Relevant Impurity Toluene in Formulations

DAPA Small Scale Study R-204-87-12

Small Scale Collaborative Study for the Determination of the relevant Impurity Toluene in Formulations by Headspace GC-FID

Report to DAPA

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1. Participants

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Dr. P. Wagener	Bayer CropScience AG	Frankfurt a.M., Germany
Dr. C. Vinke	BVL	Braunschweig, Germany
H. Unterweger	AGES	Vienna, Austria
Dr. R. Kettner	Syngenta Crop Protection Münchwilen AG	Münchwilen, Switzerland
Dr. R. Förster	BASF AG	Limburgerhof, Germany
T.J. Bowen	Bayer CropScience AG	Frankfurt a.M., Germany
Dr. U. Schaller	Agroscope	Wädenswil, Switzerland

Laboratories were identified by a confidential number prior to the trial commencing

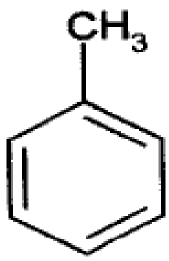
2. Active Ingredient, General Information

IUPAC name: methylbenzene

ISO common name: toluene

CAS-Nr.: 108-88-3

Structure:



Molecular mass: 92.1
Empirical formula: C_7H_8

3. Samples

In February 2013 the following formulations were sent to the 8 participants:

1. EC 250 g/l
2. EC 400 g/l
3. FS 080 g/l
4. SC 250 g/l
5. WG 50
6. Ethylbenzene internal standard

In April 2013 results were obtained from 8 participants.

4. Method

4.1 Scope

Determination of the content of the relevant impurity toluene in formulations.

4.2 Principle

Determination of Toluene with internal standard, by standard addition mode.

4.3 Procedure for the collaborative trial

Each sample should be analysed twice on two different days. The solutions should be injected twice and analysed as follows:

L_{0_1} L_{0_2} L_{1_1} L_{1_2} L_{2_1} L_{2_2} L_{3_1} L_{3_2} L_{4_1} L_{4_2} L_{5_1} L_{5_2}

Level 0	sample without toluene addition		
Level 1	2.5 µg Toluene / ml	=	0.05 % Toluene in relation to AI
Level 2	5 µg Toluene / ml	=	0.10% Toluene in relation to AI
Level 3	12.5 µg Toluene / ml	=	0.25% Toluene in relation to AI
Level 4	25 µg Toluene / ml	=	0.50% Toluene in relation to AI
Level 5	50 µg Toluene / ml	=	1.00% Toluene in relation to AI

5. Remarks of the Participants

Laboratory 1	gas syringe used
Laboratory 2	gas syringe used
Laboratory 3	gas syringe used
Laboratory 4	gas syringe used , 60 m length, 0.25 mm i.d. film thickness: 0.25 µm, stationary phase: Rtx-5; MS detector, ethylbenzene and d_8-toluene as internal standard
Laboratory 5	none.
Laboratory 6	gas syringe used
Laboratory 7	gas syringe used
Laboratory 8	gas syringe, experimental adaptions to autosampler necessary, MS-detector

6. Evaluation and Discussion

Any deviations applied by the participants were not considered to have any adverse effect on the chromatography and consequently on the results.

Various formulation types were tested to demonstrate the selectivity of the analytical method. Matrix effects are eliminated by the headspace technique and by the quantification using standard addition method

Linearity and accuracy are simultaneously determined in the standard addition mode to ensure validity of results.

Different headspace autosampler types can be used to perform the analysis. However, a fine tuning of essential parameters shall be evaluated prior to a CIPAC collaborative study. Especially for those using a gas syringe and PAL autosampler a list of parameters will be recommended.

Laboratory 4 used d8-toluene and ethylbenzene as internal standards. The data obtained with the ethylbenzene internal standard were used in the statistical evaluation. The results obtained with the d8 toluene internal standard are essentially similar.

Laboratory 8 sent back the results of one day only and was therefore not included in the statistical evaluation. Ethylbenzene as internal standard and MS detection were used. These data are in line with the results of the other labs and support those.

Laboratories 2 and 7 sent back the results of one day only for the FS 080 formulation, the data were included in the statistical evaluation.

GC-MS with ethylbenzene or d8-toluene as internal standard can be used as alternatives to GC-FID, as shown by laboratories 4 and 8. Comparable results were obtained with both detection techniques.

The statistical evaluation was done in accordance with DIN ISO 5725.

9 sample sets were sent out with 8 laboratories sending back results within the requested timeframe. The results, statistical evaluation and figures are to be found in appendix A.

Five results were identified as outliers (Dixon test and Cochran variance homogeneity test). It is assumed that headspace autosampler parameters may be responsible for these outliers and that they need to be specified more precisely to cover the different types of Headspace sampling.
No results were eliminated for the EC 400 formulation which contained toluene at a very low concentration level (approx. 0.16 g/kg related to the active ingredient).

After having eliminated outliers from the data set, the evaluation of RSD showed that both the repeatability and reproducibility are within an acceptable range for determination of the relevant impurity toluene at low levels although the Horwitz criteria is met in one case only.

Based on the feedback of the study participants, it was decided to modify chromatographic parameters and the sample preparation scheme in order to speed up analysis time and to reduce workload for the personnel.

The DAPA-group is convinced that this Headspace-method is able to quantify toluene in all kind of formulation types and can be used with different Headspace-sampling devices and with FID or MS detection.

7. Conclusions

Update of the analytical method with the essential parameters for various autosampler types.

Update of the chromatographic and sample preparation parameters to speed up analysis and preparation time.

Based upon the results of this Pilot Study it is proposed to perform a CIPAC collaborative study to determine the relevant impurity toluene at low levels in various formulation types.

8. Appendix A
Tables and Figures for the relevant impurity Toluene

Table 1: Toluene content of the formulations [g/kg]

	EC 250		EC 400		FS 080		SC 250		WG 50	
	Day1	Day2	Day1	Day2	Day1	Day2	Day1	Day2	Day1	Day2
Laboratory 1	0.6400	0.6848	0.0550	0.0580	0.0120	0.0110	0.1000	0.1040	0.2200	0.2120
Laboratory 2	0.5580	0.6190	0.0680	0.0570	0.0120		0.0900	0.0980	0.2300	0.2130
Laboratory 3	0.6780	0.6770	0.0490	0.0600	0.0120	0.0120	0.1100	0.1210	0.2340	0.2280
Laboratory 4	0.3700	0.3450	0.0280	0.0303	0.0100	0.0100	0.0790	0.0900	0.2600	0.2260
Laboratory 5	0.5175	0.5743	0.0300	0.0279	0.0105	0.0100	0.0789	0.0894	0.1875	0.2042
Laboratory 6	0.7270	0.6820	0.0710	0.0840	0.0220	0.0210	0.1830	0.2100	0.4880	0.5190
Laboratory 7	0.6770	0.5890	0.0650	0.0310	0.012		0.0970	0.0890	0.2390	0.1560
Laboratory 8	0.5370		0.0540		0.0110		0.0940		0.2060	

Table 2: Mean values of the toluene concentration [g/kg]

	EC 250	EC 400	FS 080	SC 250	WG 50
Laboratory 1	0.6624	0.0565	0.0115	0.1020	0.2160
Laboratory 2	0.5885	0.0625	0.0120	0.0940	0.2215
Laboratory 3	0.6775	0.0545	0.0120	0.115	0.2310
Laboratory 4	0.3575++	0.0292	0.0100	0.0845	0.2430
Laboratory 5	0.5459	0.0290	0.0103	0.0942	0.1959
Laboratory 6	0.7045	0.0775	0.0215++	0.1965++	0.5035++
Laboratory 7	0.6330	0.0480	0.0120	0.0930	0.1975+
Laboratory 8					

\+ outlier according to the Dixon test
++ outlier according to the Cochran variance homogeneity test

Table 3: Summary of the statistical evaluation
no elimination of any outliers

	EC 250	**EC 400**	**FS 080**	**SC 250**	**WG 50**
Xm[g/kg]	0.596	0.051	0.013	0.100	0.262
L	7	7	7	7	7
Sr	0.0371	0.0106	0.0004	0.0094	0.0263
S_L	0.1151	0.0159	0.0039	0.0391	0.1078
S_R	0.1210	0.0191	0.0040	0.0402	0.1110
r	0.1041	0.0298	0.0011	0.0262	0.0736
R	0.3387	0.0535	0.0111	0.1126	0.3108
RSD_r	6.24	20.86	3.14	8.51	10.18
RSD_R	20.31	37.45	31.06	36.57	42.96
$RSD_{R(Hor)}$	6.12	8.85	10.91	7.89	6.94

x_m = overall sample mean
L = number of laboratories
s_r = repeatability standard deviation
s_L = “pure” between laboratory standard deviation
s_R = reproducibility standard deviation
r = repeatability limit
R = reproducibility limit
RSD_r = relative repeatability standard deviation
RSD_R = relative reproducibility standard deviation
RSD_R(Hor) = relative reproducibility standard deviation (Horwitz equation)

Table 4: Summary of the statistical evaluation elimination of outliers according to Dixon- and Cochran-test

	EC 250	**EC 400**	**FS 080**	**SC 250**	**WG 50**
Xm[g/kg]	0.635	0.051	0.011	0.100	0.221
L	6	7	6	6	5
Sr	0.0395	0.0106	0.0003	0.0064	0.0135
S_L	0.0521	0.0159	0.0009	0.0109	0.0148
S_R	0.0654	0.0191	0.0010	0.0127	0.0200
r	0.1106	0.0298	0.0009	0.0180	0.0378
R	0.1831	0.0535	0.0027	0.0355	0.0561
RSD_r	6.22	20.86	2.86	6.73	6.10
RSD_R	10.30	37.45	8.46	13.27	9.05
$RSD_{R(Hor)}$	6.06	8.85	11.11	8.06	7.10

x_m	=	overall sample mean
L	=	number of laboratories
s_r	=	repeatability standard deviation
s_L	=	“pure” between laboratory standard deviation
s_R	=	reproducibility standard deviation
r	=	repeatability limit
R	=	reproducibility limit
RSD_r	=	relative repeatability standard deviation
RSD_R	=	relative reproducibility standard deviation
RSD_R(Hor)	=	relative reproducibility standard deviation (Horwitz equation)

Fig. 1: Results of the sample EC 250 (see table 3 for the evaluation)

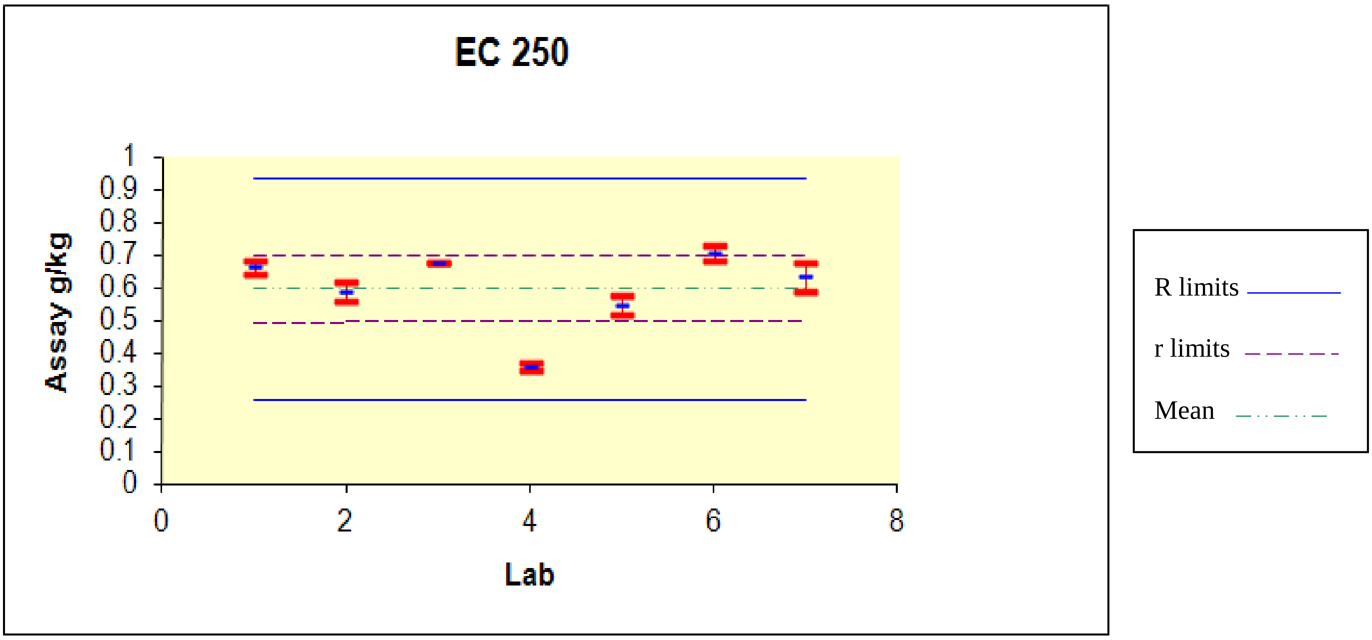


Fig. 2: Results of the sample EC 400 (see table 3 for the evaluation)

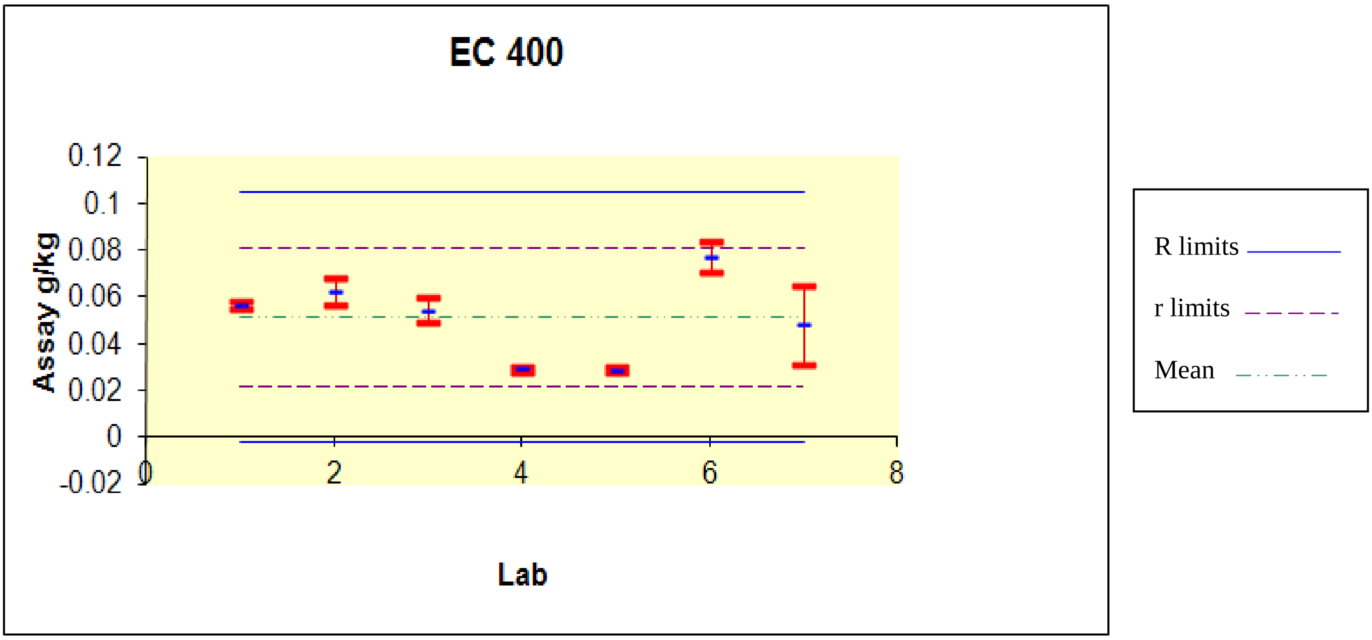


Fig. 3: Results of the sample FS 080 (see table 3 for the evaluation)

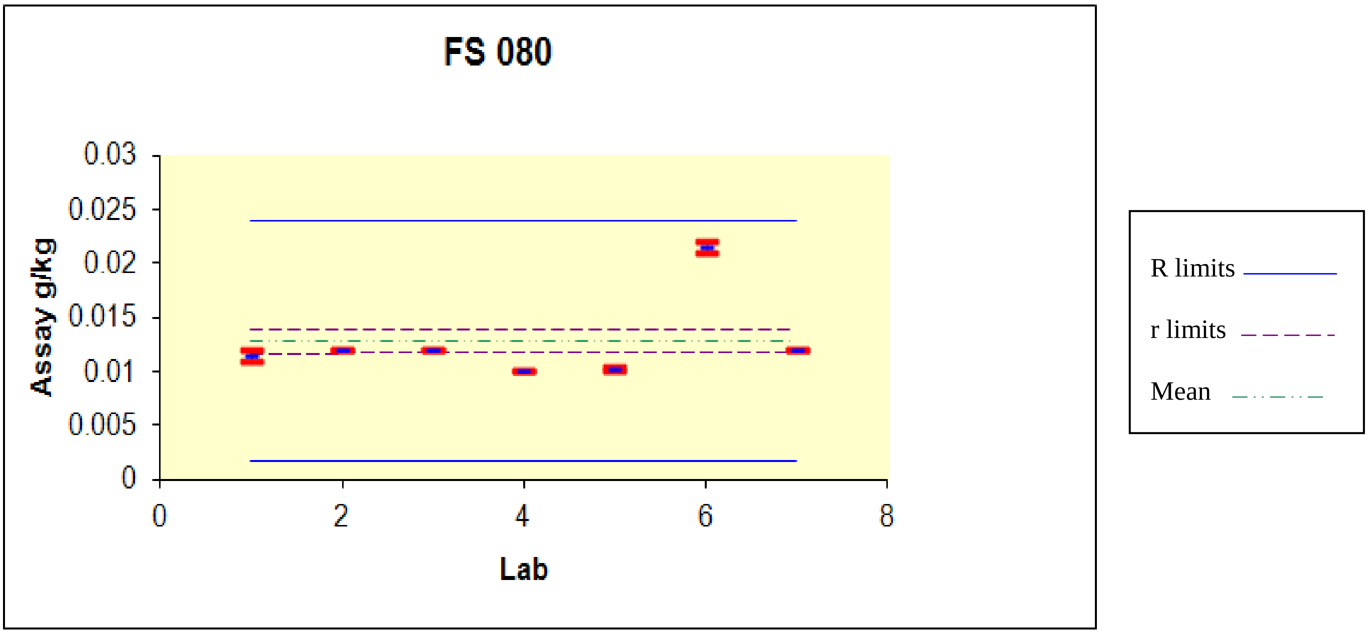


Fig. 4: Results of the sample SC 250 (see table 3 for the evaluation)

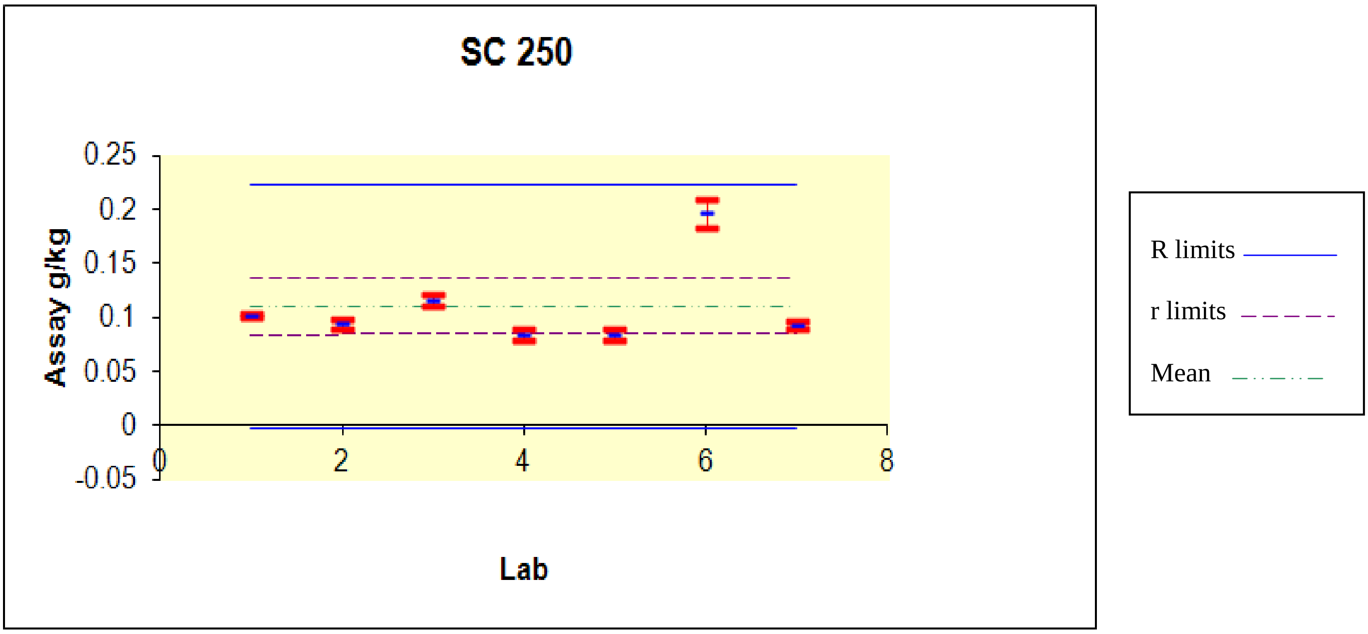


Fig. 5: Results of the sample WG 50 (see table 3 for the evaluation)