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Measured air concentrations of pesticides for the estimation of exposure to vapour in European risk assessments

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ABSTRACT

There is an identified need to revise the default air concentration values and assumptions applied in assessing vapour exposure in the risk assessment of bystanders and residents to plant protection products. To address this, we evaluated inhalation exposure via vapour using previously unpublished data from 29 field and wind tunnel studies. The database comprises 35 trials with 11 active ingredients covering a wide range of scenarios with respect to vapour pressure, crops, application rates and European regions. Of the 961 individual measurements, 634 were below the Limit of Detection (LOD), 282 were between the LOD and Limit of Quantification (LOQ) and only 45 (4.7%) were quantifiable. Ten individual non-normalized samples exceeded 0.1 μg/m^3. Of the 81 first-day measurements after the application, 36 were <LOD, and quantifiable mean, 75th and 95th percentiles values were 0.114, 0.083, 0.552 μg/m^3/kg AI applied/ha, respectively. No robust correlations between air concentration and temperature, leaf coverage, humidity, wind speed, and field size were identified; there is very limited correlation between air concentration and vapour pressure and Henry's constant in a subset of the data. These data indicate that potentially inhalable pesticide vapour within or near fields occurs only at very low concentrations in real scenarios.

1. Introduction

Non-dietary risk assessments for agrochemicals in Europe consider four different exposure populations, i.e., operators, workers, bystanders, and residents (EFSA, 2014a; EFSA, 2014b; EFSA et al., 2022). The associated model assumes bystander and resident exposure to spray drift during application plus exposure to vapour, surface deposits, and foliar residues in treated crops after application. The two population groups otherwise differ in assumed exposure duration.

Vapour refers to the gaseous forms of substances that are usually liquid or solid at a temperature and pressure below the critical point where the different phases cease to coexist. The fraction of a substance in the vapour phase could be inhaled, which makes vapourization relevant for risk assessment.

With respect to the vapour exposure pathway in European non-dietary risk assessment, active ingredients (AI) are categorized according to their inherent vapour pressure (VP) at room temperature, which is used to set one of two default air concentrations.

Accordingly, AIs are categorized as being of 'low volatility' and being 'moderately volatile', with VP $< 5 \times 10^{-3}$ Pa and VP $\geq 5 \times 10^{-3}$ Pa, respectively. AIs with VP $\geq 10^{-2}$ Pa are described as 'volatile' and, as such, are not covered by the EFSA guidance (EFSA, 2014a); an acceptable refinement option was recently introduced which uses the saturated vapour concentration calculation (EFSA et al., 2022). In case of unacceptable exposure, *ad hoc* data are necessary to prove acceptable exposures as part of their risk assessment. The strict application of categorizing AIs as 'low volatile' and 'moderately volatile' and the associated default values (see below) makes inhalation exposure to

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vapour a significant exposure pathway and thus, in practice, a spurious cut-off criterion.

A recent report reviewing the background data used to derive the vapour exposure default values highlighted the need to revise the default air concentration values and assumptions applied in assessing vapour exposure (Felkers et al., 2022). It was shown that the current grouping in European risk assessment is not supported by the underlying data from studies which utilized AIs with very similar VPs. The grouping used for pesticides in the EFSA 2014 (EFSA, 2014a) and 2022 (EFSA et al., 2022) guidance documents also differs from the characterization of AI volatility in other guidance documents and regulations for chemicals (e.g. EU (EU, 2006; EU 2008), ECHA (ECHA, 2016), Martin et al. (2008)). It was further pointed out that the current default values are independent of the application rate, while the underlying dataset allows this refinement. Importantly, when these data were normalized to the application rate, the air concentrations were in the same range for all tested AIs, while there is an excessive 15-fold difference in default values between the current VP groups in regulatory use. Also, the data appear to have been partly collected during application, which is not addressing the relevant exposure scenario. Due to lack of normalization for application rate, as it stands currently in the EFSA guidance (EFSA, 2014a; EFSA et al., 2022), the AOELs of 0.00107 and 0.01605 mg/kg bw/day become cut-offs for 'low volatility' and 'moderately volatile' substances, respectively, for the resident child. Felkers et al. further discussed that LOD and LOQ values should be handled appropriately and that the dependence of air concentration on environmental conditions, crop type and the impact of foliage density should be factored in. Additionally, appropriate population-relevant inhalation rates and durations should be considered.

Another critical issue highlighted by Felkers et al. was that air sampling should only be done after, not during application, and volatilisation behaviour should be reconsidered. Notably, resident and bystander exposure durations and inhalation rates are assumed to be the same (EFSA, 2014a; EFSA et al., 2022), meaning a constant 24 h exposure, which mismatches the exposure to spray drift where different assumptions are applied for residents and bystanders. For residents, this 24 h exposure to vapour is assumed to occur daily for an extended (sub-chronic) period. Considering that the values are based on measurements taken during and soon after application, this approach is very unrealistic.

Clearly, the current default values and approach for estimating inhalation exposure to AIs in plant protection products (PPPs) is limited, which is also recognized by EFSA (2014a): " .... any future possibility of modifying the VP value and the concentration in the air will allow a refinement of the exposure calculations" and it is recommended to "collect/produce data on relevant daily air concentrations (based on vapour pressure) of substances". Hence, member companies of industry association CropLife Europe (CLE) collected multiple state-of-the-art regulatory field and wind tunnel studies previously used in PPP registration processes. The data allow a refinement of inhalation exposure assumptions and, ultimately, a revision of the current default average air concentration values used in non-dietary risk assessment for exposure to pesticides via vapour drift.

2. Materials and methods

A total of 29 Good Laboratory Practice (GLP) studies (35 trials) on 11 AIs with VPs ranging from 1.1×10^{-8} to 9×10^{-3} Pa were conducted by CLE member companies between 2015 and 2019 (see Supplementary Table 1 for key study information).

2.1. Locations and application details

Trials (n = 35) were conducted in various locations across Europe: Spain (n = 11), Italy (n = 6), France (n = 5), Germany (n = 5), Poland (n = 3), UK (n = 2), Ireland (n = 1), Lithuania (n = 1), Switzerland (n = 1). In these locations, 32 trials were conducted in field and 3 trials in wind tunnels (2 in Germany, 1 in Switzerland). Applications took place on a wide variety of crops relevant to European situations; pome fruit (n = 8), vineyard (n = 8), bare soil (n = 6), spring/winter barley (n = 5), wheat/ winter wheat (n = 4), lettuce (n = 2), maize (n = 1) and pre-emergence (n = 1). BBCH stages were between 16 and 75 for low crops, 53–91 for pome fruit and 13–81 for vineyard, covering early and late stages for these high crops, i.e. minimal to dense foliage. The indications for applied pesticides were herbicide (n = 9), insecticide (n = 7), fungicide (n = 19). Application methods were spreading granules by hand in furrow (n = 6), drill in soil (n = 1), tractor broadcast air-assisted (n = 16), manual/research/tractor boom sprayer (n = 12). Field sizes ranged from 100 to 88000 m^2 and application rates from 0.011 to 0.986 kg AI/ ha.

2.2. Environmental conditions

Temperature and relative humidity measurements were available for individual sampling periods for 14 trials. The overall range of temperature across these 14 trials was 6.44–31.69 °C; during the first 24 h after application, the range was the same as for all measurements. The overall range of relative humidity across the 14 trials was 16.41–95.00%; during the first 24 h after application, the range was 25.22–95.00%. The overall range of wind speed (measured at 2 m above ground) across all trials was 0–10.83 m/s; during the first 24 h after application, the range was 0.178–9.10 m/s. Rainfall measurements or reporting of irrigation events were available for individual sampling periods for 15 trials. The overall range of rainfall across 14 field trials was 0–0.89 mm; in wind tunnels, 3 out of 76 individual sampling periods reported irrigation events. During the first 24 h after application, the range of rainfall was 0–0.2 mm; minor rainfall occurred for 4 out of 81 first 24 h after application.

2.3. Sampling setup and measurements

For field trials, static sampling pumps with sorbent tubes were placed at 4 points around the treatment area. The sample from the side of the plot with the maximum residue was reported for each occasion since this represents the worst-case depending on the wind direction (i.e. exposure is measured full time downwind). In wind tunnel trials, the sampling pumps were placed downwind.

For 32 trials, air sample measurements were taken at two heights representing child (0.5 and 0.7 m) and adult (1.5 m); for 3 trials, the sampling was done at 1.4 m height. Across all trials, distances from the treated area ranged from 0 m (mid field), 1, 2, 3, 5, 10 m for low crops; and 10 m for high crops. Pump flow rates were set at 0.5 (n = 7), 1 (n = 25) or 2 (n = 3) L/min. Starting time of sampling for spray applications was either just after the applications had been finished, i.e. 0 h, or when spray had been considered dried, i.e. 0.33–2 h after application. In one instance where a granular (GR) formulation was used, sampling commenced after purging the wind tunnel of dust so that only vapour was sampled. Total continuous monitoring times for 34 trials were of different durations: 24 h (n = 2), 48 h (n = 5), 72 h (n = 7), 96 h (n = 10), 168 h (n = 10). Monitoring time for 1 trial was in total 697 h long, however, continuous sampling took place between 0 and 12 h, then 24-h sampling on day 8, 15, 22 and 29 after application. Individual sampling durations were 2 h (n = 3), 6 h (n = 3), 8 h (n = 879), 12 h (n = 28) and 24 h (n = 48). From each sorbent sampling tube, the sorbent material was extracted with appropriate solvent, the extract then was analysed using LC-MS/MS according to validated analytical method for each AI. Each study in the database contains an analytical phase report, where GLP-compliant analytical methods are described for each AI. Analytical methods have been validated for determination of residues of each AI in relevant matrices.

2.4. Physico-chemical properties of AIs and formulation types

Air concentrations were measured for 11 different active ingredients. The molecular weights ranged from 221.03 to 440.82 g/mol. VPs were $1.1 \times 10^{-8} – 9 \times 10^{-3}$ Pa at 20/25 °C (depending at which temperature the VP was available). Water solubility for these 11 AIs were 0.016–24300 mg/L; Henry's law constants were 1.71×10^{-10} – 166 Pa m^3/mol, however, water solubility and Henry's law constants were available at different temperatures and pH. The AIs were applied formulated in 6 different formulation types: emulsifiable concentrate (EC) (n = 6), granule (GR) (n = 7), oil dispersion (OD) (n = 1), suspension concentrate (SC) (n = 11), soluble concentrate (SL) (n = 2), water dispersible granule (WG) (n = 8).

EFSA (2014a) recommends collecting data on relevant daily air concentrations based on VP, Table 1 shows the VPs covered by the studies presented when compared to EFSA's current volatility criteria. For a more level comparison, VPs (expressed as Pa) covered in studies are presented mostly at 20 °C, since most AIs had VP available at this temperature.

2.5. Derivation and normalization of air concentrations

Field and wind tunnel trials were grouped together, and their data treated equally, because conditions (i.e. VP, application rate, field size, sampling setup, temperature, humidity, wind speed, etc.) in wind-tunnel studies were in the same range as those observed in the field studies.

As sampling times differed between the pumps used in the various trials, raw air concentration measurements in μg/m^3 were used to calculate daily average air concentrations. For most days, the values are a mean of equal sampling durations (i.e. 3 × 8 h or 2 × 12 h or 1 × 24 h); for 3 studies, a time-weighted average (TWA) was calculated for 24 h as sampling times were of varied duration (i.e. 2, 6, and 8 h); for one study the sample values have been adjusted to the field recovery of 65%. For other studies, no adjustments for recoveries were made, as recoveries were in the range 70%–120%, which is recommended in Europe (Commission, 2021).

The measured air concentration values were further normalized with respect to application rate (μg/m^3/kg AI applied/ha), see Felkers et al. (2022). This normalization approach was taken as such a plausible relationship could be expected between the application rate and air concentration. This approach is in agreement with the risk assessment principles/toxicological axiom that dose drives exposure/risk.

Since LODs and LOQs vary between studies, a simple algorithm was applied to assure comparability between trials. In estimating the average air concentrations, the non-detects (values < LOD) have been assumed to be '0' (zero), or taken as a full LOD value, to evaluate the impact of those two extreme assumptions. Values between LOD and LOQ are treated as ½ of LOQ, and values > LOQ have been used as measured.

Table 1
VPs covered in the studies, compared to EFSA 2014 and 2022 trigger values and grouping.

AI	Vapour pressure, Pa	
	Study data[a]	EFSA, 2014 & 2022
		Volatile, cut-off 1×10^{-2}
AI5	9×10^{-3}	Moderately volatile, (15 μg/m^3)
AI8	8.4×10^{-3}	
		5×10^{-3}
AI1	1.43×10^{-3}	Low volatility, (1 μg/m^3)
AI9	1.2×10^{-5}	
AI11	9.9×10^{-6}	
AI2	5×10^{-6}	
AI10	2.3×10^{-6}	
AI6	4.00×10^{-7}	
AI3	3.22×10^{-7}	
AI7	3.60×10^{-8}	
AI4	1.10×10^{-8}	

[a] Vapour pressures (Pa) mostly at 20 °C.

3. Results

A total of 961 samples were collected from all 35 trials in field and wind tunnel studies. The air concentration measurements in wind tunnel studies were all < LOD, hence the data were not further stratified. In total, 634 samples were below the LOD and 282 were between the LOD and LOQ. Hence, 916 (95%) of the samples were not reliably quantifiable. The data include a total of 356 cumulative measurement days, and 81 datasets with first-day measurements, when considering all sampling heights and distances from the treated field. For 36 of the 81 datasets with first-day measurements, all samples on the first day were "non-detects", i.e. <LOD. The air concentration was only sufficiently high for reliable quantification in 45 out of 961 samples (4.7%). These were as follows: during the first 24 h measured, 26 samples (11.2% of first day samples (n = 229)), 58% of all measured samples (n = 45); during the second 24 h measured, 14 samples (6.8% of second day samples (n = 207)), 31% of all measured samples (n = 45); during the third 24 h measured, 5 samples (2.7% of third day samples (n = 186)), 11% of all measured samples (n = 45). After the third sampling day, there were no more measured samples above LOQ.

Fig. 1 visualizes the dataset over the sampling period and at all heights and distances from the treated field. It shows that the dataset becomes unbalanced from Day 2 on and increasingly unbalanced after Day 3. Only 10 of 961 individual non-normalized sampling values exceed an air concentration of 0.1 μg/m^3, 7 of the samples being during the first 24 h after application. The highest individual non-normalized sampling value is 0.427 μg/m^3 for a 0–2 h sample just after the application. Due to the low number of quantifiable air concentrations, a statistical evaluation is strongly affected by the selected assumptions and biased by the unbalanced nature of the dataset after Day 1, hence standard parametric statistical modelling is considered to be inappropriate, and the data considered to be too sparse for reliable imputation. Nevertheless, simple linear model fits were added to some graphs to aid a visual assessment of the different LOD algorithms.

3.1. Average air concentrations

Fig. 2 shows an overview of the normalized air concentrations for all values in μg/m^3/kg AI applied/ha. Shown are empirical cumulative distribution function (ECDF) plots on the data (A), ECDF on the log-transformed data (B), histograms (C) and kernel density plots, which provides a more homogenous profile (D). Fig. 2A and C highlight the high number of values where no residue could be measured, and which are not included in the figures with log-transformed x-axes (Fig. 2B and D). The plots also show the effect of considering different values for LODs – for the current dataset, this is profound as most of the values could not be robustly determined as they were below the LOD. When the LOD is considered to be zero, it indicates a density distribution that approximates log-normal, which can be expected for a reasonably large dataset. Fig. 2D shows how considering LODs as "full" distorts the data, the effect is more pronounced for measurements including data after Day 1 (compare dashed vs solid lines).

Fig. 3 shows normalized air concentrations over the total observation period. Only 3 of 81 values exceed 1 μg/m^3/kg AI applied/ha, and none of the measurements exceed 1 μg/m^3/kg AI applied/ha after Day 1. The high value in the plot for Day 1 (1.69 μg/m^3/kg AI applied/ha), for AI4 with VP 1.10×10^{-8} Pa, illustrates the effect of the LOD assumption, it is actually four non-detects (<LOD) in one study at different sampling heights and distances from the field, that are artificially increased so much by the generic algorithm that they become the maximum values on that Day. There was a decline of air concentrations, as well as a decline of the number of data points, over time. As expected, the value decreases over time when an LOD of 0 is assumed but it approaches the

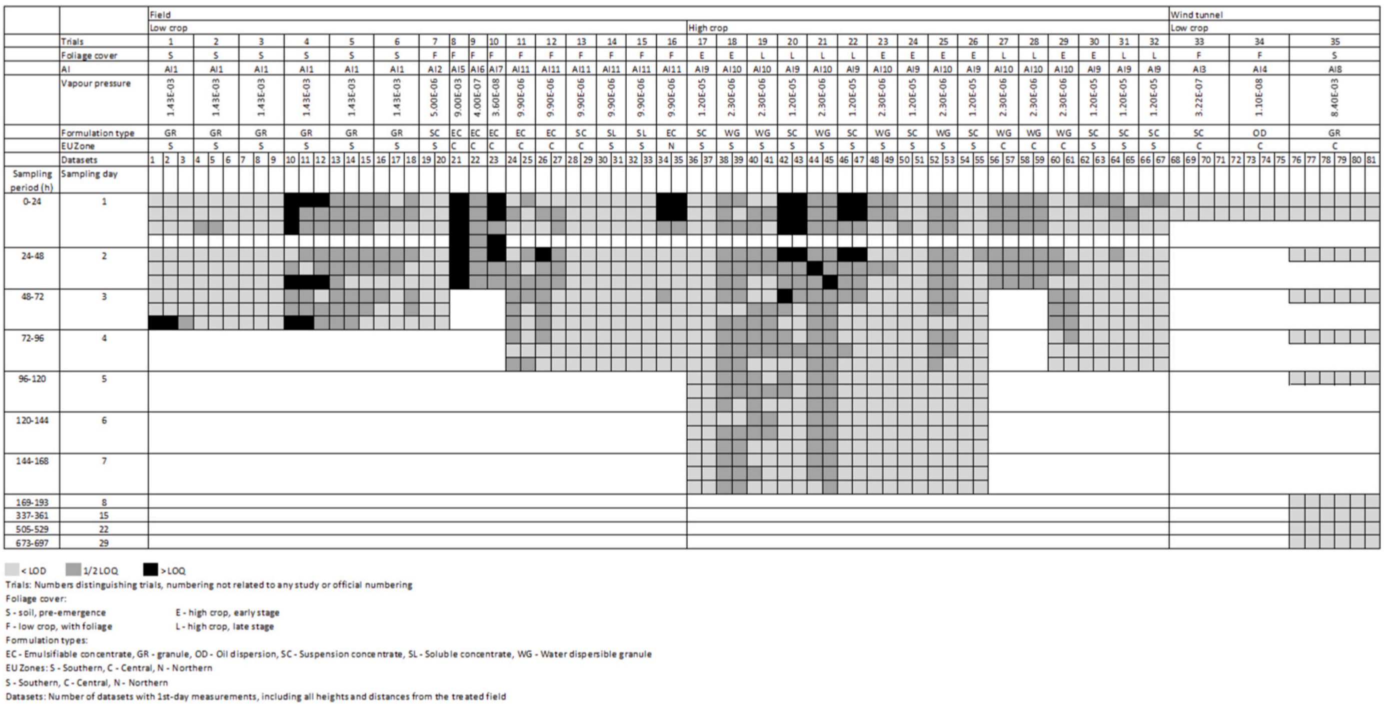

Fig. 1. Conceptual visualization of sampling during various time periods. Note: each time period presents the number of samples per 24 h, not the length of measurement for each sample; the same shading of cell does not indicate the lack of dissipation, shading classifies the cell.

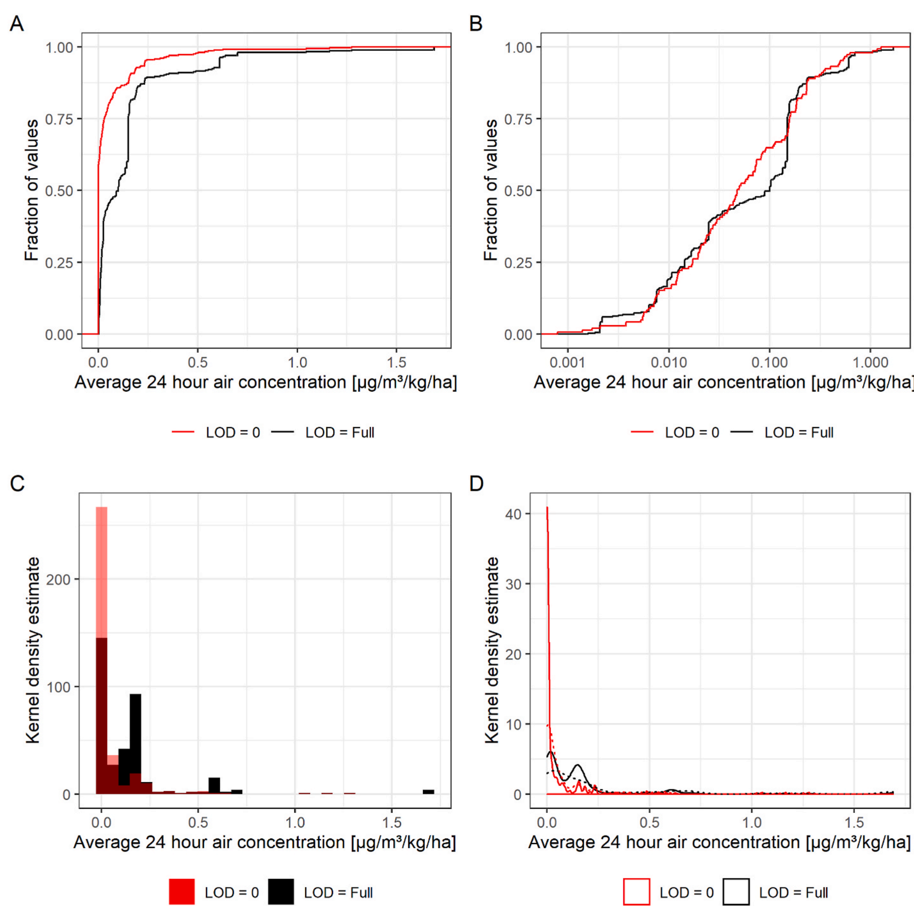

Fig. 2. Overall distribution of values expressed in µg/m^3/kg AI applied/ha. (A) empirical cumulative distribution function (ECDF); (B) empirical cumulative distribution function (ECDF) x log transformed; (C) Histogram; (D) kernel density estimates, with dashed lines representing kernel density estimates of Day 1 only. Note: the plots with the log10-transformed x-axes do not contain the values assumed to measure 0 residue.

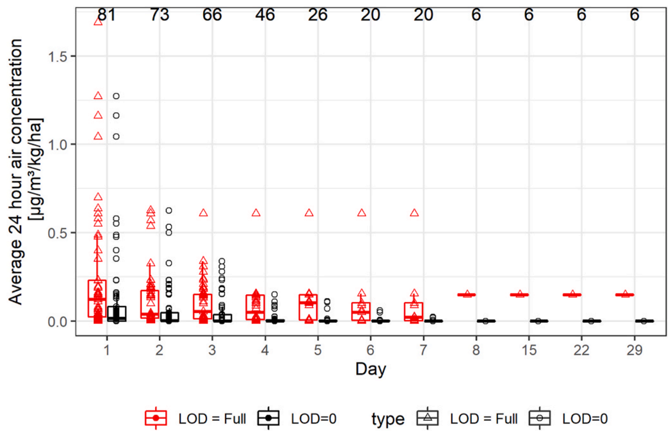

Fig. 3. Decline of air concentrations over observation days. Boxplots but without outlier highlights as those assume roughly normal distribution, which is not applicable here.

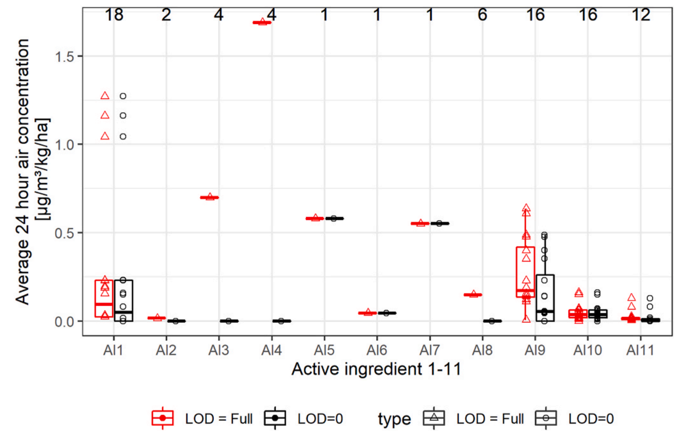

Fig. 4. Average normalized air concentrations (µg/m^3/kg AI applied/ha) in the first 24 h after application of different AIs. Values are shown using LOD set to zero and the full LOD value.

LOD if it is considered as a full LOD value. Sampling days after Day 7 do not contain any values over 0 or the LOD. Table 2 shows the summary statistics over the individual sampling days using 0 as the LOD and the full LOD.

The Day 1 air concentrations for all 11 AIs are shown in Fig. 4. Out of 81 first-day average air concentration values, when considering all sampling heights and distances from the treated field, 36 values are '0' (i.e. non-detects). The highest observed values are from AI4, as observed in Fig. 3, due to this calculation. This illustrates that the value inappropriately distorts the investigation of factors contributing to air concentration. The same effect can be observed for AI2, AI3 and AI8. Hence the highest measured values are from either AI1, AI5, AI7 or AI9. The maximum values of AI1 can however be attributed to extremely dry and warm conditions during the field study that grossly deviate from the conditions of the other studies.

Table 3 shows summary statistics for the results of Day 1 considering approaches other than normalization for µg/m^3/kg AI applied/ha. When the LOD = 0 is considered, the mean of Day 1 is 0.114 µg/m^3/kg AI applied/ha at all sampling distances and heights, which is the highest mean of all days. The mean is higher than the corresponding 75th percentile value of 0.083 µg/m^3/kg AI applied/ha and almost twice as

Table 3
Summary statistics of air concentrations during the first 24 h after application.

Group	All individual samples, LOD = excluded[a], µg/m^3	All individual samples, LOD = 0[b], µg/m^3	Average air concentration, LOD = full, µg/m^3/kg AI applied/ha	Average air concentration, LOD = 0[b], µg/m^3/kg AI applied/ha
Mean	0.029	0.012	0.272	0.114
SD	0.0419	0.0259	0.423	0.245
Min	0.0002	0	0.00208	0
Median	0.01	0.00223	0.123	0.0157
'75th'	0.0318	0.00827	0.232	0.083
'90th'	0.076	0.03	0.7	0.354
'95th'	0.13	0.076	1.27	0.552
Max	0.169	0.13	1.69	1.27
'n()'	81	81	81	81

[a] Values < LOD were considered as "non-detects" and have been excluded from the assessment.
[b] Values < LOD were considered as "non-detects" and have been assumed to be '0' (zero).

Table 2
Summary statistics of air concentrations in µg/m^3/kg AI applied/ha over sampling days.

Day	Mean	SD	Median	75th	90th	95th	Max	n
				LOD = 0				
1	0.114	0.245	0.0157	0.083	0.354	0.552	1.27	81
2	0.0665	0.127	0.00174	0.0475	0.203	0.271	0.626	73
3	0.0454	0.0851	0	0.0362	0.182	0.239	0.34	66
4	0.0138	0.033	0	0.00697	0.0496	0.0888	0.151	46
5	0.0124	0.032	0	0.00392	0.0422	0.0985	0.113	26
6	0.00883	0.0196	0	0.00374	0.0498	0.0508	0.0612	20
7	0.00381	0.00847	0	0.000197	0.0209	0.0239	0.025	20
8	0	0	0	0	0	0	0	6
15	0	0	0	0	0	0	0	6
22	0	0	0	0	0	0	0	6
29	0	0	0	0	0	0	0	6
				LOD = Full				
1	0.272	0.423	0.123	0.232	0.7	1.27	1.69	81
2	0.118	0.151	0.0399	0.172	0.228	0.551	0.626	73
3	0.107	0.125	0.0551	0.151	0.222	0.302	0.609	66
4	0.0915	0.128	0.0494	0.148	0.152	0.156	0.609	46
5	0.119	0.157	0.103	0.149	0.156	0.496	0.609	26
6	0.106	0.18	0.05	0.103	0.201	0.609	0.609	20
7	0.101	0.182	0.0222	0.103	0.201	0.609	0.609	20
8	0.149	0	0.149	0.149	0.149	0.149	0.149	6
15	0.149	0	0.149	0.149	0.149	0.149	0.149	6
22	0.149	0	0.149	0.149	0.149	0.149	0.149	6
29	0.149	0	0.149	0.149	0.149	0.149	0.149	6

high as the mean of Day 2 (0.0665 μg/m^3/kg AI applied/ha). The mean of average non-normalized air concentrations during the first 24 h after application is 0.012 μg/m^3 and 95th percentile is 0.076 μg/m^3.

3.2. Effect of environmental and physico-chemical parameters on air concentrations

The three highest values on Day 1 (and 2) are from the same active substance, AI1 (see Fig. 4). This AI has a relatively high VP; however, there are other AIs in the dataset with higher VP values which exhibit lower air concentrations. Furthermore, these values were from either 0.7 or 1.5 m high sampling and were sampled in the middle of the field or at a distance of 1 m from the treated area. The lowest value is from 0.7 m height in the middle of the field, hence there is no obvious relationship between VP and measured exposure observed in the available dataset. Excluding the three values for AI1 would substantially reduce Day 1 estimates, e.g. mean, 75th, and 95th percentile of day 1 would decrease from 0.144, 0.083 and 0.552 to 0.0742, 0.0713 and 0.412 μg/m^3/kg AI applied/ha, respectively (note the skewed distribution, with mean ≫ 75th percentile for the full dataset, see Table 3). Therefore, the effect of environmental conditions and physico-chemical properties relating to AI1 and the entire dataset was evaluated to investigate potential drivers of the air concentration measurements.

Fig. 5 shows the effect of temperature, relative humidity, field size, wind speed and application rate on the average 24 h air concentration. Fig. 6 shows the same data but excluding AI4, AI3 and the high values for AI1, to investigate their influence on the linear model depicted in the figures. Sub-setting the dataset has some effect on the visual

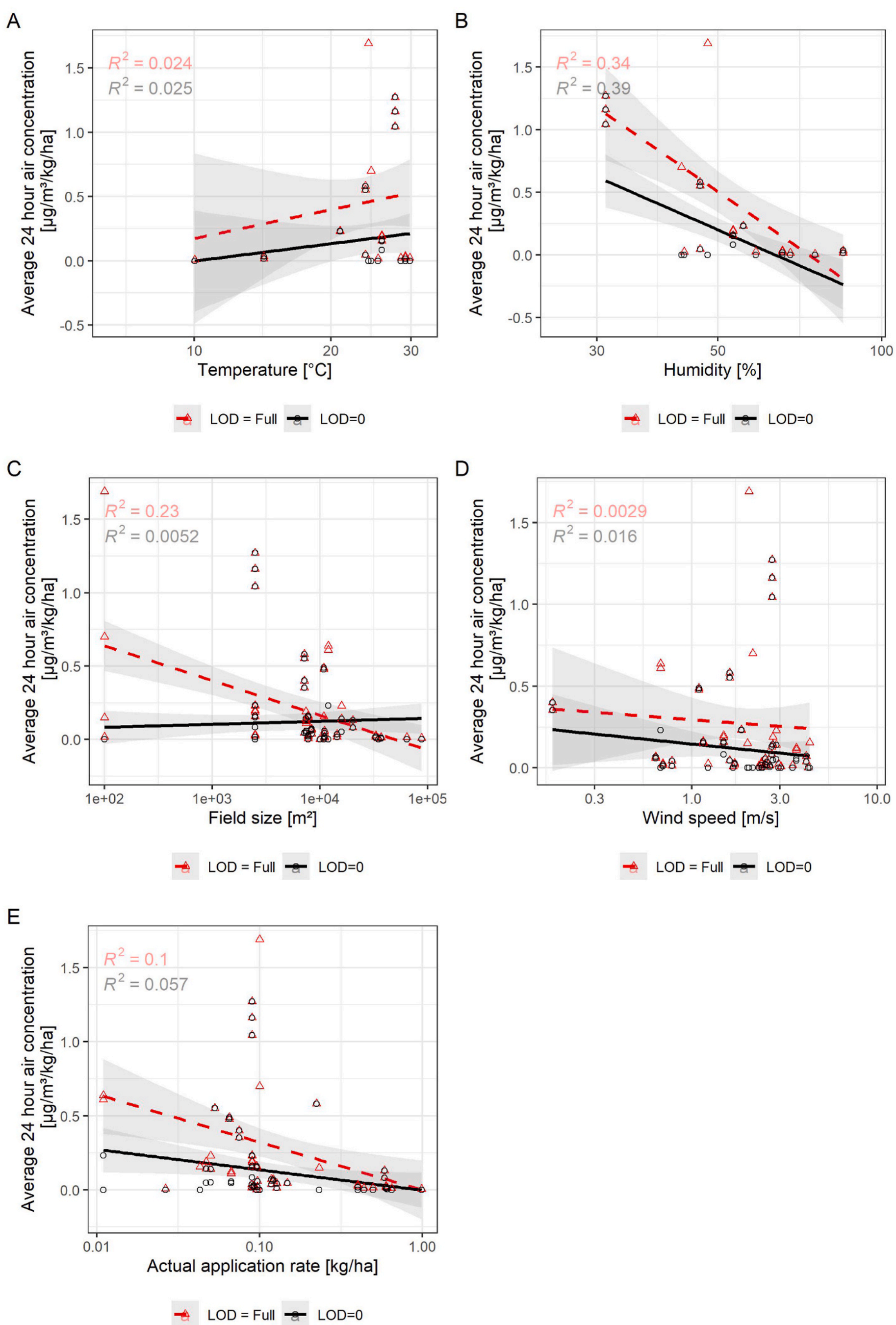

Fig. 5. Effects of temperature, humidity, field size, wind speed, application rate on average air concentration. Linear models overlayed.

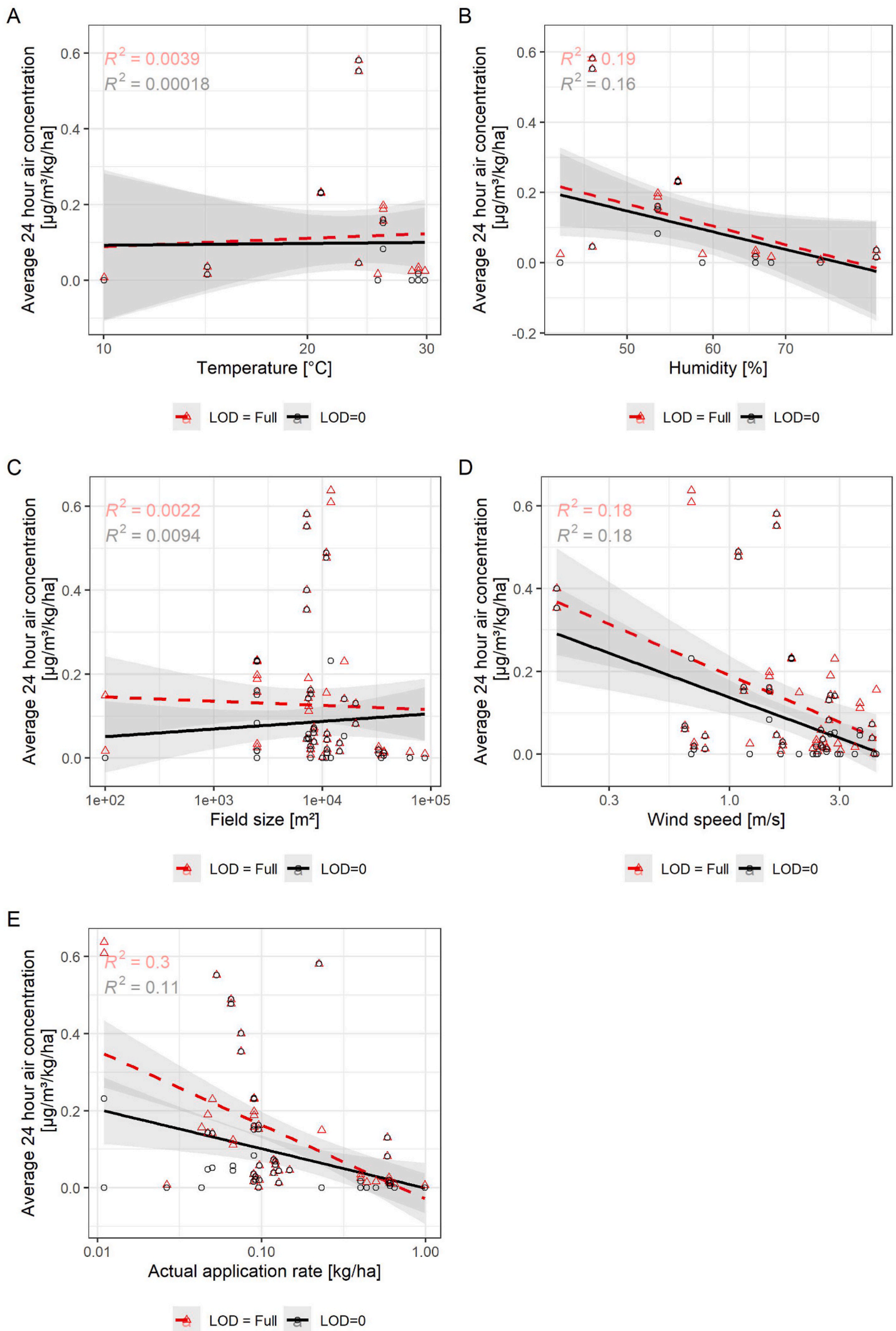

Fig. 6. Effects of temperature, humidity, field size, wind speed, application rate on average air concentration excluding AI3, AI4 and the three high values of AI1.

representation in the plots. Overall, the effect of temperature, field size and application rate are not pronounced. There seems to be some effect of humidity and wind speed. However, in Fig. 6, the only slopes statistically significantly different from 0 are for log10-transformed Wind speed and Application rate, with −0.20546 and, −0.102688 respectively, for the dataset subset. Hence, e.g. a 1% increase in wind speed decreases the air concentration by 0.002 μg/m^3/kg applied/ha. The strongest visual effect is observed for humidity, where a 1% increase decreases the air concentration by 0.007 μg/m^3/kg applied/ha.

When physico-chemical parameters are investigated over the whole dataset (Fig. 7), air concentration increases visually with VP and Henry's constant; the effect is reduced for the subset excluding the high values of AI1, AI3 and AI4 (Fig. 8). The effect is however very small with slopes <0.05, VP has the highest slope of 0.03481 when log10-transformed, which is the only slope statistically significantly different to 0. All models using VP and Henry's constant have R^2 values < 0.05, thus VP and Henry's constant are not considered to be relevantly predictive of air concentration in this dataset.

Additionally, air concentrations for AI5, AI6, and AI7 were measured in the same field study; therefore, these AIs have been subject to the same formulation, application, crop, and environmental conditions. The VP for AI5 is 9.00×10^{-3} Pa, AI6 4.00×10^{-7} Pa, AI7 3.60×10^{-8} Pa, however, the normalized measured air concentrations on Day 1 do not correspond to the VPs (see Fig. 4). Also, the non-normalized air concentration values do not correspond to the VPs of these AIs (not shown).

Figs. 4–8 demonstrate again the effect of the LOD assumptions, i.e. the consideration of full LODs completely skews the theoretically plausible relationship of the physico-chemical parameters with air

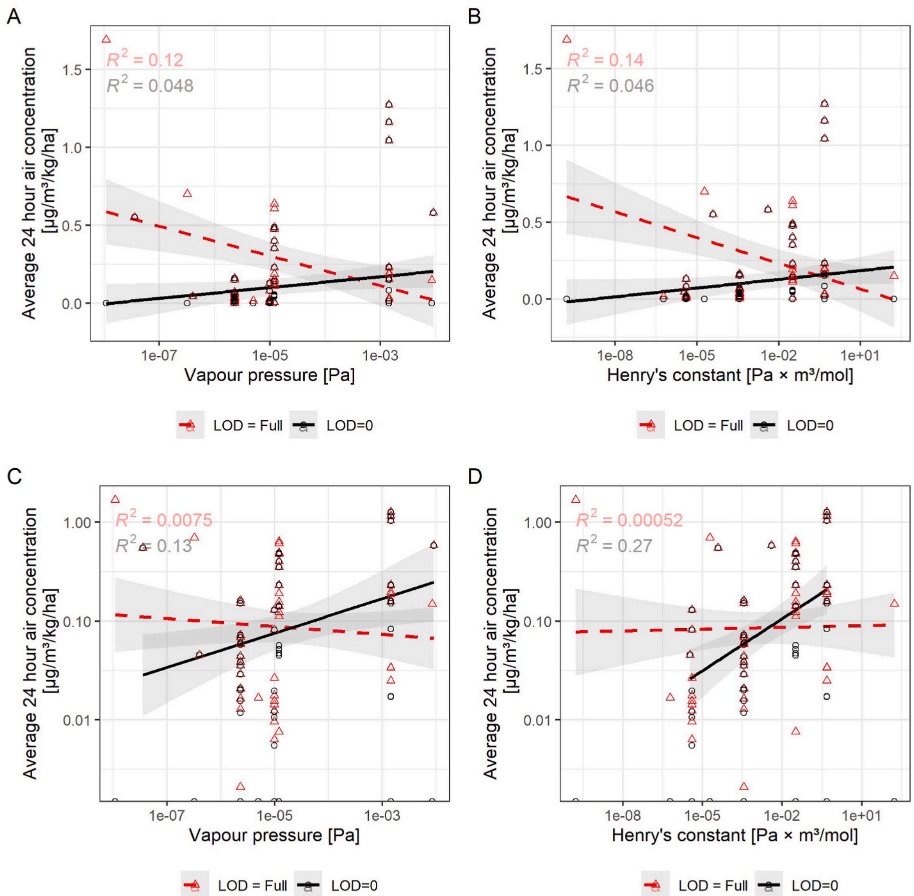

Fig. 7. Effects of VP and Henry's constant on average air concentration, normal and log10 transformed responses. Linear models overlayed.

concentration.

3.3. Effect of crop stage and foliage on air concentrations

A difference in normalized air concentration during the first 24 h could be observed when comparing early and late-stage development (i.e. minimal and dense foliage) for high crops, and bare soil versus foliage cover for low crops (Fig. 9). Since for high crops the database (16 trials) is relatively homogeneous, i.e. two AIs, two crops (pome fruit and vineyard), two development stages (early and late) for both crops, a comparison of air concentrations between stages could be made. The mean air concentrations during the first day after the application are 0.0530 µg/m^3/kg AI applied/ha for early stage, 0.2515 µg/m^3/kg AI applied/ha for late stage for vineyards; and 0.0223 µg/m^3/kg AI applied/ha for early stage, 0.0761 µg/m^3/kg AI applied/ha for late stage for pome fruit.

For low crop bare soil ("no" in Fig. 9), air concentrations are available for AI1 and AI7. For AI1, all air concentrations involve the same application method, formulation type and zone (Southern Europe). Outlying data points are from 1 trial out of 6 in total (Fig. 4), which had a marginally higher average temperature of 28.43 °C compared to 21.35–26.32 °C in other trials, and a much lower relative humidity of 29% compared to 56.31–75.31% in other trials. The application method for the outlier samples is a granule application on soil surface. For low crop with foliage ("yes" in Fig. 9), the highest air concentration value is for AI5 with VP 9 × 10^{-3} Pa at 20 °C, however the next highest value is for AI7 with VP 3.6 × 10^{-8} Pa at 20 °C, the lowest value is for AI6 with VP 4.0 × 10^{-7} Pa at 20 °C. Neither VP nor Henry's law constant seem to be correlating with foliage cover, suggesting a random distribution.

4. Discussion

As a likely consequence of strict and impractical VP and air concentration criteria (as commented during the peer-review of EFSA (EFSA, 2014a; EFSA, 2014b), as well as during public consultation of EFSA (EFSA et al., 2022)), the exposure to vapour has developed from a lesser concern to a significant exposure pathway, especially due to a lack of variable parameters and implied cut-off criteria, e.g. the acceptable operator exposure level (AOEL) for a given AI, against which exposure is assessed. This is similar to the impact of the revised assumptions made in the EFSA guidance (EFSA, 2014a) on worker re-entry exposure estimations (Kluxen et al., 2021). Consequently, CLE member companies have conducted 29 GLP studies on vapour concentrations to refine product specific risk assessments for PPP registration purposes. This is a substantially larger dataset than the one used to set the current default values. Hence, it should allow the derivation of refined default values to determine more realistic inhalation exposure to volatilized pesticides.

One major issue with the current default values is that they are independent of the application rate, which is not compatible with exposure-based risk assessment. Therefore, air concentration measurements were normalized according to sampling time and application rate. Furthermore, it has been suggested that in order to establish a VP classification for risk assessment purposes, it is important to define high and low VP (EU 2008). Non-dietary exposure assessment tends to rely on air concentrations measured during the first 24 h as a worst case, even where exposure on consecutive days is considered. However, as shown here, these air concentration values for first 24 h do not correlate with VP. When comparing the normalized air concentrations for AIs with VPs categorized according to EFSA criteria, the mean values of first-day average air concentrations for AIs with VPs that could be classified as

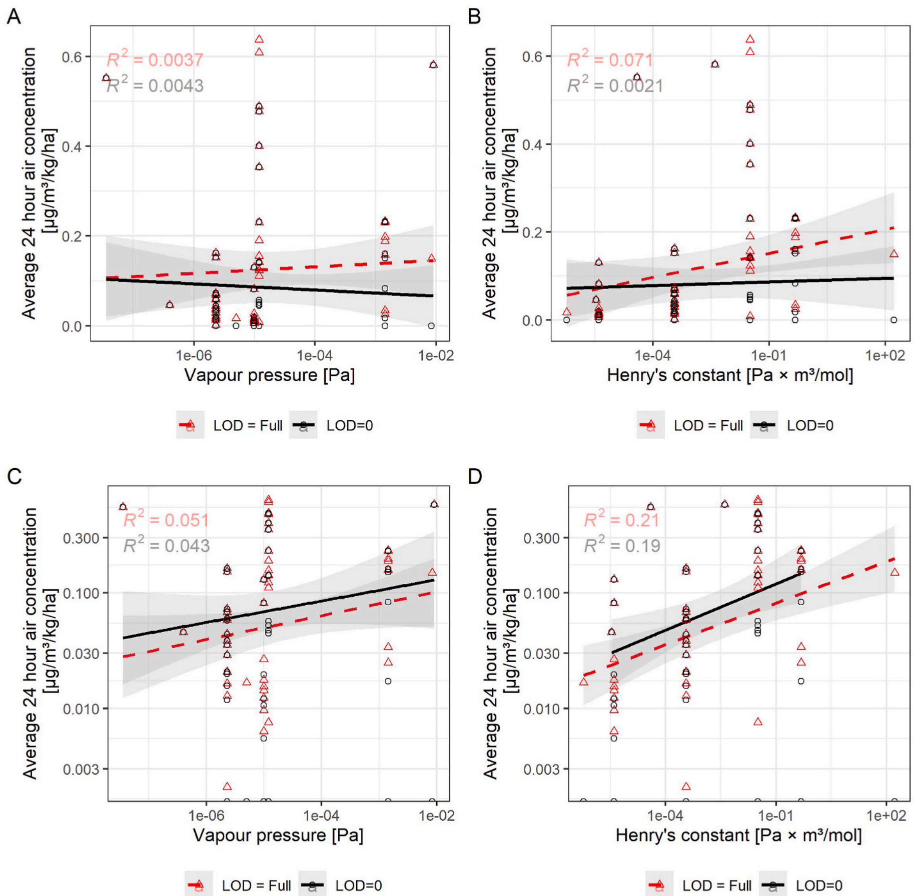

Fig. 8. Effects of VP and Henry's constant on average air concentration excluding AI3, AI4 and the three high values of AI1, normal and log10 transformed responses. Linear models overlayed.

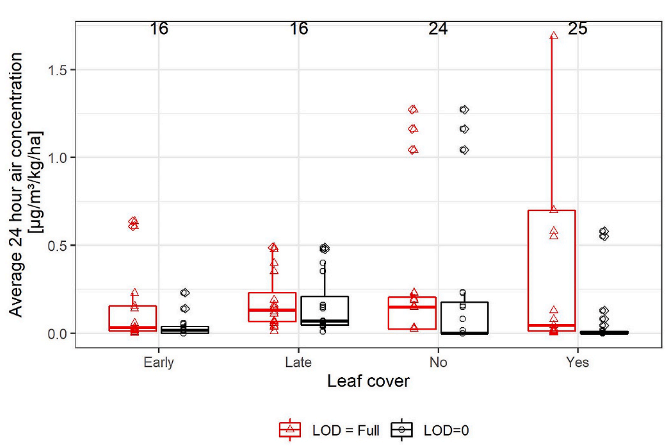

Fig. 9. Air concentration measurements (μg/m^3/kg AI applied/ha) depending on early and late stage development for high crops, and bare soil (no) and foliage (yes) cover for low crops, as individual values and histograms (counts).

'low volatility' is 0.11733 μg/m^3/kg AI applied/ha and for 'moderately volatile' 0.08301 μg/m^3/kg AI applied/ha. Hence, the new data reported here do also not support a 15-fold difference in average air concentrations, which is similar to the underlying data of the current default values (Felkers et al., 2022). It should be noted that some of the lowest air concentrations observed in the presented dataset were for AI8, which also has one of the highest VPs (8.4×10^{-3} Pa at 20 °C). This AI was applied as a sub-soil solid granule and the fact that it would be assigned the higher EFSA default of 15 μg/m^3 demonstrates that not accounting for application method and physical state of the formulation makes for a very crude and unrealistic risk assessment.

Effects of temperature and soil/air humidity have been discussed previously (EU 2008). Although the humidity of soil and air has an indirect influence on the volatilisation rate of a semi-volatile organic substance, and drying of the soil can result in a reduced VP because of increased sorption, in general, temperature enhances volatilisation, as does low air humidity (EU 2008). VPs are determined at "room temperatures", however in the environment the actual VP is influenced by the dilution of the substance and by temperature among other factors. Therefore, actual VPs under field conditions may vary even during a single sampling time, but this is not normally determined (EU 2008). Previously, Siebers et al. (2003) suggested to explore the potential impact of VPs, application rates, size of treated area, treated crop type, and effect of formulation type. All these aspects were explored with the current dataset. Since air concentrations were normalized to μg/m^3/kg AI applied/ha, the application rate was considered, in contrast to approaches suggested by EFSA (2014a) or previously by Martin et al. (2008) and PSD (2008). Although higher VP correlates with higher air concentration measurements in individual samples (μg/m^3), as also suggested by (EU 2008), it does not correlate in this way for the first 24 h period (in μg/m^3/kg AI applied/ha), which gives the highest average air concentration estimate. A difference in normalized air concentration during the first 24 h could be observed when comparing early and late-stage development (i.e. minimal and dense foliage) for high crops, and bare soil and foliage cover for low crops; notably, for high crops the database (16 trials) is homogeneous enough to compare the air concentrations between development stages. The mean air concentrations during the first day after the application for vineyards and pome fruit are higher at late development stage than at early stage, possibly due the greater leaf surface area from which evaporation may occur. Only AI11 has been applied in different formulation types, i.e., EC, SC, and SL, however, no effect of formulation type could be determined on the normalized air concentration during the first 24 h.

EFSA (2007) suggests that dry deposition downwind is a function of upwind length of the field. Also Siebers et al. (2003) and European Union regulatory authorities have suggested to consider this parameter. However, in the studies presented here, the samples considered in air concentration estimates were collected from the side of the field with the maximum residues. Since wind directions change over the monitoring time, the upwind length of the field changes depending on the dimensions of the treated plot. Consequently, the way the air concentration measurements are considered for risk assessment purposes, the field sizes or upwind length do not impact the air concentration estimates. A general trend between normalized air concentration during the first 24 h and field size was observed, which is inversely correlated to field size except for the very small plots.

The sample from the side of the plot with the maximum residue, instead of averaging samples from all sides of the field, is used for each sampling period since this represents the worst-case for potential inhalation exposure depending on the wind direction (i.e. exposure is always measured downwind). The 24 h average air concentrations are determined at a static location directly adjacent to the field (in contemporary studies that being 0–10 m). It is extremely unlikely that any person, be it bystander or resident, would spend a full 24 h in a single outdoor location which is also constantly downwind from the treated field. According to EFSA (2007) and (EU 2008), if the wind speed increases by a factor of two, the concentration in the air will decrease by a factor of two, as the same emitted amount is diluted. Since sampling values from the side of the plot with the maximum residue are considered, the impact of wind direction together with wind speed cannot be determined.

Overall, the presented data highlight the fact that there are a number of factors which contribute to vapour concentrations in the air. As shown above, air concentration may correlate to some extent with temperature and leaf coverage for high crops, and inversely with humidity, field size, and leaf-coverage for low crops, but the data indicate that there is a lack of impact of the VP on the first day normalized air concentration estimate. Although attempts have been made to determine correlations, it is a highly complex area, and it is very difficult to determine the impact of each factor/parameter without more focused and standardised experimental design. The presented data indicate relationships between various parameters/conditions, but these were not dedicated experiments to explore this.

The use of means as default values has been discussed previously (Crowley and Holden, 2019; Kluxen et al., 2021); it has the benefit of considering that exposure varies with high exposures on some days and low exposure on others, regressing to an average exposure. It also considers that residents' risk is assessed with reference values based on repeated exposure. Since the Day 1 mean of the current experiment exceeds the 75th percentile, it is also inherently conservative. Other conservatisms are driven by risk assessment assumptions, using, for example, an AOEL of a 90-day study in non-dietary risk assessment corresponds to the same exposure on 90 consecutive days and constant inhalation exposure for 24 h with continuous high breathing rates. The exposure scenario additionally considers 100% retention and absorption via inhalation exposure, i.e. disregarding physico-chemical properties of the volatilized AI that may affect inhalation exposure and consequently systemically available dose (Morris, 2012). The mean value of 0.144 μg/m^3/kg AI applied/ha observed here is similar to normalized air concentrations from sources currently used in setting the default air concentration values (Felkers et al., 2022), e.g. in Siebers et al. (2003), lindane 1.95048 μg/m^3/kg AI applied/ha, parathion 0.50284 μg/m^3/kg AI applied/ha, and pirimicarb 0.2 μg/m^3/kg AI applied/ha; in California EPA (1998), chlorpyrifos 0.73254 μg/m^3/kg AI applied/ha. Hence, a default mean value of 0.144 μg/m^3/kg AI applied/ha for inhalation exposure to vapour, independent of vapour pressure or other factors seems to be supported by the available data.

Comparison of the EFSA (2014, 2022) exposure to vapour calculation approach (i.e. separation for VP, but not kg AI applied/ha) with the new data (i.e. all AIs grouped together, and normalization for kg AI applied/ha applied) for Day 1 exposures for child resident as an example are shown Fig. 10A. This shows the relevance and impact of the application rate in exposure assessment, which is lacking in EFSA guidance. As mentioned above, the current risk assessment approach is that exposure is the same for 90 consecutive days. Assuming an application rate of 1 kg AI/ha, a comparison of the EFSA exposure to vapour calculation approach with the new data on 7 consecutive days for child resident as an example are shown Fig. 10B. This shows the relevance and impact of the decline of air concentration in exposure assessment, which is lacking in EFSA guidance.

The presented dataset is the largest and presumably most robust dataset of measurements taken in the vicinity of the treated area and attributable to a specific application event relevant for European non-dietary risk assessment in realistic scenarios; however, *ipso facto* associated with some caveats:

- The studies were designed for risk assessment refinement of specified products and AIs in realistic scenarios and are not dedicated experiments to investigate factors driving air concentrations for generic models. Hence, the dataset is not balanced, and some critical measurements are missing for some studies, e.g. humidity and temperature, which does not allow us to robustly qualify the effect of these on the air concentration. In addition, the impact of VP on air concentration cannot be investigated without significant bias, i.e. other confounding factors. However, the dataset shows the range of realistic air concentrations due to the variety of physico-chemical properties and environmental conditions covered in the studies.
- Considering LODs as measured values would substantially skew the dissipation: LODs would eventually exceed and outweigh the measured values, as also discussed in Felkers et al. (2022). The difference between the set LOD and LOQ for individual substances was between 3- and 105-fold; therefore, assuming ½ LOQ, the 'estimated' air concentration may add a factor of 1.5–52.5.
- The presented data do not cover AIs with VPs $\geq 10^{-2}$ Pa; however, the data indicate that there is a lack of impact of the VP on the first day normalized air concentration estimate, which was also observed by Carlsen et al. (2006). Consequently, considering the range of VPs covered in the current studies, it can be recommended that an overall average air concentration value is derived without distinguishing VP ranges or grouping. Furthermore, first 24 h air concentration values are the highest compared to the other sampling days, adding to the protective approach.

5. Conclusions

We show that a single default exposure value can be derived for realistic estimates for bystander and resident exposure, which considers the application rate. Although the studies included were designed for risk assessment refinement for specific PPPs, causing the dataset to be heterogeneous, the data generated are relevant to bystander/resident risk assessment since the air concentrations were monitored within the parameters defined by the EFSA guidance (EFSA, 2014a; EFSA et al., 2022) regarding the height, distance, and locations of samplers, and represent relevant climatic conditions and crops for Europe. This provides a level of consistency in the analysis of these data, relevant to determining a refined default value.

For the air concentration value for the first 24 h, which would be used in the non-dietary exposure assessment as a worst case, no robust correlations with VP, temperature, leaf coverage, humidity, and field

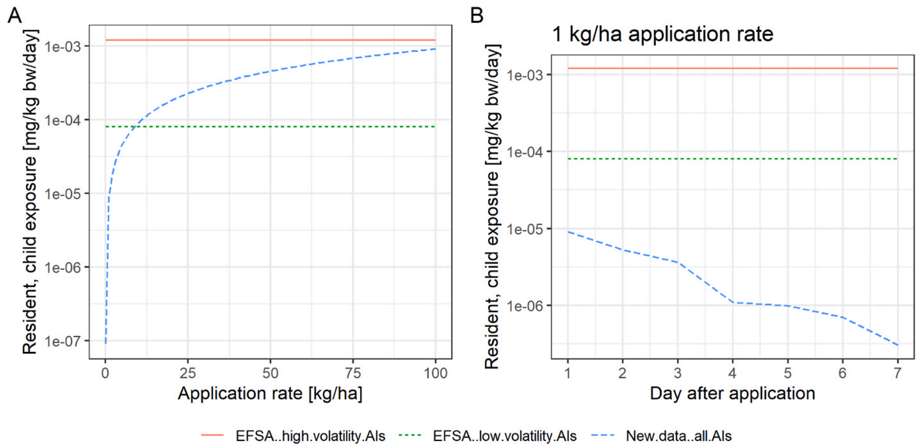

Fig. 10. Comparison of the EFSA (2014, 2022) exposure to vapour calculation approach with the new data for Day 1 exposures for child resident; and a comparison of the EFSA exposure to vapour calculation approach with the new data on 7 consecutive days for child resident assuming an application rate of 1 kg AI/ha.

size were identified.

While the data should allow for robust exposure assessment, more refined modelling approaches would require specific and standardised experimental design to evaluate the effects of temperature, crop type, foliage density, formulation type and other parameters.

In conclusion, this investigation shows that current assessment paradigms considerably overestimate exposure. Data from 29 GLP studies with 11 AIs with VPs ranging from 1.1×10^{-8} to 9×10^{-3} Pa show that a single default air concentration value of 0.144 μg/m^3/kg AI applied/ha can be derived for more realistic inhalation exposure estimates for bystander and resident exposure.

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CRediT authorship contribution statement

Edgars Felkers: Conceptualization, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Felix M. Kluxen:** Conceptualization, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization, Writing – review & editing, Visualization. **Sarah Adham:** Resources, Data curation, Writing – review & editing. **Anne-Kim Vinck:** Resources, Data curation, Writing – review & editing. **Nicola J. Hewitt:** Writing – review & editing. **Neil Morgan:** Resources, Data curation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Edgars Felkers , Felix M. Kluxen, Sarah Adham, Anne-Kim Vinck and Neil Morgan are employees of companies that conduct and evaluate risk assessments for regulatory purposes in the context of authorization and marketing of their companies' products. They contribute as scientific experts to the industry association CropLife Europe for evaluation and development of the state-of-the-art methodology. Nicola Hewitt is a scientific consultant.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2022.105285.

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