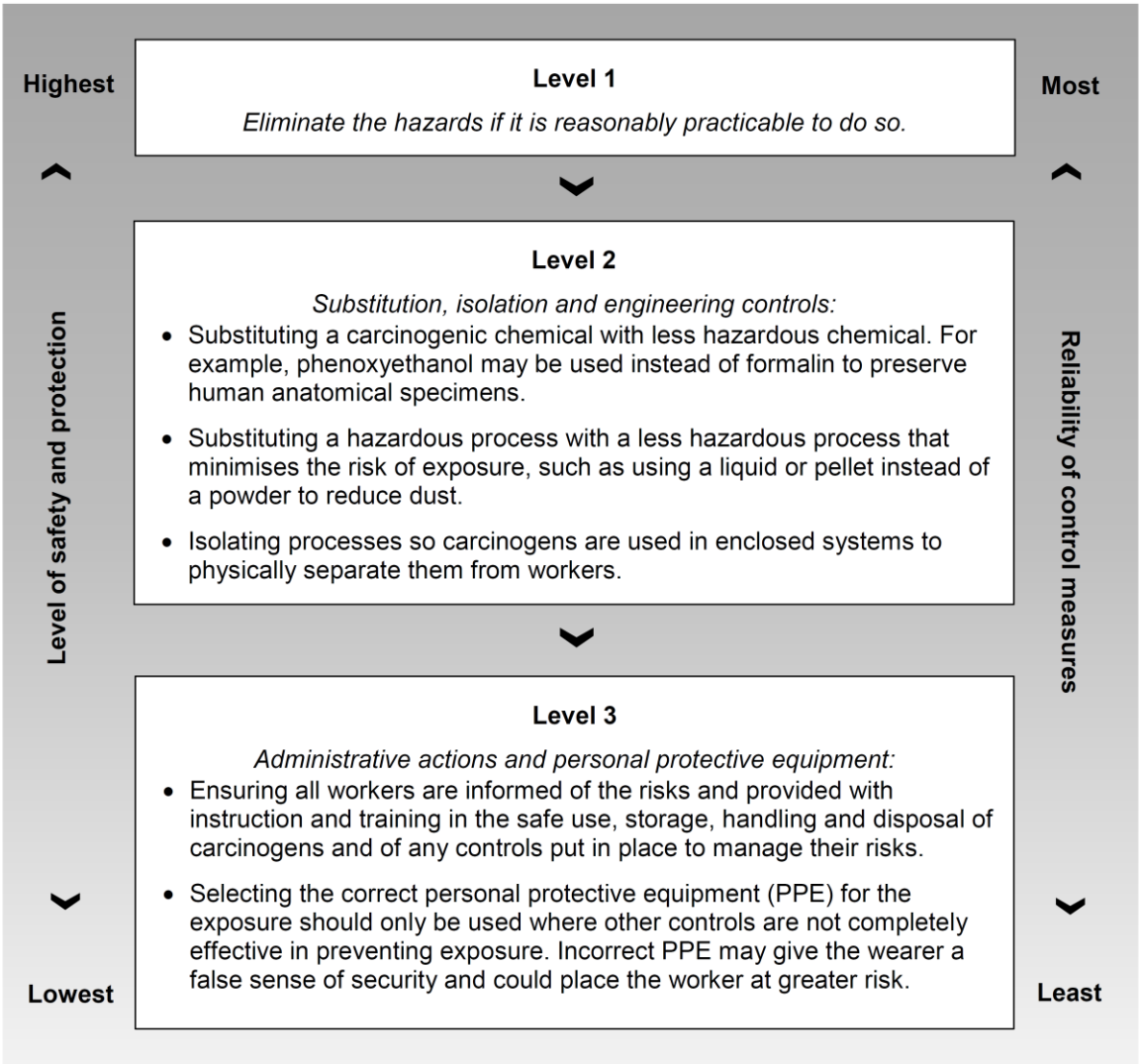


Figure 1 Hierarchy of risk control measures (from SWA, 2016)

As tools to eliminate or minimise injury and illness, exposure standards are used to:

- provide information to duty holders about the health risks of work-related exposures to chemicals
- provide guidance to work health and safety professionals (for example industrial hygienists, occupational physicians and safety engineers)
- help select effective risk controls, and
- determine the effectiveness of existing controls.

Australia's current list of 644 exposure standards has not been reviewed since the early 2000s. A recent review of the workplace exposure standards revealed that almost a third of Australia's exposure standards may be out-of-date and may not be adequate to protect the health of workers in some cases (SWA, 2015). As such, the workplace exposure standards are currently being reviewed and updated.

Review of the workplace exposure standards

A methodology to update the exposure standards based on scientific reports from trusted domestic and international bodies that derive workplace exposure standards is being developed. This will ensure the Australian workplace exposure standards are based on the highest quality, most up-to-date, health-based information and supported by a rigorous, scientific approach.

International agencies that will be sources for workplace exposure standard information include:

- American Conference of Governmental Industrial Hygienists (ACGIH®)

- EU Scientific Committee on Occupational Exposure Limits (SCOEL)
- German Research Foundation (Deutsche Forschungsgemeinschaft; DFG)
- American Industrial Hygiene Association (AIHA) and its successor for the establishment of workplace exposure standards, the Occupational Alliance for Risk Science (OARS), and
- Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands.

Exposure standards are set to prevent occupational diseases or other adverse effects. For many substances, it is accepted that toxicological effects are not observed if the exposures are sufficiently low; a no observed adverse effect level (NOAEL) or threshold exists (Figure 2). Many health-based workplace exposure standards are derived from the lowest relevant NOAEL and are generally considered to be protective for adverse effects for most workers. In Australia, workplace exposure standards are also expected to be protective for carcinogenic effects (Australasian Faculty of Occupational Medicine, 2003).

However, the majority of the international agencies listed above (SCOEL, DFG and DECOS) do not set exposure standards for a subset of chemicals, the non-threshold based genotoxic carcinogens (Nielsen and Øvrebø, 2008; SCOEL, 2013; Health Council of the Netherlands, 2012; DFG, 2014).

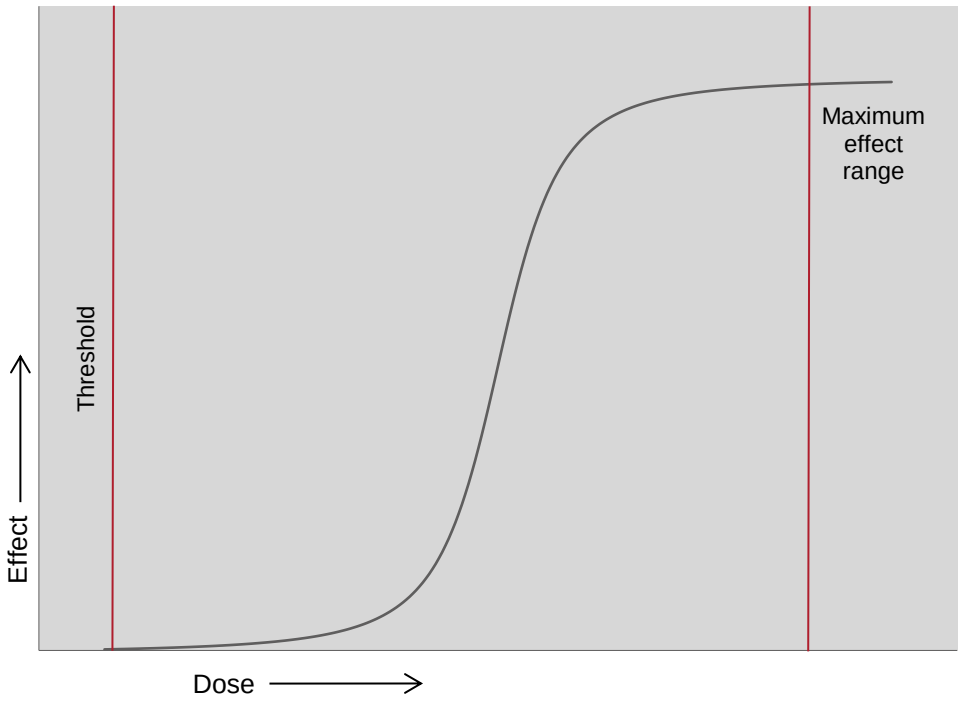


Figure 2 Stylised dose-response curve for the majority of toxicity findings

What are non-threshold based genotoxic carcinogens for the purposes of workplace exposure standards?

Carcinogenic compounds have been shown to result in an increase in tumours in animals and/or human subjects following exposure to the compound.

The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) defines the hazard categories for carcinogens as follows:

- **Category 1A**: Known to have a carcinogenic potential for humans; the placing of a substance is largely based on human evidence
- **Category 1B**: Presumed to have carcinogenic potential for humans; the placing of a substance is largely based on animal evidence

- **Category 2**: Suspected human carcinogens; the placing of a substance is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1.

Tumours can arise due to genotoxic or non-genotoxic mechanisms of action. The GHS criteria do not specifically differentiate carcinogens that act *via* a genotoxic or non-genotoxic mechanism. The GHS classification system provides an indication of the hazard but does not provide an indication regarding risk. A more potent carcinogen, which has been used less widely, could be classified as a Category 1B carcinogen according to the GHS criteria whereas a less potent carcinogen, with more widespread use, could be classified as Category 1A because there is more evidence of carcinogenicity in human subjects with the latter carcinogen. Some individuals may consider the Category 1A carcinogen as having a higher risk than the Category 1B carcinogen, but this may not be the case. Therefore, the GHS classification in isolation cannot be used to determine comparative risk between carcinogens.

'Genotoxic' is a broad term applied to agents or processes which alter the structure, information content or segregation of DNA. Genotoxic compounds can be further divided into mutagens, clastogens (causing structural aberrations) and aneugens (causing numerical aberrations). Mutagens are DNA-reactive substances that have the potential to directly cause DNA damage (e.g. alkylating agents or DNA intercalators) and are generally detected in a bacterial reverse mutation assay. Compounds causing chromosomal aberrations are detected in mammalian chromosomal aberration tests and rodent micronucleus tests. A genotoxic carcinogen increases the tumour incidence in animals or human subjects as a result of DNA or chromosomal damage.

For mutagens, it is generally accepted that a no effect dose (or threshold) at the cellular or molecular level does not exist and there is a linear relationship between tumour incidence and dose that goes through a zero dose (Figure 3); any exposure, no matter how small, carries a finite risk for carcinogenic effects.

In the case of aneugens and clastogens, carcinogenicity by these mechanisms is generally considered to have a biologically plausible threshold (Lovsin Barle et al., 2016; Nielsen and Øvrebø, 2008; SCOEL, 2013).

There are a variety of non-genotoxic mechanisms that can result in tumour formation, including hormonal changes, chronic irritation, chronic inflammation, immunosuppression and the induction of metabolic processes (reviewed in Hernández et al., 2009). Tumour formation by these non-genotoxic mechanisms is considered to have a threshold, or a dose associated with no risk for tumour formation (Figure 3). For example, if tumour formation occurs as a result of chronic irritation, prevention of the initiating irritation will prevent tumour formation.

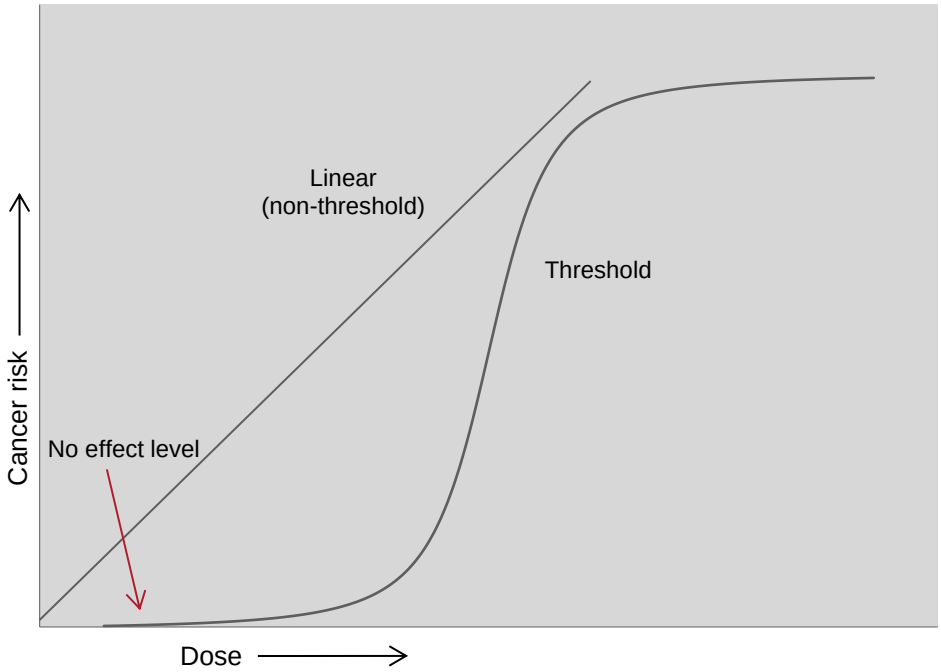


Figure 3 Stylised dose-response curves for non-threshold based genotoxic (Linear) and threshold based genotoxic and non-genotoxic (Threshold) carcinogens. Doses without a carcinogenic risk (no effect levels) can be determined for threshold based carcinogens. For non-threshold based genotoxic carcinogens, a no effect level would be a dose or exposure of zero.

Mechanistic studies (e.g. assessment of hormone levels or induction of metabolic pathways) may be performed to ascertain a threshold-based mechanism for tumour formation.

For the purposes of the workplace exposure standards, a ‘confirmed’ non-threshold based genotoxic carcinogen will be a hazardous chemical that has:

1. clear and unambiguous positive results from adequately conducted mutagenicity test or tests
2. positive results from adequately conducted carcinogenicity study or studies, and
3. confirmation of a non-threshold based genotoxic mechanism of action in the formation of tumours (e.g. demonstration of DNA-adduct formation at affected sites, mechanistic data cannot confirm threshold mechanisms are involved in tumour formation).

Positive mutagenicity (1) and carcinogenicity (2) results alone do not confirm a hazardous chemical is a genotoxic carcinogen. Mechanistic data indicating a non-threshold mechanism as the major carcinogenic mechanism is required to confirm a chemical is a non-threshold based genotoxic carcinogen. However, for some genotoxic and carcinogenic chemicals (1 and 2) there are insufficient data to ascertain the mechanism of tumour formation (3). These compounds will be assumed to be genotoxic carcinogens until data have been provided to suggest otherwise. A link between mutagenic activity and tumour formation is a reasonable assumption to make in the absence of mechanistic data. This is consistent with the policy taken by trusted international sources (SCOEL, 2013; Health Council of the Netherlands, 2012).

Chemicals that have proven to be positive in mutagenicity studies (1), but adequate data to determine the carcinogenic potential of the compound are lacking (2), will not be considered to be non-threshold based genotoxic carcinogens[3]. A compound may have positive findings in genotoxicity assays (1) but not induce tumour formation in animals and/or human subjects in adequately conducted studies. Chemicals with unknown mutagenic potential will be considered non-mutagenic and non-carcinogenic until data have been provided to suggest otherwise. These data may include data from a chemically-related compound.

The definition of a non-threshold based genotoxic carcinogen for the purposes of workplace exposure standards is outlined in Figure 4.

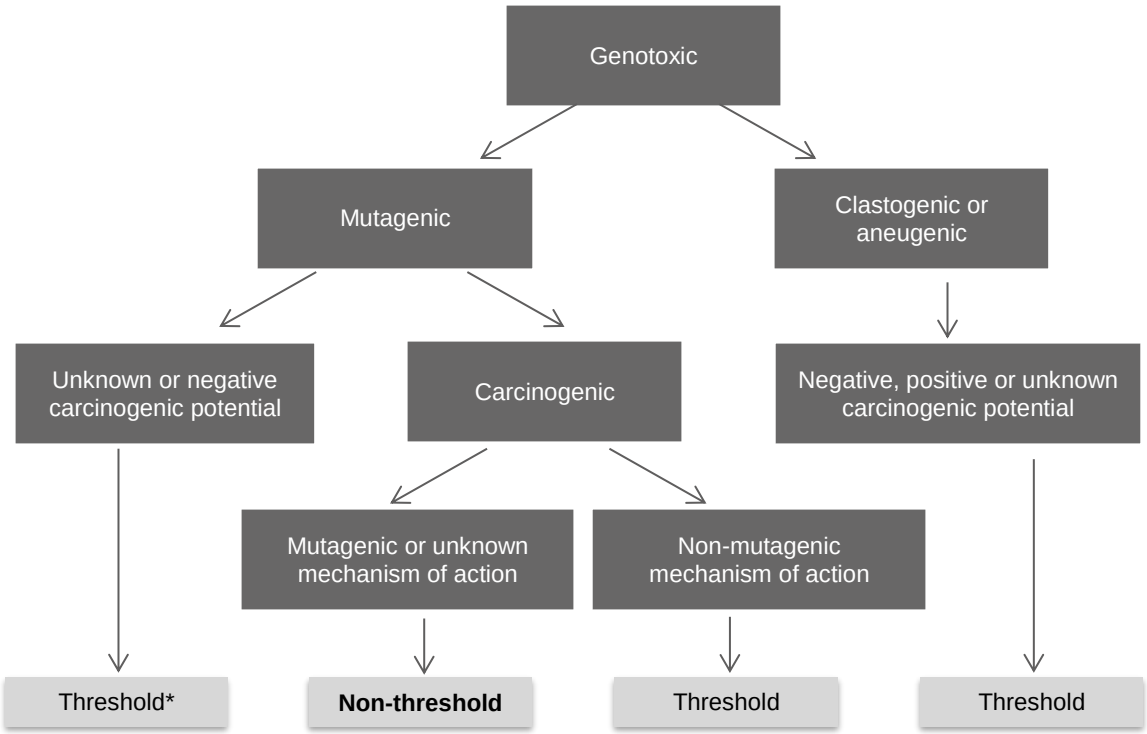


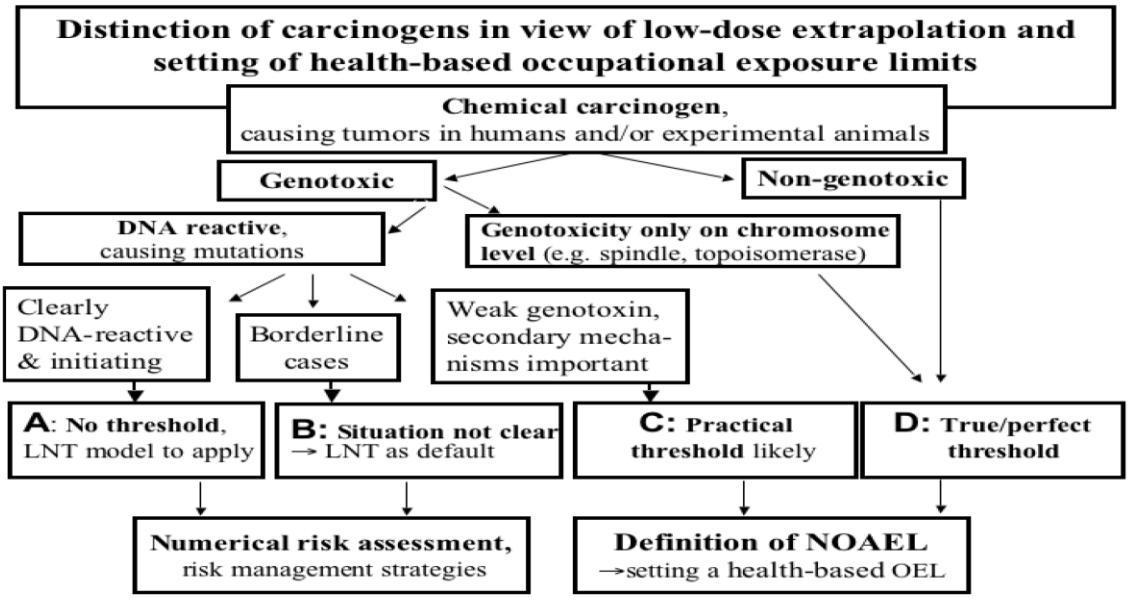
Figure 4 Definition of a non-threshold based genotoxic carcinogen.
***** Threshold for non-carcinogenic effects.

[3] Exception: If a chemically-related compound has been shown to be both mutagenic and carcinogenic and the two compounds have the same mechanism of mutagenicity (e.g. both chemicals have the same DNA-reactive group), it may be reasonable to assume the compound is carcinogenic in the absence of empirical data.

Why is there a need for a policy position on non-threshold based genotoxic carcinogens?

Internationally, health-based workplace exposure standards (or occupational exposure limits) are generally derived from NOAELs identified in experimental studies or reports. As a NOAEL cannot be determined for non-threshold based genotoxic carcinogens, DECOS, DFG and SCOEL do not set occupational exposure limits for these compounds (Nielsen and Øvrebø, 2008; SCOEL, 2013; Health Council of the Netherlands, 2012; DFG, 2014). For carcinogens that are considered to have a threshold, occupational exposure limits are derived from NOAEL values (or low observed adverse effect levels) determined from studies or reports.

The following diagram summarises the SCOEL approach when setting health-based occupational exposure limits (OELs) for carcinogens (Figure 5; SCOEL, 2013). A similar approach is undertaken by DECOS and DFG (Nielsen and Øvrebø, 2008; DFG, 2014; Health Council of the Netherlands, 2012).



Group A: Non-threshold genotoxic carcinogens; for risk low-dose assessment the linear non-threshold (LNT) model appears appropriate.

Group B: Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases the LNT model may be used as a default assumption, based on the scientific uncertainty.

Group C: Genotoxic carcinogens for which a practical threshold is supported.

Group D: Non-genotoxic carcinogens and non-DNA reactive carcinogens; for these compounds a true ("perfect") threshold is associated with a clearly founded NOAEL.

Figure 5 Health-based occupational exposure limits are set for subsets of carcinogens based on mechanism of action underlying carcinogenic action (from SCOEL, 2013). NOAEL = no observed adverse effect level

As DFG, DECOS and SCOEL do not set workplace exposure standards for non-threshold based genotoxic carcinogens, it proves problematic when reviewing the Australian workplace exposure standards, as standards may only be available from ACGIH®. The estimated working lifetime cancer risk for some chemicals at the ACGIH® workplace exposure standards is unacceptably high (cancer risks greater than 1 in 1000 and sometimes greater than 1 in 100; Health Canada, 2004; ECHA, 2012; NIOSH, 2016b). To protect workers from the effects of non-threshold based genotoxic carcinogens there is a need to lower the workplace exposure standard. However, there is no clear policy position as to what 'minimal' cancer risk level might be considered acceptable for workplace exposure standards in Australia.

How are limits for non-threshold based genotoxic carcinogens determined in a regulatory setting?

In general, agencies that set health-based occupational standards are not the legislative bodies that enforce the standards. While SCOEL, DFG and DECOS do not determine health-based exposure standards for non-threshold based genotoxic carcinogens, regulatory bodies have assigned pragmatic exposure standards for these chemicals, generally at a concentration associated with a specific cancer risk. The methods for determining cancer risk differ across agencies and the selected cancer risk level or margin also differs across agencies (see Table 1).

There is no overall international scientific consensus on an 'acceptable' cancer risk for substances that are non-threshold based genotoxic carcinogens. Most regulatory agencies in the food, drinking water, pharmaceutical and environment industries generally set acceptable or regulatory limits between 1 in 100,000 (a risk of cancer in 1 individual per 100,000 individuals) and 1 in 1,000,000. Within the occupational setting, the target working lifetime cancer risk level is generally between 1 in 10,000 and 1 in 100,000. For some agencies, analytical technical feasibility is considered when assigning exposure limits for non-threshold based genotoxic carcinogens. Further details are provided in the following sections.

Table 1 Cancer risk levels assigned by different regulatory agencies

Organisation	Cancer risk level	Comments
Occupational setting		
Committee of Hazardous Substances of the German Federal Ministry of Labour and Social Affairs (AGS)	4 in 100,000	From 2018. An 'acceptable' risk of 1 in 10,000 was assigned for a transitional period (2013-2018). A risk of 1 in 1000 may be tolerated under the condition that the employer is continually aiming to reduce levels to an 'acceptable' level.
European Chemical Agency (REACH)	1 in 100,000	
European Chemical Agency (Existing Industrial Chemicals)	1 in 100,000 1 in 1,000,000	Different values used for different chemicals. (e.g. 1 in 100,000 for 2-nitrotoluene for workers; 1 in 1,000,000 for 2,3-epoxypropyltrimethyl-ammonium chloride for workers)
Health Council of the Netherlands	4 in 100,000	Considered a 'target' level. The OEL Subcommittee of the SER, an advisory body of the Dutch government, assigns OELs at the 'target' level if technically feasible. Otherwise the limit will be between the 'target' level and the 'prohibitive' level of 1 in 1000, with an ultimate aim to reduce the limit to the 'target' level.
Japanese Society for Occupational Health (JSOH)	1 in 1000 1 in 10,000	JSOH does not recommend these values as a safety exposure level or that these cancer risks are acceptable. The reference values are considered by the Ministry of Health, Labour and Welfare.
UK Committee on Carcinogenicity	1 in 100,000	This level is 'unlikely to be a concern' and is recommended for risk communication and risk management processes but is not a legislated level.
US National Institute for Occupational Safety and Health (NIOSH)	1 in 10,000	This level should be considered a starting point for continually reducing exposures to minimise the residual risk.

Organisation	Cancer risk level	Comments
Food industry and drinking water		
European Food Safety Authority (EFSA)	1 in 100,000	
US Food and Drug Administration (US FDA)	1 in 1,000,000	
World Health Organization (WHO)	1 in 100,000	For drinking water.
Pharmaceutical industry		
International Guidelines (ICH M7)	1 in 100,000	
Remediation of contaminated soil sites		
French Ministry of the Environment	1 in 100,000	A higher level of 1 in 10,000 may be acceptable provided techniques to achieve lower levels are unavailable and based on the strength of a detailed technical-economic study.
Health Canada	1 in 100,000	This includes a working lifetime cancer risk for workers at industrial properties with contaminated soil.
Environment		
enHealth, Australian Department of Health	1 in 100,000	
National Environment Protection Council (Australia)	1 in 100,000	Air quality guidelines.
New South Wales Department of Environment and Conservation	1 in 1,000,000	Considered an 'acceptable' risk. Cancer risks greater than 1 in 10,000 are considered 'unacceptable'. Between the 'acceptable' and 'unacceptable' limits, proponents must demonstrate 'best practice' for development applications.
US Environmental Protection Agency (US EPA)	1 in 1,000,000	
Victorian Environmental Protection Agency	1 in 1,000,000	For planning purposes.
World Health Organization (WHO)	1 in 10,000 1 in 100,000 1 in 1,000,000	Air quality guidelines. The concentrations provided at the various cancer risks are to support authorities in the decision-making process. The WHO does not make a comment regarding acceptability of risk.

Cancer risk levels or margins across agencies

Occupational setting

The SCOEL recommendations form the scientific basis for policy discussion at the EU level for the development of occupational exposure limits under the Chemical Agents Directive (European Council Directive 98/24/EC) and the European Council Directive on the protection of workers from the risks related to the exposure to carcinogens and mutagens at work (Council Directive 2004/37/EC) (SCOEL, 2013). While SCOEL does not assign exposure limits for non-threshold based genotoxic carcinogens, the reports from SCOEL are used by the European Commission to decide on limit values for these chemicals and the level of a tolerable risk (European Council Directive 2004/37/EC; Health Council of the Netherlands, 2012). These limits are considered the minimum requirements. Member states can then apply more stringent requirements if they so choose. Some EU Member States have applied a working lifetime cancer risk.

The European Chemical Agency (ECHA) is an agency of the European Union which is responsible for the implementation of REACH (Registration, Evaluation and Authorisation of Chemical substances). Under REACH, manufacturers, importers and downstream users should ensure that they manufacture/place on the market/use substances in such a way that they do not adversely affect human health. According to REACH, the Derived No-Effect Level (DNEL) is a level of exposure above which humans should not be exposed. As a DNEL is not appropriate to set for a non-threshold based genotoxic carcinogen, REACH recommends an applicant develop a derived minimal effect level (DMEL), a reference risk that is considered to be of very low concern. The cancer risk or margin at the DMEL is 1 in 100,000[4] (ECHA, 2012).

EU risk assessments for industrial chemicals carried out under EU regulation 793/93 (applies to evaluation of risks of existing substances to humans, including workers and consumers, and to the environment) by ECHA, cancer risks between 1 in 100,000 and 1 in 1,000,000 for some non-threshold based genotoxic carcinogens were considered of low concern (cited in ECHA 2012). These cancer risks were endorsed by the EU Scientific Committees on Health and Environmental Risks and Toxicity, Ecotoxicity and the Environment (SCHER and CSTEE) (SCHER/SCCP/SCENIHR, 2009).

In Germany, the Committee for Hazardous Substances of the German Federal Ministry of Labour Social Affairs (AGS) introduced a risk-based approach for assigning acceptable limits for non-threshold based genotoxic carcinogens. At the time (2013), ‘acceptable’ limits assigned to non-threshold based genotoxic carcinogens were associated with a working lifetime cancer risk of 4 in 10,000. During the transitional period of 2013 and 2018, these limits were to be reduced further to an associated working lifetime cancer risk of 4 in 100,000, considered an ‘acceptable’ working lifetime cancer risk from 2018 onwards. A ‘tolerable’ limit associated with a 4 in 1000 working lifetime cancer risk has also been assigned. Concentrations higher than the tolerable limit should be avoided. At levels below the acceptable risk, employers are not obliged to put in place additional protective measures. Concentrations between the tolerable and acceptable limits may be allowed under the condition that they are continually reduced with the aim of reaching an ‘acceptable’ limit. The employer is expected to make various operational risk-reduction measures, for example technical measures, spatial separation, exposure minimisation and minimising the duration of exposure and number of people exposed (BAuA, 2014; Degen and Nies, 2008; Kayser and Henn, 2013). If the acceptable concentration cannot be determined by measurement, it is set at the limit of detection (BAuA, 2014)

In the Netherlands, the Health Council of the Netherlands calculate a ‘target’ risk limit, associated with a working lifetime cancer risk of 4 in 100,000, and a ‘prohibitive’ risk limit, a limit that must not be exceeded, associated with a 4 in 1000 working lifetime cancer risk. At concentrations below the target value (associated with a 4 in 100,000 cancer risk), no additional protective measures need to be taken. The Occupational Exposure Limit Subcommittee of the SER[5] considers the technical feasibility of implementing a legal limit value at the target risk level and subsequently advises the Minister of Social Affairs and Employment who sets a new legally binding occupational exposure limit. Based on the technical feasibility findings, this value may be between the target (4 in 100,000)

[4] BMDL10/10,000 is an equivalent principle to a 1 in 100,000 cancer risk (Nielsen and Øvrebø, 2008).

[5] The main advisory body to the Dutch government and the parliament on national and international social and economic policy. It is independent from government and represents the interests of trade unions and industry (SER website).

and the prohibitive (4 in 1000) risk levels (Health Council of the Netherlands, 2012). The ultimate aim in the Netherlands is to reduce the exposure limit to the target level, and the limits selected will be reviewed on a relatively frequent basis to help assist this.

Because of uncertainties associated with extrapolating from experimental data to determine a dose associated with a specific cancer risk, the British government and its advisory committees (including the Health and Safety Executive [HSE]) do not use this method. The British government recommends exposure to non-threshold based genotoxic carcinogens should be kept to as low as reasonably practicable. However, a margin of exposure (MOE) approach (see method in the next section) could be used for risk communication and risk management processes (Committee on Carcinogenicity[6], 2012; 2014). When using the MOE approach, the Committee on Carcinogenicity, an advisory committee to the British government, consider a margin of less than 1 in 100,000 unlikely to be of concern (Committee on Carcinogenicity, 2004).

In the USA, the Occupational Safety and Health Administration (OSHA) is the regulatory agency responsible for setting and enforcing standards to help ensure workplace health and safety. Many of the occupational exposure limits (termed permissible exposure limits, PELs) determined by OSHA have not been updated since 1970. Recognising that their current PELs may not be protective for workers, OSHA recommends that employers consider using alternative occupational exposure limits and cites standards determined by the National Institute for Occupational Safety and Health (NIOSH; a scientific research agency focused on worker health and safety), and ACGIH®[7]. NIOSH has recently developed a Chemical Carcinogen Policy which involves assigning a Risk Management Limit for Carcinogens (RML-CA) (NIOSH, 2016a). An RML-CA is a limit that is associated with a risk estimate of one excess cancer case in 10,000 in a working lifetime, if it is analytically feasible[8]. If measurement of the occupational carcinogen at the RML-CA is not analytically feasible at the 1 in 10,000 risk estimate, NIOSH will set the RML-CA at the limit of quantification of the analytical method for that carcinogen. NIOSH will revise the RML-CA when the limit of quantification for a NIOSH or OSHA validated or partially validated analytical method is reduced. NIOSH recommends keeping exposures within a 1 in 10,000 risk level, but this should be considered a starting point for continually reducing exposures to minimise the residual risk.

In Japan, the Ministry of Health, Labour and Welfare (MHLW) regulate occupational exposures in the working environment and maintains a list of mandatory exposure standards (termed Administrative Control levels; AC levels) for approximately 100 hazardous chemicals. The AC values are determined at an expert meeting that is assembled when the MHLW deems it necessary. Occupational exposure limits recommended by ACGIH® and the Japanese Society for Occupational Health (JSOH) are considered when assigning AC values for chemicals (Takahishi and Higashi, 2006). JSOH is a non-governmental society of occupational health professionals (academics and practitioners) that recommends occupational exposure limits or reference values. Where there is sufficient scientific information, JSOH will assign reference values corresponding to excess working lifetime cancer risks of 1 in 1000 and 1 in 10,000 for non-threshold based genotoxic carcinogens (Takahashi and Higashi, 2006; Kaneko et al., 1998; JSOH, 2016). JSOH clearly state that they do not recommend these reference values as safety exposure levels or that the working lifetime cancer risks are acceptable (JSOH, 2016).

Other settings

Non-threshold based genotoxic carcinogens can be found in food, pharmaceuticals and the environment. To minimise the cancer risk from these sources, regulatory agencies have taken different approaches. In general, cancer risks between 1 in 10,000 and 1 in 1,000,000 are generally considered acceptable, with a 1 in 100,000 risk commonly considered acceptable in the food and pharmaceutical industries for the general population and when considering the remediation of contaminated soils, whereas a more stringent risk of 1 in 1,000,000 seems to be common for risks from the environment to the general public (Table 1).

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[6] The terms of reference for the COC do not include the provision of risk management advice; that is the responsibility of regulators and policy makers.

[7] These limits are not legally binding.

[8] Based on a NIOSH or OSHA analytical method.

Food industry and drinking water

Non-threshold based genotoxic carcinogens can be found in food as a result of being an inherent natural constituent in the food plant or as a contaminant from the environment or through preparation processes. A committee of the European Food Safety Authority (EFSA) stated that a 1 in 100,000[4] cancer risk would be of low concern with respect to food safety (EFSA, 2005). In 1970, the US Food and Drug Administration (FDA) adopted a criterion of 1 in 1,000,000 cancer risk for food additives as an 'essentially zero' risk (Kelly, 1991). The WHO provides guideline concentrations for non-threshold based genotoxic carcinogens in drinking water with an associated lifetime cancer risk of 1 in 100,000 (WHO, 2011).

Pharmaceutical industry

Non-threshold based genotoxic carcinogens are sometimes used in the synthesis of pharmaceuticals and hence may be found as impurities in the final medicine. The ICH M7 guideline (ICH, 2015) which has been adopted internationally by pharmaceutical regulators was developed to provide guidance regarding safety risk management in establishing levels of non-threshold based genotoxic carcinogenic impurities that are expected to pose a negligible carcinogenic risk. A 1 in 100,000 cancer risk is considered an acceptable cancer risk, in comparison with the background overall lifetime cancer incidence.

Remediation of contaminated soil sites

Health Canada has deemed a cancer risk of 1 in 100,000 to be 'essentially negligible', compared with the background cancer incidence, when considering the remediation of contaminated sites. This includes a working lifetime cancer risk of 1 in 100,000 for workers at industrial work sites (Health Canada, 2004).

The French Ministry of the Environment has assigned the same cancer risk of 1 in 100,000 for the general population and workers on site, though a higher level of 1 in 10,000 may be acceptable provided techniques to achieve lower levels are unavailable and based on the strength of a detailed technical-economic study (Darmendrail, 2001).

Environment

The World Health Organization (WHO) in its Air Quality Guidelines for Europe provide airborne concentrations of non-threshold based genotoxic carcinogens associated with an excess cancer risk of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000, including a working lifetime cancer risk (WHO, 2000). The WHO does not make any reference to acceptability of risk, stating that this decision should be made by national authorities within the framework of risk management. The concentrations provided at the various cancer risks are to inform authorities in the decision-making process. However, as the WHO provides concentrations at cancer risks between 1 in 10,000 and 1 in 1,000,000, it may be inferred that cancer risks above 1 in 10,000 are considered unacceptable.

The US Environmental Protection Agency (US EPA) has stated that concentrations of non-threshold based genotoxic carcinogens in water associated with a 1 in 1,000,000 lifetime cancer risk are acceptable for the general population (US EPA, 2000).

Australian environmental regulatory authorities generally aim for a cancer risk of 1 in 100,000 or 1 in 1,000,000 which includes contamination in or exposure from air, soil and water (NSW Environmental Protection Agency, 2005; Victorian Environmental Protection Authority, 2001; enHealth, 2012; National Environment Protection Council, 2011).

Methods used for determining margins or risk

The method used to derive a margin or risk for cancer effects due to non-threshold based genotoxic carcinogens depends on the data available and the quality of such data:

- If only animal data are available, the two main approaches taken are the margin of exposure (MOE) method and the linear extrapolation method,
- If quality epidemiological data are available, linear extrapolation or absolute or relative risk factors are used, and
- If no adequate animal or epidemiological data are available, the threshold of toxicological concern is used by some agencies.

The approaches taken differ across agencies (Table 2).

Table 2 Summary of methodologies for risk assessment of non-threshold based genotoxic carcinogens

Agency	Approach	Point of departure	Reference
AGS	Absolute or relative risk (human data)	—	BAuA, 2014
AGS	Linear extrapolation	BMD10 BMD01 T25 (if BMD10 cannot be determined)	BAuA, 2014
European Chemicals Agency (ECHA)	MOE	BMDL10 T25	ECHA, 2012
ECHA	Linear extrapolation	BMDL10 T25 (preferred)	ECHA, 2012
EFSA	MOE	BMDL10 T25 (if BMDL10 cannot be determined)	EFSA, 2005
Health Canada[9]	Linear extrapolation	TD05 TC05	Health Canada, 2004
Health Council of the Netherlands	Linear extrapolation	BMD10	Health Council of the Netherlands, 2012
Health Council of the Netherlands	Relative risk (human data)	—	Health Council of the Netherlands, 2012
ICH M7 (pharmaceuticals)	MOE	TD50	ICH, 2015
JSOH	Relative risk (human data; extrapolation from animal data generally not performed)	—	JSOH, 2016
Scientific Committee on Occupational Exposure Limits (SCOEL)	Linear extrapolation	unclear	SCOEL, 2013
UK Committee on Carcinogenicity	MOE	BMDL10	Committee on Carcinogenicity, 2014
US EPA	Linear extrapolation (animal or human data)	BMDL10 BMDL01	US EPA, 2005
US EPA	Relative risk (human data)	—	US EPA, 2005
WHO	Linear extrapolation	BMDL10	WHO, 2000
WHO	Relative risk (human data)	—	WHO, 2000

[9] The approach adopted for contaminated sites; it is also the approach that was used in the assessment of substances on the Second Priority Substances List under the Canadian Environmental Protection Act.

Starting point for extrapolation to derive a margin or risk

The margin of exposure and linear extrapolation methods begin with a selected point of departure (POD). In the case of a substance inducing multiple tumour types or having been tested in multiple studies, the POD selected is usually the lowest of all modelled values. The various PODs include:

- the benchmark dose representing a 10 per cent tumour response from lifetime exposure (BMD10) or the lower 95% confidence interval of this benchmark dose value (BMDL10),
- the dose resulting in 25% of animals having tumours in a study (T25 method), and
- a dose resulting in 50% of the animals having tumours (TD50 approach)

See Appendix 1 for more detail about these PODs.

Of the three PODs mentioned above, the most widely used, if adequate data are available, is the BMD/BMDL approach. This is also the method less prone to error and less influenced by study protocol, such as dose spacing. However, it should be noted that different modelling methods and data can result in different values obtained. If this approach were to be taken, a specific BMD model and POD (BMDL or BMD) will need to be decided.

Margin of Exposure method (MOE)

The basis of the margin of exposure method is to divide a POD from animal studies by a factor to derive, generally, a 1 in 100,000 margin. This factor is independent of the chemical or its carcinogenic potency. The points of departure, BMD10/BMDL10, T25 and TD50, are divided by 10,000, 25,000 and 50,000, respectively, to derive a 1 in 100,000 margin or risk. As a margin of exposure resulting in a 1 in 100,000 risk is generally derived for a lifetime, a margin of exposure resulting in a 1 in 10,000 to 1 in 14,000 risk may be more appropriate for the occupational setting, given the standard working lifetime duration is 14 per cent of the whole lifetime (SCOEL, 2002). This would be consistent with the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) recommendation of a 10-fold lower margin when deriving standards for workers compared with the margin used for consumers (ECETOC, 2002); ECHA recommends a 2-fold lower margin for workers (ECHA, 2012).

Linear extrapolation approach

As the cancer risk at low doses cannot be determined directly either by animal experiments or by epidemiological studies, a number of mathematical models and procedures have been developed for use in extrapolating from high doses (such as those used in animal studies) to low doses.

The linear extrapolation method is driven by the assumption of a linear dose response relationship between tumour formation and exposure, and a threshold for carcinogenic effects does not exist (i.e. a ‘zero’ tumour response is associated with a ‘zero’ dose). The starting point for linear extrapolation is usually a point of departure such as a BMD/BMDL or T25 (ECHA, 2012). The high to low dose response assessment is generally performed in two steps:

- assessment of the dose response in the observable range for the tumour type under consideration to derive a POD, and
- extrapolation from the POD to lower dose levels.

Generally, allometric scaling is performed to correct a dose from an animal study to a human equivalent dose.

There are several models used for low dose extrapolation (EFSA, 2005; Edler et al., 2002). The most significant models that have been used are the linearised multistage method (LMS) (previously used by the US EPA, 1986) and the low dose linear extrapolation method (currently used by the US EPA; US EPA, 2005). The low dose linear extrapolation method used by the US EPA extrapolates from a human equivalent point of departure (generally the BMDL10[10]; corrected for background incidence) to the origin.

The slope of this extrapolated line is called the cancer slope factor (upper bound estimate of risk per increment dose). Unit risk estimates express the slope in terms of $\mu g/m^3$ or ppm of air and assumes standard daily intake (Unit risk = risk/($\mu g/m^3$ or ppm)). Risk-specific doses (for a lifetime or

[10] Termed LED10 by the US EPA

working lifetime duration) can be derived from the slope factor or unit risk. The slope factor and/or unit risk is generally cited in US EPA Integrated Risk Information System (IRIS) reports.

The LMS model employed a maximum likelihood estimation of parameters (US EPA, 1992; Kodell, 1988). The model approaches a 100 per cent risk at high doses and the shape at lower doses is described by a polynomial function which approximates a linear relationship between dose and cancer risk at low doses. The cancer slope factor or inhalation unit risk value is determined from the slope of the line at low doses. Due to non-linearity, it is considered inappropriate to determine doses associated with cancer risks greater than or equal to 1 in 100 using the cancer slope factor or inhalation unit risk factor determined by the LMS model (US EPA, 1992).

The linear extrapolation methods used by the WHO, Health Council of the Netherlands, AGS and Health Canada differ from the approach used by the US EPA by the POD or the extrapolation model used. Cross-comparison of estimates from various agencies can provide an indication of the confidence in estimates.

There are some potential errors or uncertainties associated with the low dose linear extrapolation method and LMS model (US EPA, 2005). Sources for uncertainty include the use of animal models as surrogates for humans (e.g. the relevance of the observations in animals to humans as well as differences in sensitivity to substance induced effects), model uncertainty and uncertainty surrounding the POD used as a starting point for extrapolation.

However, some of these uncertainties also exist for the margin of exposure method, most notably the reliability of the POD and the chosen animal model. Another consideration is the assumption of low dose linearity which may or may not be correct (Sielken et al., 1995).

No other validated non-linear mathematical models for non-threshold based genotoxic carcinogens are widely used by regulatory or standard setting agencies. The estimated cancer risk should not be considered an absolute or definitive risk. There are uncertainties surrounding the estimated values and these uncertainties should be clearly articulated in any accompanying documentation regarding risk communication or risk management (Committee on Carcinogenicity, 2012; US EPA, 2005).

Relative risk approach based on epidemiological data

If adequate epidemiological data are available, The WHO, Health Council of the Netherlands, AGS and the US EPA will use a relative risk approach as the preferred option to estimate airborne concentrations at different cancer risk levels. There are many advantages to this approach:

- The use of human data avoids uncertainties concerning interspecies extrapolations
- Compared with animal studies, data from larger group sizes may be available, and
- The extent of dose-effect extrapolation is lower as doses at which subjects are exposed will generally be lower than the high doses used in animal studies.

There are some potential shortcomings with this approach largely related to the quality of the available epidemiological data:

- adequacy of exposure data,
- definitive cause-response relationships,
- differing tumour classifications, and
- data on past exposure (either to the chemical of interest or to other potentially confounding confounding factors or effect modifiers).

Nonetheless, each agency has a set of criteria to gauge the quality of the study (US EPA, 2005; BAuA, 2014; Health Council of the Netherlands, 2012; WHO, 2000; SCHER/SCCP/SCENIHR, 2009).

Relative risk measures (risk ratio [RR], odds ratio [OR], Standardised Mortality Ratio [SMR] and Standardised Incidence Ratio [SIR]) are calculated depending on the study design (cohort or case control study) and end points examined (incidence or mortality). The relative risk is an expression of the strength of the association between exposure and the occurrence of the disease and can be used to calculate a concentration at a particular cancer risk value.

Threshold of Toxicological Concern

The threshold of toxicological concern (TTC) is a concept largely used in the food and pharmaceutical industries (US FDA, 1995; EFSA, 2012; ICH M7). The TTC concept was developed

to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects. An oral intake of 1.5 µg/day is considered to be associated with no more than a theoretical 1 in 100,000 excess lifetime risk of cancer, for most genotoxic compounds. It is noted that several potent compounds are excluded from this threshold due to their high carcinogenic potency (e.g. aflatoxin-like-, N-nitroso- and alkyl-azoxy compounds) (ICH M7; Committee on Carcinogenicity, 2014). Most agencies that use the TTC concept state that the TTC should only be used when there are insufficient chemical-specific data to calculate carcinogenic risk or a sufficient margin of exposure (ICH M7; EFSA, 2012).

The TTC concept is generally used for chemicals taken by the oral route of administration but there have been attempts to derive an inhalation TTC value for occupational health purposes (Lovsin Barle et al., 2016). Using the rationale provided in Lovsin Barle et al. (2016), based on a standard acceptable intake of 1.5 µg/day for a lifetime exposure (365 days, 70 years) and accounting for a shorter occupational exposure duration (eight hours/day, five days/week, 48 weeks/year, 40 years) with a volume of 10 m^3 of air respired in an eight hour period, this equates to an occupational inhalation TTC of 0.4 µg/m^3 associated with a theoretical 1 in 100,000 risk.

Given potent carcinogens, which may include chemicals on the workplace exposure standard list (for example, aflatoxin), should be excluded from the TTC concept and many times the TTC value is higher than a value for a 1 in 100,000 cancer risk estimate for a chemical based on experimental data (Lovsin Barle et al., 2016), this concept is not considered appropriate for deriving workplace exposure standards in Australia. In the case of the UK, a similar conclusion was reached by the Committee on Carcinogenicity (2014).

Proposed approach — workplace exposure standards for genotoxic carcinogens

For workplace exposure standards, there were several approaches considered with respect to non-threshold based genotoxic carcinogens (see Appendix 2 for details). Based on consistency with other international agencies and health-based and risk management reasons, the preferred option is to derive a workplace exposure standard at a ‘minimal’ cancer risk level. The term ‘minimal’ risk rather than ‘acceptable’, ‘tolerable’ or ‘negligible’ risk will be used.

This will indicate that there is still a residual risk at the target level and that PCBUs still have a responsibility to keep concentrations as low as reasonably practicable (ALARP). The estimated numerical risk at the target concentration will not be published to prevent any misleading indications regarding the accuracy of the risk estimate.

When using animal data, the linear extrapolation method will be used to determine an airborne concentration at this minimal cancer risk level. The limitations with this method (described above) are noted but it is considered the preferred option for the following reasons:

- This is the approach taken by comparable international agencies that derive occupational exposure limits, AGS, SCOEL and the Health Council of the Netherlands[11]. Therefore, a valid comparison between the value derived and the values obtained by the other agencies can be made to gauge the confidence in the estimate. Values within an order of magnitude will be considered comparable, given the potential errors and uncertainties in the estimates.
- Cancer slope factors and inhalation unit risk values are readily available from the US EPA for many genotoxic carcinogens. As the US EPA has already decided a BMD/BMDL, there would be no need for complicated determinations of BMD/BMDL, a process that could potentially introduce errors if performed by inadequately trained or inexperienced individuals. Cancer slope factors and inhalation unit risk values will not be used from other sources as these may be determined by a different means to that used by the US EPA.

If adequate epidemiological data are available, cancer slope factors and inhalation unit risk factors determined by the US EPA will be used.

The ‘minimal’ cancer risk level for workplace exposure standards for non-threshold based genotoxic carcinogens will be approximately 1 in 100,000, noting potential errors in the calculation. This is similar to that used by organisations that set limits for these chemicals in food, pharmaceutical products and the environment. It is also generally in the same order of magnitude with the targets of

[11] While SCOEL and the Health Council of the Netherlands do not derive exposure limits, when adequate data are available, these Agencies may determine concentrations at various cancer risk levels.

other agencies when setting occupational exposure standards. Australian workers should be afforded the same protections against occupational carcinogens as those in other developed countries. Likewise, people have the same right to protection at work as they do in other activities. This target is also insignificant compared with the overall cancer risk/incidence (1 in 3; Cancer Council Australia, 2016) and is within the range of work-related traumatic injury fatalities (1.5 in 100,000 Australian workers in 2016[12]; SWA, 2017). Setting an estimated cancer risk of 1 in 100,000 is consistent with the workplace exposure standards being protective for most workers.

While a 1 in 100,000 working lifetime cancer risk is similar to a whole of lifetime cancer risk for non-threshold based genotoxic carcinogens in food or pharmaceutical products (1 in 100,000), the actual dose per day is much higher for workers as a working lifetime is approximately 14 per cent of a whole of lifetime (SCOEL, 2002); the risk is associated with dose and exposure duration.

Working lifetime cancer risk calculation

The concentration at the minimal risk level of approximately 1 in 100,000 will be recommended using the US EPA calculated inhalation cancer slope factor or inhalation unit risk value for a particular chemical. Slope factors and unit risk values determined using either the LEDx/linear[13] or LMS method for the adult population will be used. If slope factors are available from both methods, the slope factors and inhalation unit risk factors determined using the LEDx/linear method is preferred over those determined using the LMS method (the latter method is no longer used by the US EPA). If slope factors or inhalation unit risk factors are estimated from high quality epidemiological data, this will be preferred over values determined from animal data.

The slope factors and unit risk values are calculated assuming continuous lifetime exposure (70 years) and need to be adjusted to the shorter working lifetime duration. Consistent with values used by other international agencies (Table 3), the following assumptions regarding a working lifetime are made:

- eight working hours per day
- five working days per week
- 48 working weeks per year, and
- 40 working years per lifetime.

Table 3 Comparison of values used by various agencies for calculating a working lifetime cancer risk

Agency	Working lifetime values	'Target' or 'acceptable' cancer risk	Reference
AGS	8 hours/day 240 days/year (equivalent to: 5 days/week 48 weeks/year) 40 years	4 in 100,000	BAuA, 2014
ECHA	8 hours/day 5 days/week 48 weeks/year 40 years	1 in 100,000	ECHA, 2012
European Commission	8 hours/day 5 days/week 50 weeks/year	—	European Commission Public Health
Health Canada (for contaminated sites)	8 hours/day 5 days/week 48 weeks/year 35 years	1 in 100,000	Health Canada, 2004

[12] The highest incidence was in the Agricultural industry with a fatality rate of on average 17 per 100,000 per year between 2003 and 2016. The fatality rate in all other industries was less than 10 per 100,000 workers.

[13] LEDx = BMDLx

Agency	Working lifetime values	'Target' or 'acceptable' cancer risk	Reference
Health Council of the Netherlands	8 hours/day 5 days/week 48 weeks/year 40 years	4 in 100,000	Health Council of the Netherlands, 2012
JSOH	40 years	—	Takahasi and Higashi, 2006
NIOSH	8 hours/day 5 days/week unspecified number of weeks/year 45 years	1 in 10,000	NIOSH, 2016a
SCOEL	8 hours/day 240 days/year (equivalent to: 5 days/week 48 weeks/year) 45 years	—	SCOEL, 2002
WHO	8 hours/day 240 days/year (equivalent to: 5 days/week 48 weeks/year) unspecified number of years	—	WHO, 2000

A 40 year working lifetime is considered appropriate to cover most workers. There are examples of welders working in the one industry for at least 36 years in other countries (Li et al., 2004). Many workers begin apprenticeships in their teenage years and stay in the same industry for their working lifetime. As the risk of cancer is associated with the overall duration of exposure, a working lifetime of 40 years, eight hours/day and 240 days/year is equivalent to a lower number of working lifetime years if the working day was longer or there were a greater number of working days per week (Table 4). Assuming a working lifetime of eight hours/day, 240 days/week and a total of 40 years and a cancer risk of 1 in 100,000 is considered to be protective to cover various exposure duration scenarios for most workers.

Table 4 Equivalent exposure duration scenarios

Years	hours/day	Days/year
40	8	240
32	10	240
38	8	250
31	10	250

Calculation of a minimal cancer risk using slope factors

Due to the assumed linear dose-response association for tumours induced by genotoxic carcinogens, an estimated cancer risk at a given dose can be calculated using the cancer slope factor (CSF). Estimation of cancer risk is based on the following simple equation:

$$Cancer\ risk = Exposure\ (mg/kg/day) \times CSF\ (1/(mg/kg/day))$$

As the US EPA cancer slope factors assume a continuous lifetime exposure (24 hours/day, 365 days/year, 70 years), modification of this equation is necessary to calculate a working lifetime (WL) exposure (eight hours/day, five days/week [240 days/year], 40 year working lifetime).

$$WL\ cancer\ risk = Exposure\ (mg/kg/day) \times CSF\ (1/(mg/kg/day)) \times \frac{40\ years}{70\ years} \times \frac{8\ h}{24\ h} \times \frac{240\ days}{365\ days}$$

Workplace exposure standard (WES) parameters are expressed as a concentration (ppm or mg/m^3). To convert this to an exposure parameter suitable for the above equation, the WES concentration is converted to a mg/kg/day dose, assuming a 70 kg individual and a 10 m^3 volume of air respired in eight hours (values used by agencies such as the ACGIH®, SCOEL, AGS and DFG, and consistent with the *Australian Exposure Factor Guide*[14]). Therefore, the working lifetime cancer risk of a genotoxic carcinogen at a particular airborne concentration can be calculated by the following equation:

$$WL\ cancer\ risk = Concentration\ (mg/m^3) \times \frac{10\ m^3/day}{70\ kg} \times CSF\ (1/(mg/kg/day)) \times \frac{40\ years}{70\ years} \times \frac{8\ h}{24\ h} \times \frac{240\ days}{365\ days}$$

Conversely, the airborne concentration at a given working lifetime cancer risk can be determined by rearrangement of the above equation as follows:

$$Concentration\ (mg/m^3) = \frac{WL\ cancer\ risk}{CSF\ (1/(mg/kg/day))} \times \frac{70\ kg}{10\ m^3/day} \times \frac{70\ years}{40\ years} \times \frac{24\ h}{8\ h} \times \frac{365\ days}{240\ days}$$

Calculation of a minimal cancer risk using an inhalation unit risk

Estimation of a cancer risk for the whole of lifetime exposure using the inhalation unit risk (IUR) is performed with the following equation:

$$Cancer\ risk = Concentration\ (\mu g/m^3) \times IUR\ (1/(\mu g/m^3))$$

Using the conversion factors described above, a working lifetime (WL) cancer risk can be calculated by the following equation:

$$WL\ cancer\ risk = Concentration\ (\mu g/m^3) \times IUR\ (1/(\mu g/m^3)) \times \frac{40\ years}{70\ years} \times \frac{8\ h}{24\ h} \times \frac{240\ days}{365\ days}$$

By rearrangement of the above equation, the airborne concentration at a given working lifetime cancer risk can be calculated as follows:

$$Concentration\ (\mu g/m^3) = \frac{WL\ cancer\ risk}{IUR\ (1/(\mu g/m^3))} \times \frac{70\ years}{40\ years} \times \frac{24\ h}{8\ h} \times \frac{365\ days}{240\ days}$$

Comparison of concentrations at the minimal risk value across agencies

Concentrations of selected non-threshold based genotoxic carcinogens at the minimal working lifetime cancer risk level determined using the equations in the previous section were compared with concentrations determined by SCOEL, DECOS and AGS (Table 5). In general, the values determined using the equations above were within an order of magnitude of values determined by other agencies, thus supporting the proposed approach above.

[14] The hourly inhalation rate for outdoor workers is cited as 1.3 m^3/hour. A 10 m^3 volume of air respired in eight hours is equivalent to 1.25 m^3/hour.

Table 5 Airborne concentrations for various chemicals determined by different agencies at the minimal cancer risk level

		Concentration at the minimal cancer risk level (µg/m^3)			
Compound	**CAS No.**	**SWA[a]**	**SCOEL**	**DECOS**	**AGS[b]**
Acrylamide	79-06-1	0.8	—	0.4	1.8
1,3-Butadiene	106-99-0	2.7	2.0	25	12.5
Epichlorohydrin	106-89-8	67	—	—	58
Vinyl chloride, monomer	75-01-4	18	78	2.5-25	—

[a] determined using inhalation unit risk factors from the US EPA.
[b] values derived from values in the GESTIS International Limit Values database; minimal cancer risk value, estimated 1 in 100,000; — = not determined.

Mixtures of non-threshold based genotoxic carcinogens

Workers may be exposed to multiple non-threshold based genotoxic carcinogens at one time or at various times throughout their working lifetime. The action of any particular chemical could potentially be influenced by other chemicals to which an individual is exposed, either simultaneously or at a different time. The UK Committee on Carcinogenicity (2010) has reviewed the different types of interactions:

- Simple similar action (non-interaction, dose addition)
  - The chemicals target the same organ and act via the same mechanism of action.
  - The effect of the components of the mixture is determined by respective doses and potencies.
- Simple dissimilar action (non-interaction, response addition)
  - The chemicals have different modes of action and possibly a different nature and site of action. The effect of each chemical does not modulate or contribute towards effects of other constituents of the mixture.
  - The health effects of exposure to these chemicals are expected to be qualitatively and quantitatively similar to those produced by the individual components when administered alone.
- Interaction (synergism/potentiation or antagonism/inhibition)
  - This refers to the situation where the observed effect of two or more exposures differs from the effect that would be expected if the exposures had additive effects.
  - The interaction could be due to direct chemical-chemical interactions, toxico/pharmacokinetic or toxico/pharmacodynamic mechanisms. The nature of the interaction could change depending on altered exposure conditions.

Because of the many possible combinations and complexities in terms of modes of action, target organs, relative exposure levels, different potencies and different timings of exposure, a prescriptive method to adjust workplace exposure levels for mixtures of non-threshold based genotoxic carcinogens is not possible at this stage.

However, adjusting a workplace exposure standard to a minimal cancer risk (estimated 1 in 100,000) for each non-threshold based genotoxic carcinogen is expected to provide some buffer to accommodate the possible interactions described above.

Risks associated with skin absorption

As with most workplace exposure standards, the minimal cancer risk adjusted workplace exposure standard for non-threshold based genotoxic carcinogens will be based largely on inhalation data. Therefore, for compounds where significant dermal absorption is possible at the workplace exposure standard, the associated cancer risk is potentially higher than the ‘minimal’ cancer risk. For these compounds, as with other chemicals where dermal absorption is significant at the exposure standard, a skin notation will accompany the exposure standard. Extra precautions would be necessary to minimise dermal absorption.

What are the implications for workplace exposure standards for non-threshold based genotoxic carcinogens?

A preliminary**,** peripheral examination[15] of the workplace exposure standard (WES) list revealed the following:

- 96 chemicals have a carcinogenicity notation (classified according to GHS as a category 1A, 1B or 2 carcinogen)
    - 18 of these chemicals are known to have a genotoxic mechanism of action resulting in tumorigenic effects (confirmed genotoxic carcinogens), and
    - 28 of these chemicals have an unknown mechanism underlying the tumorigenic effects, but are assumed to be genotoxic carcinogens based on positive genotoxicity findings.
- Inhalation Unit Risk values are only available for 19 of the confirmed or assumed non-threshold based genotoxic carcinogens
    - three of these chemicals are listed in Schedule 10.2 of the model WHS Regulations, and
    - of the remaining chemicals, 6 of the chemicals have no clearly demonstrated use in Australia (according to National Industrial Chemicals Notification and Assessment Scheme Inventory Multi-tiered Assessment and Prioritisation reports).

The proposed approach would likely result in WES values for several of the 19 confirmed or assumed non-threshold based genotoxic carcinogens being lowered considerably.

Following adjustment according to a minimal cancer risk, the WES value for some chemicals may be a concentration that is not practical to measure. This will have some impact on the ability of duty holders to use, handle and store these chemicals and for regulators to conduct compliance and enforcement activities. Chemicals for which the calculated WES is impractical to measure will be included in the WES list with an annotation stating that the value may be below the LOD.

For a number of assumed or confirmed non-threshold based genotoxic carcinogens there will be insufficient information to calculate a cancer risk. An interim WES will be recommended for these chemicals based on available data and applying uncertainty factors. The data may include data from analogue compounds and information regarding relative potency. Priority assessment of these chemicals in the next review of the workplace exposure standards will be recommended. An overview of the proposed approach for setting workplace exposure standard values for non-threshold based genotoxic carcinogens is shown in Figure 6.

[15] The numbers may change after the definitive assessments have been conducted.

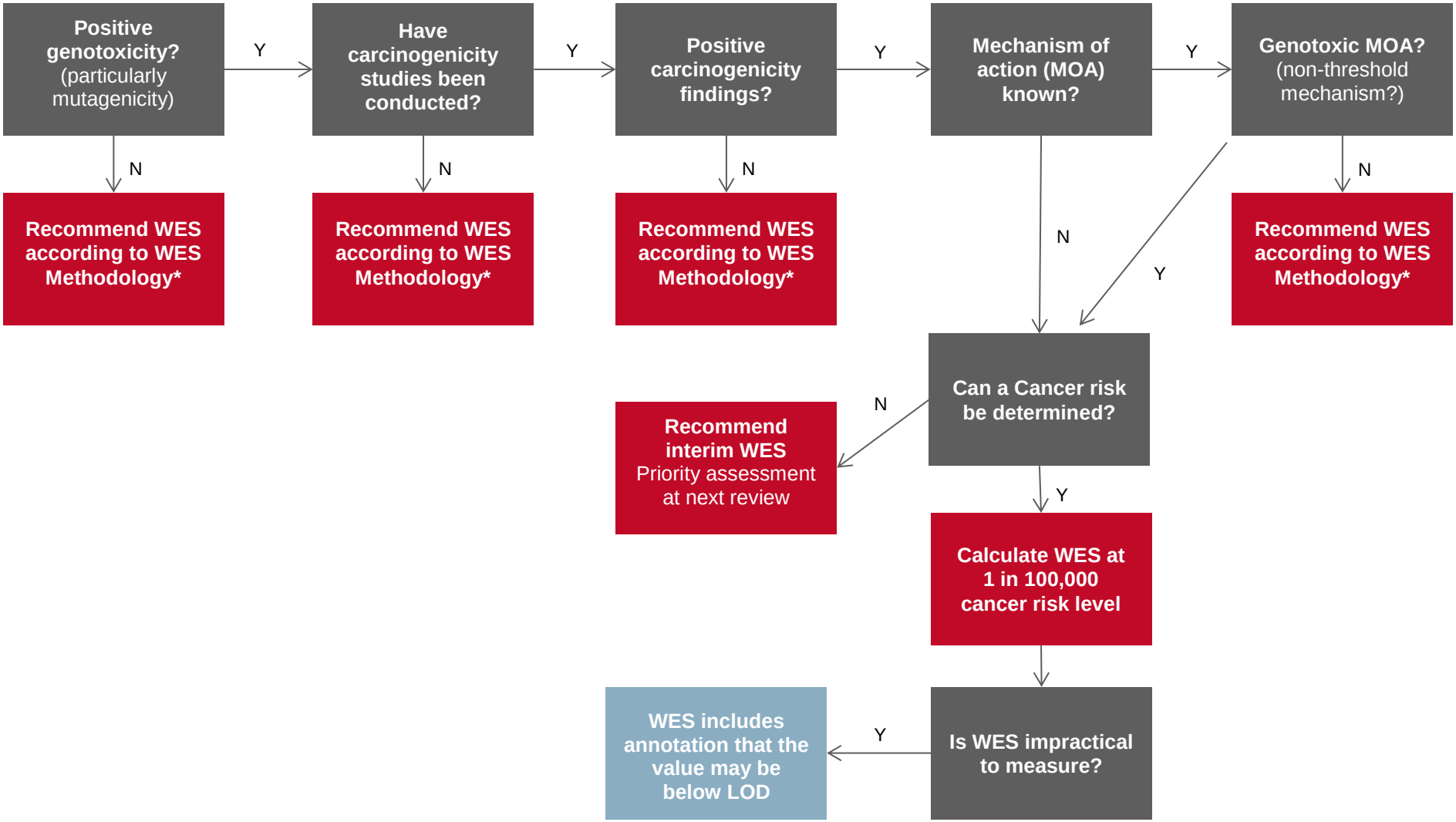

Figure 6 Overview of approach to setting workplace exposure standards for non-threshold based genotoxic carcinogens
*[*WES Methodology: Recommending health-based workplace exposure standards and notations*]

What are the implications for not taking cancer risk into consideration for workplace exposure standards?

If considerations for cancer risk for non-threshold based genotoxic carcinogens were not undertaken, workers may be exposed to occupational genotoxic carcinogens at unacceptably high cancer risks. Workers and PCBUs will be unaware of the potential risks associated with occupational exposures to these compounds. WES values are expected to be protective for carcinogenic effects and not addressing the occupational causes of cancer could ultimately lead to an extra strain on healthcare systems and an increase in workers' compensation claims.

Conclusion

- There is a responsibility for PCBUs and duty holders to eliminate or minimise the exposure of workers to carcinogens. A hierarchy of control measures is provided by the model WHS Regulations to help guide the management of risks associated with exposure to carcinogens in the workplace. This hierarchy of controls includes elimination and substitution, but this may not always be reasonably practicable. Workplace exposure standards, which are expected to be protective for carcinogenic effects, provide duty holders with information to design risk management plans for workers handling or exposed to carcinogens.
- Currently, there is no policy position for setting workplace exposure standards for a set of carcinogens, the non-threshold based genotoxic carcinogens. The estimated cancer risk associated with the current workplace exposure standard value for the majority of these compounds is at a level above international and national benchmarks.
- Based on similar approaches taken by international bodies, a policy is proposed to set a workplace exposure standard value at a minimal cancer risk level for a working lifetime. This will be determined with standard approaches used by the US EPA.
- The minimal cancer risk level is in a similar incidence range to that of traumatic fatal injuries sustained in Australian workplaces.
- It is acknowledged that cancer risk assessment is an evolving field and different mathematical models are being developed taking into account biological factors involved in defending against carcinogens (for example). As new models are being developed, validated and adopted by standard setting agencies, so too should Safe Work Australia's approach.
- Despite a workplace value being assigned to a non-threshold based genotoxic carcinogens, the principles of ALARP should always apply.

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Appendices

Appendix 1 — Points of departure

There are generally three points of departure used for linear extrapolation or margin of exposure methods. The advantages/disadvantages of these methods are shown in Table 6.

BMDx/BMDL10

BMDx/BMDLx values are not always available for chemicals and will generally need to be derived. The BMDx is defined as the dose that corresponds to a specific change (%) in response compared to the (modelled) response in control animals or subjects, the benchmark response (Crump et al., 1995). The BMD is determined by fitting a mathematical curve to the dose-response data over the range of observable responses from animal studies or human studies (if available). To take experimental uncertainty into account, the lower 95% confidence bound on the benchmark dose (BMDLx) is used as the point of departure by the US EPA. Prior to modelling, consideration should be given to the choice of data which would be used as the basis for the model. BMD analysis then involves model selection, model fit assessment and data reporting. There are various models for BMD determination with different software available to perform the calculation (Committee on Carcinogenicity, 2014; US EPA, 2012; EFSA, 2009; 2011; WHO/IPCS, 2009). BMDx/BMDLx values can differ depending on the data used for modelling and the method for modelling. These are potential sources of error and inaccuracy. The BMDx/BMDLx should only be determined by experts skilled in the interpretation of toxicological and epidemiological data (for the choice of data inputs) and experts who have a clear understanding of BMD models and their limitations to minimise the risk of errors in the final BMDx/BMDLx value determined.

T25 method

Compared to the BMDx/BMDLx method, this is a much simpler method, requiring only a single data point from the dose-response curve from a single study and does not require elaborate statistical methods. The T25 is defined as the dose eliciting a 25% increase in the incidence of a specific tumour above the background level. The T25 value is determined by interpolation or sometimes extrapolation from the dose-response curve to identify the dose resulting in a 25% increase in the background tumour incidence. The T25 value from a rodent carcinogenicity study is then converted to a human T25 value using allometric scaling factors. There have been several criticisms of this method (covered in Committee on Carcinogenicity, 2014; ECETOC, 2002). The choice of a single data point from a single study has the potential to introduce error in any extrapolations from the value, compared with a benchmark dose approach. The T25 is determined from the most sensitive tumour site and the dose level that gives the lowest T25 estimate. The most sensitive tumour site might be difficult to discern as it depends on the magnitude of the background incidence for that tumour in the rodent study. The human relevance of the tumour findings is uncertain if the most sensitive tumour occurs in an organ not found in humans, for example the rat forestomach, Zymbal's glands or Harderian glands, taking into account the mechanism of tumour formation is due to a direct interaction with DNA. The most sensitive rodent species may not be the best animal model for human susceptibility. While the derivation of a T25 value may be simple, the choice of the most relevant species and most relevant tumour site requires extensive toxicological expertise. The T25 method has been used in the EU in the past but has been abandoned because of the limitations and inaccuracies in this approach (ECETOC, 2002). Given the potential errors associated with the use of T25 values and that this approach is not used by most other agencies, use of the T25 value as a point of departure is not considered suitable when deriving workplace exposure standards for genotoxic carcinogens in Australia.

TD50 approach

The TD50 is defined as the chronic dose which would induce tumours in a given site(s) in 50% of the test animals. TD50 values have been estimated for many chemicals and are listed in the Carcinogenic Potency Database (developed by Gold et al., 1984; 1997). A description of the TD50 methodology and the complex statistical analysis involved in the derivation is provided on the Toxnet site. The TD50 values are determined from multiple studies, regardless of administration route, and the TD50 values from individual studies can vary greater than 10-fold. No data are provided to gauge the quality of the cited studies in the database. As the majority of studies from which the TD50 values are derived involved oral administration of the chemical, the relevance of the derived TD50 value to the inhalation route (necessary when deriving workplace exposure

standards) is questionable. Also, given the significant variability in TD50 values determined, the reliability of the data to derive a workplace exposure standard is of particular concern and an indication of the quality of the underlying experimental data is not provided (both potential sources of error). The Committee on Carcinogenicity (2014) recommends the use of TD50 values for ranking the carcinogenic potency of genotoxic compounds rather than to be used as a point of departure. However, the TD50 approach is used in the pharmaceutical setting where the oral administration route is more common (ICH M7). The TD50 approach is not used by reputable regulatory or policy agencies that set workplace exposure standards and is not considered an appropriate approach to use in setting workplace exposure standards in Australia.

Table 6 Advantages and disadvantages of various points of departure

Method	Advantages	Disadvantages
BMDLx/BMDx	• Considers several sources of data. • Recommended point of departure used by most agencies.	• BMDLx/BMDx values are not readily available and will need to be derived. • Different BMDLx/BMDx values can be determined depending on the choice of data and the choice of BMD model, thus leading to potential sources of error.
T25 method	• Simple method to calculate. • Does not require elaborate modelling or statistical programs.	• The T25 value would need to be derived. This will require considerable toxicological expertise and effort to select the most relevant rodent species and most relevant tumour site from which to derive the T25 value. • Use of a single data point, rather than considering multiple sources of data and data points, is a potential source of error and inaccuracy. • This method has been criticised.
TD50	• TD50 values do not need to be derived.	• TD50 values available have been derived from studies following predominantly oral studies, which are not considered relevant to workplace exposure standards. • The TD50 values inherently have large errors, as TD50 values derived from different studies can vary greater than 10-fold. • The TD50 values are better considered as an indicator of relative carcinogenic potential rather than used as a numerical value to derive workplace exposure standards. • This method is not used by any agency that assigns workplace exposure standards for genotoxic carcinogens.

Appendix 2 — Potential approaches considered when setting workplace exposure standards for non-threshold based genotoxic based carcinogens

1. **Maintain status quo — Adopt the standard from the ACGIH®**
   This was not considered a satisfactory option for the following reasons:

   a. This approach is not expected to adequately protect workers from the risk of carcinogenicity; the estimated cancer risk at some of the ACGIH® standards for genotoxic (non-threshold-based) carcinogens is considered unacceptably high. This is in conflict with the role and expectations of workplace exposure standards.
   b. The cancer risk for carcinogens at the set workplace exposure standard levels will be variable.

2. **Do not apply a workplace exposure standard for these chemicals**
   This was not considered a satisfactory option for the following reasons:

   a. This approach is generally inconsistent with the approach adopted by international regulators.
   b. This approach does not differentiate a potent carcinogen from a carcinogen with lower potency. No information is available regarding relative potency for different carcinogens.
   c. It does not provide sufficient information for risk management plans as no information regarding the relative risk at various concentrations would be available.
   d. As PCBUs have a duty of care to provide a relatively safe working environment for their employees, this approach does not provide sufficient safety information for PCBUs to fulfil their duties in terms of Workplace Health and Safety for workers.

3. **Adopt the standard from the ACGIH® and communicate the cancer risk at the given airborne concentration**
   This was not considered a satisfactory option for the following reasons:

   a. The mandated workplace exposure standard may represent an ‘unacceptable’ cancer risk.
   b. While this option does provide more information for duty holders and regulators to inform decision making, education, compliance and enforcement activities, it may cause confusion for duty holders about compliance expectations.

4. **Calculate a WES at a minimal cancer risk level**
   This was the favoured option for the following reasons:

   a. It is generally consistent with other regulatory bodies.
   b. The level of risk would be expected to be similar for all non-threshold based genotoxic carcinogens, regardless of potency, at the calculated workplace exposure standard.
   c. It is a pragmatic approach that can provide PCBUs and workers with appropriate information for risk management processes.
   d. The approach aligns with the role and expectations of workplace exposure standards.
   e. Models are available to effectively and consistently calculate working lifetime cancer risks.

5. **Adopt the standard from the ACGIH®, communicate the working lifetime cancer risk at the mandated airborne concentration, and communicate the exposure standard at which there is a minimal working lifetime cancer risk**
   This was not considered a satisfactory option for the following reason:

   a. This option provides multiple airborne concentrations to duty holders to inform decision making; however, it may cause confusion around which standard is mandated and which is advisory and again carries the risk surrounding mandating an ‘unacceptable’ cancer risk.

6. **Set an exposure standard solely based on technical feasibility**
   This method would involve setting an exposure standard at the limit of detection (LOD) for the analytical method. Action would be required if airborne concentrations are above the LOD. This approach may be a useful pragmatic approach if the airborne concentration at a minimal cancer risk level was impractical to measure due to limitations in analytical techniques.
   This was not considered a satisfactory option for the following reasons:
   a. Limits based on technical feasibility alone do not provide adequate protection from adverse health effects. The aim of workplace exposure standards is to protect workers against risks to their health and safety.
   b. The extent of risks would differ from one carcinogen to another at the exposure standard if levels were based solely on technical feasibility.
   c. It would need to be clearly articulated that the limit is based on technical feasibility.
   d. Currently, there is no framework to mandate measurement methods.
   e. This approach may lead to ‘method shopping’.
   f. There are concerns regarding advances in technology and analytical methods occurring at a faster rate than the Regulations can be updated or reviewed.

Appendix 3 — Abbreviations and acronyms

Abbreviations	
ACGIH®	American Conference of Governmental Industrial Hygienists
AGS	The Committee for Hazardous Substances of the German Federal Ministry of Labour Social Affairs
AIHA	American Industrial Hygiene Association
ALARP	As low as reasonably practicable
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German Federal Institute for Occupational Safety and Health)
BMD	Benchmark dose
BMDLx	Lower 95% confidence bound on the benchmark dose
BMDx	Dose that corresponds to a specific change (x%) in response compared to the (modelled) response in control animals or subjects
COC	Committee on Carcinogenicity
CSF	Cancer slope factor
CSTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment
DECOS	Dutch Expert Committee on Occupational Safety
DFG	German Research Foundation (Deutsche Forschungsgemeinschaft)
DMEL	Derived minimal effect level
DNA	Deoxyribonucleic acid
DNEL	Derived No-Effect Level
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemical Agency
EFSA	European Food Safety Authority
EU	European Union
GESTIS	Information system on hazardous substances of the German Social Accident Insurance
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HSE	Health and Safety Executive
ICH	International Conference on Harmonisation
ICH M7	International Conference on Harmonisation M7 Guideline
IRIS	Integrated Risk Information System

Abbreviations	
IUR	Inhalation unit risk
JSOH	Japanese Society for Occupational Health
LEDx	Effective dose corresponding to the lower 95% limit on a dose associated with x% response
LMS	Linearised multistage method
LOD	Limit of detection
LOQ	Limit of quantification
m^3	Cubic metre
Methodology (b)	Recommending health-based workplace exposure standards and notations
mg/kg/day	Milligrams per kilogram per day
mg/m^3	Milligrams per cubic metre
MHLW	Ministry of Health, Labour and Welfare
MOE	Margin of exposure
NIOSH	US National Institute for Occupational Safety and Health
NOAEL	No observed adverse effect level
OARS	Occupational Alliance for Risk Science
OEL	Occupational exposure limit
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
PCBU	Person conducting a business or undertaking
PEL	Permissible exposure limits
POD	Point of departure
PPE	Personal protective equipment
ppm	Parts per million
REACH	Registration, Evaluation and Authorisation of Chemical substances
RML-CA	Risk Management Limit for Carcinogens
RR	Risk ratio
SCCP	Scientific Committee on Consumer Products
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental Risks

Abbreviations	
SCOEL	Scientific Committee on Occupational Exposure Limits
SER	Main advisory body to the Dutch government and the parliament on national and international social and economic policy
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
STEL	Short-term exposure limit
SWA	Safe Work Australia
T25	The dose eliciting a 25% increase in the incidence of a specific tumour above the background level
TD50	The chronic dose which would induce tumours in a given site(s) in 50% of the test animals
TTC	Threshold of toxicological concern
TWA	Time-weighted average
UK	United Kingdom
US EPA	US Environmental Protection Agency
US FDA	US Food and Drug Administration
WES	Workplace exposure standard
WHO	World Health Organization
WHS	Work Health and Safety
WL	Working lifetime