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Original Article

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Extrapolating the Applicability of Measurement Data on Worker Inhalation Exposure to Chemical Substances

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Abstract

Measured data are generally preferred to modelled estimates of exposure. Grouping and read-across is already widely used and accepted approach in toxicology, but an appropriate approach and guidance on how to use existing exposure measurement data on one substance and work situation for another substance and/or work situation is currently not available. This study presents a framework for an extensive read-across of existing worker inhalable exposure measurement data. This framework enables the calculation of read-across factors based on another substance and/or work situation by first evaluating the quality of the existing measurement data and then mapping its similarity or difference with another substance and/or work situation. The system of read-across factors was largely based on the determinants in ECETOC TRA and ART exposure models. The applicability of the framework and its proof of principle were demonstrated by using five case studies. In these case studies, either the 75th percentiles of measured exposure data was observed to lie within the estimated 90% confidence intervals from the read-across approach or at least with the increase in the geometric mean of measured exposure, geometric mean of estimated exposure also increased. Testing and re-evaluation of the present framework by experts in exposure assessment and statistics is recommended to develop it further into a tool that can be widely used in exposure assessment and regulatory practices.

Keywords: determinants of exposure; exposure assessment for existing substances; exposure assessment methodology; exposure data evaluation; exposure estimation; read-across

Introduction

In industry, new chemical substances are continually being introduced (Herber *et al.*, 2001). These chemicals may pose a broad range of potential health hazards to the workers who are prone to their exposure during the production and use of chemicals in workplaces (ILO, 2014). In 2007, the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) was introduced as an effort to regulate the risks inherent to working with, or producing chemical substances. Under REACH, companies are obligated to register any chemical (apart from several exemptions) they wish to sell on the European market, which is to be accompanied with proof that risk from working with the chemical can be controlled with the use of exposure measurements or modellings. Obviously, collecting exposure measurements for the specific exposure situation is considered the gold standard for exposure assessment and should be encouraged. However, measuring worker exposures can be time consuming and expensive, and the use of exposure models is prone to user bias (Schinkel *et al.*, 2014).

Instead, methods that can maximize the use of available data for both estimating exposure and benchmarking exposure model predictions can prove to be more useful or cost-effective (ECETOC, 2009; Adami *et al.*, 2011; Lavelle *et al.*, 2012; Hristozov *et al.*, 2014). One approach can be to use read-across from a substance or situation with sufficient data to support an exposure assessment to a similar substance or situation where measurement data are unavailable or too weak to support an exposure assessment, as similarly practiced in toxicology. The acceptability of such a read-across in toxicology depends on the comparability of aspects such as e.g. physico-chemical characteristics of a substance and the applied safety factor that takes into account the uncertainty in the read-across. In exposure assessment, however, there are other factors to account for such as substance emission potential (substance properties related to exposure), activity emission potential (energy of the activity leading to exposure), ventilation, and engineering controls. In addition, a framework for identifying relevant exposure measurement datasets, assessing data quality and quantifying the effect of differences between the situation to be assessed (hence called target situation) and the situation(s) from which the data are derived (hence called source situation(s)) is required. A set of robust criteria can, assist in extending application of exposure measurements obtained for a specific substance(s) and use conditions to other substances under similar use conditions. Through the development of a scientific, credible framework for extending measurement datasets to similar exposure scenarios, the reliance on exposure modelling in data-poor exposure scenarios may be reduced.

In this study, we present an approach which enables such a read-across of worker inhalation exposure measurement data. It allows risk assessment based on measured exposure levels for situations and substances for which such measured exposure levels are not (or insufficiently) available. Lastly, the proposed approach is tested using five extensive case studies.

Read-across approach

The approach used in the proposed read-across framework consists of three steps: evaluation of source data quality (Step 1); evaluation of similarity between source and target situations, based on mapping the two situations for relevant read-across parameters (Step 2); calculation of target situation exposure level (Step 3). Before the framework can be implemented, it is assumed that the user is aware of the target situation information and that in an initial pre-requisite step (Step 0) measurement data of a similar situation (i.e. source situation data) is available with the user. The full approach, including the process flow and the input data used is summarized in Fig. 1.

Step 1: Evaluation of source data quality

In Step 1, it is assessed whether the source dataset is adequate and appropriate to be used for read-across. Within the scope of this study, 'adequate' should be interpreted as containing sufficient information to address key characteristics and uncertainties in the data that need to be known to use the data for read-across.

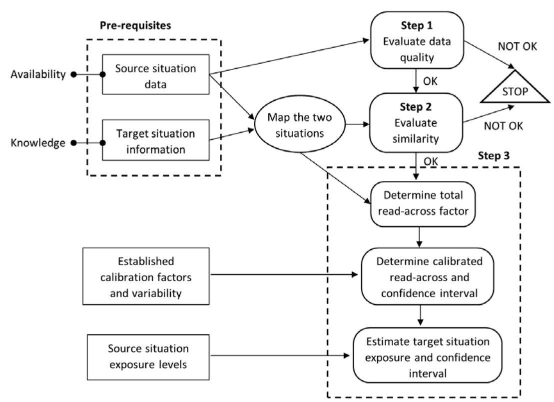

Figure 1. Illustration of the framework for read-across of exposure data.

While all exposure information can be relevant, exposure information of different quality has a different weight in the exposure assessment process (Money and Margary, 2002). However, a minimum quality level of a dataset is needed before it can be used for the purpose of read-across. The different aspects that influence the adequacy of measured datasets, disregarding any statistical factors, can roughly be categorized into two types of aspects:

(i) Technical aspects, related to the actual sampling and analytical methods used; this is called technical adequacy;
(ii) Contextual aspects, related to the description of the situation that was measured; this is called contextual adequacy.

Measurement strategy, including choices of how many samples and when to sample, can have an important effect on the results of the measurements. The number of samples influences the (un)certainty of the resulting statistical outcomes. This will be accounted for in the estimation of uncertainty of the read-across approach. Another important aspect of measurement strategy is what and when to sample. This includes the choice to sample at random or e.g. focusing on worst-case situations. It also includes the choice to sample during one activity or for a longer period. The sampling strategy in relation to random sampling, focused sampling (e.g. on worst-case situations) or stratified sampling is covered in the read-across approach via the mapping of the source and target situations. The choice for either random, focused (e.g. on worst-case situations) or stratified sampling will result in different values for contextual information, which will be taken into account in determining the read-across factor. The influence of duration of sampling in relation to duration of activities is accounted for in decision scheme on adequacy of the dataset.

The overall approach for evaluating the adequacy of measured datasets is shown in Fig. 2. In case new information is gathered to fill data gaps, the evaluation should restart from the top of the decision scheme with the total dataset, including the new information.

Technical adequacy

The technical adequacy of methods used for measurements needs to be ensured. There are many documents, including standards from standard setting bodies, such as CEN and ISO, that describe aspects of technical adequacy when performing measurements (e.g. EN482). In general, the technical adequacy of the measurements can be considered sufficient if:

(i) A method (fit for the type of exposure and substance) is used which is published by national authorities or renowned institutes, such as NIOSH (USA), IFA (Germany) or HSE (UK) and includes a validation exercise and descriptions of accuracy, precision and validity boundaries of the methods they publish;
(ii) Or an in-house specific method is used which has been developed and validated according to the same standards as the methods published by renowned institutes;
(iii) And there are no conditions which can be expected to lead to significant interference, such as the presence of substances known to influence the results of the measurements or conditions such as very high temperatures, high humidity or low pressures (e.g. measurements at high altitude) for which the methods may not have been tested.

Contextual adequacy

To allow measured data from a source situation to be used for assessing exposure in a target situation, it is necessary to have the context of the measurements sufficiently known. The context describes the parameters that determine the exposure levels. The context also provides users with the information needed to map the similarity of the source situation to the target situation. Therefore, to allow proper interpretation and use of measured values, the most important determinants in the context should be known. The relevant determinants for which the sufficient contextual information should be known on the measured data have already been shown in Fig. 2 (summary in Supplementary Table S1, available at *Annals of Work Exposures and Health* online). These determinants were derived from previous work (Lippmann *et al.*, 1996; Rajan *et al.*, 1997; Money and Margary, 2002; Tielemans *et al.*, 2002) and ECETOC TRA.

Deciding on adequacy and its categorization

The critical issue that decides technical and contextual adequacy is the availability of sufficient information and its quality to allow evaluation whether the source substance and source situation can be compared with their target counterparts. The sufficient information can be quantitative or semi-quantitative information or categorical data that can be directly compared between source and target situation. Based on the earlier categorization systems (Klimisch *et al.*, 1997; Money *et al.*, 2013), we suggest the adequacy categories in Table 1. For read-across of exposure data, only data with adequacy score of 1 or 2 should be used.

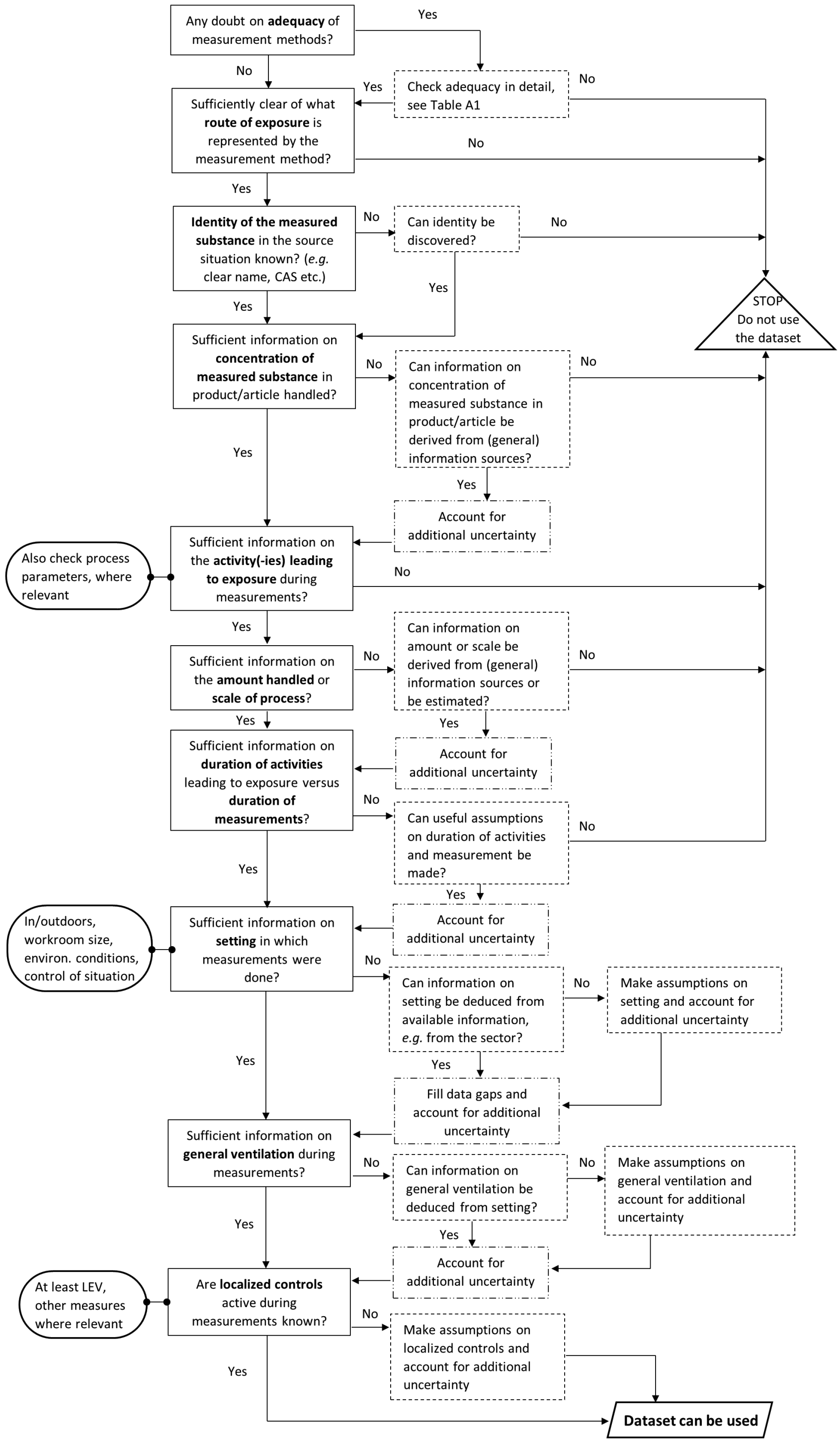

Figure 2. Decision scheme on adequacy of the dataset; ▭ indicate the basic determinants to be evaluated; ⬭ indicate possible additional detail needed for some determinants; ⬚ indicate questions on adequacy or possibilities to fill data gaps by gathering specific information or making assumptions; ⬚ indicate that filling data gaps via additional information or assumptions may lead to additional uncertainty, which may need to be accounted for in the actual read-across estimations; △ indicate that the data quality was found insufficient to proceed with the next step in the framework; ▱ indicates that the data quality was concluded to be sufficient.

Table 1. Criteria for evaluating and assigning reliability scores to exposure data.

Score	Adequacy assignment	General criteria	Examples
1	Adequate without restriction	Data of good technical and contextual adequacy is available	Completely documented measurement studies, performed with validated measurement methods (published by renowned institutes) and with all information on each data point in annexes
2	Adequate with restrictions	Data of at least acceptable technical adequacy and information on contextual adequacy is available or can be evaluated based on the expert judgement and reasonable assumptions	Well documented measurement studies, performed with validated measurement methods (published by renowned institutes) or methods that resemble such methods closely and for which sufficient information on validity, accuracy, precision, and boundaries is available; sufficient description of context to either directly know the values for relevant factors or to make informed and justified expert judgement on a number of factors; activities may need to be categorized, based on descriptions, assumptions on scale and setting may need to be based on expert judgement, data on substance and product characteristics may need to be found in other sources or estimated
3	Not adequate	Data with inadequate technical adequacy and/or data that do not allow separation of situations with important differences in context	Dust measurements with incorrect sampling techniques; measurements with imprecise and insufficiently selective indicator tubes; statistical summaries of data (vapour pressure of measured substances, concentrations of substances in products or largely different settings) that are not stratified; studies in which only the jobs of sampled workers are indicated without any indication of activities being sampled
4	Not assignable	Data for which the technical adequacy cannot be evaluated or that are described too insufficiently to allow evaluation of several factors related to contextual adequacy	Studies in which the sampling method is not described (e.g. no reporting of whether respirable dust, inhalable dust or total dust has been measured); the method for measuring solid/liquid aerosols is not described; studies in which no information is given on e.g. the use or no use of localized control measures, the concentration of measured substances in articles, the duration of activities within shift-based measurements, the containment of sources, etc.

Step 2: Mapping of similarity between source and target situations

For the evaluation of the similarity between source and target situations, six rules are suggested to indicate sufficient similarity or lack of similarity:

(i) The physical state of the measured and target substances should be the same, e.g. either both liquids (measured as vapour or mixed-phase aerosol) or both solids (measured as dust).

(ii) The exposure route should be the same, i.e. inhalation.

(iii) The source and target situations should fall in the same process category (PROC), as defined and described by ECHA (2015) and applied in ECETOC TRA (ECETOC, 2004, 2009, 2012, 2014, 2018), with some exceptions as described in Supplementary Material (available at *Annals of Work Exposures and Health* online; based on the similarity between PROCs) or the same Advanced REACH Tool (ART) activity class (AC) and subclass. ECETOC report TR No. 131 (ECETOC, 2018) provides some additional explanation to assist the allocation of an appropriate PROC. When the data do not allow the allocation of PROCs, or ACs the categorization in more broad and qualitatively described categories is also possible, provided that the activities of both the source and target situations should fall in the same general activity description.

(iv) The substance use rates in the source and target situations should be sufficiently similar, i.e. differ by no more than two categories as used in ART (Supplementary Table S2, available at *Annals of Work Exposures and Health* online) (Marquart et al., 2011).

(v) In case of a minor fraction of volatile substances (as the substances of interest) within a complex matrix, both the vapour pressure of the substances in source situation and target situation should be similar. The product matrix should also be similar.

(vi) The read-across is not to be performed over generally different types of localized control measures. It is currently allowed within certain localized control measures groups (e.g. different LEV systems).

(vii) The duration of important exposure causing activities, in case of measurements and estimates covering a full-shift, should be sufficiently similar in source and target situation. If the full-shift is not sampled, it should be ensured that there are no important exposure causing activities during non-measured periods in the source data. If the source data and the target assessment are both activity-based, it should be ensured that the source data cover only the actual activity and not a substantial period outside of the activity that is a target of the assessment.

If all of the above six rules are met, one can go to the next step, i.e. map the source situation to the target and calculate read-across factors.

Step 3: Calculation of target situation exposure level

The actual statistical read-across consists of the mapping and mathematical comparison between the determinants of exposure for the target and source situations. For this, four exposure determining categories were differentiated, namely: (i) substance emission potential, (ii) activity emission potential, (iii) engineering control measures, and (iv) workplace configuration. Several key parameters which underlie each category were identified. Based on these key parameters, a read-across factor between 0 and 1 is calculated for each of the four categories. Next, an overall read-across factor is derived from each category read-across factor using equation (1).

$$\begin{aligned}\text{Read-across factor}\\ &= (\text{Substance read-across factor})\\ &\quad\times(\text{Activity read-across factor})\\ &\quad\times(\text{Engineering control read-across factor})\\ &\quad\times(\text{Workplace configurations read-across factor})\end{aligned} \tag{1}$$

Substance emission potential

For the substance emission potential, two parameters were identified to be influencing. They are dustiness (for solids) or volatility (for liquids) and weight fraction of the substance in a product. These parameters are also used in exposure models such as ART and ECETOC TRA, and are also identified in ECHA guidances (Fransman et al., 2011; ECETOC, 2012; ECHA, 2016).

The dustiness of powders can be directly measured using varying validated techniques such as the rotating drum test (Breum, 1999; Jensen et al., 2009; Tsai et al., 2009) or the continuous drop test (Bach and Schmidt, 2008). The read-across factor for the dustiness can be calculated by dividing the dustiness value at the target situation by its value at the source situation for the same dustiness fraction. In case dustiness measurements are not performed, or unknown, the target and source situations can also be compared categorically on the basis of the categories which are handled by the ART, as shown in Supplementary Table S3 (available at *Annals of Work Exposures and Health* online). Similar to dustiness, the read-across factor for the volatility can be calculated by dividing the vapour pressure of the target substance by that of the source substance. While the situation in mixtures can be much more complicated and the linear influences of vapour pressure and weight fraction only are valid in ideal mixtures, for pragmatic reasons, we assume a linear effect when the substance is in a mixture. For weight fraction, it is suggested to divide the weight fraction of the target substance by that of the source substance. When the parameters between the source and target situations are matched and read-across factors are assigned, a substance read-across factor can be calculated using equation (2) (DV is the dustiness or volatility read-across factor and WF is the weight fraction read-across factor).

$$\text{Substance read-across factor} = \mathrm{DV}\times\mathrm{WF} \tag{2}$$

In the assessment of the dustiness and the volatility, the values for these parameters in the actual (source and target) situations should be used. For example, if the source product is used at high temperature, the vapour pressure at that temperature should be taken into account. If a powdered product is moist and therefore less dusty, the choice of dustiness value should take account of that fact.

Activity emission potential

For the activity emission potential, two parameters were identified as being relevant for comparison between source and target situations: activity description and amount of substance used.

To calculate an activity read-across factor, the ECETOC TRA exposure estimate (Supplementary Table S4, available at *Annals of Work Exposures and Health* online) for the assigned PROC of the target situation can be divided by that of the source situation. The read-across factor, corresponding to the amount of substance used (or use rate) can be calculated by dividing the amount of substance used in the target situation by the amount of substance used in the source situation. When the exact amount is not precisely known, the corresponding exposure modifiers (derived from ART) can be divided to obtain the read-across factor. According to the rules set in Step 2, the amount of substance used (expressed in ART modifiers) should not differ by more than two categories (Supplementary Table S2, available at *Annals of Work Exposures and Health* online). An overall read-across factor for the activity emission potential can thus be calculated by using equation (3) (A_t is the activity type read-across factor and A is the amount of substance used read-across factor).

$$\text{Activity read-across factor} = A_t \times A \times D \quad (3)$$

In equation (3), duration of exposure or activity duration (D) can also be considered as a relevant parameter when a period of non-exposure has to be accounted for in which case the exposure is a time weighted sum of zero exposure and a period of exposure.

Engineering control measures

For the engineering control measures, two parameters were identified and considered relevant for the comparison between the source and target situations. These parameters are general (room) ventilation (Jafari et al., 2008; Saraga et al., 2014) and localized control measures (Fransman et al., 2011; ECETOC, 2012; ECHA, 2016). In theory, it is expected that the exposure is related to the degree of dispersion of airborne substances which is a direct function of both number of air change per hour (ACH) and room volume (Cherrie et al., 2011). Therefore, the read-across factor corresponding to the mechanical ventilation can be calculated by dividing the respective exposure modifiers at the source and target situations (Fransman et al., 2011).

For the second parameters, i.e. localized control measures, it is proposed that two different types of localized control measures cannot be compared when applying the read-across method, e.g. a situation with a containment system should not be used for read-across to another situation where a certain LEV system is in place. For the current framework, the exposure modifiers from the ECEL library, as used as the basis for multipliers in the ART model (Fransman et al., 2011), were used as a measure to compare the different efficiencies of localized control measures (Supplementary Tables S5.1 and S5.2, available at *Annals of Work Exposures and Health* online). For the calculation of an engineering controls read-across factor, equation (4) can be used in which GV is the general ventilation and RMM is the risk management and local control methods.

$$\text{Engineering control read-across factor} = \text{GV} \times \text{RMM} \quad (4)$$

Data on the effectiveness of localized control measures are still scarce, so when more data will be available (in databases such as the ECEL), the engineering control read-across factors should be revised accordingly.

Workplace configuration

Workplace configuration is the factor which is comprised of information about the premises where the measurements have been collected, e.g. indoor or outdoor, industrial or professional setting, etc. Two key parameters for the workplace configuration are environmental conditions and premise setting. The environmental conditions are related to whether the task is performed indoors or outdoors. Tasks which are performed outdoors, results in an estimated 30% reduction in exposure (ECETOC, 2004, 2009; ECHA, 2015). The premise setting can either be an industrial setting (advanced systems to instruct, train, and supervise workers, proper installation, operation, maintenance, and cleaning of equipment and regular cleaning of workrooms) (Fransman et al., 2011; ECETOC, 2012; ECHA, 2016; ECETOC, 2018) or professional setting (managing controls are less effective due to the constant change of working environment, or more limited resources available when the workplace is stationary to implement these management controls).

The read-across factor for the workplace configuration can thus be calculated using equation (5) in which P is the premise setting and EC is the environmental conditions read-across factors, respectively.

$$\text{Workplace configuration read-across factor} = P \times \text{EC} \quad (5)$$

Uncertainty and calibration analysis

The uncertainty in read-across of exposure data was calculated on the basis of the measured exposure data sets in "similar" situations. A comparison was made between the read-across factors (which are ratios of determinants in the scenarios) of situations and the ratios of geometric means (GMs) of measured data. The primary information source for calibrating the read-across approach and quantifying the uncertainty in the exposure data was the ART database (Schinkel et al., 2013). It currently contains 2007 exposure measurements, arranged into 122 exposure situations. To validate the calibration approach, the SUVA database (Savic et al., 2017) was used. It contains 585 exposure measurements. It, thus, has smaller numbers of measurements per situation which translates into greater uncertainty associated with estimates of exposure summaries based upon the measurements. A six-step approach was implemented for the calibration of the read-across approach:

(i) The 122 exposure situations in the ART database were coded using the appropriate determinants. The coding was conducted by one team member with every scenario subsequently checked by a second team member. In a small number of cases where there was disagreement a final coding was made by consensus. For each situation, the model central estimate of the GM (8-h TWA) was obtained. All the determinants, associated with each exposure scenario, were recorded using the same scheme as Savic et al. (2017).

(ii) The GM and geometric standard deviation (GSD) were estimated from the measurements available on these 122 exposure situations. Based on an assumption that measurements were log-normally distributed, the 75th, 90th, and 95th percentiles (i.e. α) were estimated for each situation from equation (6), where z_α= 0.674, 1.282, and 1.6449 for the 75th, 90th, and 95th percentiles, respectively.

$$Y_\alpha = \exp\{\log(\mathrm{GM}) + z_\alpha \times \log(\mathrm{GSD})\} \quad (6)$$

(iii) The exposure situations were also split into four substance classes: aerosol, dust, liquid vapour, and dust resulting from abrasive processes. Only comparisons of situations within a substance class were made. For each pair of exposure situations (within a substance class), the ratio of ART scores ($X_{i,j}$) was calculated.

$$X_{i,j} = \frac{\text{ART score for scenario } i}{\text{ART score for scenario } j} \quad (7)$$

While ART has been used as the tool for coding the scenarios for practical reasons (speed of computation and to minimize the possibility of coding errors), the ratio in equation (7) depends upon the underlying determinants and is thus independent of the (calibrated) ART model. For 'similar' scenarios, the determinants within the two ART scores should also almost totally cancel: the ratio in such cases is based only upon the determinants where the two scenarios differ. Thus, the approach, based upon the theory of determinants, is model independent. Read-across can be applied to exposure scenarios based upon both ART activity classes and ECETOC TRA PROC classes.

(iv) Each pair of datasets from the ART database (within a common substance class) was compared to assess for similarity—a binary coding of similar/dissimilar. This exercise was based upon expert judgement, which involved a comparison of ART determinants in the situations and the textual descriptions. This was blind to exposure measurements associated with the two scenarios and the ART scores themselves.

Table 2. Results from calibration of the read-across factors.

Metric	β (SE)	σ	r^2
GM	0.44 (0.05)	1.21	0.37
75th percentile	0.38 (0.05)	1.23	0.30
90th percentile	0.34 (0.06)	1.32	0.22
95th percentile	0.11 (0.09)	2.00	0.02

(v) The calibrations of the read-across factors were made using equation (8), in which $Y_{i,j}$ denotes the ratio of GMs (or respective percentiles for calibration of 75th, 90th, or 95th percentiles) and $\varepsilon_{i,j} \sim N(0, \sigma)$. The results from this calculation for the summaries considered are given in Table 2.

$$\log(Y_{i,j}) = \beta \times \log(X_{i,j}) + \varepsilon_{i,j} \quad (8)$$

The calibrated GM for situation j (i.e. target situation) and a confidence interval are given in equations (9) and (10), respectively. Similar calculations for percentiles result from substituting the appropriate coefficients from Table 2.

$$\mathrm{GM}_j = \mathrm{GM}_i \times \exp\{\beta \times \log(X_{i,j})\} \quad (9)$$

$$\text{Confidence interval} = \mathrm{GM}_i \times \exp\{\beta \times \log(X_{i,j})\} \times \exp(\pm z_\alpha \times \sigma) \quad (10)$$

(vi) The validation was done on the basis of a similar dataset of ratios of ART scores and summary statistics from the SUVA database.

A comparison of the ratio of GMs and read-across factors ($X_{i,j}$) is shown in Fig. 3a for the full set of pairwise comparisons (including both similar and dissimilar exposure situations—against the rule set in Step 2 of the approach) in the cases of all four distinct substance classifications. The 1:1 line (solid black) indicates that on average, $X_{i,j}$ is consistent with the ratio of GMs. For a given value of $X_{i,j}$, the ratio of GMs covers four orders of magnitude. A similar comparison is shown in Fig. 3b, but only for similar exposure situations. The 1:1 line is also shown with the best fit line (dashed black), estimated from equation (8) (coefficient and associated standard error are given in Table 2). The range of GMs, for a given value of $X_{i,j}$, is approximately two orders of magnitude for all substance classes, representing a substantial reduction in uncertainty compared with Fig. 3a.

The $X_{i,j}$ values are compared with the 75th, 90th, and 95th percentile ratios in the Fig. 4a,b, and c, respectively

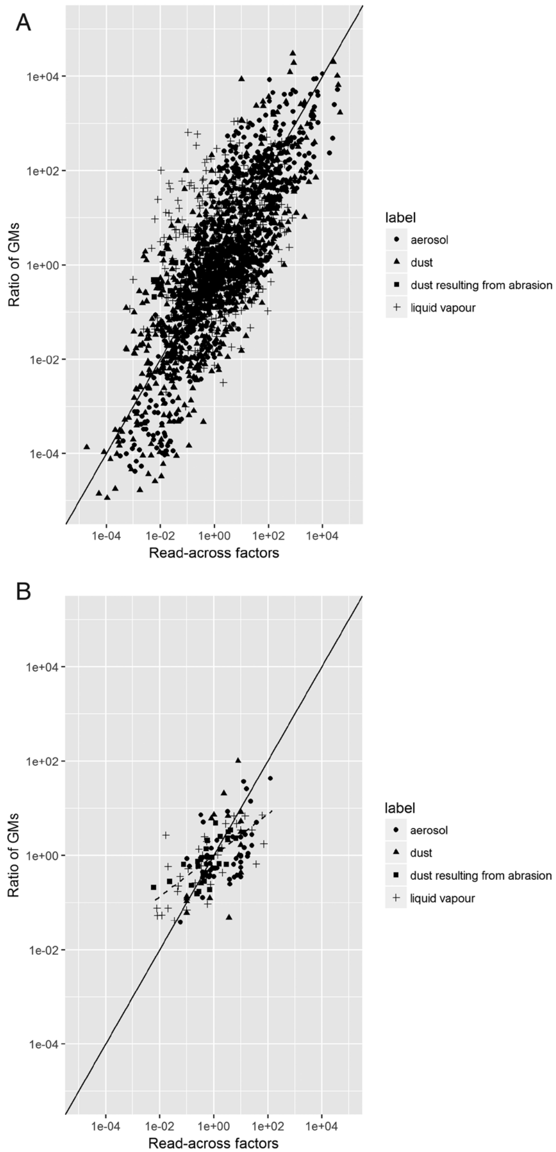

Figure 3. Pairwise comparisons of the ratios of read-across factors and ratios of GMs within each substance class for (a) all exposure situations (similar or dissimilar); (b) similar exposure situations. The 1:1 (solid) and calibrated (dashed) lines are also shown.

for similar exposure situations. The 1:1 and best fit [equation (8)] lines are indicated on the plots. For the 75th and 90th percentiles (Fig. 4a,b), the two ratios positively correlate. Moreover, the data scatter around the fitted line is greater for these two percentiles than in the case of GM which suggests greater uncertainty in read-across for these percentiles of the exposure distribution compared with the GM. The ratio of 95th percentiles, however, do not correlate with the read-across factor ratios, as shown in Fig. 4c. The read-across for the 95th percentile is, therefore, not currently justified.

Due to small numbers of measurements in the SUVA database, only the GMs of those datasets were studied which correspond to the substance classes of dust and liquid vapour. A pairwise comparison of the GM and read-across factor ratios, for all exposure situations (similar or dissimilar), is shown in Fig. 5a, while similar situations are compared in Fig. 5b. The fitted line is estimated from calibration data in Table 2. The relationship estimated from calibration data was consistent with the validation data (Fig. 5b), however, a greater variability in the ratio of GMs can be observed in Fig. 5b for a given ratio of determinants (quantified through a standard deviation of 1.31). This reflects the smaller numbers of measurements for each exposure situation and hence greater uncertainty in the estimates of GMs for these exposure scenarios.

Proof of principle by case studies

The proof of principle of the developed framework for read-across of exposure data was demonstrated by using five case studies. Summary information of these case studies is provided in Table 3. To demonstrate the wide applicability of the stepwise read-across framework, five different substance classes were considered in these case studies, two of which (vapour and respirable dust) are not explicitly supported by the ART and ECETOC TRA. The source (and target) scenarios in case studies were also formulated around different sources of measurement data that in principle could be leveraged for the purposes of read-across. These included source (and target) scenarios provided by industry (Case 1), compiled from site visit reports (Case 2), from the published literature (Case 3) and taken from the ART database (Cases 4 and 5).

Adequacy check

For each of the case studies, as a first step, the adequacy check of the source contextual information, against the decision scheme (in Fig. 2), was done. The contextual information was available for the source dataset and hence the quality scores of 1 was assigned to all dataset in Case studies 1, 3, 4, and 5, respectively. In Case study 2, relatively sparse details were available in the source dataset. However, its technical adequacy was found to be reasonable and sufficient information was available for selecting the PROC for use with the ECETOC TRA. Consequently, quality scores of 2 were assigned in

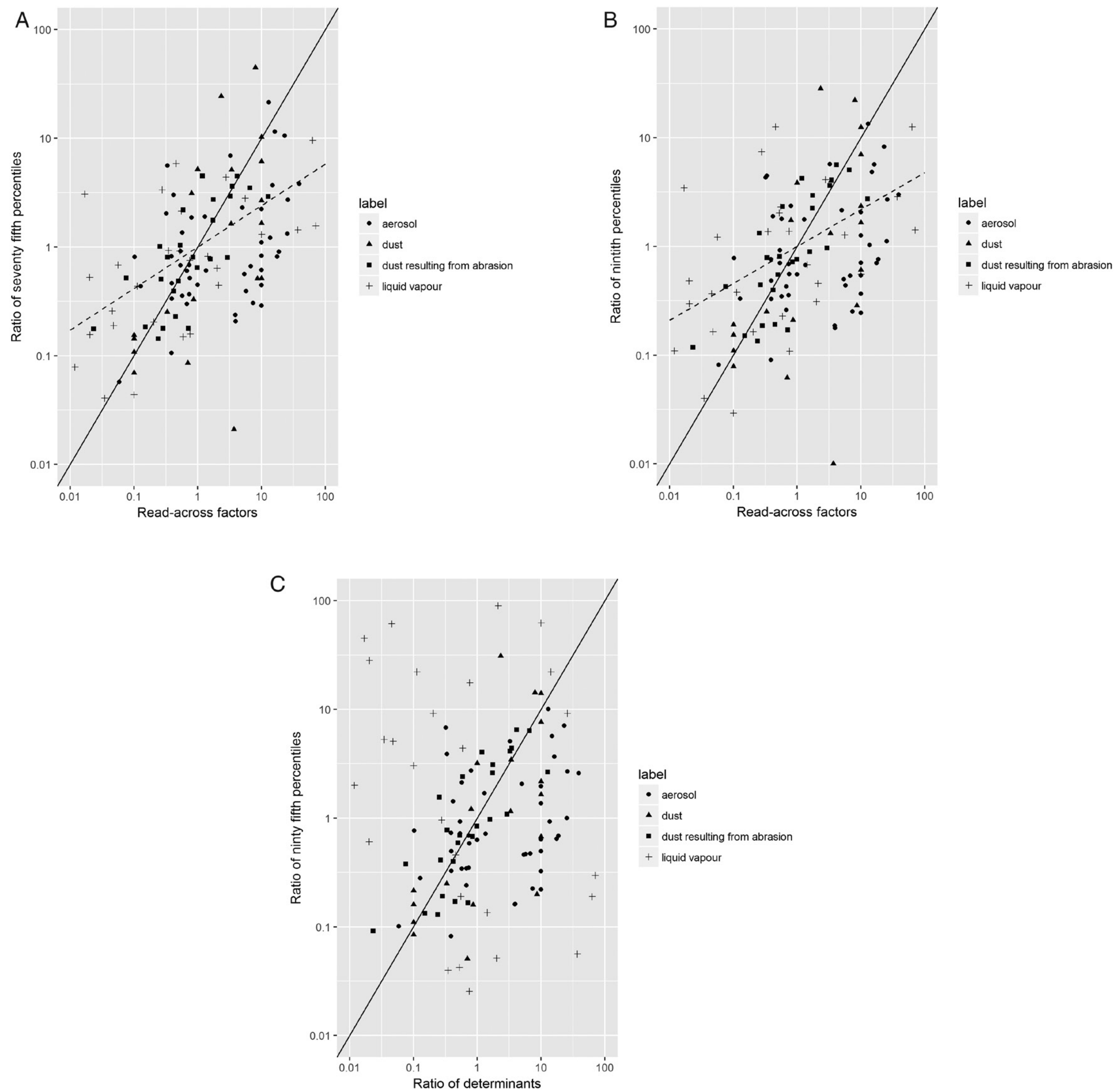

Figure 4. Pairwise comparisons of the read-across factors ratios and ratio of (a) 75th; (b) 90th; and (c) 95th percentiles for the subset of similar exposure situations.

Case study 2. The detailed information on the quality checks, transcription, and coding of the case studies in appropriate PROCs and ART activity classes is shown in Supplementary Table S6 (available at *Annals of Work Exposures and Health* online).

Calculation and verification

In Table 4, a working example is shown for Case study 1 in which the appropriate process characteristics, levels, and read-across factors are derived for seven determinants. For example, the source dataset in Case study 1 belongs to the PROC2. In addition to six determinants, PROC2 is considered to be similar and conservative for PROC1 situations. Therefore, a read-across from the PROC2 source situation to PROC1 was considered in this case study. Other six determinants could be varied in the target situation—their levels and associated read-across factors are also given in Table 4. The multipliers have been normalized such that the multiplier is unity when the source situation is identical to the target situation, which simplifies the subsequent calculations. The vapour pressure and weight fraction are continuous parameters that could be varied and the read-across factor is the ratio

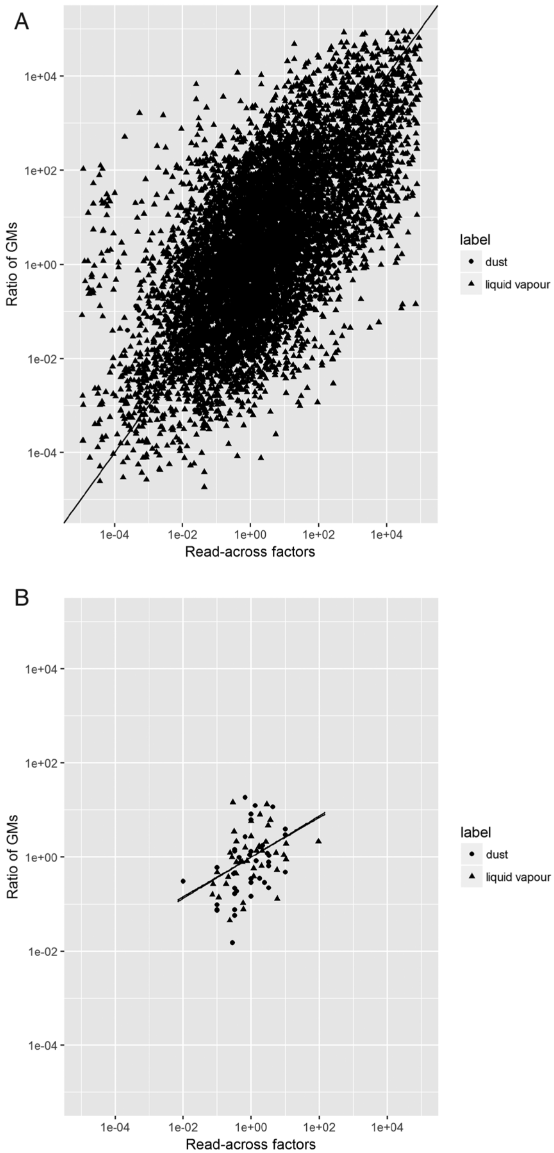

Figure 5. Pairwise comparisons of the read-across factor and GM ratios within each substance class of dust and liquid vapour for (a) all exposure situations (b) similar exposure situations. The fitted line is estimated using the coefficients which are determined from the calibration data.

of the target and source situations. The process characteristics, levels, and read-across factors for the applicable determinants in the remaining four case studies can thus be calculated in a similar way as shown in Supplementary Tables S7–S13 (available at *Annals of Work Exposures and Health* online). The verification of the calibrated target exposure in all five case studies was done using the measurements from both the source and the target situations which were task-based.

For Case study 1, the 75th percentile was extracted from the available measurement data for the target situation (empirically derived rather than a modelled percentile). The 75th percentile, calculated from full shift exposure measurements (85 measurements from five sites), was 0.1 ppm with site specific 75th percentiles varying between 0.068 and 0.15 p.p.m. As given in Table 5, five target situations have been proposed within Case study 1 to map with the source situation, which represent the full dataset. The read-across factors for these five target situations (calculated using Table 4) are also given in Table 5 with contributing determinant levels (adjacently mentioned in parenthesis) and interquartile ranges (IQR). For the verification, two datasets were used which included 25 full shift exposure measurements of ethylene oxide and 32 measurements of 1,3-butadiene from two sites, respectively. In both datasets, the plants were outdoors which implies no LEV and default ventilation. The first and second datasets correspond to the Target situations 4 and 5, respectively in Case study 1. A comparison between the two 75th percentiles (calculated from data on the verification situations) with the estimates based upon read-across (and confidence interval) is made in Table 5. For the Target situation 4, Table 5 shows 75th percentile from read-across to underestimate the 75th percentile from the exposure data, although the 75th percentile from the exposure data is within the calculated IQR. For the Target situation 5, 31 of the 32 measurements in second dataset were below the LOD of 0.003 ppm. Therefore, the 75th percentile from the exposure data is reported as <0.003 p.p.m. and it is over-estimated by the read-across approach.

For Case study 2, the 75th percentile, estimated using data on the source situation (35 measurements from 15 sites), was 15.9 mg m^{-3}. The calculations of the read-across factors are given in Table 5 for six proposed target situations which cover the full 35 measurements. For case studies 3, 4, and 5, the GM and 90th percentiles of the exposure distribution at the source situations were deduced using log-normal fit models (more details in Supplementary Material, available at *Annals of Work Exposures and Health* online). Their values are also given in Table 5 with the read-across factors for respective target situations in each case study. Note that in Case study 5, the consideration of a non-exposure period is necessary. This is accounted for by rescaling the read-across estimate i.e. taking 80 and 90% of derived GM and 90th percentiles for Target situations 1 and 2, respectively to account for the 20 and 10% respective periods of non-exposure in the target situations.

The verification data were available for all six target situations in Case study 2 which included 36 full shift

Table 3. Summary information on five case studies.

Case study no.	Source substance	Source dataset	Target substance(s)	Substance class	Source situation	Target situation(s)	Characteristics	Extrapolations	Data quality	Variation in target situation	Activity parameterization	Calculated target values	Other issues
1	Propylene oxide	See below[a]	Same substance or other gases	Vapour (pure substance)	Synthesis/ manufacturing process: use in closed, continuous process with occasional controlled exposure—PROC2	Same as source situation; more closed activity (PROC1)	• Industrial production • Far-field • Indoors • Containment	• Dispersion • Containment • Substance • Indoors/ outdoors	Very high (quality score 1)	• Substance • Environment • Activity	PROCs (simple)	75th percentile and interquartile range calculated	Limited uncertainty, therefore narrow confidence limits used
2	Inhalable dust	See below[b]	Respirable dust	Dust from abrasive processes	Grinding, cutting, and polishing of stone	Same as source situation	• Professional use • Near-field • Indoors	• Indoor/ outdoor • Engineering controls • Dispersion	Sufficient after making assumptions (quality score 2)	• Ventilation and localized ventilation • Activity • Other localized controls	PROCs (simple)	75th percentile and 90% confidence interval calculated	None
3	Toluene in lubricating oil	See below[c]	Same substance	Aerosol (complex mixture)	Machining metal parts/high speed processes	Same as source situation	• Near-field • Indoors • Single company	• Engineering controls • Dispersion	Very high (quality score 1)	Ventilation and localized ventilation	ART (more detailed)	GM and 90th percentile with 90% confidence interval calculated	Account for uncertainty due to single company source data
4	Inhalable dust	See below[d]	Same substance	Dust	Wrapping of bread in industrial bakeries	Same as source situation	• Near-field • Indoors	• Contamination • Dispersion • Dustiness	Very high (quality score 1)	No variation (target situation highly similar to source situation)	ART (more detailed)	75th percentile and 90% confidence interval calculated	None
5	Benzene from gasoline	See below[e]	Same substance	Vapour (complex mixture)	Top-loading of gasoline; filling of drums with gasoline	Same as source situation	• Far-field • Outdoors • Multiple source datasets	• Use-rate • Distance to source • Benzene concentration • Controls	Very high (quality score 1)	• Detailed activity parameters • Non-exposure period • Partial containment	ART (more detailed)	GM and 90th percentile with 90% confidence interval calculated	Weighting source data based on variability

[a]Source dataset available in Case study 1: The source situation is the industrial-scale manufacture of propylene oxide in a closed continuous production process. The workers performed a range of tasks in the far-field of the source. Some prospect of controlled exposure to propylene oxide was possible. The production of propylene oxide was of the order of several tons per hour and was in the industrial setting. The manufactured product was 100% propylene oxide at a vapour pressure of ~74 kPa. The exposure measurements represents exposure to propylene oxide. A dataset of 85 full-shift exposure measurements from five sites were available.

[b]Source dataset available in Case study 2: The source situation is based upon data collected in the HSE silica baseline survey (Easterbrook and Brough, 2009). This specific situation is developed from the stonemasonry sector. The workers (hand masons) were involved in the production of a variety of natural stone (granite, limestone, sandstone, and marble) products, such as kitchen work surfaces, gravestones, and ornamental pieces. The tasks involved cutting, grinding, and polishing of stone using manual and power tools. All measurements were taken indoors where the mechanical general ventilation systems were not implemented but LEV was in use. A dataset for workers performing tasks with LEV (31 measurements from 13 companies) were available with sampling times of 163–341 min.

Table 3. Continued

[c]Source dataset available in Case study 3: The source dataset is taken from an ART validation study by Savic et al. (2017). Following are the key information sufficient for determining the characteristics of read-across: ART AC5: application of liquids in high speed processes; liquid product; concentration of substance in mixture: 3.8%; room temperature; vapour pressure: 3800 Pa; near-field exposure; small-scale activities involving high speed movements; open process; LEV: other enclosing hoods; good house-keeping processes (although this is of sufficiently small influence to be discounted in the read-across calculations); indoors; room volume: 1000 m^3; ACH: 3. A dataset of 12 measurements from 1 site was available for this exposure situation.

[d]Source dataset available in Case study 4: The source situation is based upon data reported in Meijster et al. (2007). The situation describes the work of packaging workers in industrial bakeries. The warehouse workers were sampled during the full shift (8 h). During the shift, the warehouse workers were wrapping bread or doing order picking work for ~95% of the time. The workers were involved in the handling of contaminated objects with limited surface contamination. The flour, a fine dry powder, was used as a product or is the surface contaminant during handling activities. The exposure measurements reflect exposure levels to total inhalable dust. The work is performed in rooms of between 1000 and 3000 m^3 volume with general ventilation. A dataset of 13 measurements from 8 sites site were available for this exposure situation.

[e]Source dataset available in Case study 5: This situation describes the filling of drums with gasoline. The operators were sampled for 150–600 min and filled drums for ~100% of the time, at a rate of 100–1000 l min^{-1}. There localized controls were not implemented. The filled product was gasoline, containing 2.5% benzene with a vapour pressure of 10 000 Pa. The exposure measurements reflect exposure to benzene. The activity was performed outside without any information on the weather conditions at the time of sampling. The measurements for this situation are in the ART database. A dataset of 23 measurements from three sites were available for this exposure situation.

exposure measurements at 20 sites from SUVA database. As can be seen in Table 5, the 75th percentile from read-across overestimates the 75th percentile from the exposure data for all target situations. In fact, for Target situations 2 and 3, the 75th percentile estimate from the exposure data is even lower than the lower bound of the 90% interval. The verification data for three target situations in Case study 3 consisted of 17 full shift exposure measurements at three sites from SUVA database. As given in Table 5, and like Case study 2, the estimate from read-across overestimates the GM from the exposure data for all target situations with lower bound of the estimated 90% CI exceeding the GM from the exposure data. However, the ranking of the GMs is consistent with that from read-across.

For Case study 4, the verification data consisted of 11 full shift exposure measurements at eight sites from Meijster et al. (2007). For both target situations, the GM from the exposure data is underestimated by the read-across approach but it lies within the 90% CI (Table 5). For Case study 5, the verification data included 112 full shift exposure measurements at 36 sites. The GM and 90th percentile from the exposure data in Table 5 are generally underestimated by the read-across approach but they lie within the 90% CI in both target situations.

Thus, 15 verifications were made for five case studies. In three cases, the actual measured value was observed to be below the CI of the estimations by read-across. For these case studies, there was an overall tendency for the estimate from read-across to over-predict exposures, although the summary statistics calculated from data were generally within the limits of confidence intervals. The read-across approach is not inherently conservative in the approach and this broad trend was driven by two different processes. For the third case study the measurements in the source scenario appeared to be higher relative to the three identified similar scenarios and the adjustments from the large GM exposure in this scenario were insufficient; for Case study 2, the adjustments from the source scenario appeared to be insufficiently large. For this latter case, in principle further refinement of the framework may result in better estimates.

Discussion

The current study has developed a three-step framework for read-across of inhalation exposure data. A decision scheme was created indicating the steps and elements to evaluate the data quality of the source data, and a theoretical framework for read-across was developed and tested in five case studies and were shown to be workable for these case studies.

Table 4. Process characteristics, levels, and read-across factors for the seven determinants in Case study 1.

No.	Determinant	Level at source situation	Level at target situation	Read-across factor
1	PROC	PROC 2	PROC 1	0.0004[a]
			PROC 2	1
2	Amount of substance used (kg min^{-1})	>1000 kg min^{-1}	>1000 kg min^{-1}	1
			100–1000 kg min^{-1}	0.33
			10–100 kg min^{-1}	0.1
			1–10 kg min^{-1}	0.03
			0.1–1 kg min^{-1}	0.01
			<0.1 kg min^{-1}	0.003
3	Percentage of substance in preparation	Continuous		$\frac{\text{\% at target situation}}{\text{\% at source situation}}$
4	Volatility	Continuous		$\frac{\text{Volatility at target situation}}{\text{Volatility at source situation}}$
5	Setting	Indoors	Indoors	1
			Outdoors	0.7
6	General ventilation	10 ACH	0.3 ACH	10
			1 ACH	5
			3 ACH	2
			10 ACH	1
			30 ACH	0.4
7	LEV	With LEV	With LEV	1
			Without LEV	10

[a]For volatiles, the ratio between the PROC1 and PROC2 estimates is dependent upon the volatility of the substance—the PROC1 estimate does not vary with volatility whereas the PROC2 estimate does.

Based upon a comparison of determinants in the source and target scenarios, an adjustment via a calibrated read-across factor can be made to a summary statistic calculated from measurement data on the source scenario. Different calibration factors were derived for the GM, 75th and 90th percentiles and account for the deviation of the linear regression from 1:1 line. The resulting 'corrected' summary statistic represents an estimate of exposure in the target scenario. Differences between multiple determinants are simultaneously accounted for within this composite read-across factor with an implicit assumption of linearity between the parameters, and their relation to exposure—this may not be appropriate for all parameters.

While an approach that corrects on a determinant-by-determinant basis is more desirable, exposure scenario datasets that differ in only a single determinant would be required to inform such an approach for every determinant. The methodological approach developed thus far, while less desirable from a theoretical viewpoint, is able to work within the limitations of the sparse database of exposure-scenarios. However, in future refinements of the approach adjustments for specific determinants such as the efficacy of engineering control or the effect of room volume and ventilation, where sufficient data are available for studying the effect of these determinants in isolation, may be possible.

The expression of contextual information about an exposure scenario using determinants is common to the read-across approach developed in this work and to exposure models. Furthermore, the underlying scoring of determinants from the TRA and ART models has also been utilized in the read-across approach. It is therefore reasonable to view the read-across methodology as a modelling approach. The key difference of the approach, compared with exposure models, is that instead of translating a given set of determinant scores into an estimate of (inhalation) exposure via a model, an estimate is instead derived for a source scenario based upon measurements. An adjustment, based upon correcting for small differences in determinants between source and target scenarios, is subsequently made. Therefore, while this approach builds upon the theory of exposure determinants, which underpin exposure models, it represents a substantially weaker requirement compared to the direct mapping from determinants to an estimate of exposure. The read-across approach may represent a stronger assumption when a large set of good quality exposure measurement data are available for a similar scenario, but will represent a weaker assumption compared with exposure models when limited data are available and the target scenario is less similar to the source scenario. Furthermore, the read-across approach is expected to

Table 5. Example calculations for all read-across situations in five case studies and their verification through their comparison with available exposure data at target situation; n/a, not available.

Case study	Target situation		Read-across factor
1	1	Alternative gases (such as Ethylene Oxide, Acetaldehyde, and 1,3-Butadiene) within the same production process	1 (PROC 2)
	2	Indoors; enhanced general ventilation (10 ACH) but no LEV	1 (indoor) × 1 (10 ACH) × 10 (without LEV) = 10
	3	Indoors; good general ventilation (3 ACH); LEV	1 (indoor) × 2 (3 ACH) × 1 (with LEV) = 2
	4	Outdoors (which implies no LEV and default ventilation)	0.7 (outdoor) × 5 (1 ACH) × 10 (without LEV) = 35
	5	Read-across to PROC 1 for a similar production process occurring outdoors (which implies no LEV and default ventilation)	0.0004 (*PROC* 1) × 0.7 (outdoor) ×5 (1 ACH) × 10 (without LEV) = 0.014
2	1	Room volume of 300 m^3 and 1 ACH.	0.275 (room volume of 300 m^3 with 1 ACH)
	2	Fixed LEV. No suppression. Room of 100 m^3 with 1 ACH	0.1 (fixed capturing hood) × 1.43 (no suppression) × 0.45 (room volume of 100 m^3 with 1 ACH) = 0.064
	3	Moveable LEV. No suppression. Room of 300 m^3 and 1 ACH	0.5 (moveable capturing hood) × 1.43 (no suppresion) × 0.275 (room volume of 300 m^3 with 1 ACH) = 0.2
	4	Outdoors. No suppression.	0.7 (outdoor) × 1.43 (no suppression) = 1
	5	Wetting at the point of release. 1000 to 3000 m^3 and 1 ACH	0.14 (wetting at the point of release) × 0.2 (room volume of 1000 to 3000 m^3 with 1 ACH) = 0.028
	6	Mechanical treatment of large surfaces. Far-field. Wetting at point of release. Room of 1000 m^3 and 1 ACH	3.33 (mechanical treatment or abrasion of large surfaces) ×0.85 (far field) × 0.14 (wetting at the point of release) × 0.0294 (far field of room volume of 1000 m^3 with 1 ACH) = 0.012
3	1	Room volume of 1000 m^3 with 1 ACH	1 (room volume of 1000 m^3 with 1 ACH)
	2	Movable capturing hood. Room volume of 1000 m^3 with 1 ACH.	5 (movable capturing hood) × 1 (room volume of 1000 m^3 with 1 ACH) = 5
	3	No LEV. Room volume of 3000 m^3 with 3 ACH.	10 (no LEV) × 0.875 (room volume of 3000 m^3 with 3 ACH) = 8.75
4	1	Handling of objects with limited residual dust	3.33 (handling of objects with thin visible residual layer of dust)
	2	Handling of objects with limited residual dust	3.33 (handling of objects with thin visible residual layer of dust)

75th percentile from read-across		75th percentile from exposure data at target situation
Calibrated read- across factor[a]	Target (IQR)[b]	
$\exp(0.382 \times \log(1)) = 1$	$0.1 \times 1 = 0.1$ (0.0436, 0.23)	n/a
$\exp(0.382 \times \log(10)) = 2.41$	$0.1 \times 2.41 = 0.24$ (0.11, 0.55)	n/a
$\exp(0.382 \times \log(2)) = 1.3$	$0.1 \times 1.3 = 0.13$ (0.06, 0.3)	n/a
$\exp(0.382 \times \log(35)) = 3.89$	$0.1 \times 3.89 = 0.389$ (0.17, 0.89)	0.76 p.p.m.
$\exp(0.382 \times \log(0.014)) = 0.195$	$0.1 \times 0.195 = 0.02$ (0.009, 0.045)	<0.003 p.p.m.
75th percentile from read-across		
Calibrated read- across factor*b*	**Target (90% CI)*c***	
$\exp(0.382 \times \log(0.275)) = 0.61$	$15.9 \times 0.61 = 9.7$ (1.28, 73.4)	1.95 mg m^{-3}
$\exp(0.382 \times \log(0.064)) = 0.35$	$15.9 \times 0.35 = 5.56$ (0.74, 42)	0.57 mg m^{-3}
$\exp(0.382 \times \log(0.2)) = 0.54$	$15.9 \times 0.54 = 8.59$ (1.13, 64.96)	0.54 mg m^{-3}
$\exp(0.382 \times \log(1)) = 1$	$15.9 \times 1 = 15.9$ (2.1, 120.3)	4.87 mg m^{-3}
$\exp(0.382 \times \log(0.028)) = 0.26$	$15.9 \times 0.26 = 4.13$ (0.55, 31.2)	1.52 mg m^{-3}
$\exp(0.382 \times \log(0.012)) = 0.18$	$15.9 \times 0.18 = 2.86$ (0.38, 21.6)	0.43 mg m^{-3}
GM from read-across		
Calibrated read-across factor*d*	**Target (90% CI)*e***	
$\exp(0.437 \times \log(1)) = 1$	$11.25 \times 1 = 11.25$ (1.54, 82.30)	0.85 mg m^{-3}
$\exp(0.437 \times \log(5)) = 2.02$	$11.25 \times 2.02 = 22.73$ (3.1, 166.3)	1.38 mg m^{-3}
$\exp(0.437 \times \log(8.75)) = 2.58$	$11.25 \times 2.58 = 29.02$ (4.0, 212.2)	1.90 mg m^{-3}
GM from read-across		
Calibrated read-across factor	**Target (90% CI)*f***	
$\exp(0.437 \times \log(3.33)) = 1.7$	$0.47 \times 1.7 = 0.8$ (0.11, 5.86)	0.91 mg m^{-3}
$\exp(0.437 \times \log(3.33)) = 1.7$	$0.47 \times 1.7 = 0.8$ (0.11, 5.86)	3.56 mg m^{-3}

Table 5. Continued

Case study		Target situation	Read-across factor
5	1	Transfer rate of ~1000 l min^{-1}. Non-exposure period of 20%.	3.33 (transfer rate of over 1000 l min^{-1})
	2	Transfer rate 10–100 l min^{-1}. Near-field. Partial containment of source. Non-exposure period of 10%.	0.33 (transfer rate $10 - 100$ l min^{-1}) $\times 26$ (near field) $\times 0.3$ (partial containment) $= 2.57$

[a]Calibration factor (β) from the calibration of the read-across scores for the 75th percentile, see Table 2.
[b]Interquartile range confidence interval calculated as the central estimate multiplied by exp ($\pm 0.6745 \times 1.23$).
[c]CI calculated as the central estimate multiplied by exp($\pm 1.6449 \times 1.23$).
[d]Calibration factor (β) from the calibration of the read-across scores for the GM, see Table 2.
[e]CI calculated as the central estimate multiplied by exp($\pm 1.6449 \times 1.21$).
[f]CI calculated as the central estimate multiplied by exp($\pm 1.6449 \times 1.21$).
[g]Rescaled factor, based on the calibration of the read-across and the correction for a non-exposure period.

perform better than models in situations where models often substantially under/overestimate. Studies have shown that this often occurs at either low or very high exposure levels (Lamb et al., 2015; Marquart et al., 2017). The broad theory of utilizing 'similar' (measurement) data to support a target exposure scenario has been previously described by McNally et al. (2014).

We should note that collecting exposure measurements for the specific exposure situation is the gold standard and should be encouraged before this read-across or any other modelling approach is applied. However, while it is theoretically possible for an assessor to set up a measurement campaign and obtain measurement data from downstream user companies for every substance and every exposure situation, the reality is that this is so complicated that it will hardly ever happen. In addition, this read-across framework that extracts more value from measurement campaigns in comparison to exposure modelling may well encourage industry to take measurements and share data. The ultimate goal is to improve the exposure assessment for regulatory risk assessments, where usually neither the time, nor the access to exposure situations is available to perform an appropriate set of exposure measurements before the assessment results need to be submitted.

The case studies were largely based on situations with very good quality data, with just a few elements needing assumptions or estimations to fill small data gaps. Five different substance classes were studied, including gas and respirable dust, which are supported by neither the ECETOC TRA nor ART exposure models. The source (and target) scenarios in case studies were also formulated around different sources of measurement data that in principle could be leveraged for the purposes of read-across. These included source (and target) scenarios provided by industry (Case 1), compiled from site visit reports (Case 2), from the published literature (Case 3) and taken from the ART database (Cases 4 and 5). Through these case studies, a reasonable breadth of exposure scenarios were considered and a range of extrapolations from source to target have been made. The performance of the approach appears to be broadly reasonable, with predictions from read-across generally consistent with measurements. However, a number of areas in need for further research and/or refinement have been identified: these are briefly discussed here. In the first case study, an extrapolation from a PROC 2 to PROC 1 class was made and required the baseline estimates from the TRA tool for the respective PROC classes—this correction is therefore predicated on reliable estimates from the TRA

75th percentile from read-across				75th percentile from exposure data at target situation
Calibrated read- across factor[a]		Target (IQR)[b]		
Calibrated read-across factorg		Target (90% CI)	Target (90% CI) (after rescaling for non-exposure period)	GM and 90th percentile from exposure data at target situation
GM	$\exp(0.43 \times \log(3.33)) = 1.67$	$0.645 \times 1.67 = 1.08$ (0.147, 7.88)	0.85 (0.12, 6.3)	0.94 mg m^{-3}
90th percentile	$\exp(0.38 \times \log(3.33)) = 1.58$	$1.84 \times 1.58 = 2.91$ (0.33, 25.51)	2.32 (0.26, 20.41)	4.43 mg m^{-3}
GM	$\exp(0.43 \times \log(2.57)) = 1.58$	$0.645 \times 1.58 = 1.02$ (0.139, 7.46)	0.92 (0.13, 6.71)	0.85 mg m^{-3}
90th percentile	$\exp(0.38 \times \log(2.57)) = 1.50$	$1.84 \times 1.50 = 2.76$ (0.31, 24.2)	2.48 (0.28, 21.78)	3.28 mg m^{-3}

tool and clearly represents more uncertainty compared to a correction based upon determinants. Unless an additional uncertainty associated with this extrapolation can be quantified, between-PROC class extrapolations should not be allowed, and this should be clearly mentioned in the rule base. In the second case study, the estimate from read-across was an over-estimate compared with measurements in all five target scenarios. This result appears to be a consequence of 'anchoring', where insufficient adjustments from the source scenario were made. In this case study, it was necessary to account for large differences in room volume which is a determinant that appears to have been insufficiently covered in the calibration dataset. An adjustment for room volume and ventilation outside of the composite (calibrated) read-across factor may be warranted. Between PROC class extrapolations and adjustments for room volume are areas of current research.

A third area of ongoing research is on how to accommodate single-company/site exposure measurement datasets. Due to uncertainty as to whether such datasets are representative of 'average' exposures, it is unclear whether single-company datasets should be acceptable. However, we have explored the performance of the read-across approach in the third case study, for which the source and all three target scenarios were single company datasets. In this case study, the target scenario was over-estimated in all three studies, however the calculations take no account of the single company datasets. This is not a problem that is unique to read-across. Direct use of single-company/site exposure measurement datasets to support the source scenario itself also poses the question of representativeness of data. To date, we have explored adjustments to the calculated summary statistic from source scenario measurements based upon the characterization of between-company variability in McNally et al. (2014), however more work in this area is required.

Another aspect that was explored within case studies was of the choice of summary statistic and the level of uncertainty in read-across to be accounted for. The calculations used a variety of summary statistics and widths of confidence interval to demonstrate the flexibility of the approach. For source scenarios developed on PROC categories, the 75th percentile would perhaps be a logical summary statistic to be used and the read-across estimate might be interpreted as working as a tier one screening approach, whereas for source scenarios based upon ART activity classes, the read-across estimates can be interpreted as being equivalent to a Tier 2 approach, with an appropriate choice of summary statistic for the exposure scenario of concern selected. The appropriate width of confidence interval to be used is less straight-forward. The number of measurements and unique companies within the source measurement dataset, degree of extrapolation (number of different determinants), hazard posed by the substance, and the direction of extrapolation (i.e. are exposures in the source dataset viewed as being conservative for the target scenario) may influence this choice. Furthermore, in cases where there are multiple source datasets available, which have been demonstrated as being consistent using the read-across framework, then predictions made for a target scenario might be made with greater confidence. Further work and consultation with stakeholders is required before practical use.

Further testing with data sets of more limited quality would be useful to determine the boundary between sufficient and insufficient quality. Also, such a test with lower quality data could indicate possible simplifications of the data quality evaluation. Furthermore, the recalculation to control for differences between source and target situations was largely done on the basis of relevant parameters on exposure as used in ECETOC TRA and ART. Once the ECEL 2.0 library is finalized, which aims to provide factors for control efficiencies of localized control measures, it can be used to improve the recalculation factors for localized controls. Further testing and re-evaluation of the present framework by experts in exposure assessment and statistics is recommended to develop it further into a tool that can be widely used by experts in exposure assessment and regulatory practices. Similar to the recommended use of exposure assessment models, we do not envisage that this read-across approach be used by non-experts in the field of exposure assessment or occupational hygiene.

The present work focuses on the inhalation exposure of workers. Most elements presented in the study can also be used in similar ways for dermal exposure of workers. However, dermal exposure data is limited to just a few types of exposure situations and therefore the scope of such a framework for read-across will also be limited. A read-across framework for consumer exposure can theoretically also be developed, especially when activities are similar to workplace activities (e.g. rolling and brushing). However, it will be difficult to calibrate and verify because of the scarcity of relevant exposure data.

Conclusions

The findings from the present study suggest that it may be possible to perform read-across from source inhalation exposure data to the target situations and to estimate both central tendency as well as confidence limits, although further refinement and guidance is required prior to practical use. The present approach works well if the source and target situations are relatively similar. Even for larger differences in some situation parameters, the tested approach is valid with high quality data (including sufficient contextual information). The measurements on a source situation taken over multiple sites are (in general) preferable. The read-across between largely different activities, e.g. indicated by different PROCs, is more uncertain than read-across within the same general activity. The choice of percentile and confidence level to be estimated and used by the framework could depend on e.g. the size of the source dataset and the difference between source dataset and target situation. The case studies generally showed good agreement between the estimated and measured exposure levels. While the approach is not fully developed yet, substantial potential was shown for a very useful framework that can expand the use of measured exposure levels in regulatory risk assessment. The availability of good quality source data is critical to fully use this potential.

Supplementary Data

Supplementary data are available at *Annals of Work Exposures and Health* online.

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