Minimizing operator exposure: field data analysis of three Closed Transfer Systems for pesticide mixing and loading

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Supplementary materials S1

Test items

The formulations were SC (suspension concentrate) with 5 L in 5 L containers containing 212 g/L Xylitol (actual content, nominal was 200 g/L) and SL (soluble concentrate) with 10 L in 9000 L containers containing 920 g/L Sorbitol (actual content, nominal was 800 g/L). These were stored at ambient temperature at each location and used within ~1 month of receipt in each country.

Predicted exposure without CTS using the AOEM

The predicted operator exposure for occupational exposure to Sorbitol and Xylitol after M&L was calculated using the AOEM (Großkopf et al. 2013). It was assumed that 100 % of the active substance (a.s.) was bioavailable. The values used were according to the actual amounts (rather than nominal) used in the study.

Study design

The study was conducted under GLP conditions and according to Regulation (EC) No 1107/2009 (EC, 2009) and OECD Guidance Document No. 9 for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application (OECD 1997).

The study was conducted in the second half of 2021. A total of 12 operators in 36 monitoring units at various sites within Europe were monitored for all the activities associated with M&L. 12 operators tested each CTS, which in turn was used to test both products. When Xylitol was tested, the operator handled 3 Xylitol containers and when Sorbitol was tested, each operator handled 25 Sorbitol containers.

To cover a broad range of agronomic conditions and farmer habits within Europe, the study took place in 4 countries at similar times of the year: Bad Sassendorf, Germany (11.10.2021), Polinyà de Xúquer, Spain (08.11.2021), Fresnes-sur-Marne, France (15.11.2021) and Abbenes, The Netherlands (22.11.2021). All samples were sent to a single laboratory for analysis. Air temperature, wind speed and relative humidity were recorded at regular intervals during the monitored activities in all locations.

The number of M&L events performed by each operator was representative of an application to 50 ha, which is considered to be representative of a typical day's work. The monitored activities were conducted using commercial equipment according to their normal procedures under the close supervision of the associated representative of the test facility conducting the study (AgroChemex International Limited). The operators were experienced in the work activities conducted in the study and were given 30 to 60 min training for each CTS, just prior to the monitoring.

The study monitored the M&L for 2 theoretical spray tank volumes (1000 L and 5000 L), which represent the lower and upper range of spray tank volumes which are in regular commercial use. The idea of the 2 tank sizes was to produce data that would show whether there is a statistically relevant difference when the same amount of product is loaded in 2 sessions or in 10 sessions. Half of the 12 operators / CTS system mimicked the use of a 1000 L spray tank to mix the spray solution for the 50 ha target, and the other half of the operators mimicked the use of a 5000 L spray tank to mix the spray solution for the 50 ha target. Each operator performed multiple fillings. The number of mixing/loading events for each operator was based on a theoretical application to 50 ha, which is considered to be representative of a typical day's work. This meant that the number of mixing/loading events was 2 for a spray tank volume of 5000 L and 10 for a spray tank volume of 1000 L. When the operator performed 2 mixing events, each mixing was performed by adding 1.25 x 5 L containers of Xylitol and 12.5 x 10 L containers of Sorbitol. When the operator performed 10 mixing events, each mixing was performed by adding nominally 0.25 x 5 L containers of Xylitol and 2.5 x 10 L containers of Sorbitol.

Operator details

Each operator was given a separate ID number for each CTS type they tested. For example, Operator ID numbers 1, 2 and 3 refer to the same person conducting the test using easyconnect, easyFlow and GoatThroat, respectively. The details of each operator and their ID number are listed in Supplementary Table S1.

Supplementary Table S1 Operator details

Operator identification	Sex	Height (cm)	Weight (kg)	Location
1+2+3	Male	187	103.4	59505 Bad Sassendorf, Germany
4+5+6	Male	185	111.3	59505 Bad Sassendorf, Germany
7+8+9	Male	181	62.2	59505 Bad Sassendorf, Germany
10+11+12	Male	165	93.8	46688 Polinyà de Xúquer, Spain
13+14+15	Male	185	88.2	46688 Polinyà de Xúquer, Spain
16+17+18	Male	180	98.5	46688 Polinyà de Xúquer, Spain
19+20+21	Male	182	77.0	77410 Fresnes-sur-Marne, France
22+23+24	Male	171	76.0	77410 Fresnes-sur-Marne, France
25+26+27	Male	178	80.4	77410 Fresnes-sur-Marne, France
28+29+30	Male	190	86.3	2157 LH Abbenes, The Netherlands
31+32+33	Male	183	90.0	2157 LH Abbenes, The Netherlands
34+35+36	Male	186	109.3	2157 LH Abbenes, The Netherlands

Dermal exposure monitoring

Dermal exposure was measured by operators wearing 2 layers of whole-body dosimeters (pre-washed on a short washing cycle (~60 min) without detergent). The inner dosimeter consisted of full-length cotton underwear garments covering the arms, legs and torso. This was worn over the operator's regular underwear and directly under the outer dosimeter. The outer dosimeter consisted of a cotton (35 %)/polyester (65 %) coverall. This was worn directly over the inner dosimeter. The operators were allowed to wear a cap (at the discretion of the operators), which was not sampled as a dosimeter (only one operator wore a cap). At the end of the monitoring period, the whole-body dosimeters were removed from the workers and either kept whole or sectioned (into arms, legs, front torso and back torso). Each set of body part dosimeter specimens was wrapped in aluminium foil, transferred into a dry polyethylene bag and double bagged. The specimens were placed in temporary frozen storage as soon as possible (within 1 h after completion of the monitored activities) and remained frozen until they were transported under frozen conditions to the analytical laboratory. Specimens were maintained in frozen storage until analysed.

Protective nitrile gloves were worn during the whole M&L activities. Hand exposure was measured by a hand wash method. Since there were no breaks during the monitoring, the operators performed a monitored hand wash at the end of the respective M&L procedure. For each hand wash, 2 x 500 mL of 0.01 % Aerosol OT solution was used to wash the operators' hands. The first 500 mL of the Aerosol OT solution was poured into a stainless-steel bowl and the operators washed their hands in the bowl for approximately 30 seconds. Then, the second 500 mL of the Aerosol OT solution was carefully poured over the operators' hands (whilst the operator washed his hands) and combined with the 500 mL already in the bowl. The combined solutions were mixed and a 100 mL sub-sample was taken into a polyethylene bottle (HDPE) for analysis. The remaining solution was discarded.

Exposure of the head was monitored by collecting face/neck wipe specimens at the end of the respective M&L procedure. For each sample, the face and neck were wiped with 2 gauze pads (each pre-wetted with 4 mL of 0.01 % Aerosol OT solution). The gauze pads were then placed into polyethylene bottles (HDPE) and transferred to freezer storage. The gauze pads were 8 ply, 10 cm x 10 cm (Medicare Plus, Type 13, Light BP).

Field fortifications

Field fortifications were performed on 3 days during the 5 days of monitoring in each country coinciding with the first day of monitoring for each operator. These were performed to demonstrate the stability of xylitol and sorbitol under the environmental conditions existing during the exposure monitoring period. Inner and outer dosimeter material, gloves, hand wash solutions and face wipes were fortified in triplicate at a low, medium and high fortification rate (0.1, 10 and 1000 µg/mL, respectively). A single control sample was also added for each matrix. These specimens were exposed to the same environmental conditions and for the same period of time as the respective operator dosimeters. The overall mean field recovery at each level for the 3 days of fortification in each country was used for any possible correction of the operator results, since the environmental conditions are considered similar during the monitoring in each country (i.e., the monitored activities were performed under cover within a barn in each country).

The field fortification values performed on 3 days of monitoring in each country for inner and outer dosimeter material, nitrile gloves, face wipes and hand wash samples are shown in Supplementary Table S2. As for the travel fortification values, the lower fortification rates were impacted by the background values; therefore, the recovery could not be calculated. However, the results at these fortification levels are generally not relevant for the correction of the operator samples, except for some hand wash samples and outer dosimeter samples. This result was considered not to impact the study outcome. The mean recovery of Sorbitol and Xylitol for the 2 higher fortification rates ranged between 93–135 % and 90–141 %, respectively.

Supplementary Table S2 Results of the field fortification experiments

Country	Matrix	Fortification rate (µg) / (µg/L)	Mean recovery (%) Sorbitol				Mean recovery (%) Xylitol			
			Day 1	Day 2	Day 3	**Mean**	Day 1	Day 2	Day 3	**Mean**
Germany	Inner dosimeter	0.01	[1]	[1]	[1]		[1]	[1]	[1]	
		0.1	[1]	[1]	[1]		[1]	[1]	[1]	
		10	128[2]	117[2]	125[2]	**123**	124[2]	105[2]	110[2]	**113**
	Outer dosimeter	0.01	[1]	[1]	[1]		[1]	[1]	[1]	
		1	[1]	[1]	[1]		[1]	[1]	[1]	
		100	112[2]	116[2]	118[2]	**115**	128[2]	1252	169[2]	**141**
	Gloves	0.1	[1]	[1]	[1]		[1]	[1]	[1]	
		10	95[2]	89[2]	95[2]	**93**	99[2]	95[2]	96[2]	**97**
		1000	98[2]	93[2]	89[2]	**93**	95[2]	89[2]	93[2]	**92**
	Face wipe	0.02	[1]	[1]	[1]		[1]	[1]	[1]	
		2	123[2]	[1]	113[2]	**118**	123[2]	[1]	126[2]	**125**
		200	117[2]	116[2]	112[2]	**115**	119[2]	115[2]	115[2]	**116**
	Hand wash	0.4	[1]	[1]	[1]		[1]	[1]	[1]	
		40	101[2]	107[2]	100[2]	**103**	106[2]	113[2]	109[2]	**109**
		4000	99[2]	99[2]	102[2]	**100**	99[2]	98[2]	107[2]	**101**
Spain	Inner dosimeter	0.01	[1]	[1]	[1]		[1]	[1]	[1]	
		0.1	[1]	[1]	[1]		[1]	[1]	[1]	

		10	128[2]	122[2]	120[2]	**123**	122[2]	127[2]	139[2]	**129**
	Outer dosimeter	0.01	[1]	[1]	[1]		[1]	[1]	[1]	
		1	[1]	[1]	[1]		[1]	[1]	[1]	
		100	117[2]	124[2]	128[2]	**123**	126[2]	124[2]	128[2]	**126**
	Gloves	0.1	[1]	[1]	[1]		[1]	[1]	[1]	
		10	88[2]	106[2]	111[2]	**102**	97[2]	106[2]	102[2]	**102**
		1000	94[2]	99[2]	88[2]	**94**	93[2]	93[2]	84[2]	**90**
	Face wipe	0.02	[1]	[1]	[1]		[1]	[1]	[1]	
		2	118[2]	117[2]	121[2]	**119**	127[2]	123[2]	125[2]	**125**
		200	107[2]	108[2]	111[2]	**109**	110[2]	111[2]	110[2]	**110**
	Hand wash	0.4	[1]	[1]	[1]		[1]	[1]	[1]	
		40	97[2]	96[2]	98[2]	**97**	106[2]	101[2]	115[2]	**107**
		4000	96[2]	93[2]	101[2]	**97**	98[2]	97[2]	105[2]	**100**
France	Inner dosimeter	0.01	[1]	[1]	[1]		[1]	[1]	[1]	
		0.1	[1]	[1]	[1]		[1]	[1]	[1]	
		10	145[2]	136[2]	125[2]	**135**	132[2]	113[2]	133[2]	**126**
	Outer dosimeter	0.01	[1]	[1]	[1]		[1]	[1]	[1]	
		1	[1]	[1]	[1]		[1]	[1]	[1]	
		100	123[2]	122[2]	117[2]	**121**	114[2]	113[2]	118[2]	**115**
	Gloves	0.1	[1]	[1]	[1]		[1]	[1]	[1]	
		10	116[2]	108[2]	109[2]	**111**	113[2]	105[2]	110[2]	**109**
		1000	102[2]	104[2]	87[2]	**98**	98[2]	98[2]	95[2]	**97**
	Face wipe	0.02	[1]	[1]	[1]		[1]	[1]	[1]	
		2	130[2]	129[2]	117[2]	**125**	131[2]	123[2]	120[2]	**125**
		200	113[2]	110[2]	103[2]	**109**	114[2]	114[2]	106[2]	**111**
	Hand wash	0.4	[1]	[1]	[1]		[1]	[1]	[1]	
		40	102[2]	96[2]	112[2]	**103**	116[2]	114[2]	114[2]	**115**
		4000	102[2]	94[2]	97[2]	**98**	95[2]	97[2]	99[2]	**97**

[1]The background levels of sorbitol and xylitol relative to the fortification level have significantly interfered with the recovery, therefore, the results are compromised and unusable.

[2]The background levels of sorbitol and xylitol are ≤ 10 % of the fortification rate (except day 1 and 2 for outer dosimeters where there seems to be a contamination of the control samples), therefore the fortification results are considered valid and demonstrate the stability of xylitol and sorbitol under the environmental conditions during monitoring and during shipment and storage prior to analysis. These fortification levels generally reflect the residues detected in the operator samples.

Travel fortifications

Travel fortifications were performed on the first day of monitoring in each country for the inner and outer dosimeters and gloves only. These travel fortifications were performed to demonstrate the stability of xylitol and sorbitol under the transportation and storage conditions prior to the start of the analytical phase. Each matrix (dosimeter) type was fortified in triplicate at the low and high rate. A single control sample was also added for each

matrix. These specimens were frozen immediately after fortification and were used to determine the stability of Xylitol and Sorbitol under the conditions of frozen shipment and storage prior to analysis. The travel fortifications were analysed after all the operator dosimeter specimens were analysed. Packaging, storage and shipment of the travel fortification specimens was conducted in the same way as for the operator specimens.

The travel fortification values performed on the first day of monitoring in each country for inner and outer dosimeter material and nitrile gloves are shown in Supplementary Table S3. For the lower fortification rates, the background levels of Sorbitol and Xylitol relative to the fortification level significantly interfered with the recovery and therefore could not be used to conclude on their stability. By contrast, the background levels of Sorbitol and Xylitol are ≤ 10 % of the higher fortification level (except in Germany for outer dosimeters where there was a contamination of the control samples). The mean recovery of Sorbitol and Xylitol ranged between 91–136 % and 88–135 %, respectively. These demonstrate the stability of Sorbitol and Xylitol under the transportation and storage conditions prior to the start of the analytical phase.

Supplementary Table S3 Summarized results of the travel fortification experiments

Country	Matrix	Fortification rate (µg)	Sorbitol Mean recovery (%)	Xylitol Mean recovery (%)
Germany	Inner dosimeter	0.01	[1]	[1]
		10	1362	1182
	Outer dosimeter	0.01	[1]	[1]
		100	1132	1162
	Gloves	0.1	[1]	[1]
		1000	912	902
Spain	Inner dosimeter	0.01	[1]	[1]
		10	1262	1302
	Outer dosimeter	0.01	[1]	[1]
		100	1162	1212
	Gloves	0.1	[1]	[1]
		1000	962	882
France	Inner dosimeter	0.01	[1]	[1]
		10	1402	1352
	Outer dosimeter	0.01	[1]	[1]
		100	1132	1082
	Gloves	0.1	[1]	[1]
		1000	962	922
The Netherlands	Inner dosimeter	0.01	[1]	[1]
		10	1172	1182
	Outer dosimeter	0.01	[1]	[1]
		100	1162	1142
	Gloves	0.1	[1]	[1]
		1000	932	952

[1]The background levels of sorbitol and xylitol relative to the fortification level significantly interfered with the recovery, therefore, the results are compromised and unusable.
[2]The background levels of sorbitol and xylitol are ≤10% of the fortification level (except in Germany for outer dosimeters where there seems to be a contamination of the control samples) and therefore the fortification results are considered valid.

Background residues

The background levels of sorbitol and xylitol are summarised in Supplementary Table S4.

Supplementary Table S4 Background levels of sorbitol (a) and xylitol (b) in inner and outer dosimeters

(a) Background values for Sorbitol

	Outer Dosimeter					**Inner Dosimeter**				
	dosimeter		**patch**			**dosimeter**		**patch**		
	µg Total	µg per g	µg Patch	µg per g	equivalent to µg per dosimeter	**µg Total**	µg per g	µg Patch	µg per g	equivalent to µg per dosimeter
maximum	76438	83	63	25	23028	187	0.5	1.1	0.5	191
median	1498	1.6	2.5	1.0	919	36	0.1	0.7	0.4	128
25thcentile	334	0.4	0.9	0.4	337	27	0.1	0.5	0.3	95
5thcentile	211	0.2	0.5	0.2	145	18	0.0	0.4	0.2	70
minimum	143	0.15	0.39	0.16	145	14	0.04	0.39	0.20	70

(b) Background values for Xylitol

	Outer Dosimeter Xylitol					**Inner Dosimeter Xylitol**				
	dosimeter		**patch**			**dosimeter**		**patch**		
	µg Total	µg per g	µg Patch	µg per g	equivalent to µg per dosimeter	**µg Total**	µg per g	µg Patch	µg per g	equivalent to µg per dosimeter
maximum	10499	11	166	66	61163	61	0.2	1.4	0.7	257
median	103	0.1	3.4	1.4	1255	22	0.1	0.6	0.3	103
25thcentile	62	0.1	0.4	0.2	141	19	0.1	0.5	0.2	87
5thcentile	45	0.0	0.2	0.1	76	15	0.0	0.4	0.2	59
minimum	29	0.03	0.21	0.08	76	13	0.04	0.33	0.16	59

Analytical methods

The inner and outer dosimeter samples were extracted with water/acetonitrile (75/25; v/v) using a ratio of 10 mL extraction solvent per gram of dosimeter matrix. Clean-up was performed by filtration using a PTFE syringe filter and an aliquot of the extract was diluted into isotopically labelled internal standard. The nitrile glove samples were extracted with water using a ratio of 200 mL extraction solvent per glove. An aliquot of the extract was diluted into isotopically labelled internal standard. The face and neck wipes samples were extracted with water/acetonitrile (75/25; v/v) using a ratio of 40 mL extraction solvent per two gauze pads. An aliquot of the extract was diluted into isotopically labelled internal standard. An aliquot of the hand wash sample was concentrated (if necessary) until dryness and dissolved into isotopically labelled internal standard, or an aliquot was directly diluted into isotopically labelled internal standard. Four replicates of the outer dosimeter and one replicate for the remaining measurements were conducted.

Quantification was by LC-MS/MS. Isotopically labelled internal standards (10 ng/mL [$^{13}C_6$]Sorbitol and 50 ng/mL [$^{13}C_5$]Xylitol) were used for quantification so that possible matrix effects on determination are automatically

accounted for when using the response ratio of analyte and internal standard for quantification. The HPLC system was an Agilent Infinity 1290 Series HPLC system (vacuum solvent degasser, binary HPLC pump, Multisampler, Multicolumn Thermostat). LC was performed in the gradient mode using 0.1% acetic acid in 10 mM ammonium formate (solvent A) and acetonitrile/Water (9/1, v/v) containing 10 mM Ammonium Formate (solvent B); the pump flow rate was set at 600 µL/min between 0.0 and 2.5 min and increased to 600 µL/min by 5.0 min until the end of the run. The gradient was as follows: Initial = 30 % A; 2.0 min = 45 % A; 2.5 min = 45% A; 5.0 min = 75 % A; 6.0 min = 75 % A; 6.1 min = 30 % A; 8.0 = 30 % A. Separation was performed on a Waters BEH Amide column (150 mm x 3 mm, 1.7 µm) and Phenomenex C18 guard column heated to 40°C. The sample injection volume was 10 µL. Mass spectrometry was performed on a TripleQuad SelexION 6500+ System, SCIEX (Triple quadrupole mass spectrometer) equipped with an Electrospray ionisation (ESI, TurboIonSpray) connected to a PC running standard software. Samples were analysed in the negative ionization mode. The MS was operated in the full scan MS/MS Multiple Reaction Monitoring (MRM) mode. The m/z values for the [M-H]- ion of Sorbitol and Xylitol were 181→89 and 151→89, respectively. Due to chromatographic interference of Xylitol at the mass transition m/z 151→89, the mass transition m/z 151 → 101 was used for the quantification of OPEX matrices inner dosimeter, face/neck wipes, gloves and hand wash solutions.

The limits of quantification (LOQ) and limit of detection (LOD) for Xylitol and Sorbitol were the same for each type of sample collected. For patches, the LOQ was 0.1 µg/100 cm^2 patch and the LOD was 0.022 µg/100 cm^2 patch for inner dosimeter material and 0.028 µg/100 cm^2 patch for outer dosimeter material. For gloves, the LOQ and LOD were 1.0 µg/glove and 0.27 µg/glove, respectively. For gauze pads, the LOQ and LOD were 0.2 µg per two gauze pads and 0.053 µg per two gauze pads, respectively. For liquids, the LOQ and LOQ were 0.4 µg/L and 0.080 µg/L, respectively.

All specimens were analysed in suitably sized batches together with control specimens fortified with sorbitol and xylitol which acted as procedural recoveries. The overall mean procedural recoveries for each matrix and for each analyte were all between 97% and 109%. The RSD ranged between 6% and 11%. Therefore, the analytical efficiency is proven on the days of sample analysis. The calibration curves obtained for both analytes and all matrices were shown to be linear over the range 0.80 to 75 ng/mL for hand wash and 1 to 100 ng/ml for inner and outer dosimeter, nitrile gloves and face/neck wipes, with correlation coefficient, $R^2 \geq 0.99$.

Calculations

The reduction in (potential and actual) exposure using the three CTS forms were calculated as follows:

$$\%\ Reduction\ in\ exposure\ = \left(1 - \frac{Measured\ exposure}{AOEM\ predicted\ exposure}\right) \times 100$$

EC (2009) Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 Oct 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC

Großkopf C, Mielke H, Westphal D, Erdtmann-Vourliotis M, Hamey P, Bouneb F, Martin S (2013) A new model for the prediction of agricultural operator exposure during professional application of plant protection products in outdoor crops. J Verbrauch Lebensm 8(3):143-153. https://doi.org/10.1007/s00003-013-0836-x

OECD (1997) Series on Testing and Assessment No. 9 ”Guidance document on the conduct of studies of occupational exposure to pesticides during agricultural application ”, Paris 1997. OCDE/GD(97)148, SANTE/2020/12830, rev.1