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# 5 Batch Analysis

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## Guidance to the manufacturer and the testing laboratories

The term **'5 – batch analysis'** originates from the US EPA guidelines for testing of pesticides. The term is accepted now by most regulatory bodies like EEC, Indian registration authorities namely CIB & RC and other countries as well. There are no guidelines of OECD for this study. The study is essential to determine the composition of the product with respect to the active ingredient and its associated impurities.

**Background**

In the early framing of the guidelines for the composition of the technical grade pesticides ( With respect .to) the active ingredient and its associated impurities up to the level of 0.01% were suggested by US EPA. However, industries showed their inability to comply with this and suggested 0.1% levels for impurities. For toxic impurities ( like dioxins, nitroso amines ) the levels will be lower be than this. For impurities that cannot be characterized easily a gross description is accepted. E.g. 'polymeric impurities containing carbon, nitrogen, hydrogen and oxygen'. The main concern is the consistency of the product that should be maintained by the manufacturer of the technical grade pesticide.

**Introduction**

The 5 – batch analysis is that first step in determining the composition of a technical grade product of a manufacturer. The study is useful in setting up the specification of the impurity levels ( at least maximum content ). The report of the study are also required for registration of a technical grade pesticide.

## Performing the 5-Batch Analysis

The 5-batch analysis may be performed while registering a new product developed by a manufacturer[6-9] or for an existing product of another manufacturer made by still another manufacturer. The second case is commonly required for a generic product (the product that is out of patent validity period ). There are me too registrations permitted in most countries. In this case, one has also to match the composition wrt to the composition of the material that is previously registered. The data may be generated on the 5-batches of the final process developed in R&D. It is preferable to use pilot plant batches to the development samples from R&D.

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One of the batches can also be used for physic chemical properties and the safety(toxicity) data generation. It is still better to use the manufacturing plant bathes for this purpose. The data needs to be generated **again** if there are changes in the process, equipment or raw material quality that can result in different composition e.g., the Dow had a process of Chlorpyrifos Technical based on the chlorination of pyridine forming the penultimate intermediate 3,5,6-Trichloropyridin-2-ol(TCP). That process in now replaced with acrylonitrile and trichloroacetyl chloride telomerisation process for the penultimate intermediate – TCP.

**Selection of Batches for the 5 –Batch Analysis Study**

The selection of the five batches of a technical grade pesticide is from the manufacturing produced by the standard process using the raw materials supplied by the approved vendors and passing the specifications. The pilot plant or R&D batches(that are standardized and finalized) may also be used in the development Phases. For a continuous process the lots produced at different time may be used.

## 5 BATCH ANALYSIS – Guidance to the Manufactures and the Testing laboratories

**Developing the method of Analysis for the 5-Batch Analysis**

The methods of analysis of the 5-Batches are one that are selective and specific to the contents. Different complementary methods may be used e.g. HPLC with UV or preferably a DAD (PDA) detector with complementary LC-MS/MS or GC with FID/ECD/NPD/FPD with complementary GC-MS/MS, ICP with complementary ICP-MS Techniques like HPTLC have their use in many analyses where non-eluting impurities like residual solvent and decomposition products that are volatile in nature. At least two methods are to be used for identification and quantitation of the components.

In developing the methods of 5-Bathc analysis it is necessary t ensure that all the possible impurities can be analysed by the methods should be preferably complementary like GC-FID and GC-MS-MS or GC-ECD(Complementary ) and HPLC UV-VIS(DAD) complimented by LC-MS-MS.

A PRODUCT LIKE Chlorpyrifos Technical can be analysed by GC- FID because all impurities are stable to heat and volatile enough to be analysed. An HPLC UV (300nm)method of CIPAC can be used with the advantage for the same analysis but a toxicologically very significant imparity like sulfotep is not UV active at 300nm. It is then possible to use an LC-MS/MS method for analysis of this impurity at low levels(less than 0.3% w/w) using similar LC conditions. An excellent GC method is already published for determination of sulfotep in Chorpyrifos by the international organizations.

| Methods of Analysis of Active and Impurities | Complementary methods | Supplementary methods | Remarks |
|---|---|---|---|
| HPLC – UV photo diode array | LC-MS-MS | GC-FID/ECD; HS-GC/ GC-MS | Thermally unstable ingredients |
| GC- FID | GC-MS-MS | HPLC; HPTLC | All thermally stable ingredients |
| HPLC-UV photo diode array | LC-MS-MS | HPTLC; TLC - MS | Polymeric non-elutable ( in small pore size column ) impurities |
| X –ray fluorescence ion – chromatography | ICP; ICP-MS | ASS Flame photometer | For inorganics like AIP, $CuSo_4.5H_2O$ |

Analysis of Cypermethrim technical for 5- batches poses different issues. The normal phase HPLC UV – method published for Cypermethrin cannot resolve the enantiomers. The 4 pairs of diastereomers are separated on the normal phase silica column using non – polar solvent along with some polar solvents like

propan -2 ol- or diisopropyl ether and many such solvent systems. However, it can not resolve the isomers fully. Chiral column are needed for the resolution. The methods are available for the same. The volatile solvent can be analysed by HS- GC or HS-GC-MS/MS.GC methods are also suitable for diastereomers and impurities. The molecular peaks of the active isomers and the impurities are usually small and need to be indentified carefully subtracting the background. The major fragments in GC give lot of information about the impurity structure. HPTLC is a useful technique for determining the polymeric impurities in Cypermethrin technical and arriving at the mass balance. Recently mass spectrometry is being used with HPTLC.

## Analytical Method Validation (AMV) for the 5 – Batch Analysis

The methods used are validated using SANCO 3030 rev.42000 guidelines. Other guidelines can be used on merit.

## 5 BATCH ANALYSIS
## – Guidance to the Manufactures and the Testing laboratories

**Identification of the A.I. and the impurities in 5- Batch Analysis**

Identification of the impurities can be done by matching the retention time of A.I and other parameters like the UV spectrum in the PDA or mass spectrum in GC-MS/MS and LC- MS/MS or high resolution mass matching.

If the certified reference materials ( traceable to some national or international standard ) are available then the confirmation of the a new impurity the chemical structure can be determined using the standards spectroscopic methods like UV- VIS, FTIR, NMR, Mass Spectra, Single Crystal X- ray and Elemental Analyses or empirical formula derived by high resolution GC/LC/MS.

**Determination of A.I. in the 5 Batch Analysis**

The active ingredients are analysed preferably by a known published method of analysis. The standard Method like CIPAC and AOAC methods can be used without validation provided that the specificity wrt impurity interference is passing the test. Chiral methods should be used to quantify the enantiomers, if a new method is developed and used the method needs to be validated

**Determination of impurities in the 5-Batch Analysis**

The method for A.I. may be suitable for the impurities. However, the methods are developed as per the properties of the impurities. The low level impurities can be analysed by trace analysis methods. Adequate sampling and enrichment are suggested for determining the trace level toxic impurities. If a new method is developed for impurities and used then the method to be validated.

**Other parameters for ascertaining the quality of the technical material**

The parameters of quality control like acidity/alkalinity, insoluble material, ash content, moisture content, melting point and appearance by using the standard methods.

**Reporting the result**

The data of the analysis of the 5 Batches are to be presented in the report with appropriate uncertainty associated with the measurement. The data should be rounded using significant rules; Summarized data should be presented with statistical evaluation as appropriate. The mass balance to be achieved should meet the 98-102% criterion.

**Conclusions form the 5 Batch Analysis**

Result need to be presented in such a way that it will help th manufacture prepared the composition of the technical material. The specifications of the product can be laid down using the data.

**Setting Up limits of A.I and impurities**

The certified limits can be proposed in the report to help the sponsor or the manufacture of the material for its registration. Due consideration is to be given the stability of A.I during the storage and the possible degradation products.

**5 BATCH ANALYSIS**
**– Guidance to the Manufactures and the Testing laboratories**

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