

# CIPAC MT STATUS REPORT

28/10/2015

## MT 198 Toluene-relevant impurity in formulations

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Allocated to DAPA

CIPAC methods published in:

Not published

**CIPAC** 58<sup>th</sup> meeting, June 2014 in Liège

Mr Kettner presented the results of a **full scale** collaborative study on the determination of toluene in formulations by headspace GC with FID or MS detection. The study was conducted in collaboration with DAPA.

Two samples of EC, 1 sample of FS, 1 sample of WG and 1 sample of SC were provided. Each formulation contained different active ingredients and was therefore predicted to contain a different level of toluene. 13 laboratories participated in the trial.

The following remarks were received from the laboratories:

- Lab 4: Nitrogen instead of helium used as carrier gas. Recommendation to extend the time of the temperature program (formulation EC2)
- Lab 5: Injection volume 500 µl instead of 1000 µl; chromatography shortened due to MS detection, toluene-d8 used as internal standard.
- The data were also evaluated by external calibration (using the internal standard D<sub>8</sub>-toluene). The results generated were comparable to those obtained by standard addition.  
Column: DB5, 30 m, 0.32 mm, film thickness 0.25 µm – temp program adjusted.
- Lab 6: Column: ZB-624, 60 m, 0.32 mm, film thickness 1.8 µm; Split ratio: 15:1
- Lab 8: Carrier gas: hydrogen, shaking time: 12 s, split ratio 5:1
- Lab 9: Analysis also performed with MS detection
- Lab 10: Column: BGB 5, 30 m, 0.32 mm, film thickness 0.25 µm - temp program adjusted.  
Split ratio: 50:1
- Lab 12: Column: DB-624, 30 m, 0.25 mm, film thickness 1.4 µm
- Lab 13: Hold time of final column temperature increased.

A mixture of fixed transfer line (5 labs) and gas syringe (8 labs) auto samplers and FID (9 labs) or MS (4 labs) detection were used.

The statistical evaluation was carried out according to the CIPAC guidelines. The following outliers and stragglers were identified:

For the EC1 Lab 7 was identified as a Mandel's k-straggler

For the EC2 Lab 6 and Lab 12 were identified as Mandel's k-stragglers

For the FS Lab 5, Lab 9 and Lab 12 were identified as Mandel's k-stragglers

For the SC Lab 12 was identified as a Mandel's k-outlier

For the WG Lab 6 was identified as a Mandel's k-straggler

All results were initially included in the evaluation. In the initial evaluation the Horwitz criteria were not met for any samples. When the outliers were removed from the statistical calculations the Horwitz criteria were met for the FS, SC and WG sample. The % RSD<sub>R</sub> for both EC-formulations tested was slightly above the Horwitz value after elimination of stragglers/outliers.

Mr Kettner proposed that due to the universal applicability of the method (all formulation types), the use of different sampling devices for the headspace-technique (fixed transfer line or gastight syringe) and the use of different detectors (FID or MS), a slightly higher coefficient of variation in this collaborative trial is acceptable.

Based on the results of this CIPAC collaborative study, DAPA consider this method to be fit for use and recommend that it be accepted as a provisional CIPAC MT-method for the determination of toluene as relevant impurity of the active ingredient at low levels in solid formulated products and in aqueous and organic solvent based liquid formulated products

The following comments were received from the meeting:

- Why do you recommend that labs use heavy toluene as an internal standard instead of ethylbenzene which is cheaper? Mr Kettner replied that it is only a recommendation for labs to use this if it is available

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- It would be preferred if you do not mention “relevant” impurity in the title of the method. It is outside of the remit of CIPAC to address whether an impurity is relevant or not, CIPAC’s role is to develop and collaboratively test methods.
- You mention that for one a.s there is a limit of maximum 0.5% toluene. This seems odd to me. Mr Kettner replied that the limits are set as part of the regulatory process in the EU.
- On the basis of all the results using either GC-FID or GC-MS could you see any significant difference between the two detection techniques? Mr Kettner replied that there was no significant difference and that if laboratories had both detection systems either would be suitable to use.

The closed meeting discussed the comments received during the open meeting.

It was agreed that CIPAC should not state that the method is for a relevant impurity in the title as whether or not a compound is a relevant impurity is for regulatory authorities to decide and not CIPAC. It was agreed that the method will be published as an MT method for the determination of toluene in certain formulation types.

Decision: The headspace GC method (CIPAC/4944) for the determination of toluene in formulations was accepted as a **provisional** CIPAC MT method.

**CIPAC** 59<sup>th</sup> meeting, June 2015 in Athens

At the 58<sup>th</sup> meeting, 2014 in Liège the method was adopted as provisional. Mr Hänel remarked that the method target is not residue or impurity testing. No further comments were received.

Decision: The method can be promoted to a **full CIPAC method**.