Regulatory risk assessment approaches for synthetic mineral fibres

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A B S T R A C T
Exposure to synthetic mineral fibres (SMF) may occur in a number of workplace scenarios. To protect worker health, a number of different organisations worldwide have assessed the health risk of these materials and established workplace exposure limits. This paper outlines the basic principles of risk assessment and the scientific methods used to derive valid (justifiable) occupational exposure limits (OELs) and goes on to show how, for SMF, and particularly for refractory ceramic fibre (otherwise known as aluminosilicate wool, RCF/ASW), the methods used and the associated outcomes differ widely. It is argued that the resulting differences in established OELs prevent consistent and appropriate risk management of SMF worldwide, and that development of a transparent and harmonised approach to fibre risk assessment and limit-setting is required.

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1. Introduction

Synthetic mineral fibres (SMF) — alternatively known as man-made mineral fibres (MMMF) — constitute a complex group of materials including synthetic vitreous fibres (SVF) and certain non-vitreous materials such as polycrystalline wools (PCW). SVFs include glass wool, rock/stone wool, slag wool, alkaline earth silicate (AES) wool and aluminosilicate wool (ASW) — also known as refractory ceramic fibre (RCF). The composition of these materials differs according to their intended use, though they typically include silicates and other mineral oxides. They may be manufactured from processed or un-processed mineral raw materials; fibres are normally produced by spinning or blowing the molten material, or by a sol—gel process. Most SMF are used for acoustic or thermal insulation, fire protection, reinforcement and filtering applications. ASW/RCF, along with AES wools and PCW, constitute a family of fibres known as High Temperature Insulation Wools (HTIW)1 that are used in specialist industrial high temperature applications such as furnace linings. Worker exposure by inhalation to these fibres may occur during fibre production, product manufacture (processing) and assembly or installation operations, and during plant decommissioning or demolition. Exposure of the general public is generally low and for HTIW is negligible as these materials are not used in consumer products.

The toxicity of SMF is driven not by chemical constitution but — because of their fibrous nature — by their size, shape and biopersistence, as reflected in the so-called ‘3Ds’ paradigm (Brown and Harrison, 2012; see Section 4.1). This makes the risk assessment and regulation of SMF rather more complex than for bulk

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The principal objective of this review is to describe and assess specifically the approaches that have been applied to SMF, and to ASW/RCF in particular. We also consider the need for harmonisation of the regulatory processes applied to SMF globally — including the derivation of OELs for ASW/RCF — to enable consistent and appropriate risk management. The first part of the paper briefly describes some general principles of risk assessment, followed by a description of the processes and procedures used to set occupational exposure limits. The next section looks at specific issues in risk assessment and leads into consideration of regulatory approaches to SMF in Europe and the USA. Finally, leading up to the discussion section, there is a detailed ‘case study’ reviewing regulatory approaches to ASW/RCF in different jurisdictions across the world.

2. Principles of risk assessment

Risk assessment traditionally constitutes three steps — hazard identification, hazard characterisation (or dose-response assessment), and exposure assessment. A fourth step, risk characterisation, is then applied to integrate the findings (Finer, 2006; NRC, 2009). Any attendant uncertainties relating to the first three steps are integrated into the risk characterisation step and it is this information that is drawn on for the related, but distinct, process of defining the necessary risk management measures (RMM) required to ensure safe use of the substance. Chemical risk assessment usually incorporates both qualitative and quantitative evaluation (Harrison and Holmes, 2006); these are briefly described below. The process is widely and comprehensively documented elsewhere by authoritative bodies (for example, EFSA, 2014; COC, 2012a; COC, 2012b; ECHA, 2012a; ECHA, 2012b; WHO, 2010; EFSA, 2009; EC, 2000a; US EPA, 2005).

Hazard identification is concerned with identifying the specific potential adverse effects of a chemical or mixture through consideration of its chemical and physical properties in conjunction with toxicological and toxicokinetic data. Hazard characterisation entails the evaluation of available data to develop a ‘weight of evidence’ (WoE) argument in support of a link between exposure to a chemical and the likelihood and severity of any adverse effect (the apical endpoint). Where a number of different endpoints are observed, the one that occurs at the lowest exposure level is usually selected as being ‘critical’ for risk assessment purposes. For the majority of chemicals it is possible, on the basis of mechanistic knowledge and available experimental data, to define a threshold dose/concentration — such as the ‘no observed adverse effect level’ (NOAEL) or benchmark dose (BMD) — that can be used as the point of departure (POD) (also referred to as Reference Point) for risk extrapolation (discussed further in Section 2.2). If the dataset does not allow definition of an effective ‘no effect’ threshold then, provided understanding of the toxic mechanism is sufficient to support the theoretical existence of a threshold, it may be possible to define a dose at which only a minimal level of effect is apparent, termed the lowest observed adverse effect level (LOAEL). Due to the implicitly greater degree of uncertainty associated with a LOAEL, an additional assessment factor is incorporated into the risk assessment process (Section 2.2).

For a few types of toxic effect (e.g. cancer, mutation and sensitisation), the underlying mechanism may determine that it is theoretically not possible to establish a threshold below which no adverse effect will occur; in other words, any exposure to the chemical might elicit some degree of response (COC, 2012a). Such chemicals are treated differently from threshold chemicals in the risk assessment process (Section 2.1). It is to be noted, however, that the supposed absence of a threshold for genotoxic carcinogens is increasingly disputed (Greim and Albertini, 2015). Indeed, it can reasonably be argued that all substances (including genotoxic carcinogens) are likely to have some kind of threshold of effect — the problem is determining where this lies.

Human data for use in risk assessment can be sourced from case reports, epidemiology, and occupational and clinical studies. However, each of these sources has certain limitations (Devlin et al., 2005), and may not be available at all. For these reasons, data from studies on intact animals are often utilised; these have the advantage of being designed, controlled and conducted to address specific gaps in knowledge or use specific disease models to specific criteria and protocols (e.g. OECD guidelines for the testing of chemicals). However, as responses of humans and animals to a given exposure may be substantially different (both physiologically and behaviourally), there are always inherent associated uncertainties when extrapolating from animals to humans. Further, animal studies have historically investigated dose-response relationships over a much higher concentration range than would be likely to occur for humans, necessitating extrapolation of the findings to lower dose levels, leading to further uncertainty. Importantly, animal studies can nonetheless provide valuable information on the Mode of Action (MoA) and Adverse Outcome Pathway (AOP) to complement the determination of a quantitative reference point for hazard characterisation (Devlin et al., 2005; EFSA, 2014). Supporting this aim, a number of in vitro models, in silico tools (e.g. (Q)SARs and ‘read-across’ methodologies) and ‘omics’ technologies (transcriptomics, proteomics, metabolomics) have been developed to investigate toxicokinetic and toxicodynamic processes at the organism, organ, cell and molecular levels (described more fully in EFSA, 2014; EC, 2011; Grant et al., 2010; EC, 2009; NRC, 2006; Devlin et al., 2005; Holme and Dybing, 2002).

2.1. Carcinogens and thresholds of effect

With potential carcinogens and mutagens (also sensitising agents), it is important to consider the MoA by which the chemical acts and the relationship between dose and adverse response so that the risk assessment process can allow for the presence or absence of a threshold. Conventionally, a distinction is made between ‘genotoxic carcinogenicity’ and ‘non-genotoxic carcinogenicity’ (COC, 2012a), and it is now further recognised that there is a difference between ‘primary’ and ‘secondary’ genotoxic carcinogenicity, where the latter has a measurable threshold. This is the case, for example, with certain fibres (see below) where the induction of reactive oxygen species (ROS) is responsible for a secondary genotoxic effect for which a threshold exists. There are a number of structured frameworks available for the assessment of the overall WoE for a postulated MoA (Cohen et al., 2003, 2004; Meek et al., 2003; Boobis et al., 2006).

For primary (DNA-reactive) genotoxic carcinogens considered

2 ASW/RCF is categorized under the chemical abstracts service registry number (CAS Number) 142844-00-6 and EC List number 604-314-4. In Europe, under European Regulation 1907/2006 (REACH), ASW/RCF is defined as a type of UVCB (chemical substance of unknown or variable composition, complex reaction products and biological material).

3 For most chemicals, POD is expressed as the dose (e.g. mass per kilogram bodyweight in a given period, e.g. mg/kg bodyweight/day) or as a concentration (e.g. mg/m³ for atmospheric exposure) to which an organism is exposed.

not to have a threshold of effect, it is assumed that increases in DNA damage occur in a linear fashion related to dose, so that any level of exposure might result in a mutation and hence some measure of increased risk (SCHER et al., 2009). Under EU Directive 2004/37/EC5 workers’ exposure to such chemicals must be prevented by replacing the carcinogen or mutagen or by using a closed process. If not technically possible, then risk must be lowered by ensuring that exposure of workers is ‘reduced to as low a level as is technically possible’ (SCHER et al., 2009). Similarly, as complete prevention of exposure of the general population to carcinogens is not always feasible, a widely accepted approach to reduce risk from genotoxic carcinogens is to ensure that levels are controlled so that exposure is as low as reasonably achievable (ALARA). This may mean preventing exposure entirely or identifying a practical ‘minimal risk level’ through application of appropriate uncertainty factors to a POD (e.g. the lower 95% confidence limit of the BMD for a 5% response over control levels – BMDL5) from dose-response data for carcinogenicity (Constable and Barlow, 2009: COC, 2012b). In the US and some European countries, risk from an environmental genotoxic carcinogen is estimated by the extrapolation of dose-response data from epidemiology and/or experimental animal studies to give an estimate of excess lifetime risk (e.g. 1 cancer case in a population of 1 million). This approach has not been adopted in the UK as the Committee on Toxicity (COC) considers that the derived estimate generates a false sense of precision which cannot be justified (COC, 2012b).

Non-genotoxic carcinogens are chemicals for which there is no evidence for a MoA involving genotoxicity as the primary biological mechanism (COC, 2012a). Many of these chemicals induce tumours as a consequence of a primary toxic effect (e.g. induction of reactive oxygen species) for which a threshold dose such as a NOAEL can be identified and used as the PoD (Ashby et al., 1996 — cited in COC, 2012a).

2.2. Risk characterisation

The final step of the risk assessment process, risk characterisation, involves ‘the quantitative or semi-quantitative estimate, including attendant uncertainties, of the probability of occurrence and severity of adverse effect(s)/event(s) in a given population under defined exposure conditions based on hazard identification, hazard characterisation and exposure assessment’ (EC, 2000a).

In practice, risk characterisation is usually accomplished by comparing the POD values (e.g. NOAEL/LOAEL) for the most critical (sensitive) toxic endpoint with the dose or concentration to which humans are exposed. Historically it has been common to express this relationship as the ‘Margin of Safety’ (MoS; i.e. the ratio of the predicted exposure to the POD, FLOYD, 2006), with values < 100 normally interpreted as indicating a need for a more comprehensive evaluation of risk (COC, 2012b).

Alternatively (and now more usually), the experimental POD may be adjusted to determine an exposure level in humans that would be ‘acceptable’, through the use of assessment factors (sometimes termed ‘uncertainty factors’). The derived ‘acceptable’ exposure level may be referred to – depending on the jurisdiction, and the type and nature of exposure – by terms such as acceptable daily intake (ADI), tolerable daily intake (TDI), tolerable concentration (TC), minimal risk level (MRL), reference dose (RfD) or reference concentration (RfC). Acceptable exposures for workers are generally termed ‘permissible exposure levels’ (PELs), ‘occupational exposure levels’ (OELs) or ‘recommended exposure levels’ (RELs).

Assessment factors not only account for exposure differences and limitations in datasets, but also address inherent uncertainties in the extrapolation process itself (Dourson et al., 1996). Historically, regulatory systems addressed uncertainty pragmatically, for example applying a default 100-fold factor to a NOAEL from a chronic (lifetime) animal study to determine the acceptable exposure for humans (reflecting a 10-fold inter-species variability in sensitivity and 10-fold intra-species variability in sensitivity). Additional factors might be included because of limitations in datasets (e.g. from 1- to 100-fold, on a case-by-case basis) when extrapolating from short-to longer-term durations or if using a LOAEL rather than a NOAEL as the POD. Further adjustment might be applied to address severity of effect and reservations on dataset quality, based on professional judgement (Dourson et al., 1996).

Characterisation of the scientific basis underlying use of assessment factors now permits replacement of one or more default values with chemical-specific values where specific toxicokinetic and/or toxicodynamic data are available (Pieters et al., 1998; Renwick, 1991, 1993, 1999; Renwick and Lazarous, 1998; EVM, 2005).

3. Setting occupational exposure limits

Occupational Exposure Limits (OELs) have been a feature of the industrialised world for over fifty years. In the EU it is the responsibility of SCOEL to recommend ‘health based’ OELs where a review of the total available scientific database leads to the conclusion that it is possible to identify a clear threshold dose/exposure level below which exposure to the substance in question is not expected to lead to adverse effects’ (SCOEL, 2013). SCOEL advises that OELs may principally be used ‘to provide standards or criteria against which measured exposure levels in existing workplaces may be compared in order to ensure that, as far as the current state of knowledge permits, control is adequate to protect health’. However, OELs can also be used for designing new plants and processes to ensure that they ‘are engineered in such a way that exposures can be controlled at levels which will not damage health’ (SCOEL, 2013).

‘Risk-based’ OELs may be recommended for substances that are genotoxic, carcinogenic or respiratory sensitisers where, at least according to current paradigms, it is not possible to define a threshold of activity and where it must, therefore, be assumed that any level of exposure, however small, might carry some finite risk. It is the responsibility of the European Commission to set ‘risk-based’ OELs, which requires consultation with interested parties (SCOEL, 2013).

OELs may be established using human and/or animal data and are intended to be protective under realistic workplace exposure conditions (e.g. by mandating controls on the maximum exposure during a working day or on peak short-term exposures). Various approaches exist, such as the previously discussed MoS concept where, depending on the endpoint considered, a low MoS may suggest a need for further evaluation. However, in some circumstances, and in some organisations/jurisdictions, there may also be the need to consider aspects such as practicality and achievability. Depending on the particular socio-economic, legislative and political environment, different regulatory regimes may reach somewhat differing conclusions as to what constitutes the appropriate OEL for a substance, even using the same scientific evidence.

Since 2010 in the EU, following the implementation of REACH, the concepts of ‘derived no effect level’ (DNEL) for threshold effects and ‘derived minimal effect level’ (DMEL) for non-threshold effects have also been applied to protect workers and other population groups; the latter is intended to represent an exposure level where the likelihood that an adverse effect would occur in a population is
considered to be sufficiently low as to be of essentially no concern. Unlike the traditional OEL setting process, DNEL or DMEL setting for workers under REACH is a purely risk-based procedure that involves applying various assessment factors to the POD, mostly involving the use of default values. DNEL and DMEL values are compared against estimates of human exposure to decide if the risks are acceptable. For threshold effects, a risk is considered acceptable if the ratio DNEL:Exposure (termed the risk characterisation ratio, RCR) is <1. For non-threshold substances, however, REACH is less clear cut, since the regulation does not specifically define an ‘acceptable’ risk and, in its guidance, ECHA fails to give a specific value, instead stating “Based on these experiences, cancer risk levels of $10^{-5}$ and $10^{-6}$ could be seen as indicative tolerable risks levels when setting DMELs for workers and the general population, respectively” (ECHA, 2012a). This lack of clear guidance has been the subject of criticism (Puringer, 2011; Losert et al., 2011).

A somewhat different approach continues to be taken by SCOEL which, under Council Directive 80/1107/EEC as amended by Council Directive 88/642/EEC, is tasked with developing proposals for either binding or indicative occupational exposure limit values (BOELVs or IOELVs respectively); the former refer to situations where a “no-effect” level of exposure cannot be reliably identified. If there is a threshold, health-based OELs are recommended but ‘risk-based’ OELs may be established for non-threshold phases (particularly genotoxicity, carcinogenicity and respiratory sensitisation). For each substance, SCOEL establishes assessment factors on a case-by-case basis and distinguishes four types of carcinogen on mechanistic grounds, namely:

**Group A:** Non-threshold genotoxic carcinogens – for low-dose risk assessment linear non-threshold (LNT) modelling is applied;

**Group B:** Genotoxic carcinogens – where a threshold cannot be sufficiently established, LNT modelling is used as a default assumption;

**Group C:** Genotoxic carcinogens – for which a practical threshold is supported; and

**Group D:** Non-genotoxic carcinogens and non-DNA reactive carcinogens – a true threshold may be established associated with a NOAEL.

SCOEL seeks to derive health-based OELs for carcinogens in Groups C and D and, if possible, apply risk-based assessments to Category A and B substances (Bolt, 2008; Bolt and Huici-Montagud, 2008; Bolt and Degen, 2004; SCOEL, 2013).

As a consequence of the differences in approach between REACH and SCOEL, safety margins determined through the REACH procedures are, on average, approximately six-times higher than those derived by SCOEL. This may be a consequence of its reliance on default assumptions and ‘rule-based’ processes without the expert deliberation that is an integral part of the SCOEL approach (Schenk and Johanson, 2011).

For non-threshold substances (e.g. genotoxic carcinogens), the risk associated with a particular exposure (e.g. the incidence of cancers that would arise in a given population; Dorne and Renwick, 2005) can be used to set exposure limits. However this requires a judgement by policy makers on the disease frequency (e.g. of cancer) that would be societally acceptable for an exposed group. Defining such a risk level is a policy matter not a scientific decision and, consequently, values are likely to vary between jurisdictions and depending on the populations affected.

The choice of model used to determine the dose-response relationship has a critical impact on the risk estimate derived; linear dose-response assumptions generally give more conservative estimates than nonlinear models (NRC, 2006; Gold et al., 2003). Ideally, model selection should be driven by an understanding of the underlying MoA.

A summary of the principles that apply in deriving OELs is given in Table 1.

### 4. Fibre-specific considerations

#### 4.1. Toxicological considerations

In the case of fibres, the factors that influence toxicity and carcinogenic potency are much more complex than simply the chemical composition and mass of material to which an organism is exposed. Instead, the toxicity of a fibre is critically influenced by the intrinsic properties of length, diameter and solubility (chemical stability in a biological environment). The paradigm that describes the potential for a fibre to produce a toxic response in the lung has been referred to as the ‘3Ds’, which stands for *dose, dimension* (where diameter essentially determines fibre respirability and deposition in the lung, and length influences ease of removal by macrophages), and *durability*, (or, more properly, ‘biopersistence’, which relates to the propensity of fibres to dissolve and/or break in the lung milieu; Hesterberg and Hart, 2001; Maxim et al., 2006; Moore et al., 2001). Chemical composition of a fibre is generally regarded as important only in so far as it influences biopersistence (Brown and Harrison, 2012).

As noted by SCOEL (2011), for humans, fibres with a diameter of >3 μm are essentially non-respirable, whilst pulmonary deposition is greatest for fibres of diameter about 1 μm and length about 8 μm. Clearance of deposited fibres is also a function of length and diameter, with fibres with a length smaller than the diameter of the macrophages (<15–20 μm) being readily phagocytised and removed by dissolution and/or transport to local lymph nodes. Longer fibres reaching the alveolar region are cleared more slowly, depending on their biopersistence. Fibres that are sufficiently thin (<0.1 μm) and durable can penetrate the epithelial surface of the alveoli and be translocated to the lung parenchyma and pleural space, where fibres greater than 5 μm may be trapped by their inability to traverse the parietal stomata, causing inflammation (Lippmann, 2014; Murphy et al., 2013). Inhaled fibres that are deposited higher up the respiratory tract are removed by the mucociliary system.

Fibre dimension also plays a critical role in determining consequent pathological responses in the respiratory tract, which are different according to whether the fibre is in the lung parenchyma or has been translocated to the pleura. Looking critically at the relationship between fibre dimension and disease, Lippmann (2014) found the critical minimum fibre lengths for asbestosis (interstitial fibrosis), mesothelioma (malignant tumour of the mesothelium) and lung cancer to be ~2 μm, ~5 μm and ~15 μm, respectively. With regard to fibre diameter, for asbestosis and lung cancer, fibres with diameters >0.15 μm appear to be of predominant significance (as thinner fibres can be more readily cleared via the lymphatics) whilst for mesothelioma (and other lesions of the mesothelium), fibres ~<0.1 μm seem to be the most pathogenic. Overall it can be concluded that pulmonary diseases are caused predominantly by inhaled fibres thicker than about 0.1 μm and longer than about 20 μm, while the for pleural diseases, fibres thinner than ~0.1 μm and longer than ~5 μm are the most important.

Fibre chemistries that lead to breakage and/or dissolution in the extracellular lung fluid (pH 7.4–7.5) or within macrophages (pH 4.5–5.0) convey low biopersistence (Bernstein, 2007). As has been well documented elsewhere (Brown and Harrison, 2012), this knowledge has led to the development of fibre products such as the
AES wools that have low biopersistence and therefore are less hazardous to the lung.

4.2. Toxicological testing of fibres

Standard toxicological assessment of fibrous materials is performed using inhalation, intratracheal and/or intrapleural/intrapерitoneal methodologies. In the absence of human epidemiological data, inhalation testing in experimental animals is generally regarded as the ‘gold standard’ for this purpose. Intratracheal experiments are known to suffer from problems of fibre agglomeration during dosing and of irregular deposition of the test material in the lung (the ‘bolus effect’) but the technique is still recommended by some regulators for biopersistence testing, for example.

Despite the use of the intrapерitoneal (IP) test by certain regulatory authorities for cancer risk assessment purposes (see Section 5.2.1), results derived by this procedure are of limited value compared to findings from inhalation tests for assessing the possible carcinogenicity of inhaled substances in humans, principally because the IP test bypasses the animal’s respiratory system. The lung is an extremely efficient particle filtering/clearance system, so that while certain sized particles can and do reach the deep lung, the translocation of fibres from the lung parenchyma to the pleural space (by mechanisms that have not yet been fully elucidated) involves a certain ‘dwell time’ which is likely to result in the modification (e.g. by dissolution and/or fragmentation) of the number and nature of fibres that eventually reach the pleura. This will further attenuate any relationship between number/type of fibres inhaled and those reaching the pleural (and/or peritoneal) mesothelium. Further, findings based on the delivery of fibres direct to the peritoneum are of questionable relevance to human risk assessment for parenchymal lung cancer. In addition it is possible, or in some cases likely, that the dose delivered to the mesothelium may contain non-respirable fibres.\(^6\) Given that such coarse fibres are established irritants and that irritation is a well-established tumour promoting mechanism, their presence is likely to confound the IP test. Together, such arguments suggest that fibre hazard potential determined by IP tests is of little or no value for inferring human risk; suggestions that IP testing is more sensitive and superior to inhalation testing run counter to the reasoned assessments of several authoritative bodies (e.g. IARC, ILSI, NIOSH and NRC)\(^7\) which concluded that inhalation studies constitute the best available model for assessing human risks from exposure to fibres, although it is understood that reservations exist in some quarters about results obtained with asbestos in rodent studies compared to the human experience (e.g. Wardenbach et al., 2000).

4.3. The measurement and characterisation of fibres

Throughout this paper, reference to a ‘fibre’ generally means a standard fibre as defined (for monitoring/measurement purposes) by the World Health Organization. A ‘WHO fibre’ is any particle that has a length greater than 5 \(\mu\)m, a diameter less than 3 \(\mu\)m and length:diameter ratio greater than 3:1. The standard method of measuring and counting fibres uses phase contrast optical microscopy (PCOM) although this method is poor at identifying fibres

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<th>Table 1</th>
<th>Principles and considerations that apply in determining an OEL.</th>
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<tr>
<td><strong>Definition of OELs</strong></td>
<td>OELs are used to provide standards or criteria against which measured exposure levels may be compared in order to ensure that, as far as the current state of knowledge permits, control is adequate to protect health, or for designing new plants and processes to ensure that they are engineered in such a way that exposures can be controlled at levels that will not damage health.</td>
</tr>
<tr>
<td><strong>Margin of safety (MoS)</strong></td>
<td>The relationship (ratio) between the POD value (e.g. NOAEL/LOAEL) for the relevant effect(s) and the dose or concentration to which humans are exposed. Values below 100 (where the POD is based on animal data) are usually taken to indicate a need for more comprehensive risk evaluation.</td>
</tr>
<tr>
<td><strong>Point of departure (POD)</strong></td>
<td>The critical dose level, usually a NOAEL or LOAEL, derived from the key (most relevant/authoritative) study.</td>
</tr>
<tr>
<td><strong>NOAEL/LOAEL</strong></td>
<td>The ‘no’ or ‘lowest’ observed adverse effect level in an experimental study.</td>
</tr>
<tr>
<td><strong>BMD</strong></td>
<td>The ‘benchmark dose’ at which a defined level of response occurs (by convention 5 or 10%, depending on the nature of the effect); it is an alternative to the use of a N/LOAEL as a POD.</td>
</tr>
<tr>
<td><strong>T(D)10/T(D)25</strong></td>
<td>For non-threshold carcinogens the BMD may be described as a T(D)10 or T(D)25 indicating the calculated dose for a 10% or 25% tumour incidence, respectively, using actual dose response data or modelled data assuming for example a linear dose-response relationship.</td>
</tr>
<tr>
<td><strong>Assessment factors</strong></td>
<td>Deriving an OEL from health effects data invariably requires the application of ‘assessment factors’ to account for uncertainty in the process, particularly in relation to various extrapolations and assumptions that need to be made, for example in using animal data to predict human risk.</td>
</tr>
<tr>
<td><strong>DNEL</strong></td>
<td>The ‘derived no-effect level’ for threshold substances, calculated for REACH purposes according to ECHA guidance (Chapter R8). This guidance gives various default values for the assessment factors that are to be applied, differentiating between workers and the general public and for different routes of exposure. An airborne DNEL for workers may be taken as equivalent to an OEL.</td>
</tr>
<tr>
<td><strong>DMEL</strong></td>
<td>The ‘derived minimal effect level’ – similar in principle to a DNEL but calculated differently and applied to substances with non-threshold effects, such as genotoxic carcinogens. A DMEL for workers may be taken as equivalent to an OEL.</td>
</tr>
<tr>
<td><strong>MoA</strong></td>
<td>The ‘mode of action’ of a substance that indicates whether a threshold or non-threshold approach should be used in establishing the DNEL/DMEL and/or OEL. For non-threshold substances a so-called ‘risk-based’ OEL is set.</td>
</tr>
<tr>
<td><strong>Acceptability of risk/ tolerable risk</strong></td>
<td>For threshold effects, a risk is usually considered acceptable if the ratio DNEL:Exposure (the risk characterization ratio) is less than 1. For non-threshold substances such as genotoxic carcinogens, risk levels ranging between 10(^{-3}) and 10(^{-6}) for workers and/or the general public may be considered ‘tolerable’.</td>
</tr>
<tr>
<td><strong>IOELV</strong></td>
<td>An ‘indicative occupational exposure limit value’ is a health-based limit conventionally established only for substances for which it is possible to establish a threshold or a no-effect level considered to be protective of health. They are, in essence, OELs recommended by SCOEL.</td>
</tr>
<tr>
<td><strong>BOELV</strong></td>
<td>A ‘binding occupational exposure limit value’ may be formally established by the Council and European Parliament in cases where an appropriate limit of exposure can be identified based on risk as well as socio-economic impact assessment. BOELVs primarily apply to non-threshold substances covered by the EC Carcinogens and Mutagens Directive (CMD), and are also recommended by SCOEL.</td>
</tr>
<tr>
<td><strong>WoE</strong></td>
<td>‘Weight-of-evidence’ is an approach involving the assessment of the strengths and weaknesses and relative weights of different pieces of information. It requires expert judgement and is influenced by a variety of factors including data quality and consistency, nature and severity of effects, and relevance. Reliability, relevance and adequacy for purpose must always be taken into account in the WoE approach.</td>
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\(^6\) Dr Geoff Pigott – personal communication.  
with diameter less than 0.25 \( \mu m \) and is unable to differentiate between different fibre types. Also the POCOM protocol does not provide length and diameter distributions for visualized fibres longer than 5 \( \mu m \) (Lippman, 2014). Thus the most hazardous fibres — if present — may not be counted. These important issues of fibre identification and quantification can have considerable practical implications for routine accurate monitoring of health-relevant fibres in the workplace (Lippmann, 2014). Further, it must be understood that the WHO definition covers a very wide range of fibre sizes and thus respirability — for example, fibres of 0.1 \( \mu m \) diameter will be considerably more respirable than thicker fibres of 3 \( \mu m \) diameter.

It is assumed that fibre count figures referred to by the various regulatory/standard-setting bodies in the following sections reflect the WHO definition and the use of POCOM (rather than electron microscopy) for measurement purposes.

5. Regulatory risk assessment of SMF in Europe

5.1. Current classifications for SMF

In the EU, man-made vitreous (silicate) fibres were classified under the ‘Dangerous Substances Directive’ 67/548/EEC (as amended by 97/69/EC) as carcinogenic unless they are continuous (filamentous) thick fibres (with length-weighted geometric mean diameter less two standard errors greater than 6 \( \mu m \)). Thinner fibres containing more than 18\% by weight of alkaline and alkaline earth oxides\(^8\) may also be exonerated from classification if certain bioassays demonstrate low biopersistence and/or lack of pathogenicity, as described in Note Q of the Directive (which refers to the assessment of short-term biopersistence by inhalation or intratracheal instillation, and of carcinogenicity by appropriate IP tests or suitable long-term inhalation tests) (Brown and Harrison, 2012). The biopersistence protocols incorporated into Note Q of the Directive were developed and standardised by the European Commission using the results from chronic inhalation studies (Bernstein and Riego-Sintes, 1999). In line with the recognition of the importance of biopersistence in fibre carcinogenicity, Note Q mandates that fibres should not be classified as carcinogenic where short-term inhalation biopersistence testing establishes that the weighted clearance half-time for fibres longer than 20 \( \mu m \) is less than 10 days — or less than 40 days in the case of intratracheal testing (Bernstein, 2007). These rules have now been transferred to the EU Classification, Labelling and Packaging (CLP) regulation.

It is noteworthy that the adoption of this formal Directive (and latterly the CLP regulation) served as a major stimulus to European SMF manufacturers to develop, test and market fibres that had low biopersistence and could meet the criterion for exoneration from identification as a carcinogen in the absence of data from chronic bioassays. The development of a regulatory paradigm that avoided the need for conducting long-term studies using large numbers of animals was also consistent with the growing movement around the world to minimise the number of laboratory animals used in research (Hesterberg et al., 2012).

However, there remains some concern about how the ‘18%’ formula in Note Q was derived and whether it is truly justified. Bellmann et al. (2010), for example, investigated the chemical composition of glass and stone wools in the light of the then available toxicity database. Data for about 60 different fibres investigated in the intra-tracheal biopersistence test standardised in the EU were analysed, leading to a model that enabled prediction of half-times based on chemical composition. The authors concluded, however, that for regulatory purposes the model is not sufficient to replace biopersistence tests completely, and the question still remains about the scientific derivation and justification of the chemical composition definition in Note Q.

In Germany (see also Section 5.2.1.), additional regulations apply to fibrous dusts as specified under technical guidance on worker protection TRGS 905,\(^9\) which contains a list of substances that can release dusts classified as carcinogenic; it includes dusts generated from substances or preparations that may not have been classified by the EU. This document gives criteria for assessing the carcinogenicity of ‘inorganic fibrous dusts’ — including vitreous WHO fibres. The rules in the document indicate that fibres can be classified by conducting IP carcinogenicity tests (with specified numbers of fibres to be injected) or by determining in vivo biopersistence in intratracheal instillation tests.

5.2. Some specific national approaches to the risk assessment of SMF in Europe

5.2.1. The German ‘Exposure-risk relationship’ concept

German authorities have adopted a system based on quantitative risk assessment in which defined levels of ‘acceptable risk’ are used to determine OELs for carcinogens. This approach, championed by the German Committee on Hazardous Substances — Ausschuss für Gefahrstoffe (AGS), an advisory body of the Federal Ministry of Labour and Social Affairs concerned with occupational safety and health measures — is known as the Exposition-Risiko-Beziehung (ERB) or exposure-risk relationship (ERR) concept. It was described in detail in AGS ‘Announcement 910\(^10\)’ and accompanying guidance documents, and subsequently published in TRGS 910.\(^11\) This methodology, which has been applied to ASW/RCF (see Section 8.2.2.), is suggested by these bodies as a means of establishing exposure-risk relationships for carcinogens, making the risk management of such substances manageable and allowing the setting of exposure limits incorporating societal judgements of the acceptability of risk (see also Wardenbach et al., 2000). However, aspects of both its underlying scientific assumptions and practical implementation are open to criticism. For example, the document notes that ‘no occupational exposure limit can currently be derived for the vast majority of carcinogenic substances’ but paradoxically makes no distinction between threshold and non-threshold (directly genotoxic) carcinogens. The Annex in which the term ‘risk’ is defined refers to ‘health damage’ and fails to clarify if the risks being considered relate specifically to cancer or the likelihood of any ‘health damage’. Also, where asbestos is given as an example of implementation of this approach, no differentiation is made between the different forms of asbestos, despite it being now well established that amphiboles are more potent than chrysotile (e.g. see Berman and Crump, 2008; Bernstein et al., 2013).

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\(^8\) I.e. \( \text{Na}_2\text{O} + \text{K}_2\text{O} + \text{CaO} + \text{MgO} + \text{BaO} > 18\% \) by weight; such fibres are termed ‘Mineral wool’ in the Directive. The scientific basis for this compositional criterion is not documented.


It is also worth considering the approach in the document ‘Exposure-risk relationship for man-made fibres’ contained in the AGS document ‘ERR (exposure-risk relationship) for aluminium silicate fibres’ — which is a reworking of ‘Exposure-risk relationship for synthetic mineral fibres’ produced by the AGS Working Group on Fibres and Dusts (AKF&S). This sets out to establish an exposure-risk relationship for man-made mineral fibres (M3MFs), which forms the basis for the ERR for aluminium silicate fibres (see also Section 8.2.2). In this document, ‘risk’ is said to be the likelihood that additional ‘adverse effects’ will occur in exposed compared to non-exposed persons. This is unhelpful given that the normal conventions of quantitative risk assessment and societally accepted levels of risk usually refer to the risk of death or serious injury rather than unspecified ‘adverse effects’. The starting point for deriving exposure-risk relationships here is the quantitative risk assessment of asbestos (all types combined), derived from epidemiological studies. The authors state that it was not appropriate to reference epidemiological findings on MMMFs given that essentially only non-positive findings have been obtained. This reveals a clear underlying bias by the authors in presuming that MMMFs are necessarily carcinogenic to humans despite the lack of any epidemiological evidence to support this view (e.g. see Greim et al., 2014). The assessment also makes the unfounded assumption that tests using IP injection permit a comparative assessment of the potential effects of asbestos and different types of MMMF (see Section 4.2). While correctly documenting the essential principles and determinants of fibre toxicity (i.e. length, diameter and biopersistence), the assessment makes a questionable assumption that IP tests are able to accurately — and in a quantitative fashion — discriminate fibres in relation to their carcinogenic potency in the lung. Moreover, the data concerning mesothelioma induction after IP injection is taken from a 1994/95 Annual Report of the German Medical Institute for Environmental Hygiene, which is unpublished and therefore not peer-reviewed.

Various calculations are presented for different size ranges of fibres. It is well known that length is important and that longer fibres (L > 20 μm) are notably more pathogenic than short fibres. Whilst acknowledging that if only fibres longer than 20 μm are taken into account the calculated risks for MMMFs relative to crocidolite are smaller, the authors choose to regard this as irrelevant and instead base their risk assessment on ‘WHO fibres’. Overall, this is likely to result in risk estimates that are too high, perhaps by a factor of 10. Furthermore, the use of the BMD50/T10 in a quantitative risk assessment approach assumes an (unproven) straight-line relationship between dose and cancer induction and is fundamentally inappropriate for application to fibres that exhibit a threshold of effect.

Methods of fibre preparation are likely to be critical to the results obtained in IP tests. The protocol involves injection of an entire fibre sample into the peritoneum (as a model for the pleural mesothelium) whereas, after inhalation, fibres will naturally undergo varying degrees of size selection, attenuation and comminution before reaching the pleural space (see Section 4.2). This further emphasises the problems with the IP test and the non-physiological nature of the exposure involved.

Arguments in the document comparing the calculated risks with epidemiological data appear to suggest that the predictions of the proposed approach cannot be verified by epidemiological study. It would thus appear that the proposed exposure-risk method — or at least its application to MMMF — is not testable using the scientific method. It can certainly be argued that the occupational risks estimated using the proposed method are highly uncertain, to the point of being speculative, and the range of estimates for any particular MMMF could vary by huge factors.

Considering the ERR approach more generally in relation to other adopted approaches (as used, for example, by SCOEL) for substances for which a non-genotoxic or a threshold genotoxic mechanism can be shown to be responsible for the carcinogenic process, there is no need and, indeed, no advantage, to be gained from seeking to calculate risk estimates as the basis for setting limits. Rather, health-based methods involving the initial definition of a no-effect level (NOAEL) are appropriate.

Unfortunately, despite the inappropriateness of the AGS/ERR approach for MMMF, this methodology has had a profound influence on the development of German ‘Technical Rules for Hazardous Substances’. Thus, TRGS 521 (Demolition, reconstruction and maintenance work with biopersistent mineral wool) has been applied to workers involved in demolition, reconstruction and maintenance work with biopersistent mineral wools where dusts classified as carcinogenic are released, and TRGS 558 (Activities involving high-temperature wool) has been applied to the protection of workers and other persons engaged in activities involving fibrous dusts classified as carcinogenic that may be released during activities involving high temperature (insulation) wools.

5.2.1.1. TRGS 521. This lists a number of activity scenarios within three different ‘exposure categories’, linking these with certain fibre dust concentrations to drive the requirement for protective measures. The ‘trigger’ concentration is 50,000 fibres/m³ — or 0.05 fibres/m³ — which is equivalent to that for asbestos and far stricter than OELs applied by other jurisdictions to SVF. This makes conforming to the limit highly problematic and requires exposure monitoring to limits far beneath those for most other countries.

5.2.1.2. TRGS 558. This applies to ASW/RCF (see Section 8.2.2) but also states, without justification, that it similarly applies to PCW. It is stated that ‘according to the current state of scientific knowledge it is not possible to discount a risk of cancer when these fibre dusts are inhaled’. As with TRGS 521, this document also establishes three levels of exposure category (low, medium and high ‘risk areas’), referring to the concept of ‘graduated risk control’ for carcinogenic substances as described in TRGS 910. These different exposure-risk levels are based on the definitions of ‘acceptable’ and ‘tolerable’ risk and the equivalent fibre concentrations that are set out in the document ‘Exposure-risk relationships for synthetic mineral fibres’. For each different ‘risk level’ a number of worker protective measures are mandated. This document is flawed not by its intentions or the suggested protective and precautionary measures, but by the assumption, driven by TRGS 910 and the ‘exposure-risk relationships for synthetic mineral fibres’ document, that HTIW (specifically ASW/RCF — see Section 8.2.2 — and also PCW) is as potently 14 Technical Rules for Hazardous Substances: Demolition, reconstruction and maintenance work with biopersistent mineral wools (TRGS 521). Version: January 2011, Committee on Hazardous Substances — AGS management — BauA — www.bau.de. Available at: http://www.bau.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/pdf/TRGS-521.pdf?__blob=publicationFile&v=2 (accessed July 2015).
16 The three levels relate to exposure risks that are below the ‘acceptable’ risk, or between ‘acceptable’ and ‘tolerable’, or above ‘tolerable’.
carcinogenic as amphibole asbestos — an assertion for which there is no justification.

5.2.2. UK HSE

UK occupational exposure limits — now named “Workplace Exposure Limits” (WELs) — are listed in the official UK Health and Safety Executive (HSE) guidance document EH40 (HSE, 2011). The current WELs for MMMF (machine-made mineral fibre\(^{17}\) except for ‘refractory ceramic fibres and special purpose fibres’) are specified as being 5 mg/m\(^3\) (8-h TWA of inhalable dust) and a fibre number concentration of 2 fibres/ml. The equivalent gravimetric and fibre number WELs for ‘refractory ceramic fibres and special purpose fibres’ are 5 mg/m\(^3\) and 1 fibre/ml, respectively (see Section 8.2.4).

EH40 states that “Machine-made (formerly ‘man-made’) mineral fibres are defined as man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na\(_2\)O + K\(_2\)O + CaO + MgO + BaO) content greater than 18% by weight. Neither the gravimetric limit nor the fibres in air limits should be exceeded. Fibre concentrations of MMMFs must be measured or calculated by a method approved by HSE” (UK Health and Safety Commission).

The gravimetric exposure limit (WEL) for mineral wool fibres in the UK is equivalent to 50% of the gravimetric concentration that is the reference point for further risk management consideration for generic dusts for which no specific WEL is set.

6. Regulatory risk assessment of SMF in the USA

The regulatory processes of the USA differ fundamentally from those of the EU. In the EU, the initial premise for classification is based on the intrinsic hazard of the material, with the specific objective of determining what protective measures are required during normal handling and use. In the USA, in contrast, the EPA uses a risk-based evaluation considering both hazard and exposure data and applying ‘weight of evidence’ considerations (Bernstein, 2007).

As of 2003, the US EPA had not classified the potential carcinogenicity of glass wool, continuous filament glass, rock wool, or slag wool, but assigned ASW/RCF to Group B2 (probable human carcinogen) based on the results of animal studies (Bernstein, 2007).

The US EPA advises that “when available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data, linear extrapolation is used as a default approach” and “A nonlinear approach should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses”.

7. Principles of precaution, feasibility and achievability relevant to the risk assessment of fibres

The precautionary principle came to form a fundamental element of German environmental law in the early-1970s (Tickner et al., 1998). Internationally, a pivotal step was its adoption in the 1992 Rio Declaration from the United Nations Conference on Environment and Development (Agenda 21; Tickner et al., 1998). The EC recommends that ‘the precautionary principle should be used by decision-makers when deciding on risk management policy but should not be confused with use of assessment factors by scientists during risk assessment’ (EC, 2000b). Some EU Member States, including France, Sweden and Denmark, have adopted the principle fairly extensively (Tickner et al., 1998), whilst several other jurisdictions apply different interpretations of the principle — for example, New Zealand (Cameron, 2006) and Australia (Gullett, 2000).

For the precautionary principle to be invoked, the EC considers that three preliminary conditions must be met: (i) there has been identification of potentially adverse effects; (ii) the scientific data available has been evaluated; and (iii) there is an understanding of the extent of scientific uncertainty surrounding the concern. In the case of fibrous material and, increasingly some nanomaterials (e.g., Hansen et al., 2013) there have been pressures to adopt an extreme precautionary approach; this has frequently resulted in ill-founded analogies with asbestos being drawn. Such arguments have ignored the fact that much has been learned about the physico-chemical properties of different types of fibre and the way these influence the underlying mechanisms of toxicity.

An important factor influencing the successful implementation of risk management decisions is that the ‘acceptable’ level derived by risk assessment should be realistic and able to be substantiated. Thus, it is important that the feasibility of achieving a desired exposure level is considered and that it is possible to measure exposure in the workplace to a sufficiently high degree of accuracy to demonstrate whether or not control has been achieved. Whilst the technical challenges for chemicals with a threshold mechanism (where under REACH a DNEL would be set) are more likely to be achievable, in the case of non-threshold chemicals the magnitude of the challenge may be considerably greater. In such circumstances, use of the ALARA concept remains appropriate in order to achieve an acceptable risk by adopting reasonably achievable control measures in a manner that balances risks and benefits. The reasonableness of the cost of control is generally evaluated using various technological criteria, such as ‘best available control technology’ (BACT) or ‘best practicable control technology’ (BPCT; Shortreed et al., 2003). Indeed, since REACH does not overrule the requirements of the Carcinogens and Mutagens Directive (CMD, 2004/37/EC), use of the ALARA approach to controlling workplace exposure remains appropriate in the EU (ECHA, 2012b).

8. Case study: regulatory approaches to assessing risk for ASW/RCF in different jurisdictions

8.1. USA

8.1.1. NIOSH and OSHA

The US National Institute for Occupational Safety and Health (NIOSH) is a non-regulatory federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness (NIOSH, 2013). It is located as part of the Centers for Disease Control and Prevention (CDC) within the U.S. Department of Health and Human Services, and can act as the “scientific research arm” of the Occupational Safety and Health Administration (OSHA). OSHA, itself part of the US Department of Labor, is primarily responsible for developing and enforcing occupational safety and health regulations (OSHA, 2011). Generally in the US, a risk of 1 × 10\(^{-6}\) is applied as the ‘de minimis’ criteria when risks to the general public are being assessed. However, when considering occupational exposure, OSHA will not introduce regulation of a substance where the incremental lifetime cancer risk to a worker exposed for his entire working lifetime is estimated to be substantially below 1 × 10\(^{-3}\) (Adler, 2007). Interestingly, experience indicates that not dissimilar risk values tend to be applied in the EU (e.g. EMA, 2006).
Building on historic controls placed on workplace exposure to ASW/RCF (OSHA, 2015), in 1999 OSHA established a PEL (8-h TWA) of 1.0 f/cc (1 f/ml) for fibreglass and mineral wools (glass wool, rock wool and slag wool) under a voluntary agreement with industry termed the Health and Safety Partnership Program (HSPP) (OSHA, 1999; ATSDR, 2004; Marchant et al., 2002). The HSPP featured the newly recommended PEL, training programmes, medical monitoring, engineering control resources, and information on appropriate respirator use. Later, OSHA (2001) also established a 5 mg/m³ (respirable) limit for all synthetic vitreous fibres, as part of regulations relating to inert or nuisance dusts, and a 15 mg/m³ limit in relation to total dust, that were intended for use by general industry.

As with fibreglass and mineral wools, the refractory ceramic fibre industry entered into several long-term voluntary agreements with various government agencies (e.g., OSHA, NIOSH and EPA). Collaborative work began as a five-year consent agreement with EPA in 1993 that was included in the industry’s Product Stewardship Program (PSP). Upon completion of the EPA agreement, the industry continued its voluntary stewardship program under OSHA oversight. The PSP was designed to specifically address the RCF-type of synthetic vitreous fibre (ATSDR, 2004; RCFC, 2015a). Under the PSP, in the absence of a lower specified regulatory limit, industry adopted a ‘recommended exposure guideline’ of 0.5 f/cc (8-h TWA) that, rather than being risk based per se, was developed by considering what would be a realistic, generally feasible level that could be attained through use of workplace engineering controls (RCFC, 2015a). The PSP also included ongoing medical monitoring, medical surveillance, development of engineering controls, use of an explicit respirator policy, preparation of handling guidelines, and training. Since the program began in the early 1990s, the weighted average of all occupational exposures to RCF in the US for both manufacturers and customers working with RCF has decreased to around 0.2 f/ml (Maxim et al., 2008).

In 2006, NIOSH published a Criteria Document on RCF (NIOSH, 2006) in which a recommended exposure limit (REL) of 0.5 fibres per cubic centimetre (f/cm³) TWA was proposed for shifts of up to 10-hr during a 40-hr working week. This level was stated as being sufficient to minimize risks of lung cancer and irritation of eyes and upper respiratory system; it was noted however, that at this level there remained some degree of cancer risk and therefore it was also recommended that there should be continued effort to reduce exposure to <0.2 f/cm³.

To inform their recommendation, NIOSH conducted an extensive review of available experimental and human data, and concluded that epidemiological studies indicate that current occupational exposure to ASW/RCF is not associated with an increased risk of pleural mesothelioma or lung cancer. However, for workers involved in its manufacture, historical associations had been found between the airborne exposures then occurring and a range of pathological changes, including pleural plaques, impairment of pulmonary function and increase in respiratory symptoms and conditions (pleurisy, dyspnea and cough). Also, increased risk of skin and eye irritation had been observed historically, even after adjusting for smoking and non-fibrous dust co-exposure. Though there was evidence of possible interactions between the risk of co-exposure to ASW/RCF and cigarette smoke, the effect on pulmonary function was still detectable in non-smoking females. Experimentally, inhalation of ASW/RCF was noted to have caused lung cancer in rats and mesothelioma in hamsters, though interpretation of these findings was difficult due to the issue of co-exposure to fibres and non-fibrous respirable particles in these experiments (see Hesterberg et al., 1995; Brown et al., 2000, 2005). Other experimental effects reported included enzyme induction, haemolysis and, possibly, impairment of cell viability and inhibition of proliferation, as well as effects on mediator release and induction of free radicals, micro-nuclei, polynuclei, chromosomal breakage and hyperdiploid cells. When determining their recommended REL for ASW/RCF, it is evident that NIOSH adopted a pragmatic approach in that they drew on the toxicological evidence from human and experimental studies but also considered evidence on the extent to which ASW/RCF exposure could now be controlled for various workplaces and activities. The resultant REL is therefore considered to be “achievable for most workplaces where RCFs or RCF products are manufactured, used, or handled”. When considering the residual risk of lung cancer at the recommended REL, an estimate of 0.073—1.2 cases per 10000 was made by extrapolation from a number of published risk models. Mesothelioma risk at this exposure standard was considered to be uncertain due to data limitations, though it was suggested to be somewhat lower than that for lung cancer risk on the basis of the lack of any evidence that mesothelioma occurred in workers exposed to ASW/RCF and as pleural plaques were considered less likely to develop in workers with lower exposure. Nonetheless, NIOSH suggested that all reasonable effort should be made to further reduce worker exposure to 0.2 f/cm³ or below, the level at which lung cancer risk was suggested to be 0.03—0.47 cases per 10000 (equating to a further reduction in cancer risk of some 40%).

Following publication of the NIOSH Criteria Document, OSHA expressed their support for the continuation of the voluntary stewardship program, initially established with the Refractory Ceramic Fibres Coalition (RCFC) (and subsequently with the High Temperature Insulation Wool (HTIW) Coalition18) as a means of achieving continued reductions in workers’ exposure to ASW/RCF (OSHA, 2007; HTIWC, 2015). The most recent version of the program (2012—2017) continues the efforts to reduce workers’ exposure to ASW/RCF (Michaels, 2012 19; HTIWC, 2015). Consequently, OSHA has not proposed a change to the standards it had previously established. However, California’s Occupational Safety and Health Standards Board has since adopted a permissible exposure limit (PEL) for ASW/RCF at the lower level suggested as desirable by NIOSH, i.e. 0.2 f/cc. This is reported to have come into effect on 3rd August 2010 (RCFC, 2015b) though it appears that other States are continuing to adhere to the existing OSHA (federal) limits.

8.1.2. The American Conference of Governmental Industrial Hygienists (ACGIH)

The ACGIH is a professional association of industrial hygienists and practitioners of related professions, with headquarters in Cincinnati, Ohio.

The ACGIH TLV—TWA for ASW/RCF is set at an intermediate level between asbestos (0.1 f/cc) and other types of SVF (1.0 f/cc). The recommended TLV—TWA of 0.2 f/cc for ASW/RCF reflects concerns based on pleural and lung function abnormalities seen among exposed cohorts, taken to indicate that the health risks of RCF are closer to asbestos than other types of SVF. Similarly, an A2 (Suspected Human Carcinogen) notation is assigned for ASW/RCF, based on the following: 1) ASW/RCF causes lung fibrosis, lung cancer, and mesothelioma in animals exposed via inhalation; 2) these health effects resemble those of asbestos (a confirmed human carcinogen); and 3) ASW/RCF exposures in humans have been too brief to date to allow an accurate assessment of the risks of lung cancer and mesothelioma. There appears to be no published detailed scientific rationale explaining the specific limit value selected.

8.2. European Union

In 1997, a European Technical Progress Committee decided that the evidence from experimental animal studies was sufficient to warrant ASW/RCF being classified as what at that time was termed an EU Category 2 carcinogen (i.e. a substance to be regarded as if it were carcinogenic to humans)\(^20\) and the risk phase R49 (‘may cause cancer by inhalation’) was applied.

Directive 97/68/EC of 5 December 1997 sets out the classifications of two types of randomly-oriented MMMF:

(a) mineral wools; and
(b) RCFs (also special purpose fibres (SPFs) which are not within the scope of this paper).

The term “randomly-oriented” was applied to distinguish these categories of MMMF from continuous filament fibres, which are generally thicker in diameter.

Under Directive 97/68/EC, mineral wools were classified as Category 3 (now called Category 2 — suspected or possible) carcinogens and ASW/RCFs as Category 2 (now Category 1b — presumed) carcinogens. The classification as a Category 2 (now 1b) carcinogen applied to fibres of a certain size only (with those greater than 6 μm length-weighted geometric mean diameter being regarded as too large in diameter to be respirable and therefore posing no carcinogenic hazard by inhalation). Mineral wools were also exempted from classification as carcinogenic if they met any of four specified conditions set out in the Directive.

8.2.1. SCOEL and DECOS

Assessments of the carcinogenicity of ASW/RCF have recently been published by the European Scientific Committee on Occupational Exposure Limits (SCOEL, 2011) and the Dutch Expert Committee on Occupational Safety (DECOS, 2011). These are notable for their consideration of the MoA of ASW/RCF and their conclusions regarding thresholds and the establishment of no-effect levels.

In considering the MoA, SCOEL acknowledged the well-established fact (IARC, 2002) that chronic inflammation contributes to cancer development and concluded that inflammation is the relevant mechanism explaining the effects of ASW/RCF in experimental animals. Since lung inflammation is known to occur and persist only at high doses, SCOEL were content to assume that the basic mechanism of fibre carcinogenicity involved a threshold, as explained and described in a number of publications that have evaluated and described this mechanistic principle of fibre toxicity and carcinogenicity (e.g. Greim et al., 2001; Schins, 2002; IARC, 2012). Moreover, the report elaborates how epidemiological studies in workers of facilities located in the US, which started ASW/RCF production in 1953, support the threshold concept of fibre carcinogenicity. Although originally workers were exposed to relatively high fibre concentrations of 10 fibres/ml or more, no additional lung cancer burden has been observed even more than 30 years after the onset of exposure (SCOEL, 2011). Since the latency of asbestos-induced mesothelioma can be up to 50 years, the relationship between RCF exposure and respiratory malignancies has not been fully determined. However, RCF and rock wool have similar airborne fibre dimensions and persistence. Based on the numerous existing cohort and case control studies, IARC (2002) concluded that there is no epidemiological evidence for the carcinogenicity (including mesothelioma induction) of rock wool. The analogy with rock wool makes it reasonable to believe that increases in lung cancer or mesothelioma incidence are unlikely to be found in RCF-exposed workers (Greim et al., 2014).

On the basis of this epidemiological evidence, SCOEL concluded that there was no evidence for exposure-related pulmonary fibrosis or cancer in ASW/RCF workers, and used findings on pulmonary function, which provides sensitive parameters for the evaluation of ASW/RCF exposure, to determine a no-effect level. Assuming a 45-year exposure and average cumulative exposure of 147.9 (all workers) or 184.8 f.mo/ml (workers >60 years old), SCOEL calculated average fibre concentrations of 0.27 and 0.34 f/ml respectively. Considering these values as no observed adverse effect levels, SCOEL therefore proposed an OEL of 0.3 f/ml. According to SCOEL, the epidemiological studies and the evidence that inflammation is the primary underlying mechanism of fibre carcinogenicity strongly indicate that genotoxic effects observed in certain experimental studies represents a secondary change arising from the induction of reactive oxygen species (ROS) and, in the case of cytogenetic effects, from the interaction of the fibres with the spindle apparatus of the cell. SCOEL thus evaluated ASW/RCF as ‘Group C’ — a genotoxic carcinogen for which a practical threshold is supported.

Similarly the DECOS Committee considered the induction of chronic inflammation to be the most plausible mechanism of carcinogenic action of ASW/RCF, and also acknowledged that this implies the existence of a threshold of effect. In addition, they concluded that it is unlikely that ASW/RCF possesses stochastic genotoxic properties via direct production of ROS, given its very low iron content.

DECOS considered the number of observational studies reporting possible associations between occupational exposure to ASW/RCF and cancer development in humans to be limited and concluded that, overall, available data are insufficient to draw a conclusion whether or not ASW/RCF is carcinogenic to humans. However, they concluded that, while not all were positive and other factors were at play, the animal studies on ASW/RCF do indicate carcinogenic activity. Their assessment was, therefore, that while ASW/RCF should be presumed to be carcinogenic to man, this was due to a non-genotoxic mechanism. Based on this conclusion, an OEL of 1 f/ml (8hr TWA) was derived, based on a NOAEL of 25 f/ml and a safety factor of 25 to take into account the seriousness of the critical effect (cancer).

8.2.2. The German approach to ASW/RCF

As mentioned earlier (Section 5.2.1), German authorities have adopted a system (ERR) based on quantitative risk assessment in which defined levels of ‘acceptable risk’ are used to determine OELs for carcinogens.

With respect to the regulatory implications for ASW/RCF, a number of statements in TRGS 910 appear to imply that ‘carcinogens’ in the context of this approach include only those substances that have been shown to have no threshold (i.e. are genotoxic). Given that ASW/RCF has been argued by authoritative sources (e.g. SCOEL, see above) to be either non-genotoxic or, at most, to show a threshold effect as a result of secondary genotoxic changes, it can be strongly argued that ASW/RCF should not be included as a carcinogen within the meaning and intention of this approach. The negative in vitro genotoxicity test results obtained for ASW/RCF\(^21\)

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\(^{20}\) Under the present EU Classification, Labelling and Packaging Regulations 2008, which contains the Globally Harmonised System (GHS) for classification and labelling, the designated carcinogen classification is 1b (presumed human carcinogen based on demonstrated animal carcinogenicity).

An 8 h OEL corresponds to an excess risk for lung cancer, at 70 years of age, and this is consistent with the occupational epidemiological evidence which shows that ASW/RCFs are not associated with elevated standard mortality ratios for either lung cancer or mesothelioma (Boffetta et al., 2014; Greim et al., 2014). In addition, TRGS 910 indicates that if acceptable concentrations cannot be determined by measurement, it is set at the limit of detection; this is the case for ASW/RCF for which the ‘tolerance’ concentration has been set at 0.1 f/ml. This conclusion and approach is certainly debatable.

As discussed earlier (Section 5.2.1), for substances such as RCF/ASW for which a non-genotoxic or a secondary (ROS-induced) genotoxin and not a direct mutagen, a linear model can be shown to be responsible for the carcinogenic process, methods involving the definition of a no-effect level should be used as the basis for setting limits, rather than approaches using calculated risk estimates.

As previously noted (Section 5.2.1), TRGS 558, referring to ASW/RCF, states that ‘according to the current state of scientific knowledge it is not possible to discount a risk of cancer when these fibre dusts are inhaled’. This runs counter to the arguments for a threshold of response for ASW/RCF made by SCOEL and DECOS (Section 8.2.1).

8.2.3. France

In France, AFSET22 has derived a recommended occupational exposure limit for ASW/RCF of 0.1 f/ml based on the assumptions of proven carcinogenicity in animal studies and of a mechanism of toxicity that has no threshold in humans. Consequent to the assumption of no threshold of effect, a linear model is applied to establish a dose-response for low dose exposures, correlated to units of excess risk. The risk values are based on a summary presented by Maxim et al. (2003). Determination of an OEL is done by evaluation of the individual additional lung cancer risk and applying medically acceptable risk values. The value of 0.1 f/ml for an 8 h OEL corresponds to an excess risk for lung cancer, at 70 years of age, of $5 \times 10^{-4}$.

Like the German approach, the French methodology hinges on the assumption that ASW/RCF is a non-threshold (genotoxic) carcinogen, and hence is open to the same criticisms (see Section 8.2.1).

8.2.4. UK: Health and Safety Executive (HSE)

Directive 97/69/EC relating to the classification, packaging and labelling of dangerous substances, including ASW/RCF and other mineral fibres (see Section 8.2), was implemented in Great Britain in 1999 by an amendment to the CHIP Regulations.

At a meeting of HSE’s Advisory Committee on Toxic Substances (ACTS) in March 2000, an HSE-commissioned report collating and reviewing airborne fibre concentrations generated in the manufacture, installation and removal of RCFs (ACTS/45/98/INF) was reviewed (ACTS/05/2000). ACTS was asked to consider the feasibility of setting a separate lower ‘maximum exposure limit’ (MEL) for ASW/RCFs because of their carcinogenic potential. ACTS agreed that HSE should carry out a Regulatory Impact Assessment (RIA) for two MEL proposals of 1 f/ml and 0.5 f/ml. HSE concluded that 1 f/ml was practicable but that reduction to 0.5 f/ml was likely to have more far-reaching implications, in particular for small companies, some of which would find this limit extremely difficult to achieve, and a MEL (now termed WEL) of 1 f/ml was adopted.

The current gravimetric and fibre number WELs for ASW/RCF — as listed in HSE guidance document EH40 — are 5 mg/m³ (total inhalable dust) and 1 fibre/ml respectively. Although in terms of health effects, it is the concentration of respirable fibres (f/ml) that relates to effects in the deep lung (fibrosis and carcinogenicity), there is also a concern for the possibility of effects in the upper airways that are more likely to relate to the total inhalable dust concentrations. Hence, in occupational situations with the potential for generating high airborne dust levels (e.g. kiln wrecking), the gravimetric limit offers a useful risk management tool in addition to the f/ml limit. However, in all circumstances, it is control to the f/ml count that is the predominant requirement.

In the UK, the WEL for ASW/RCF is based on the notion of reasonable practicality, which is not necessarily part of the OEL-setting procedure in other countries, and unlike some other regulatory authorities HSE’s approach does not involve prediction of residual risk at the limit value.

A summary of different approaches to the risk assessment of ASW/RCF is given in Table 2.

8.3. Other risk analyses of ASW/RCF

Drawing on both experimental (rat) and limited occupational epidemiological data, Maxim et al. (2003) critically reviewed previously published quantitative risk assessments that derived maximum likelihood estimates (MLE) for the incremental cancer risk associated with a working lifetime exposure to a concentration of 1 fibre/ml of ASW/RCF; these historic estimates were noted to vary between $4.1 \times 10^{-6}$ and $3.4 \times 10^{-3}$. The authors further compared these with new estimates obtained using benchmark dose (BMD) models, drawing on US EPA methods that gave MLE estimates of approximately $2.4 \times 10^{-4}$—$6.7 \times 10^{-4}$.

The authors noted that none of the quantitative risk assessments performed on ASW/RCF have explicitly adjusted for possible confounding from the effects of co-exposure to particles and fibres and, hence, may be regarded as somewhat conservative. When historic assessments lacking adequate documentation or utilising less favoured methodologies were excluded, the range of MLEs was found to be $10^{-4}$—$10^{-3}$, thus falling much closer to the estimates obtained using a BMD approach. For all estimates, however, the authors noted that the two greatest uncertainties were the assumptions used to normalise lung burden and the potential for confounding from co-exposures to particles (Maxim et al., 2003).

When considering the stringency of risk management that is to be applied for the use of a substance in workplaces, it is important for regulatory bodies to understand the nature and scale of health impacts predicted to occur so that these may be balanced against the socio-economic consequences of any regulatory measures. In the case of the EC, a report by IOM to the European Commission, the ’SHECan’ Summary Report (IOM, 2011), has assessed the scale of the potential health, environmental and socio-economic impacts that would arise from amendment of the European Carcinogens and Mutagens Directive (2004/37/EC) for a number of occupational carcinogens, including ASW/RCF. Importantly, ASW/RCF was one of eight that were shown to have ‘little or no baseline health impact’. That is, there was little evidence for any significant impact arising from current or relatively recent exposures in the EU. The projected number of cancer cases that might be attributed to occupational exposure was less than about 10 per year for the whole EU.
(between 2010 and 2069). Predicted number of deaths from past occupational exposure, based on worst-case assumptions, was also low (in 2010, no attributable deaths in manufacturing and two deaths in downstream users). Predictions of future mortality patterns suggest that, by 2050, there would be none relating to occupational ASW/RCF exposure. In considering the influence of introducing an OEL of 0.1 or 1 fibre/ml, it was found that there would be no important impact on cancer deaths or registrations for ASW/RCF. For both potential OELs, estimated disability-adjusted life years (DALYs) decrease from 29 years in 2010 to zero years by 2060; with no intervention there are two DALYs predicted in 2060. Whilst IOM did not estimate mesothelioma risk (because the authors did not believe that the human epidemiological data substantiates such a risk); if it was assumed to be an impact, under worst case assumptions there might be three or four new cases of cancer as estimated. While this would increase the total health impact, the authors concluded that this would not change their overall finding that, for ASW/RCF, an EU-wide OEL of 1.0 fibres/ml could likely be met through greater uptake of currently available techniques by industry, with associated costs being relatively low. Only a small health benefit was associated with this OEL, valued at up to €1–2 million in total over the period 2010–2069. This contrasts with estimates based on an OEL of 0.1 fibres/ml, which would have much more significant costs for industry. Achieving this exposure limit would require a degree of automation and enclosure that was considered unlikely to be feasible, especially for certain downstream users, and the associated compliance costs were estimated at €60 to €140 million (2010–2069) — to achieve minimal health gains.

8.4. Existing OELs for ASW/RCF worldwide

Before considering existing OELs for ASW/RCF, it is important to appreciate that there has been, and continues to be, significant improvement in occupational hygiene practices across most industrial sectors. Hence occupational exposure to chemicals has shown a steady decrease since the 1970’s. For example, Creely et al. (2007), looking at a range of industries, reported the level of inhalation exposure for almost all chemicals to have decreased annually by 1–32% (median 8%) while specifically for fibres, the annual decline was as much as 32%. Also, in Finland, by 2008 overall inhalation exposure to chemicals had fallen to 41% of the 1970 value and prevalence of high exposure to asbestos had decreased from 41% to <0.1% over the same period (Kauppinen et al., 2013).
Many jurisdictions have enforceable occupational exposure limits (OELs) for ASW/RCF, and other organizations have produced recommended or guideline limits for worker exposure. Examination of currently established limits shows considerable differences between authorities regarding the level of control considered necessary for the protection of workers. Established OELs vary by an order of magnitude (see Table 3), with Germany, France and Norway being notable outliers. In part this reflects the time when a particular OEL was established or last reviewed, though there also exist fundamental differences in the approaches taken across the jurisdictions in the assessment of risk posed by these materials, as discussed in this paper. Despite this, it is generally apparent that there has been an ongoing tendency to set increasingly more stringent occupational hygiene standards over recent decades. For example, a recent (2011) proposal of 0.3 f/ml by the EC’s SCOEL committee, which is based on pulmonary function changes, is not dissimilar to the 0.5 f/ml level established by NIOSH and OSHA or the 0.2 f/ml proposed by ACGIH (SCOEL, 2011). As might be expected, where exposure standards for the general public have been established (e.g. in the USA), lower values are adopted, as can be seen from the MRL of 0.03 f/cm³ set by the ATSDR, which takes account of different exposure durations. In any event, even if a relatively high OEL still exists in a particular jurisdiction, workers there may actually experience somewhat lower exposures due to industry establishing a ‘recommended’ in-house exposure limit.23

The intention is that this limit, 0.5 f/ml, should be applied in the absence of any more stringent limit mandated by the competent authority. In deriving the recommendation, industry based their considerations on prudence and feasibility criteria, rather than a specific indicator of a particular risk at a higher exposure (Maxim and Utell, 2014).24

9. Discussion

It is important for stakeholder confidence that transparent and consistent approaches to risk assessment are adopted worldwide. Without this, widely varying OELs will continue to be derived and applied, which is an unsatisfactory and confusing situation for manufacturers, workers and businesses alike (see IEH/ICMM, 2006). For ASW/RCF it has been shown that OELs vary by more than an order of magnitude, due at least in part to certain countries adopting risk assessment procedures that are out of line with other country’s approaches and which give rise to much lower values. Table 4 illustrates the differing rationales/procedures applied by various organisations in deriving limit values for ASW/RCF.

Recent authoritative assessments by various national and international bodies or groups (e.g. SCOEL, 2011; DECONS, 2011) have consistently determined that ASW/RCF is a threshold carcinogen (either non-genotoxic or a secondary genotoxin) and that it is

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23 See “What are the recommended maximum fibre exposure levels?” in the ‘Q&A’ section of the ECFIA website at www.ecfia.eu/qa.htm.

24 Note: In a recent update to the REACH registration dossier for ASW/RCF, industry presents a calculated DNEL of 1.62 f/ml, based on the procedures and assessment factors recommended in ECHA guidance document R.8.
acceptable and appropriate to set OELs based on evidence-based health risk assessment approaches. This opinion is supported by experimental data cited in the REACH registration dossier for ASW/RCF, derived from research commissioned at an independent quality-assured toxicology testing facility to determine the genotoxic potential of ASW/RCF. In regulatory-compliant mutagenicity tests using different histidine-dependent strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537 and TA102); ASW/RCF at up to 5000 μg/mL did not induce gene mutations. A similarly compliant in vitro cytogenicity assay using duplicate cultures of Chinese hamster ovary cells, investigating ASW/RCF up to and including the maximum practicable concentration of 1000 μg/mL, did not induce micronuclei in either pulse or continuous exposure regimes. These results indicate that ASW/RCF has no demonstrable mutagenic activity in standard test systems for this endpoint. Moreover, the independent ‘SHEcan’ report (IOM, 2011) provides strong evidence that current conditions of use of ASW/RCF in Europe do not pose a significant carcinogenic risk to workers.

As argued by SCOEL and previously suggested by IARC (2002), it is most likely that inflammation is the underlying effect of fibre carcinogenicity and that the genotoxic effects observed in certain studies are secondary, resulting from the induction of reactive oxygen species and, in the case of cytogenetic effects, from the interaction of the fibres with the spindle apparatus. This is the reason that SCOEL classified ASW/RCF as a genotoxic carcinogen for which a practical threshold is supported, and why the assumption in the ERR-MMMF document that ASW/RCF (and other MMMFs) are non-threshold carcinogens, with associated application of

<table>
<thead>
<tr>
<th>Source</th>
<th>Selected key study type</th>
<th>Study target organ, endpoint</th>
<th>Human endpoint</th>
<th>Anticipated risk level</th>
<th>Limit value [μg/ml]</th>
<th>Strengths and weaknesses of approach adopted</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCOEL (EU)</td>
<td>Epidemiology</td>
<td>Lung, pulmonary function</td>
<td>Chronic inflammation</td>
<td>Health-based threshold</td>
<td>0.3</td>
<td>Strengths: Science-based (considers possibility of threshold/non-threshold mechanisms, uses physiologically-relevant data, uses epidemiological evidence); transparent; conservative assessment factors used to address uncertainties; practical to monitor compliance.</td>
</tr>
<tr>
<td>DECO (Netherlands)</td>
<td>Animal inhalation</td>
<td>Lung, cancer</td>
<td>Cancer</td>
<td>Health-based threshold</td>
<td>1.0</td>
<td>Weaknesses: None identified</td>
</tr>
<tr>
<td>HSE (UK)</td>
<td>Not known/Not specified</td>
<td>N/A</td>
<td>Cancer/Fibrosis</td>
<td>Health-based threshold</td>
<td>1.0</td>
<td>Strengths: Pragmatic</td>
</tr>
<tr>
<td>NIOSH (USA)</td>
<td>Animal inhalation</td>
<td>Lung, cancer</td>
<td>Cancer</td>
<td>Risk ≤ 1:1000 (extrapolation)</td>
<td>0.5</td>
<td>Strengths: Science-based (considers animal and epidemiological data, possibility of threshold/non-threshold basis, and also addresses non-cancer endpoints); practical to monitor compliance</td>
</tr>
<tr>
<td>ACGIH (USA)</td>
<td>Not known/not specified</td>
<td>N/A</td>
<td>Cancer</td>
<td>Health-based threshold</td>
<td>0.2</td>
<td>Strengths: Highly conservative limit</td>
</tr>
<tr>
<td>AGS (Germany)</td>
<td>Animal IP injection</td>
<td>Peritoneum, cancer</td>
<td>Cancer</td>
<td>Risk ≤ 4:1000 (extrapolation)</td>
<td>0.1 (tolerance level)</td>
<td>Weaknesses: Strictly animal-based; does not consider epidemiological evidence; uses non-physiological route; does not distinguish between threshold and non-threshold mechanisms; based on limited data; adopts unvalidated assumptions; adopts not strictly scientific risk values</td>
</tr>
<tr>
<td>AFSET – now ANSES (FR)</td>
<td>Based on risk estimates review by Maxim et al. (2003)</td>
<td>N/A</td>
<td>Cancer</td>
<td>Risk ≤ 5:10,000 (extrapolation)</td>
<td>0.1</td>
<td>Strengths: Highly conservative limit</td>
</tr>
</tbody>
</table>

*a i.e. values considered ‘societally-acceptable’ rather than based on scientific concepts.
straight-line dose responses for carcinogenicity, is not supported by the currently available scientific and medical evidence.

We argue here particularly that the ERR approach is not appropriate for threshold carcinogens, and that ASW/RCF is such a substance. One premise for the assumption of a carcinogenic threshold is the fact that ASW/RCF is non-genotoxic. Moreover, there are several important factors clearly distinguishing ASW/RCF and other MMMFs from asbestos that are important in determining risk, including fibre dimension, the propensity to fracture transversely, and biopersistence. These considerations caution against the assumption – made by the German AGS – that MMMF and the various types of asbestos are equivalent in their carcinogenic potential. Several studies in ASW/RCF workers have shown that ASW/RCF has no demonstrable carcinogenicity in humans (SCOEL, 2011; Walker et al., 2012a, b; Boffetta et al., 2014; Greim et al., 2014), providing important data challenging the ERR approach for synthetic mineral fibres. It certainly seems unlikely that the results from these studies are what would be expected for a non-threshold carcinogen, which the German authorities hold ASW/RCF to be.

Specifically, the ERR method may be criticised as unsuited for use with threshold carcinogens, and the attempts to apply it to ASW/RCF and MMMF more generally contain critical scientific flaws. In particular, the application is weakened by the reliance on IP rather than inhalation study data when calculating risk and the high degree of uncertainty associated with the various assumptions and calculations undertaken.

It would be highly advantageous for risk assessment approaches for synthetic mineral fibres – and hence their OELs – to be globally harmonised, taking into account the three principal factors that drive the derivation of an OEL, namely: 1) determination of the POD from the most relevant study (animal or human); 2) application of appropriate ‘assessment factors’ to the POD; and 3) use of the available MoA data that will determine whether a threshold or non-threshold approach should be used. Currently, different jurisdictions have different systems and approaches to setting OELs. In the UK, for example, aspects of practicality and enforceability are often taken into account while other countries may simply set precautionary or aspirational targets for the future. We suggest that all OEL-setting procedures should be transparent, based on the three above-mentioned toxicological principles, and should explicitly indicate the degree to which considerations of precaution and/or practicality are incorporated into the process.

For the global harmonisation of OELs it is clearly important that the processes, principles and decisions reached when developing standards must be sufficiently transparent to enable comparability and understanding of differences between the approaches. This should result in a higher uniform quality and greater confidence in the robustness of the OELs amongst the regulatory community, industry and the labour force. It is understood, however, that achieving harmonisation may prove difficult due to the varying remits and underlying philosophies of standard-setting bodies, and because of differences in scientific belief and approaches that exist worldwide (IEH/ICMM, 2006). Nonetheless, there are some fundamental activities that can and should be coordinated and harmonised, as set out in detail in the IEH/ICMM report on the setting and use of occupational exposure limits (IEH/ICMM, 2010). A principal tenet of these recommendations, which we fully endorse, is the documentation and publication of all the key steps in the standard-setting process. Fortunately, a degree of harmonisation in the use of assessment factors is already being achieved in Europe through the publication of recommended default values for use in establishing DNEL values under the REACH regulations (ECHA, 2012b). Achieving success in the harmonisation of OELs will require considerable active cooperation and information sharing amongst regulatory bodies as well as the participation of relevant stakeholders, but this is a goal worth striving for.

Conflicts of interest

The named authors all contributed to this paper. Paul Harrison, Philip Holmes, Ruth Bevan, Leonard Levy and Helmut Greim are independent toxicology/risk assessment consultants; they are not involved in legal testimony related to the materials and products discussed and do not have any form of commercial interest in them. Paul Harrison acts an advisor to ECFIA (an association representing the high temperature insulation wool industry) in matters relating to health and safety. Klaus Kamp is Chairman of ECFIA and an employee of Unifrax GmbH, a manufacturer of high temperature insulation wools and other refractory materials.

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Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2015.07.029.

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25 The approach adopted by the EU-LCI Working Group that sets emission standards for building products (Kephalopoulos et al., 2014) is an excellent example of a scientifically valid, transparent and fully documented methodology that can act as a model for other bodies tasked with setting health based exposure limits.
pleura responses after deposition of carbon nanotubes in the pulmonary airspaces of mice. Nanotoxicology 6, 1152–1167.


