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Title:

ART, Stoffenmanager and TRA: a systematic comparison of exposure estimates using the TREXMO translation system

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Abstract

Several occupational exposure models are recommended under the EU's REACH legislation. Due to limited availability of high-quality exposure data, their validation is an ongoing process. It was shown, however, that different models may calculate significantly different estimates and thus lead to potentially dangerous conclusions about chemical risk. In this paper, the between-model translation rules defined in TREXMO were used to generate 319,000 different *in silico* exposure situations in ART, Stoffenmanager and ECETOC TRA v3. The three models' estimates were computed and the correlation and consistency between them were investigated. The best correlated pair was Stoffenmanager–ART (R^2, 0.27–0.81), whereas the ART–TRA and Stoffenmanager–TRA correlations were either lower (R^2, 0.13–0.47) or no correlation was found. Consistency varied significantly according to different exposure types (e.g. vapour vs dust) or settings (near-field vs far-field and indoors vs outdoors). The percentages of generated situations for which estimates differed by more than a factor of 100 ranged from 14–97%, 37–99% and 1–68% for Stoffenmanager–ART, TRA–ART and TRA–Stoffenmanager, respectively. Overall, the models were more consistent for vapours than for dusts and solids, near-fields than for far-fields, and indoor than for outdoor exposure. Multiple linear regression revealed how different exposure parameters influenced the models' consistency. The findings emphasize the need for a multiple-model approach to assessing critical exposure scenarios under REACH. They also provide guidance to users wishing to select the right model(s) for assessing a wide range of exposure situations and model developers seeking future improvements.

INTRODUCTION

Under the regulations of the REACH (Registration, Evaluation, Authorisation and restriction of CHemicals) framework, occupational exposure models are an indispensable element with which to assess and recommend conditions for the safe use of a wide range of different chemicals and applications in the workplace. The European Chemicals Agency (ECHA) recommends using a tiered approach (Tielemans *et al.,* 2007; ECHA, 2016) to aid exposure model selection. Tier 1 models, such as ECETOC Target Risk Assessment (TRA) (ECETOC, 2012)-the preferred Tier 1 tool (ECHA, 2016)-or EMKG-EXPO-TOOL (BAuA, 2015), are intended to provide a conservative result and discriminate between chemicals which are of some concern to workers' health and those which are not. Higher tier models are recommended when the risk to human health cannot be discounted based on Tier 1 assessment(s) (ECHA, 2016). These include, for example, Stoffenmanager (Marquart *et al.,* 2008) (Tier 1.5) and the Advanced REACH Tool (ART, Tier 2) (Fransman *et al.,* 2013). These consider more exposure factors (ECHA, 2016) and are therefore expected to be more accurate and precise.

However, the popularity of different exposure models is also driven by the fact that measurement data of adequate quality is only available for a limited number of exposure situations. This limitation raises concerns about their performance over a wide range of different workplace situations. Several studies have investigated the performance of TRA (Kupczewska *et al.,* 2011), Stoffenmanager (Schinkel *et al.,* 2009; Kopisch *et al.,* 2012) and ART (Donnel *et al.,* 2011). They found either acceptable model performance or they refined the model calibration (Schinkel *et al.,* 2009). A more extensive study, known as the eteam project (BAuA, 2015), recently showed that the conservatism of Tier 1 tools varies according to different exposure conditions (Lamb *et al.,* 2015). Overall, the study showed that the models tended to overestimate the measured exposure, although in some cases they were found to be insufficiently conservative. TRA, for example, was not conservative enough for volatile liquids (vapours) (35% of the measurements were underestimated), whereas Stoffenmanager was considered to be sufficiently conservative for this exposure type.

Different occupational exposure models are based on different concepts (Hesse *et al.,* 2015) and calibrated against different exposure data. Using the same exposure conditions, the models will therefore usually calculate different exposure estimates (Hoffstetter *et al.,* 2012). The difference between the estimates should remain within a reasonable range and align with the defined tiered approach. A recent sensitivity study (Riedmann *et al.,* 2015), however, showed that the estimates provided by the ART 1.5, Stoffenmanager 4.5 and ECETOC TRA 3 models could differ by up to several orders of magnitude, leading to significantly mismatched exposure estimates for the same exposure situation. Different conclusions about risk are thus possible because users lack instructions as to which exposure assessment model is the best choice for a given scenario. The results of the eteam project present an important basis for further model refinement and should be considered when selecting an appropriate tool for exposure assessment. However, a significant fraction of exposure conditions and situations that have still not been investigated and assessed using multiple models. The present study, therefore, provides a more in-depth analysis in order to systematically examine the differences between three well-known occupational exposure models-ART, Stoffenmanager and TRA.

Savic *et al.* (2016) recently developed the TRanslation of EXposure MOdels (TREXMO) tool in order to reinforce best practices in the use of existing occupational exposure models. A test version is available, free of charge, at http://trexmo.unige.ch, and the authors are preparing the first end-user version (for release in summer 2017). The six models applied in TREXMO (ART v1.5; Stoffenmanager (algorithm published in Schinkel *et al,.*2009); ECETOC TRA v3; MEASE v1.02.01; EMKG-EXPO-TOOL; and EASE v2.0) require less data to be in-put than if the investigator were to use the six corresponding exposure estimate tools separately (Savic *et al.,* 2016). As referenced in the guidance to ECHA's Chapter R.14 on occupational exposure assessment (ECHA, 2016), TREXMO assumes that parameters can be translated between models. Its translation system assists users in the selection of appropriate parameters for a given exposure situation (ES). Its aim is to improve between-user reliability, save time and promote the use of multiple models for the assessment of the same ES.

The present study conducted a systematic comparison of the exposure estimates provided by three frequently used models ART, Stoffenmanager (algorithm in Schinkel *et al.,* 2009), and ECETOC TRA v.3. We generated a wide and representative number of ESs, *in silico*, for the three models under investigation. TREXMO's translation system allowed the same ESs to be applied to all three models. We calculated and analysed the correlations and the degrees of consistency between the estimates generated for each ES by each model. This comparative study highlights the ESs where model selection plays an important role in further risk characterisation. Also, when assessing a wide range of ESs the investigator is more effectively guided through the models and towards the selection of a more conservative approach. Using the TREXMO multiple model is therefore encouraged for the assessment of critical exposure scenarios under REACH.

METHODOLOGY

Study design

Using the statistical and graphic R software, version 3.3.1 (R development core team, 2008) we coded a programme to generate a wide range of different combinations of model parameters to be applied to ART (v1.5), the Stoffenmanager (SM) version published in Schinkel *et al.* (2009) and ECETOC TRA v3. Each combination of model parameters represented one ES. The parameters were first combined for ART and subsequently translated into the corresponding parameters of the two other models. The translation rules were extracted from TREXMO and recoded in R. Finally, the corresponding exposure estimates were calculated for each of the generated ESs. Every ES was therefore represented by the three different parameter combinations and three exposure estimates, one for each model.

ESs were only generated if they were applicable to all three models. Parameter combinations that lead to non-applicable ESs (e.g. "glove boxes and bags" for localised controls (LCs) or vapour pressure above 30,000 Pa) were therefore not considered. The comparison study was performed for vapours (volatile liquids, P > 10 Pa, as defined in ART and SM), dusts and solids (abrasive dusts). Mists (non-volatile liquids, P ≤ 10 Pa) were not translated to TRA since it only calculates this type of exposure for vapour pressures below 0.01 Pa (ECETOC, 2012). Thus, only ART and SM were compared for mists. The results obtained are presented in Supplementary Material 1, available in the Annals of Work Exposures and Health online.

In addition, ART was not used for generating ESs involving activity coefficients or respiratory protective equipment (RPE). Activity coefficients were omitted because, in reality, properly describing this concept is rather problematic (Tongeren *et al.,* 2011) and a comparison with models that do not use this concept becomes difficult to interpret. Hence, the parameterisation of substance emission potential in ART was only performed with vapour pressures and substance concentrations, whereas the activity coefficient was set to 1.0 for all the ESs. Furthermore, RPE was not used because ART only applies this determinant after Bayesian interference (see Fransman *et al.,* 2013). None of the three models therefore involved the use of RPE.

Indoor and outdoor settings were treated separately since different sets of parameters apply for each situation. For example, indoor exposure includes parameters to address ventilation rates and workplace volumes, whereas outdoor exposure is parameterised by the source–building and source–worker distances (in far-field settings only). Furthermore, near-field (NF) and far-field (FF) exposure were also differentiated in order to address the different influences of the source–worker distances on exposure.

The correlations and consistencies between the exposure estimates were calculated for each pair of models (i.e. SM–ART, TRA–ART and TRA–SM) and for exposure types and settings. Furthermore, a multiple linear regression analysis was applied to determine how and to what extent the individual determinants (e.g. vapour pressure) affected the consistencies between the three pairs of models.

Exposure Calculation and Parameter Translations

ART and SM calculate exposure at different percentiles, i.e. 50th, 75th, 90th, 95th and 99th (only ART). TRA's estimate, though, is intended to reflect the 75th percentile (ECETOC, 2012). However, for this study, only the 50th percentile estimates of ART (Schinkel *et al.,* 2011) and SM (Schinkel *et al.,* 2009) were further analysed because both of these studies used geometric mean exposure levels to calibrate the models. It has also been shown that using a higher percentile (i.e. 75th or 90th percentile, see Supplementary Material 4, available online) for ART and SM does not change the consistency results significantly in comparison to TRA. For vapours, the TRA exposure estimates in parts-per-million (ppm) were converted into mg/m^3 in order to be able to compare its results directly with ART and SM. For this purpose, a list of 3,162 registered liquid substances and their corresponding molecular weights (MWs) was requested from ECHA. A log-normal distribution function was then defined based on the MWs provided. Finally, a MW value was assigned to each of the generated ESs according to the distribution function to convert the units into mg/m^3.

A translation from ART to the other models can result in either straightforward or multiple translation outcomes. For the latter, TREXMO defines two types of different translation options: "recommended" and "uncertain". The "recommended" translation pathway is considered to be of low uncertainty with respect to its validity, whereas the "uncertain" translation option must be considered with greater caution before applying it to an ES. Although most cases of translation (Savic *et al.,* 2016) from ART to SM are straightforward (62–74%), the user will usually have to choose between multiple translation outcomes when moving from ART to TRA. A typical instance of multiple translation options is the translation of activity parameters to the Process Categories (PROCs) of TRA. For example, the "transfer of liquids" activity class may require the user to select between six different PROCs. A semi-random selection was therefore coded in R so as to adequately address these multiple translation outcomes. The "recommended" translation was preferred to the "uncertain" pathway with a probability of 0.75. For example, for the "fracturing of powders" activity class in ART, PROC 14 (production by tabletting, compression, extraction or palletisation) was selected in 75% of cases over PROC 15 (user of laboratory reagents in a small-scale laboratory) for TRA. A sensitivity analysis was also conducted to investigate the impact of different probabilities (i.e. 0.60 and 0.90) on the results for consistency. However, for the recommended translation pathway, different probabilities of > 0.5 showed only a negligible impact on the consistencies between the three models. The selected probability of 0.75 may, therefore, be considered as representative. The detailed results of the sensitivity analysis are given in Supplementary Material 1, available online.

Correlation and Consistency

The calculated exposure estimates were compared for pairs of models (e.g. ART and SM) and a regression line and a 1:1 line were plotted to illustrate the deviation from "ideal" consistency. Furthermore, Pearson coefficients of determination, R^2, were calculated between the log-transformed exposure estimates of two models in comparison.

Log differences between their estimates, $\log(m_1) - \log(m_2)$, were calculated to compare the consistencies between the two models. Based on the magnitude of the log differences obtained, the generated ESs were classified into one of the three defined consistency classes:

1. **High:** $|\log(m_1) - \log(m_2)| < 1$;
2. **Medium:** $1 \leq |\log(m_1) - \log(m_2)| < 2$;
3. **Low:** $|\log(m_1) - \log(m_2)| \geq 2$.

Thus, a log difference of less than one refers to a difference in exposure estimates of less than one order of magnitude, and this is assigned to the high-consistency class. Similarly, a difference of greater than one but less than two orders of magnitude is assigned to the medium-consistency class, and a difference of greater than two orders of magnitude is assigned to the low-consistency class. For each ES generated, the percentage distributions over the three defined consistency classes were calculated separately for the three exposure types, the four settings and the three pairs of models. More detailed information about the percentage distributions are presented in Supplementary Material 1, available online.

Computing the consistencies between the three models was done through a sequence of iteration cycles. In a first step, for ART, each cycle generated different parameter combinations for a set of 1,000 ESs. Next, the ESs were translated to the two other models. Finally, for each pair of models, the corresponding exposure was calculated with the respective consistency results. For a given exposure determinant in ART, each parameter had an equal probability of being selected to represent an ES. For example, the five dustiness categories were each given a probability of 0.2 of being selected for an ES. After an iteration cycle was completed, 1,000 new ESs were added to the previous set and the consistency results were recalculated accordingly. These iterations were stopped at the point where an additional set of 1,000 ESs did not change the consistency results by more than 1%. For example, 24,000 ESs had to be generated to stabilise the consistency results for vapours in NF–indoor settings.

Multiple linear regression

A multiple linear regression analysis was performed to investigate how the exposure determinants and parameters of ART affect the log differences (the consistency) of the model estimates. The parameter combinations generated for consistency were also used for the regression analyses. As above, the regression analysis was applied to each of the three exposure types and the four settings, separately. Three different equations were defined for the three model pairs, i.e. SM–ART, TRA–ART and TRA–SM:

$$\log(SM) - \log(ART) = \beta_0 + \sum_{i=1} \beta_i \cdot \log d_i + \sum_{k=1} \beta_k \cdot d_k \quad (1)$$

$$\log(TRA) - \log(ART) = \beta_0 + \sum_{i=1} \beta_i \cdot \log d_i + \sum_{k=1} \beta_k \cdot d_k \quad (2)$$

$$\log(TRA) - \log(SM) = \beta_0 + \sum_{i=1} \beta_i \cdot \log d_i + \sum_{k=1} \beta_k \cdot d_k \quad (3)$$

where β_0 is the intercept, β_i and β_k are the estimated coefficients for ART's continuous (e.g. vapour pressure), d_i, and categorical (e.g. LC), d_k, determinants. Note that the log differences, as described in Eq. 1–3, correspond to the three defined consistency classes. The regression intercept (β_0) and the coefficients (β_i and β_k) therefore determine in which consistency class a

given ES will be classified. For example, high-consistency is only reached if the sum of the elements on the right-hand side of the Eq. 1–3 add up to a result between -1 and 1. The size of a regression coefficient is therefore important in order to identify how the corresponding parameter affects the log difference, whereas its sign determines which model (in Eq. 1-3) calculates a higher estimate.

Vapour pressure and substance concentration were continuous determinants. Since Eq. 1–3 calculate the log differences, the regression variance was better explained with the logarithms of the continuous determinants. The categorical determinants, however, correspond to a limited number of categorical parameters (e.g. "low-level containment" for the LC determinant). A separate regression coefficient (β_k) was calculated for every categorical parameter, whereas the parameters, d_k, were represented by dummy values (d_k=1 for each parameter). For example, regression coefficients were estimated for all of the 14 LC parameters for a vapour ES. For each of the determinants, one of the parameters was used as a referent point (β_k=0) to calculate the regression coefficients for the other parameters of the same determinant. The individual impact of each parameter on consistency can therefore be compared with the referent parameter.

In addition, R^2 was calculated to quantify the statistical significance of the regression models (Eq.1–3) and to determine how ART's determinants explain the variance in the consistency of each pair of models.

RESULTS

We generated and translated 319,000 ART parameter combinations into the two other models. Fig. 1–3 illustrate the correlations and consistencies between the models' estimates for vapours, dusts and solids. The high-, medium- and low-consistency classes are coloured dark blue, bright blue and red, respectively. The figures also show the range of model estimates (shaded area) where they fall into either the medium- or high-consistency class. The plotted regression line illustrates the deviation from the ideal 1:1 consistency line. At the point where the regression line crosses the 1:1 line, the two models calculate the same estimates and are thus considered ideally consistent. The consistency of the results decreases as the distance from the ideal line increases.

Correlation and Consistency

Vapours (Fig. 1). SM and ART were strongly correlated (R^2, 0.62–0.81), whereas their correlation with TRA was moderate (R^2, 0.27–0.47). Note that the strongest correlation (R^2, 0.81) was observed for NF–indoor (SM-ART), representing ESs often evaluated under REACH.

SM-ART were either highly or moderately consistent for 86% of the NF-indoor situations computed. Furthermore, for any ART NF–indoor estimate within the range of 0.32–160 mg/m^3 (Fig. 1), SM was either highly or moderately consistent. These consistencies between the two models, though for fewer ESs, were also found when SM calculated estimates of higher than 96 mg/m^3. Furthermore, TRA–SM results were more consistent than TRA–ART results, with 32–90% versus 1.5–63% of estimates in the two higher classes, respectively. Overall, the consistency between the model estimates was higher for NF than for FF and for indoor than for outdoor settings. For example, for SM–ART, the NF to FF and indoor to outdoor situation ratios classified in the high- or moderate-consistency classes, were 2:1 and 3:2, respectively.

Dusts (Fig. 2). Compared to vapours, estimates were less correlated in all the model pairs (R^2, 0.16–0.46), whereas the most correlated, SM–ART, were only moderately correlated, with R^2 ranged from 0.32 for FF–outdoor to 0.46 for the NF–indoor setting.

For any ART NF–indoor estimate in the range of 0.61–890 mg/m^3 (Fig. 2), SM was either highly or moderately consistent. Concentration ranges for TRA–ART and TRA–SM were impossible to define, meaning that there were no specific concentration ranges for which the two higher consistency classes were guaranteed. Compared to vapours, ART's consistency with the other two models was significantly lower, with 64–99.6% of estimates in the low-consistency class. Conversely, TRA–SM were highly consistent in 37–66% of situations; only a minority of situations were attributed to the lowest class. As for vapours, consistency decreased from the NF-indoor to FF-outdoor cases.

Solids (Fig. 3). SM–ART were moderately correlated (R^2, 0.27–0.38) across all the settings. For outdoor situations, TRA–ART were moderately correlated (R^2, 0.25 for NF and 0.22 for FF), whereas for indoor settings, this model pair was weakly correlated (R^2, 0.13 for NF and 0.14 for FF). No correlation was found for TRA–SM.

For any ART NF-indoor estimate higher than 0.83 mg/m^3 and within the range from 0.2–410 mg/m^3, when compared to SM and TRA, respectively, the generated ESs are either highly or moderately consistent. This range was narrower in SM (0.16–3.2 mg/m^3, see Fig. 3) when

compared to ART's consistency with TRA. In general, the consistency percentages found for this exposure type varied by 10% from that calculated for dust exposure, which mostly demonstrated higher consistencies. As with the two previous exposure types, more consistent ESs were found for NF than for FF and for indoor than for outdoor.

Overall, we observed a systematic deviation of the regression line (Fig. 1-3) from the ideal (1:1) line. Where calculation was possible, the regression slopes were always lower than 1, with those calculated for SM–ART (0.21–0.38) and TRA–ART (0.12–0.31) being lower than for TRA–SM (0.48–0.79). A regression slope below 1 means that moving along the x-axis (e.g. ART) causes a smaller change on the y-axis (e.g. SM). In other words, for example, an increase in the ART estimate (e.g. due to fewer controls) is, in general, not followed by a corresponding increase in the SM estimate. This was confirmed by the different ranges of estimates possible in the three models. Fig. 1–3 illustrate wider ranges (12–15 orders of magnitude) of the estimates covered in ART and lower ranges for SM (4–7) and TRA (2–8). Consequently, the three models were only consistent within a limited range of exposure concentrations, typically, at concentrations above 0.1 mg/m^3.

For a higher fraction of the generated ESs, SM was found to calculate higher estimates than ART for all exposure types (see Supplementary Material 1 and 4). For NF-indoor settings, for example, SM gave higher estimates for 66% of vapour and 97% of dust and solid ESs. Similar results were obtained for TRA–ART, where, for NF-indoor, for 80% of vapour ESs and 94% of dust and solid ESs, TRA calculates higher estimates than ART. Furthermore, for 88% of vapour ESs, TRA was found to calculate higher NF-indoor estimates than SM, however, for 56% of dust and 59% of solid ESs, SM's calculated estimates were, higher. More detailed results of the percentages (and a detailed distribution) of ESs where one model calculated higher exposure than another are provided in Supplementary Material 1 (for 50th percentile) and 4 (for 75th and 90th percentiles), available online.

Multiple Linear Regression

Table 1 shows the extent to which ART determinants (e.g. vapour pressure) individually contributed to multiple R^2 for the three multiple regression models (Eq. 1–3). Here, we present only the NF-indoor results—the other results are given in Supplementary Material 2 and 3, online. Tables 2–4 show the regression coefficients (β in Eq. 1–3) estimated for vapours, dusts and solids, respectively.

Substance properties. For vapours, the consistencies of the SM–ART and TRA–ART pairs were almost equally sensitive to the vapour pressure and substance concentration (Table 1). Due to their negative coefficients (-0.46, Table 2), increasing the two determinants increases ART's estimate more strongly than SM's and may, due to the small intercept (0.20), further increase the difference between SM–ART, in favour of ART. On the other hand, the consistency of TRA–ART improved as vapour pressure and substance concentration increased, due to the highly positive intercept (1.93). The two determinants were, however, less significant (Table 1) in explaining the consistency of TRA–SM.

For dusts and solids, substance concentration and moisture content (Table 1) were the key factors in explaining ART's consistency with the two other models; dustiness was a less significant factor. Given the high, positive, intercepts (Tables 3–4), high consistency was rarely reached with low substance concentrations and high moisture content (e.g. the "wet products"

parameter). In addition to substance concentration, dustiness (for dusts, see Table 3) also contributed significantly to the consistency of TRA–SM, with consistency improving as the concentration (Tables 3–4) and dustiness potential increase. For this model pair, the impact of moisture content is negligible.

Activity (sub)classes. For vapours, a trend was observed in the SM–ART and TRA–ART model pairs, where activities that generated higher exposures had lower coefficients (β, Table 2). In other words, higher consistency was more likely to be reached with these activities, such as "spraying of liquids in a space" (β, -0.39; Table 2), whereas lower consistency was observed with the activities that produced less exposure, such is "handling of contaminated objects" (β, 1.43). On the contrary, the TRA–SM model pair's consistency was higher with the activities that led to lower exposure concentrations. In addition, the activity parameters explained the consistency more significantly for vapours than for dusts and solids, especially for SM–ART (Table 1).

Similarly to vapours, activities that generated higher dust exposures increased the consistency of SM and TRA, individually, with ART. However, for TRA–SM, no clear conclusion could be drawn since the regression coefficients, shown in Table 3, defined a narrower range (β, -0.54– 0). This was also supported by the results shown in Table 1, where activity parameters had little significance in explaining the consistency between the two models. Overall, the consistency for dust exposure modelling was generally better explained by substance properties and LCs (see below).

No results were calculated for solids since only one activity each for wood and stone were applicable in the models.

Localised controls (LC). For vapours (Table 2), containment categories reduced consistency more significantly than Local Exhaust Ventilation (LEV) systems. Considering the intercepts for SM–ART and TRA–ART (β_0, 0.2 and 1.93, respectively), for example, "high-level containment" (β, 2.31 and 2.77) could generate estimates for SM and TRA that were two and four orders of magnitude higher than for ART, respectively. Also, for TRA–SM, due to the high intercept (β_0, 1.73) and the positive coefficients for containments, a difference of two orders of magnitude was possible, in favour of TRA. Comparing ART to the other two models, better consistency was obtained with LEV systems than with containment, although some LEV parameters, for example "fume cupboard", could significantly reduce the consistencies of the two model pairs. For TRA– SM, consistency was increased with all the LEV categories.

As for vapours, for dusts (Table 3) and solids (Table 4), mostly the same conclusion for LC can be drawn for SM–ART and TRA–ART. The containment categories may significantly increase the exposure in favour of SM and TRA, whereas the LEVs did not lead to pronounced changes between the models. One exception was the "fume cupboard " LEV parameter; this generated significant differences between ART and the other models. Unlike for vapours, and given the negative intercepts for dusts and solids (β_0, -0.51 and -0.98, respectively), the selection of containment categories may increase the consistency of TRA–SM, whereas LEV such as "canopy hoods", generated some differences up to one order of magnitude, in favour of SM.

Workplace volume and Ventilation. For vapours (Table 2) and dusts (Table 3), the consistency of SM–ART decreased as workplace volumes and ventilation rates increased. However, no such trend was observed for solids (Table 4). For all exposure types, the consistency of TRA–ART was lower with higher workplace volumes and lower ventilation rates.

For TRA–SM, due to the positive intercept for vapours and negative intercept for dusts/solids, consistency is decreased for the former and increased for the latter as workplace volume increases. However, for volumes of 100, 300 and 1,000 m^3 consistency was constant since these volumes are covered by the same SM parameter (100–1,000 m^3). Furthermore, TRA–SM may only be affected at higher ventilation rates (10 and 30 ACH), which increases the consistency for vapours and reduces it for dusts and solids.

Overall, the importance of the workplace volume and ventilation (Table 1) was significantly smaller than for other determinants.

DISCUSSION

This paper presents the results of a theoretical assessment of the correlations and consistencies between the exposure estimates of three well-known REACH exposure models. The TREXMO translation system allowed us to compare models for a wide range of different ESs, without field exposure data. Furthermore, we conducted a multiple regression analysis to explain how the different exposure parameters affected the three exposure models' estimates and thus their consistency. To the best of our knowledge, this is the first study of its kind, where a systematic, *in silico*, comparison was conducted, to use occupational exposure models.

Several generic exposure models are recommended under the REACH framework, although the limited number of studies available on their relative performance hampers the selection of the best one for each assessment. Our results show that the correlations and consistencies between the models' estimates vary significantly depending on the different exposure types and settings. For a given situation, model estimates can differ by several orders of magnitude. Unfortunately, such significant differences cannot be considered to reflect the idea of the tiered assessment approach promoted by ECHA (2016). The conclusions about risk may therefore vary significantly depending on the exposure assessment model used. This underlines the necessity of selecting the best model for assessment.

Different factors described in this study may affect the correlation and consistency between models. These include the conceptualisation of the models themselves, their size (number of determinants), resolution (number of parameters per determinant), calibration (method and database) and translation efficiency (Savic *et al.,* 2016). However, the individual impact each factor is not easy to quantify; the differences in correlations and consistencies between the models are usually due to a combination of different factors.

ART and SM are source-receptor models (Cherrie *et al.,* 1996; Tielemans *et al.,* 2008) which describe the substance's transport from its source to the recipient. The exposure pathway is divided into several theoretical compartments (e.g. source), where exposure is determined with one or more exposure determinants (e.g. vapour pressure) (Marquart *et al.,* 2011). In addition, linear mixed-effect regression was used to calibrate both ART and SM against measured exposure. Further, the translations from ART into SM were mostly straightforward (83–99% of the cases for indoor and outdoor exposure site; see Savic *et al.,* 2016), which limited the possibility of variances due to the translation step. These conceptual similarities and the high translation efficiency from ART to SM explain the strong correlations found between these two models for all the exposure types. However, different exposure data were used to calibrate SM (Schinkel *et al.,* 2009) and ART (Schinkel *et al.,* 2011) which partly explains the differences in consistency between the two models. Furthermore, the differences in consistencies are also driven by ART's greater size and resolution than SM (see also Hesse *et al.,* 2015). Since ART applies more determinants (29) than SM (17; Hesse *et al.,* 2015), not all of them have corresponding analogues in SM. Typical examples are moisture content and substance concentration in ART; these are not used for dusts and solids in SM. This implies that for ESs with different parameter combinations (e.g. with different moisture contents) and thus different estimates in ART, SM calculates the same exposure. The higher model complexity (size and resolution) of ART may, therefore, result in greater variations in exposure estimates than SM or other lower tier models. This may also explain the higher consistency found for vapours, where the source emission term represented by vapour pressure and concentration is a continuous

scale for both ART and SM. For dusts and solids, however, no analogues exist for moisture content and concentration in SM.

Moreover, model sizes and resolutions of ART and SM differ further for FF settings. Although ART can incorporate both the separation of the worker and segregation of the exposure source, SM only defines the former (named "immission"). The two models thus differ by the additional determinant (and its five parameters), which explains the weaker correlation and consistency found in FF situations. Furthermore, different levels of model complexity exist for different exposure sites, with ART and SM's determinants overlapping more in indoor than in outdoor settings. For indoor settings, both models use workplace volume and type of ventilation. However, ART also applies the ventilation rate in order to account for the dilution of exposure. The outdoor setting in SM, on the other hand, is restricted to one parameter of general ventilation, whereas ART defines a set of different parameters to address the distance of the source from the building and the worker's distance from the outdoor source (for FF). Consequently, this results in a higher variation of exposure estimates in ART than in SM, and thus may lead to lower correlations and consistencies in outdoor settings than in indoor settings.

TRA's conceptual framework deviates significantly from the source-receptor approach used in ART and SM. First, PROC, dustiness or volatility bands, types of settings and the presence of LEV are used to extract an *initial* exposure estimate from a constrained set of quantified exposure values. The EASE model is used as a basis for deriving the *initial* values, which are continually refined with new exposure data (ECETOC, 2004; ECETOC, 2009; ECETOC, 2012). Second, this *initial* value is further modified by multipliers of concentration, general ventilation, RPE and task duration in order to obtain the final TRA exposure estimate. Furthermore, TRA's size is generally smaller than SM and ART (9 determinants), its resolution is lower (e.g. 3 dustiness parameters vs 5 in ART), and the definition and application of its determinants are generally different (e.g. activity concept). For example, where ART and SM use a continuous scale for vapour pressure (high resolution), TRA introduces a limited number of volatility bands (i.e. low, medium and high) for this determinant. This implies that despite the wide range of estimates obtained with different vapour pressures in ART and SM, TRA will compute one of only three different estimates. Moreover, TRA does not differentiate between NF and FF settings and thus calculates the same exposure for both settings. This further increases the variance and thus results in weaker correlations when compared to ART and SM.

For solids, TRA showed a weak correlation with ART and no correlation at all with SM. This is mainly because the translation from ART into TRA only allows two PROCs (21 and 24) as possible outcomes. Consequently, only a limited range of possible estimates (2–4 orders of magnitude) can be calculated in TRA in comparison to the wider range of estimates in ART and SM, leading to an even lower correlation for solids.

Consistency between the three models was further affected by each model's different ranges of exposure estimates. Compared to the wide range of possible estimates in ART (12–15 orders of magnitude), SM and TRA's estimates covered significantly narrower ranges (4–7 and 2–8 orders of magnitude, respectively). Hence, it is more likely that SM and TRA show more consistent estimates, whereas ART, due to its wide range of potential exposure estimates, accounts for more distanced estimates than the two other models. Note, however, that for ART, upper cut-off exposure values were used for both vapours (10^4 mg/m^3) and non-vapours (10^3 mg/m^3); if not applied, even wider exposure ranges would have been found.

Multiple linear regression

Regression analysis allowed us to reveal the most influential sets of exposure parameters determining the consistencies between the three models. For NF–indoor settings, three exposure factors prominently affected consistency: substance properties, activity (sub)classes and LCs. This was in accordance with the sensitivity analysis performed in Riedmann *et al.* (2015), which showed that these factors had the most significant effect on ART's estimates. In the other settings (NF–outdoor and FF, see Supplementary Material 2 and 3), other determinants, such as source segregation (for FF), could also significantly affect consistency.

In general, parameters that described a low exposure potential (e.g. low concentration, "handling of contaminated objects" etc.) were likely to lead to lower consistency between ART and the two other models. These ESs are dominant in the left-hand (red) areas of Fig. 1–3, where ART calculated significantly lower estimates. This is mainly a result of ART's complexity and the model's wide range of potential estimates, where very low exposures (e.g. 10^{-11} mg/m^3 in Fig. 2) can be computed. However, increasing the exposure potential (e.g. higher concentration, less efficient LC) should, in general, improve consistency. This means that the estimates of ART, indicated by negative regression coefficients (Tables 1–3), increase by greater increments than the estimates of the two other models. Furthermore, for a sufficiently high vapour pressure (P), concentration (c) and activity emission potential (e.g. P = 1,000 Pa, c = 90%, when used in a spraying application), ART's estimates may exceed those of the other models, thus increasing inconsistencies between them. These situations are illustrated in the right-side, red areas in Fig. 1–3.

Limitations

This study was based on the theoretical comparison of three different occupational exposure models and not on field measurements. Although this enabled us to compare a large number of ESs (n = 319,000), no recommendations can be provided on the accuracy and precision of the different models.

Although TREXMO's translation design has been reviewed by several external experts (Savic *et al.,* 2016), the translation of specific ESs may still be uncertain, especially for those situations where several translation outcomes are possible. Translation rules, however, could be updated in the future due to, for example, the availability of new information on models or a different interpretation of the coding and translation of specific ESs by experts. Depending on the number of modifications to TREXMO's translation rules, the results for consistency may change. However, they are not expected to change the general findings and conclusions, but rather some specific aspects of the study results.

This study used the SM algorithm published in Schinkel *et al.* (2009). However, the model's online platform has been updated to version 6. Since its newer versions have not yet been published in a peer-reviewed journal, the present study's authors cannot guarantee the same results with Stoffenmanager's potentially updated algorithm.

Conclusion and Recommendations

This study investigated the correlation and degree of consistency between three occupational exposure models often used and studied in the framework of REACH. We showed that for the same ES, the models could compute significantly different exposure estimates, which could lead

to very distinct conclusions about necessary safety measures, with potentially serious consequences to workers' health. The study's results suggest the need to use multiple models in any assessment of ESs, particularly for cases where consistency between the models cannot be guaranteed. These results also provide useful guidance on choosing the most appropriate models for a wide range of different ESs. Furthermore, the results highlighted the ESs for which significantly different estimates (two orders of magnitude or more) were calculated and thus the future improvements which model developers should consider.

When critical exposure scenarios need to be assessed under REACH (e.g. for substances of very high concern subject to authorization) the authors recommend beginning by checking which consistency class the ES falls into, and then deciding which model could be used to best control the risks in this specific scenario. When the ESs fall into the high-consistency class, the models will probably lead to similar conclusions, whereas the medium and especially the low-consistency class ESs could lead models to produce different outcomes and thus different recommendations on relevant safety measures. The use of several models could, therefore, lead to a more cautious assessment of critical ESs. Alternatively, the user could also select the model that is expected to give the most conservative exposure estimates. For example, ART generates higher estimates for high-exposure concentrations, whereas when dealing with well-contained low vapour-pressure substances (e.g. < 100 Pa), a more conservative approach would be achieved by using Stoffenmanager and/or TRA. Furthermore, this study gives insights into how the models' consistencies change when different parameter combinations are applied to them. The model user's assessment capabilities will thus be strengthened when different exposure scenarios need to be evaluated.

Future studies should investigate whether these models' applicability ranges should be narrowed or their algorithms revised. The results of this study may provide some support to model developers in that regard.

TABLES and FIGURES

Table 1. Increase in multiple R^2 by the ART's determinants for the regression models in Eq. 1–3, the three exposure types, i.e. vapours, dusts and solids, only in NF–indoor setting.

Eq.	Fug.	log(c)	Moist.	H	LC	Vol	ACH	Su	Multiple R^2
Vapours									
1 (SM-ART)	0.12	0.11		0.27	0.24	0.03	0.03	< 0.01	0.79
2 (TRA-ART)	0.11	0.09		0.14	0.32	0.03	< 0.01	< 0.01	0.70
3 (TRA-SM)	0.02	0.01		0.10	0.24	0.01	0.05	< 0.01	0.40
Dusts									
1 (SM-ART)	0.02	0.31	0.27	0.09	0.14	< 0.01	< 0.01	< 0.01	0.83
2 (TRA-ART)	0.02	0.07	0.19	0.08	0.26	0.01	< 0.01	< 0.01	0.65
3 (TRA-SM)	0.13	0.14	< 0.01	0.04	0.21	0.01	0.04	< 0.01	0.59
Solids									
1 (SM-ART)	0.03	0.44	0.22		0.16	< 0.01	< 0.01	< 0.01	0.86
2 (TRA-ART)	0.02	0.10	0.18		0.37	0.01	0.01	< 0.01	0.69
3 (TRA-SM)	< 0.01	0.23	< 0.01		0.36	0.03	0.07	< 0.01	0.69

Fug: the logarithm of vapour pressure for vapours, dustiness for dusts or kind of dust (wood or stone) for solids; c: product concentration; Moist.: moisture content; H: activity classes; LC: localised controls; Vol: workplace volume; ACH: determinant of ventilation rate (air-exchanges per hour); Su: surface contamination/fugitive emission sources.

Table 2. Estimated regression coefficients (β) for the three regression analyses (defined in Eq. 1–3) for vapours.

Determinant	Parameters	SM−ART (Eq. 1)	TRA-ART (Eq. 2)	TRA−SM (Eq. 3)
	Intercept	0.20	1.93	1.73
Vapour pressure	$\log(P)$	-0.46	-0.57	-0.12
Concentration	$\log(c)$	-0.46	-0.55	-0.09
Activity (sub)classes[*]	Surface spraying of liquids	0	0	0
	Spraying of liquids in a space	-0.39	-0.49	-0.09
	Activities with open surfaces—undisturbed	1.03	0.41	-0.62
	Activities with open surfaces—agitated	0.57	0.15	-0.42
	Handling of contaminated objects	1.43	0.65	-0.78
	Spreading of liquid products	0.96	0.97	0.01
	Application in high-speed processes	-0.03	-0.23	-0.20
	Transfer of liquids: bottom loading	1.43	1.31	-0.13
	Transfer of liquids: falling liquids	1.50	1.45	-0.05
Localised controls[*]	No LC	0	0	0
	Low-level containment	0.72	0.94	0.22
	Medium-level containment	1.31	1.94	0.64
	High-level containment	2.31	2.77	0.45
	LEV: canopy hoods	0.02	-0.58	-0.60
	LEV: other receiving systems	0.44	-0.13	-0.57
	LEV: fixed capturing hoods	0.72	0.14	-0.58
	LEV: movable capturing hoods	0.04	-0.57	-0.61
	LEV: on-tool extraction	0.71	0.12	-0.59
	LEV: fume cupboard	1.31	1.12	-0.18
	LEV: horizontal/downward flow booths	0.71	0.13	-0.58
	LEV: other enclosing systems	0.32	0.15	-0.17
	LEV: other systems	0.04	-0.54	-0.58
	Vapour recovery systems	0.43	-0.15	-0.58
Workplace volume (m³)[*]	30	0	0	0
	100	0.14	0.37	0.22
	300	0.34	0.56	0.22
	1000	0.53	0.74	0.22
	3000	0.56	0.82	0.25
Ventilation (ACH)[*]	0.3	0	0	0
	1	0.04	0.22	0.18
	3	0.27	0.31	0.04
	10	0.44	0.10	-0.34
	30	0.52	0.18	-0.34

[*]Parameters used as categorical (dummy) values for the multiple regression analyses.

Table 3. Estimated regression coefficients (β) for the three regression analyses (defined in Eq. 1-3) for dusts.

Determinant	Parameters	SM−ART (Eq. 1)	TRA−ART (Eq. 2)	TRA−SM (Eq. 3)
	Intercept	2.18	1.68	-0.51
Dustness[*]	Firm granules, pellets or pelletised material	0	0	0
	Granules, pellets or pelletized material	-0.15	-0.50	-0.34
	Coarse dust	-0.32	-0.08	0.24
	Fine dust	-0.47	0.31	0.79
	Extremely fine dust	-0.64	-0.21	0.43
Concentration	log(c)	-1.00	-0.55	0.45
Moisture[*]	< 10%	0	0	0
	10–90%	1.02	1.02	0.01
	> 90%	2.00	2.02	0.01
Activity (sub)classes[*]	Impaction on contaminated solid objects	0	0	0
	Handling of contaminated objects or paste	0.35	0.39	0.04
	Spraying application of powders	-0.45	-0.96	-0.47
	Moving and agitation	-0.58	-0.66	-0.41
	Transfer of powders: falling powders	0.09	-0.27	-0.36
	Transfer of powders: vacuum transfer	1.07	0.60	-0.47
	Compression of material	0.07	-0.41	-0.48
	Fracturing of material	0.07	-0.47	-0.54
Localised controls[*]	No LC	0	0	0
	Low-level containment	0.68	1.00	0.33
	Medium-level containment	1.14	2.01	0.87
	High-level containment	2.11	2.96	0.85
	LEV: canopy hoods	-0.03	-0.54	-0.50
	LEV: other receiving systems	0.36	-0.13	-0.49
	LEV: fixed capturing hoods	0.66	0.16	-0.51
	LEV: movable capturing hoods	-0.03	-0.51	-0.49
	LEV: on-tool extraction	0.69	0.21	-0.48
	LEV: fume cupboard	1.13	1.19	0.07
	LEV: horizontal/downward flow booths	0.67	0.18	-0.49
	LEV: other enclosing systems	0.12	0.15	0.03
	LEV: other systems	-0.04	-0.51	-0.47
	Suppression: knockdown technique	-0.17	0.13	0.31
	Suppression: wetting at point of release	0.66	0.96	0.30
Workplace volume (m³)[*]	30	0	0	0
	100	-0.05	0.24	0.29
	300	0.10	0.42	0.32
	1000	0.20	0.51	0.31
	3000	0.16	0.52	0.35

Table 3. continued.

Determinant	Parameters	SM−ART (Eq. 1)	TRA−ART (Eq. 2)	TRA−SM (Eq. 3)
Ventilation (ACH)*	0.3	0	0	0
	1	-0.11	0.10	0.21
	3	-0.01	0.04	0.05
	10	0.08	-0.22	-0.30
	30	0.12	-0.17	-0.29

*Parameters used as categorical (dummy) values for the multiple regression analyses.

Table 4. Estimated regression coefficients (β) for the three regression analyses (defined in Eq. 1-3) for solids.

Determinant	Parameters	SM−ART (Eq. 1)	TRA−ART (Eq. 2)	TRA−SM (Eq. 3)
	Intercept	1.83	0.85	-0.98
Kind of dust	Stone	0	0	0
	Wood	0.45	0.49	0.04
Concentration	log(c)	-1.00	-0.55	0.45
Moisture[*]	< 10%	0	0	0
	10–90%	0.53	0.52	-0.01
	> 90%	1.53	1.53	0.01
Localised controls[*]	No LC	0	0	0
	Low-level containment	0.60	1.00	0.39
	Medium-level containment	0.86	2.04	1.18
	High-level containment	1.83	2.97	1.15
	LEV: canopy hoods	-0.10	-0.37	-0.27
	LEV: other receiving systems	0.30	0.04	-0.26
	LEV: fixed capturing hoods	0.62	0.36	-0.26
	LEV: movable capturing hoods	-0.10	-0.37	-0.27
	LEV: on-tool extraction	0.58	0.30	-0.28
	LEV: fume cupboard	0.86	1.35	0.49
	LEV: horizontal/downward flow booths	0.60	0.34	-0.26
	LEV: other enclosing systems	-0.14	0.34	0.48
	LEV: other systems	-0.12	-0.41	-0.29
	Suppression: knockdown technique	-0.24	0.18	0.42
	Suppression: wetting at point of release	0.61	1.03	0.42
Workplace volume (m^3)[*]	30	0	0	0
	100	-0.14	0.23	0.37
	300	0	0.34	0.35
	1000	-0.14	0.47	0.37
	3000	0.07	0.50	0.44
Ventilation (ACH)[*]	0.3	0	0	0
	1	-0.20	0.09	0.29
	3	-0.08	0.07	0.15
	10	0	-0.24	-0.24
	30	-0.08	-0.16	-0.22

[*]Parameters used as categorical (dummy) values for the multiple regression analyses

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Figure 1. Correlation and consistency between the logarithms of the estimates of the three models for the generated vapour ESs.
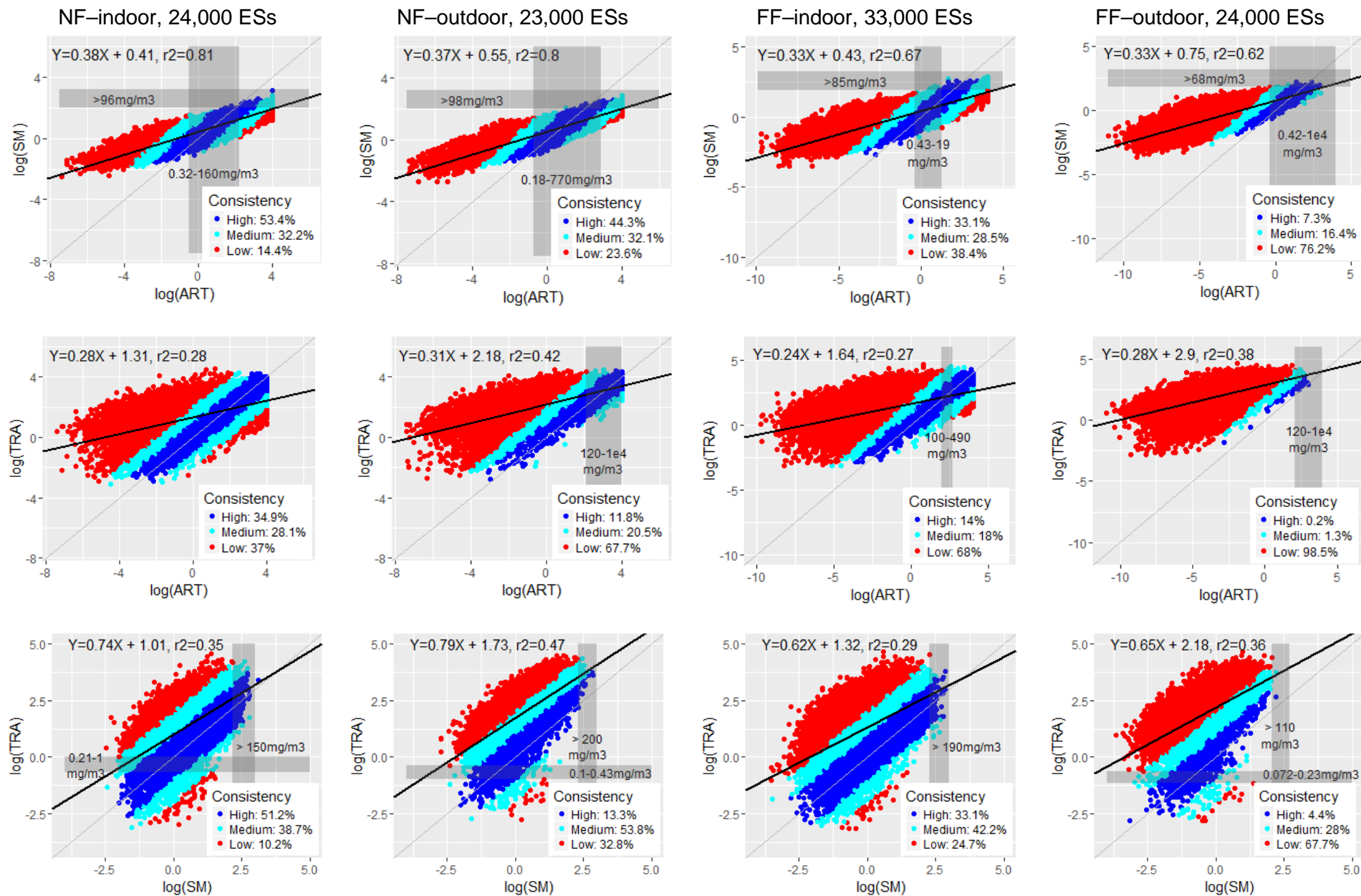
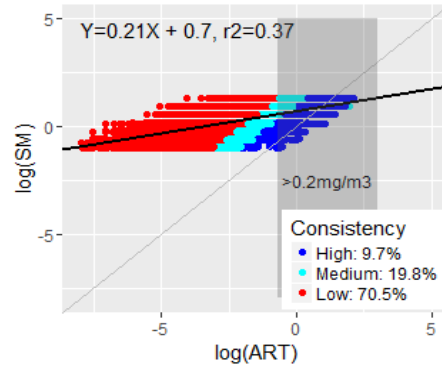**Figure 2.** Correlation and consistency between the logarithms of the estimates of the three models for the generated dust ESs.
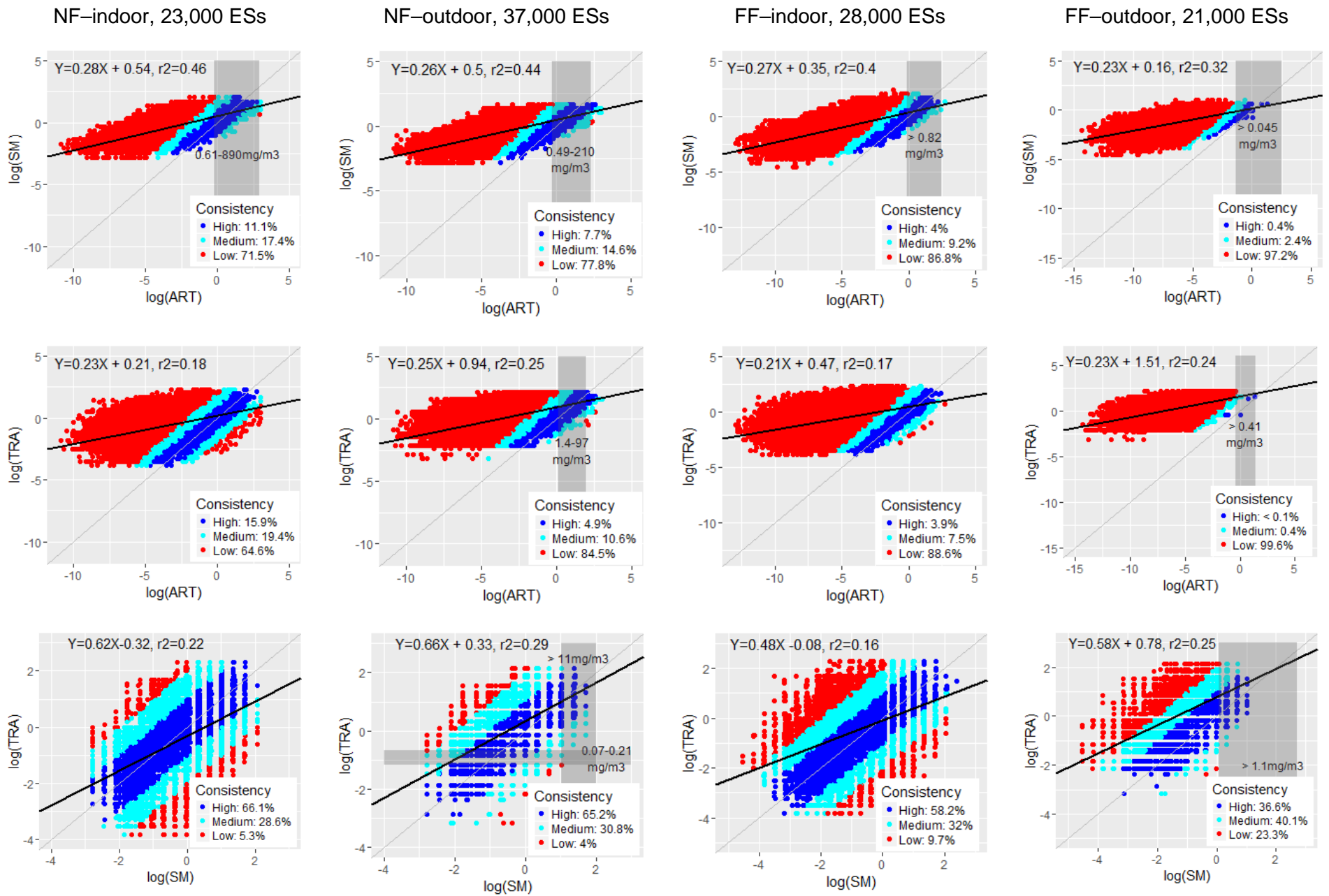
Figure 3. Correlation and consistency between the logarithms of the estimates of the three models for the generated solid ESs.
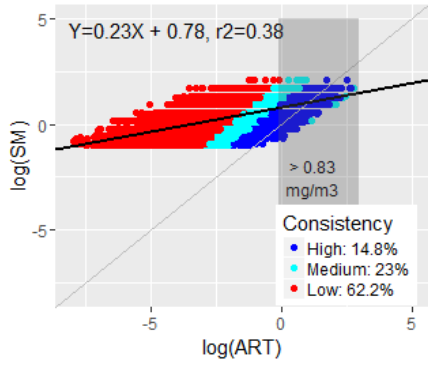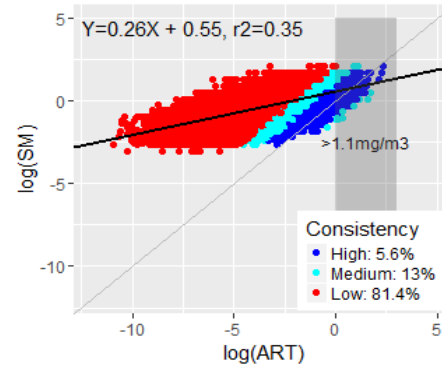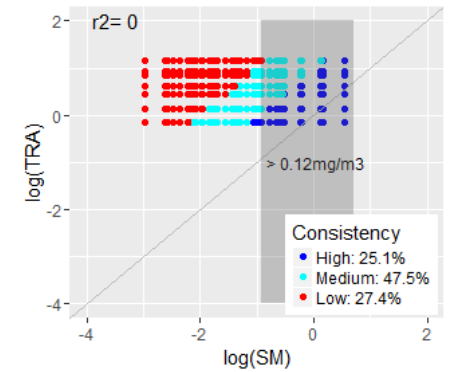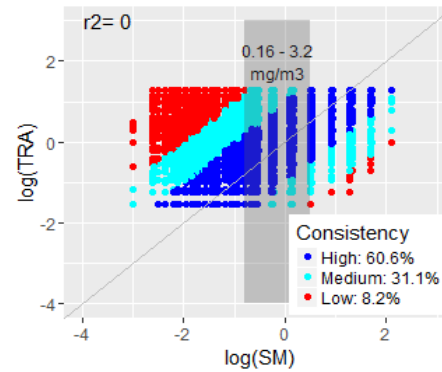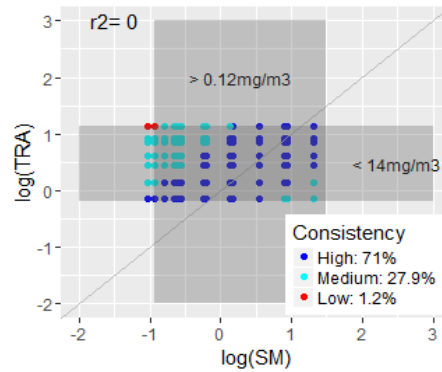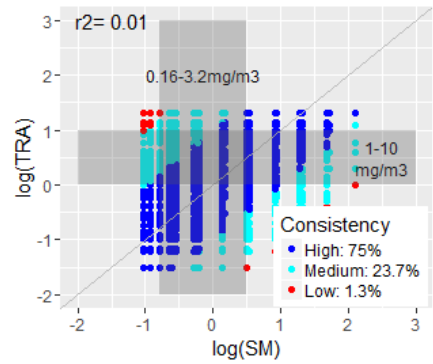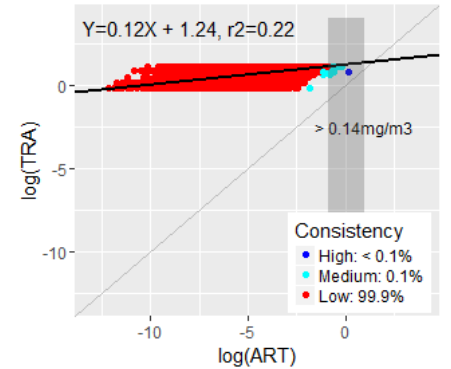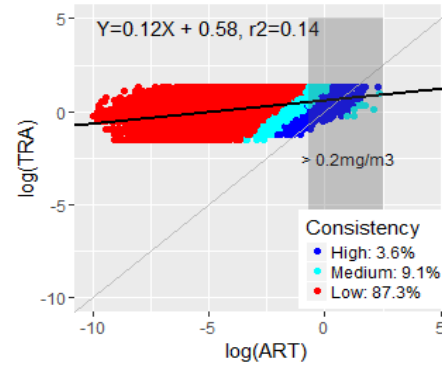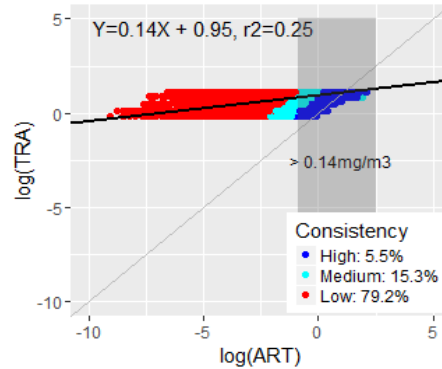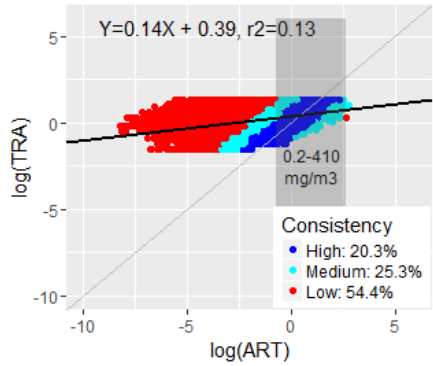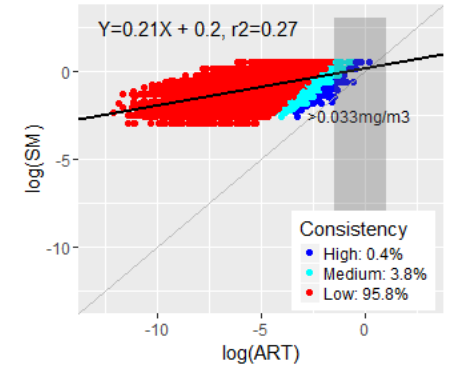
References

BAuA. (2015) Evaluation of Tier 1 Exposure Assessment Models under REACH (eteam) Project. Dortmund. Germany: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Available at http://www.baua.de/en/Publications/Expert-Papers/F2303-D26-D28.html. Accessed 21 January 2017.

BAuA. (2016) Einfaches Maßnahmenkonzept Gefahrstoffe (EMKG), Version 2.2. Dortmund: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Available from: http://www.baua.de/emkg (accessed 13 February 2017).

Cherrie J.W., Schneider T., Spankie S., et al. (1996) A new method for structured, subjective assessment of past concentrations. Ann Occup Hyg: (3), 75-83.

Donnell P., Schinkel J., Coggins M., et al. (2011) Validation of inhalable dust algorithm of the Advanced REACH Tool (ART) using a dataset from the pharmaceutical industry. J Environ Mon; 13, 1597.

ECETOC. (2004) Target Risk Assessment. Technical report No. 93. Belgium, Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals.

ECETOC. (2009) Addendum to ECETOC target risk assessment report No. 93. Technical report No. 107. Belgium, Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals.

ECETOC. (2012) ECETOC TRA version 3: Background and Rationale for the Improvements. Technical report No. 114. Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals.

ECHA. Information on registered chemicals. Finland, Helsinki: European Chemical Agency. Available from: https://echa.europa.eu/information-on-chemicals/registered-substances (accessed 28 December 2016)

ECHA. (2016) Guidance on information requirements and chemical safety assessment. Chapter R.14: occupational exposure assessment. Helsinki, Finland: European Chemical Agency.

Fransman W, Cherrie J, Van Tongeren M et al. (2013) Development of a mechanistic model for the Advanced Reach Tool (ART). Organization for Applied Scientific Research TNO, Zeist, Netherlands.

Hesse S., Hahn S.T., Schroeder K., et al. (2015) Evaluation of Tier 1 Exposure Assessment Models under REACH (eteam) project: substudy report on uncertainty of Tier 1 models. Dortmund, Germany: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA).

Hofstetter E, Spencer JW, Hiteshew K et al. (2012) Evaluation of recommended Reach exposure modeling tools and near-field, far-field model in assessing occupational exposure to toluene from spray paint. Ann. Occup. Hyg.

Koppisch D, Schinkel J, Gabriel S et al. (2012) Use of the MEGA exposure database for the validation of the STOFFENMANAGER model. Ann. Occup. Hyg; 56: 426-39.

Kupczewska-Dobecka M., Czerczak S., Jakubowski M. (2011) Evaluation of the TRA ECETOC model for inhalation workplace exposure to different organic solvents for selected process categories. J Occup Med Environ Health; 24(2): 208-217.

Lamb J., Miller B.G., MacCalman L., et al. (2015) Evaluation of Tier 1 Exposure Assessment Models under REACH (eteam) project: substudy report on external validation exercise. Dortmund, Germany: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA).

Marquart H, Heussen H, Le Feber M et al. (2008) "STOFFENMANAGER": a web-based control banding tool using an exposure process model. Ann. Occup. Hyg; 52(6): 429-4.

Marquart H, Schneider T, Goede H et al. (2011) Classification of occupational activities for assessment of inhalation exposure. Ann. Occup. Hyg; 55(9): 986-1005.

R Development Core Team. (2010) R: a language and environment for statistical monitoring. Vienna (Austria): R-Foundation for Statistical Computing.

Riedmann RA, Gasic B, Vernez D. (2015) Sensitivity analyses, dominant factors and robustness of the ECETOC TRA v.3, STOFFENMANAGER 4.5, and ART 1.5 occupational exposure models. Risk Analyses; 35(2): 211-225.

Savic N., Racordon D., Buchs D., et al. (2016) TREXMO: a translation tool to support the use of regulatory occupational exposure models. Ann Occup Hyg; 60 (8): 991-1008.

Schinkel J, Fransman W, Heussen H et al. (2009) Cross-validation and refinement of the Stoffenmanager as a first Tier exposure assessment tool for Reach. Occup. Environ. Med; 67(2):125-32.

Tielemans E., Warren N., Schneider T., et al. (2007) Tools for regulatory assessment of occupational exposure: development and challenges. J Exp Scie Environ Epid; 17: S72-S80.

Tielemans E., Schneider T., Goede H., et al. (2008) Conceptual model for assessment of inhalation exposure: defining modelling factors. Ann occup hyg: 52 (7): 577-586.

Tongeren M., Fransman W., Spankie S., et al. (2011) Advanced REACH Tool: development and application of the substance emission potential modifying factor. Ann Occup Hyg; 55(9): 980-988.