Specifications for technical grade active ingredients (TC or TK)

Learning objectives

After completing this *Learning Unit* you should:

- Understand the structure and aims of specifications for TC/TK and their role in the development of specifications for formulated products
- Understand the data requirements for developing TC/TK specifications and the need to work with incomplete information
- Understand the concept of “reference profiles”
- Understand the need for openness and transparency in decision-making, while maintaining confidentiality of secret information

Specifications for technical grade active ingredients

- Technical grade products are relatively pure active ingredients, used to prepare formulations
- TC = technical material; TK = technical concentrate
- TC and TK are not clearly distinguished; TC is usually ≥900 g/kg with solvent(s) completely removed during synthesis and no solvent added subsequently

Why distinguish between TC and TK?

TC specification has no upper limit for active ingredient content.

Increasing the purity of a TC cannot increase its overall hazard significantly and may decrease it.

TK specification has upper and lower limits because accidentally higher content may increase hazard.

What is a good TC/TK?

Correct physical appearance

Not less than the minimum content of active ingredient

Not more than the maximum content of "relevant impurities"

Acceptable physical properties, if applicable

Is a TC/TK specification required before specifications can be developed for formulations?

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Nearly all formulations are produced from a TC/TK

The approach to cases where a TC/TK is not isolated may appear to be different but the principle is the same

Specifications are related to the hazard data for the source of active ingredient under consideration, which is usually TC/TK

If the hazard data relate to a formulation (produced without isolation of a TC/TK), that formulation is unlikely to be used by other formulators

Information to support a TC/TK specification I

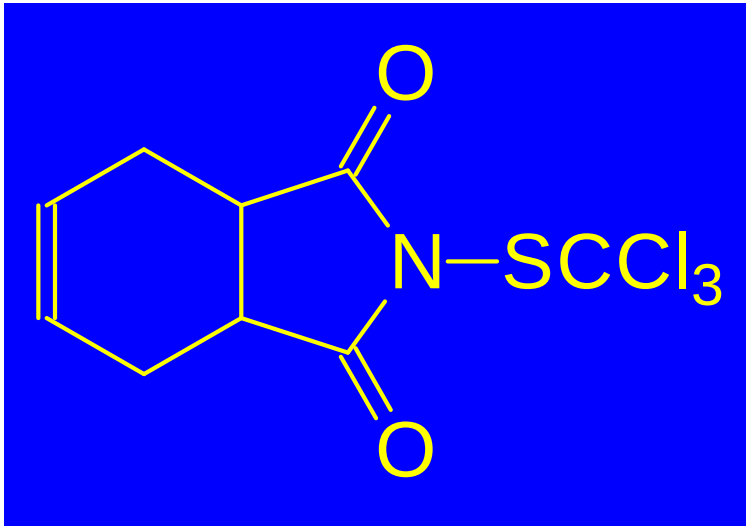
Active ingredient identity

Manufacturing route, materials, conditions (*confidential data*)

Content of active ingredient, impurities, stabilizers, etc. – manufacturing limits and data on 5 process batches (*confidential data*)

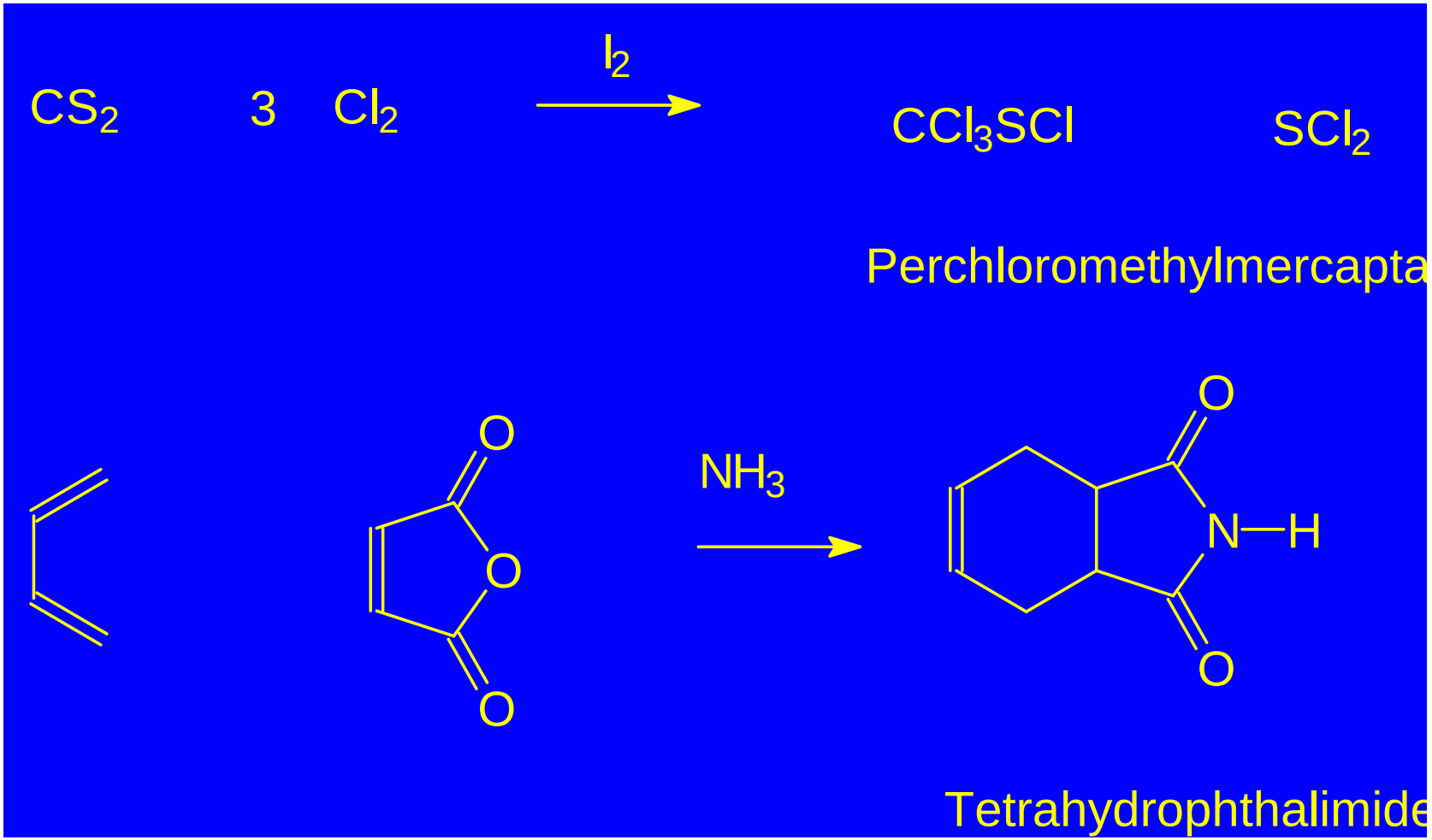
Example Captan

Important protective fungicide used in various fruit and vegetable crops

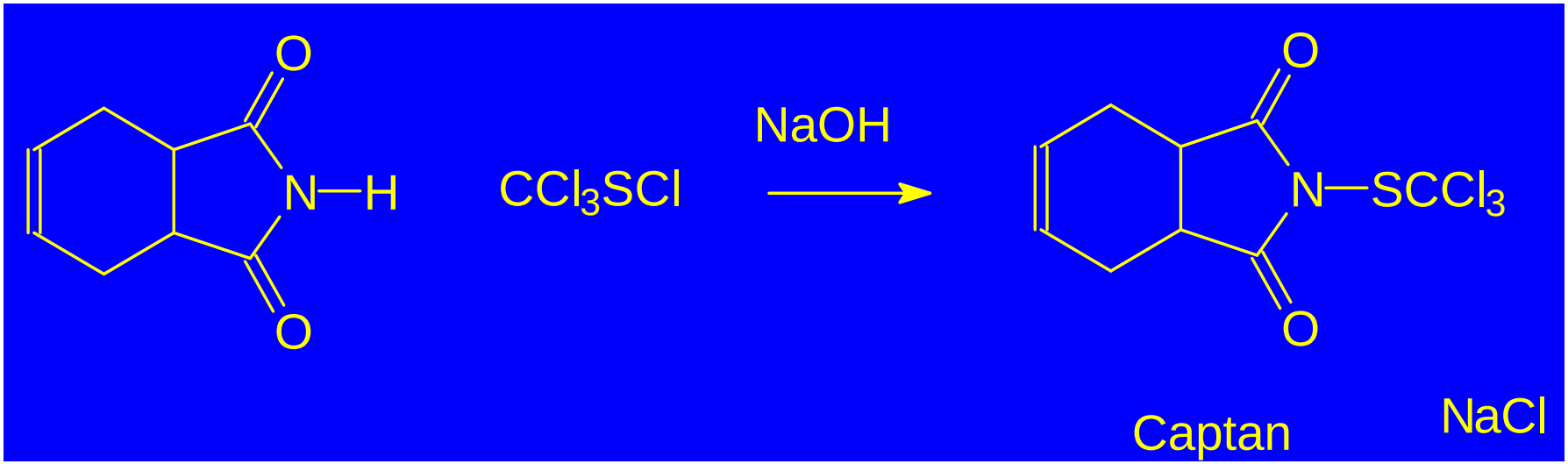


- Out of patent for long time
- Various generic manufacturers
- FAO Specification 1990 under „old procedure“

Manufacturing pathway part I



Manufacturing pathway part II



fictious but real example I

- Impurity 1:
  Folpet
- Impurity 2:
  Tetrahydrophthalimide
- Impurity 3:
  Perchloromethylmercaptan

fictious but real example (contd.)

- Impurity 4: Malonic anhydride
- Impurity 5: Excess base
- Impurity 6: Inorganics („Sulphated ash“)
- Impurity 7: Water

.2 ACTIVE INGREDIENTS

.2.1 Identity test (CIPAC 1C, 40/TC/M.3/2 p. 2013 and 40/TC/M.4/2 p. 2015)

.2.2 Captan (CIPAC 1C, 40/TC/M.3/3 p. 2013 (Referee method) or -/M.4/3 p. 2015)

The captan content shall be declared (**not less than 910 g/kg**) and,

when determined, the content obtained shall not differ from that declared by more than ± 30 g.

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3 IMPURITIES

.3.1 Perchlormethylmercaptan *

Maximum: 10 g/kg

.3.2 Loss on drying (MT 17.4.1, CIPAC 1, p. 874)

Maximum: 15 g/kg

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4 PHYSICAL PROPERTIES

.4.1 pH of 1% aqueous dispersion (MT 75, CIPAC 1A, p. 1589)

Range: 7.0 to 8.5

Captan Reference Profile

compound	11821	11855	11858	11876	11914	min/max
captan	945	938	950	947	926	920
folpet	<1	<1	<1	2	<1	5
tetrahydrophtalimide	10	8	12	11	7	20
perchloromethylmercaptan	2	4	5	8	5	10
anhydride	<1	<1	<1	<1	<1	1
sulphated ash	14	8	5	8	10	20
high mol. weight material	6	17	4	7	3	20
water	8	12	6	9	10	30
alkalinity						
Sum	985	987	982	992	961	

Information to support a TC/TK specification II

Physico-chemical characteristics:

vapour pressure, decomposition temp., water solubility, log P K_{ow}, degradation characteristics, etc.

Methods of analysis and testing used to generate reference data and for testing compliance with specifications including validation

Information to support a TC/TK specification III

Toxicology: acute, chronic, carcinogenicity, teratogenicity, mutagenicity, with purity data for the product tested

Ecotoxicology: fish, birds, bees, aquatic plants and animals, etc., with purity data for the product tested

Hazard and risk assessments made by various organizations

Data are evaluated to...

- Identify “reference profiles” of purity/ impurities and hazards
- Identify relevant impurities
- Ensure that specification clauses and limits are valid quality criteria
- Ensure that specification clauses and limits are supported by evidence

Who evaluates the data?

- Teams of scientists with sound knowledge and experience in many areas of chemistry and physical properties, toxicology and ecotoxicology
- No single person can do the job, no matter how good they are

What about missing or questionable data?

Despite the best effort of regulators and manufacturers, gaps or inconsistencies in the data are frequent

It is important to decide whether or not the gaps and inconsistencies are serious and require follow-up action

Checking questionable data

Data obtained from published literature may be of little use in assessing the TC/TK of another manufacturer

Data identical to those in published sources should be verified by checking the manufacturer's study report(s)

Other checks

- Chemical names, structures or analytical methods for impurities may be questionable, leading to errors of interpretation and mistakes in determination of equivalence – especially with highly reactive and hazardous impurities
- Check hazard assessments, especially irritation and sensitization tests, where non-standard protocols or assessments may be involved

Manufacturing limits and 5-batch analytical data

Purity/impurity profile is based on manufacturing limits, not values for individual batches

Basis of manufacturing limits should be known

Conflicts with 5-batch data are not a problem if there is a rational explanation

Some impurities may be more variable in occurrence than is shown by 5-batch data

Limits for some impurities may be lower than expected from the 5-batch data

Links between purity/impurity and hazard profiles

Conceptual rather than direct.

Manufacturing limits represent the worst-case for every component, a statistical “envelope” for purity/impurity which does not describe any single batch or blend of batches.

Hazard data represent one or more impurity profiles within the statistical envelope.

The purity of TC or TK used for hazard data may be the only information available on the link between profiles.

Links between purity/ impurity and hazard profiles

Most hazards, qualitatively and quantitatively, are derived from the active ingredient because it is by far the most abundant component of a TC

Relatively small variations in the high level of active ingredient content cannot produce big differences in hazard.

Correspondingly large variations in impurity content could produce big differences in hazard if the impurity is much more hazardous than the active ingredient

Chemical structures associated with exceptional hazards are mostly well-known.

Questionable links between purity/impurity and hazard profiles?

If the manufacturing process has evolved and/or the manufacturer sets up a new plant, manufacturing limits may be revised.

If the hazard data are purchased with process and rights to produce active ingredient, but the process is changed, manufacturing limits may be different.

The changes in manufacturing limits weaken the links with the original hazard data.

Records of evaluations

FAO/WHO evaluations are published on the Internet, recording non confidentialdata, data problems and the basis for all decisions

National/regional evaluations may not be published, but the basis for decisions should be recorded and preferably published.

TC and TK specification clauses

- Description
- Physical appearance and chemical form (e.g. salt, ester) – simplest and most rapid test.
- Stabilizer, if critical, is identified and a validated test method is provided.
- If the identity and/or quantity of stabilizer is not critical, the clause indicates only that a stabilizer is present.
- If a solvent is added (TK only), a clause and analytical method are not usually required for the solvent.

TC and TK specification clauses

- Identity - Unambiguous name … can be problematic for mixtures, especially if derived from plants or microorganism cultures – and also for some pyrethroids.
- Primary identity test usually based on measurement of active ingredient content; back-up test required for cases of doubt.
- If the active ingredient is a salt, ester or other derivative, it may be necessary to identify the derivative component.
- No external validation of identification methods required, except where the active ingredient is a mixture of defined ratio.

TC and TK specification clauses I

Active ingredient content

- Analytical methods validated by collaborative study.
- Limit based on manufacturing specification, not 5-batch data.
- Limit applies to the average of measured values.
- Content expressed as g/kg, or g/l at 20ºC, of appropriate chemical form (e.g. free acid, sodium salt, marker compound, etc.).

TC and TK specification clauses II

Relevant impurity content

- Analytical methods peer-validated in two or more laboratories.
- Limit based on manufacturing specification, not 5-batch data.
- Limit applies to the average of measured values.
- Content expressed as g/kg, or g/l at 20 ºC.

TC and TK specification clauses III

Other clauses

- Acidity, alkalinity or pH range, if required.
- Other characteristics, if critical for TC, TK or formulation quality.
- Storage stability is not specified, because manufacturers can usually re-purify an aged TC or TK.
- If a TC or TK is sold to end-users as a “formulation” (e.g. certain UL),the formulation specification applies and storage stability is specified.

HAPPYFOS TECHNICAL MATERIAL i

- WHO Specification 999/TC (December 2007*)
- *This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report(*999/2007*). It should be applicable to TC produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for TC produced by other manufacturers. The evaluation report (*999/2007*), as PART TWO, forms an integral part of this publication.*

- 1 **Description**
- The material shall consist of happyfos together with related
- manufacturing impurities and shall be a viscous yellow-to-brown
- liquid, containing not more than a trace of insoluble material, and
- shall be free from extraneous matter and added modifying agents.

HAPPYFOS TECHNICAL MATERIAL II

2 **Active ingredient**

2.1 **Identity tests** (999/TC/M/2, CIPAC X, p.193, 2003)The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Happyfos content** (999/TC/M/3, CIPAC X, p.193, 2003)

The happyfos content shall be declared (not less than 930 g/kg) and when determined, the average measured content shall not be lower than the declared minimum content.

3 **Physical properties**

3.1 **Alkalinity** (MT 31, CIPAC F, p. 96, 1995)

Maximum: 0.5 g/kg calculated as NaOH.

Note 1....

* *Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at:http://www.who.int/whopes/quality/.*

“Full” data package and reference profiles not available?

If the original manufacturer has ceased production or does not wish to provide supporting data, specifications can still be developed

Data from the most comprehensive data package available is given “temporary reference profiles” status, if the data are acceptable

Can be replaced with true “reference profiles” when original manufacturer’s data become available

Requires reassessment of equivalence when improved “reference profiles” become available