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REGIONAL NETWORK ON PESTICIDES FOR ASIA AND THE PACIFIC

DP/RAS/88/031

PEOPLE'S REPUBLIC OF CHINA

Technical report: Preparation of pesticide analytical standards*

Prepared for the People's Republic of China
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of D.W. Delo,
consultant in pesticide analysis

Backstopping officer: B. Sugavanam, Chemical Industries Branch

United Nations Industrial Development Organization
Vienna

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* This document has not been edited.

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ABSTRACT

Through lectures, and practical demonstrations with selected pesticides, the analytical staff at the Institute for the Control of Agrochemicals, Ministry of Agriculture (ICAMA), Beijing, were trained in the theoretical and practical aspects of the preparation of reference material pesticides. Details of the training, safety and apparatus requirements are incorporated in this report.

There is also a brief note of a discussion about laboratory equipment for a UNDP project for modern pesticide production at Nantong.

CONTENTS

INTRODUCTION

As a further project funded by the United Nations Development Programme (UNDP) in support of the Regional Network on Pesticides for Asia and the Pacific (RENPAP), it was agreed to send a consultant to ICAMA, Beijing, to train their personnel in the theory and preparation of pesticide analytical standards. As the selected consultant I visited Beijing 19th November to 12th December, '92, to undertake this training. The remit for this task is shown in Appendix 1.

The organizations concerned, and the background to the use of pesticides in the People's Republic of China, have already been well documented in a previous UNIDO report and will therefore not be repeated, (ref. 1.) The staff in the Pesticide Analysis Division have changed since that report and a revised organizational chart is shown in Appendix 2.

Pesticides Standards in China.

There are many pesticides used in the People's Republic of China and the bulk of the raw materials and products are manufactured locally. There is now an urgent need to have a system of centralized analytical standards which may be used to control the quality of production throughout the land. This scheme will be operated at ICAMA but will be encouraged by the Bureau of Standards of which Mr Zhang Bai Zhen, the Director of the Pesticides Analysis Division, is also a member.

There are articles which define the criteria for pesticide analytical standards, and describe procedures for preparing certain standards, published by CIPAC,(refs 2 & 3); but it was the need to reinforce these with practical experience which led ICAMA to request help in the initial stages of their project.

I. THE TRAINING PROGRAMME

Following discussions with Mr Zhang, it was concluded that there were three main courses of action to be pursued to make this assignment beneficial to ICAMA, they were:

1. To present a lecture on the steps involved in producing pesticide analytical standards. This would cover the practical work and how the observations of the analysts and their deductions eventually lead to assigning a specific strength to a standard. This would also cover the processes of storage and recording necessary to maintain the integrity of the standard once it has been produced.

2. To train selected staff in the procedures outlined in the lecture, by applying the processes to pesticides selected by ICAMA.

3. From my experiences gained at ICAMA to make recommendations which will facilitate the future development of their pesticides analytical standards system.

A. The training lectures.

An initial lecture was given to some of the staff of the Institute. The lecture was aided by a series of transparencies in English. Mr Sun Bai Zhong, who has been assigned to work on the standards project, and who studied English following his technical graduation, acted as the interpreter. Those interested in the topic stayed behind after the lecture for further discussions, and these proved to be most useful.

Mr Zhang also asked that I give a repeat lecture to ICAMA staff, some from other provinces, towards the end of my visit. As a result of my experiences during the first lecture the overheads were replaced by notes for these talks, so that staff could refer to them in the future. Members of the Pesticides Analysis Division were invited to attend again, so that they could clarify any points arising from the previous three weeks work.

The notes used for the last lecture are reproduced as appendix 3, as the contents may be of use at some later date. These were originally in capital letters and double spaced. I discovered, too late for the lectures, that the Chinese find English easier to follow when printed in lower case letters.

B. The Laboratory Training.

1. Personnel.

Two people worked with me continuously on the preparation of standards, Mr Sun Bai Zhong and Miss Ren Wei Jun; both are graduates of Shenyang College of Pharmacy They were both keen and competent, but as the Pesticide Analytical Division is only involved in analysis of raw materials and products the scale of this preparatory work was larger than they had previously handled.

Mr Ye Ji Ming, a deputy director of the laboratory, kept in touch with what was going on in the laboratory throughout my visit.

2. Equipment.

The laboratory lacked some larger pieces of apparatus which would have been suitable for the preparation of standards, because there had been no need

for such equipment in the past. Efforts were started to acquire some such items before I completed my time at ICAMA and a list of suggested equipment is included in my recommendations.

3. Safety.

The handling of concentrated solutions during recrystallization processes creates a series of hazards which need to be regulated by well defined procedures. These must specify adequate safety equipment, they must require that such equipment is worn whenever a person is processing materials and they must outline a satisfactory process for disposing of wastes, particularly waste solvents which will be generated in larger quantities than hitherto, due to the recrystallization processes and the need to thoroughly clean apparatus with solvent. Ideally an area with bench space and fumecupboards should be set aside for this work.

The application of safe working procedures and good housekeeping were the weakest points in this laboratory. The recommendations 2.5 in Mr F.H.Cottee's report (Ref1), if put into practice, have become neglected. These should be re-established then reinforced by regular safety awareness training for all of the laboratory staff. A work group of this size would benefit from regular work group safety meetings, the introduction of such meetings should be given serious consideration.

4. Sample purifications.

Three pesticides were selected for purification, for use as standards, they were phoxim, simetryn and triademefon.

Most pesticides can be purified by some form of crystallization process and this proved to be the case for these three compounds. The simetryn and triademefon from solvent systems, while the phoxim which is liquid at room temperature, was isolated from solution by freezing. The phoxim was not a good sample to use as only a small amount was available (50g) and it contained quite a lot of insoluble impurities.

It was stressed that if a pesticide is going to be purified it is advisable to start with the most pure material that is readily available, and a reasonable quantity, say 300-500g.

Two samples each of simetryn and triademefon were isolated. The first recrystallized once to be validated for use as working standards, and the second twice to be more fully characterised with the intention of assigning them primary standard status, if the purity proved to be good enough.

The purification of the phoxim proved to be more of a problem and did not proceed very far during my visit. Because of the difficulty in getting it to freeze it was necessary to locate and obtain solid carbon dioxide, a material not used previously in this laboratory. Once this had been done the phoxim was successfully isolated by cooling a 50% methanolic solution in a carbon dioxide/acetone bath which gives a temperature of about -70 deg C.

5. Standard validation.

The scheme of testing used on the purified materials was essentially that given in the text of Appendix 3 and also outlined in ref 2.

On starting the initial assessment of the recrystallized materials it was discovered that there was no satisfactory melting point apparatus available, although there were two in the department. One, a heated stage microscope, was very difficult to control so that the heating rate was generally too fast. The thermometer was extremely difficult to read, and did not appear to be the correct one for the equipment. The other melting point apparatus was a Gallenkamp instrument but the thermometer had been broken. It had a digital display operating from a thermocouple and this was used to obtain approximate melting points. The booklet for the instrument was also missing, so that the calibrations for the heating rate settings were not available.

ICAMA will need to set up a satisfactory melting point apparatus to support this work and to ensure that instrument manuals are filed in a proper system. It is a good policy to photocopy manuals as soon as they are received and lodge the copy in a separate filing system.

The infrared spectra of the materials were determined as KBr discs and showed that the purified material was of the correct identity.

A good quality reference standard of triademefon was available in the laboratory and it was used to determine the strengths of both working and primary standard materials.

The validation work on the purified materials was delayed because for three days in one week the laboratory was without electricity. A laboratory equipped with modern analytical equipment, as this one is, should have a more reliable and stable power supply, even if it means buying and running their own generator.

When determining the strengths of standards, the process requires the ultimate in chromatography precision, and this is best achieved with automatic samplers. Neither the high pressure liquid chromatographs (hplc), nor the gas liquid chromatographs

(glc) had automatic samplers. If the processing of thirty manual injections is not completed during a working day, it is possible that the analyses will not pass the statistical assessment. The purchase of automatic samplers for one gas chromatograph and one liquid chromatograph must be of prime importance to support this work.

The strength determinations showed that the working standards were of lower quality than those produced for validation as primary standards The results of 15 determinations gave the following:

		Simetryn(a)	Triademefon(b)
Working standard	mean	97.65%	98.75%
	std dev	± 0.35	± 0.32
	CV	± 0.36%	± 0.32%
Primary standard material	mean	99.27%	
	std dev	± 0.39	(c)
	CV	± 0.39%	

Notes: a. The calibration standard simetryn was of unknown origins, these values will have to be adjusted once validation of the primary material has been completed.

b. Calibration material ex Riedel de Haen certified as 99%

c. One set of results were unacceptable and the analysis will be repeated. The other results indicate a strength of about 99.4%.

The primary standard materials still have to be subjected to a variety of analyses to assess the levels of any impurities that are present in them. These tests will include capillary gc, capillary gc/mass spectrometry, hplc, possibly solvent and water contents, and any other tests which the analysts consider necessary to assign purities to the primary standards which have a high degree of certainty. This work will continue for some time after my visit.

C. <u>The storage of standards</u>.

Once the standard has been isolated it should be stored in an air tight, screw-capped bottle. Once validation is complete it needs to be filled into one gramme vials. This will minimise the chances of contaminating the standard. Both bulk stock and one gramme vials should be sealed with stretch tape and then stored in a chilled cabinet at five degrees centigrade.

The only bottles available in the laboratory were secondhand 500g bottles, and no vials. A stock of new

bottles should be obtained for standards storage. I suggest 50 x 100g capacity, screw-capped, brown glass bottles for bulk stock and 1500 x 5ml screw-capped glass vials with a suitable inert plastic seal.

There are several good quality refrigerators in the Pesticide Analysis Division, one needs to be set aside for standards storage. The shelves need to be adapted to take trays of vials to make the best use of the space in the refrigerator.

The standards should be re-assessed after five years, or earlier if there is any cause for concern about the quality of a material.

One person should be assigned the sole responsibility for issuing standards and maintaining the stock records.

D. Documentation of standards.

With Good Laboratory Practice in mind the records of each standard should be thoroughly documented in a good sized notebook. In this book should be recorded the process details of the purification, the confirmation of identity, the determinations of strength and impurities and the unique identity assigned to the standard together with the date. A stock record system will need to be introduced for the standards showing details of recipients, stock levels and the date for revalidation. An analytical certificate must be produced for each standard showing the strength of the material and other relevant facts about the standard. An example of what a certificate needs to show is at the end of my notes in appendix 3.

There is a personal computer in the Analytical Section. With suitable software it could be used to maintain stock records of standards, to print certificates of analysis, and labels for the vials. A relatively simple interactive spreadsheet and data base, such as Microsoft Works, could probably be set up to do this work.

II. A STANDARDS POLICY.

ICAMA should consider the following as a possible way of dealing with analytical standards to minimise the work of Pesticides Analysis Section. As I do not fully understand the work or organization of ICAMA these suggestions may not be of any practical use.

New pesticides owned by one company. ICAMA should request a small sample of primary standard (1g) and a larger sample of working standard (5g) from the manufacturer as part of registration procedures. This would give them sufficient material to set up their own standard if they wanted to. If they explain the large

organization involved in dealing with pesticides in China they may even persuade the manufacturer to supply more.

When the pesticide is an older chemical, not covered by patent but still produced by only one or two manufacturers, ICAMA should try to get standards from them before attempting to produce their own standards. This will leave the main effort at ICAMA to work on those chemicals being manufactured in factories in the People's Republic of China.

Occasionally, when only a small amount of standard is needed for one particular job, it might be more practicable to buy a certified reference standard from an agent. In these cases standards should only be bought from approved suppliers, for example, The Laboratory of the Government Chemist, Teddington, Middlesex, England.

III. THE PESTICIDES FACTORY AT NANTONG.

One morning was spent in discussions with Mme Jia Yangeng, the chemist in charge of the laboratories at the Nantong factory. Our meeting could have been more fruitful if I had been shown a copy of the projected scheme before the meeting, as I had no idea of the size or complexity of the project. As I understand it now, the project is to develop an existing pesticide formulation plant over the next four to five years to the state of producing modern pesticide formulations, for example, granules and suspension concentrates, and to have the scientific analytical and development services to support this work. The factory will be run on sound safety and environmental principles.

Our discussions centred mainly around the projected purchases of laboratory equipment for the coming year, future requirements, and some specific analytical problems.

They particularly wanted information on laser based particle size analysis equipment. I offered to seek the advice of those currently using the equipment to get a more expert view, and to report my findings to Mme Jia.

In the project document I noticed that just over $2000 had been allocated to buy two viscometers. On questioning Mme Jia about this, it seems that the viscometers are wanted for testing suspension concentrates for rheological properties, if this is so, then the sum allowed is far too low. I said that I would also check the suppliers and prices of suitable equipment.

Mme Jia said that they were having problems with late eluting peaks in glc analyses. It is difficult to sort out this type problem without being on the spot and

seeing the system operating, but I made some suggestions on sample and column treatment which might improve the situation and these were welcomed.

We also discussed the analysis of surface-active agents and suitable methods for assessing the quality of anionic and nonionic surface active agents used in the formulation of pesticides. I outlined the two phase titration of anionic materials using a cationic solution and methylene blue indicator; and a qualitative method for assessing the identity of non-ionic surface active agents by thin layer chromatography (tlc). I agreed to forward details of suitable references which would be helpful to them in selecting methods of analysis for assessing their surface-active agents.

I think that it might be most helpful to UNDP, and the consultants that are likely to be called to assist at Nantong in the future, if a technical expert could visit the Nantong factory to review the practical requirements of this development.

RECOMMENDATIONS

A. Apparatus.

The following apparatus to be bought by ICAMA:

1. Larger pieces of glassware, such as 2-3L beakers, Buchner funnels and flasks, Petri-dishes and large watch-glasses.

2. Rubber pressure tubing (thick walled) for use on vacuum equipment.

3. Filter papers and glass-fibre filter discs to fit the filter funnels.

4. 100g, screw-capped, glass bottles, with inert plastic seals.

5. Approximately 5ml, screw-capped, glass vials, with inert plastic seals.

B. Instruments.

ICAMA need to plan the purchase of the following:

6. A good quality melting point apparatus if existing equipment cannot be made to work properly. I will try to obtain another instrument manual for the Gallenkamp apparatus and details of possible agents in China who may be able to supply a suitable thermometer. I will let Mr Zhang know the outcome of my enquiries.

7. An automatic sampler for the glc.

8. An automatic sampler for the hplc

C. Accommodation.

9. ICAMA should consider allocating an area of laboratory, benches and efficient fumecupboards, to be cleared and kept mainly for the production of pesticide standards. The preparative hplc could also be located in the same area.

D. Chemicals.

ICAMA should consider the purchase of the following chemicals:

10. Commercial grade acetone for cleaning and drying glassware, possibly 2.5L cans. I would normally suggest 25L drums but I am worried about safe storage as the area is densely built-up, with restricted access and people living in close proximity to the laboratories. A non-flammable solvent would be safer, but increasing restrictions on the use of chlorinated solvents and their immiscibility makes their choice impracticable.

11. Filter aid.

E. Safety.

ICAMA to introduce the following safety measures:

12. To provide a stock of different sizes of nitrile safety glove for the laboratory staff.

13. To provide all laboratory staff with correctly fitted safety spectacles.

14. To provide face-shields and solvent resistant plastic aprons as additional protection to staff recrystallizing pesticides.

15. To provide a toxic waste drum for collection of waste solvent/pesticide residues.

Note: if acetone is discarded to a waste drum, chlorinated solvents, particularly chloroform should NOT be put in the same drum, as this could result in a serious explosion.

16. To provide written instructions on the correct procedures to be used to dispose of toxic waste, including solvents.

18. To provide wire-mesh safety cages for Buchner flasks and vacuum desiccators.

19. To initiate a process to monitor staff exposure to solvent vapours and pesticides.

20. ICAMA consider the possibility of making one person responsible for cleanliness and safety of all laboratory work areas. Also to nominate one person to develop the safety awareness of all staff, possibly through work group safety meetings.

F. Pesticides standards system.

21. ICAMA to introduce a system to record and control their analytical standards, incorporating the essential data detailed elsewhere in this report.

22. When ICAMA receives certified standards from and outside source they consider recording them on the same system.

23. ICAMA consider using the personal computer for stock records, analytical certificate and label printing.

G. The Nantong Factory.

24. Details of suitable particle size apparatus and viscometers and approximate prices to be sent to Mme Jia by me.

25. Details of references dealing with the analysis of surface-active agents to be sent to Mme Jia by me.

26. A technical expert should visit Nantong to assess more fully the practical requirements of the UNDP project.

V ACKNOWLEDGEMENTS.

I sincerely thank all the staff at ICAMA who through their help and co-operation made me feel that my task was worthwhile and successful.

I would particularly like to mention in my thanks Mr ZHANG BAI ZHEN for his keen support and hospitality; and the three people who bore the task of getting the standards project started at ICAMA, namely Mr YE JI MING, Mr SUN BAI ZHONG and Miss REN WEI JUN.

VI REFERENCES.

1. F.H. Cottee, UNIDO technical report DP/ID/SERA/1161, dated 1.3.89, Gas Chromatography/Mass Spectrometry (GC/MS) Analysis of Pesticides at the Institute for the Control of Agrochemicals, Beijing, P.R. of China.

2 CIPAC Handbook 1D, pp 186 - 196, Pure Pesticides, Guidelines for the Definition, Preparation and Determination of Purity of Reference Materials for the Analysis of Pesticide Products.

3 CIPAC Handbooks, 1, 1B, 1C, & 1D pp 1640-, 1928-, 2307-, & 197-, respectively. Instructions for the purification and charaterization of specific pesticides.

COPY Appendix 1

United Nations Industrial Development Organization

25th May 1990

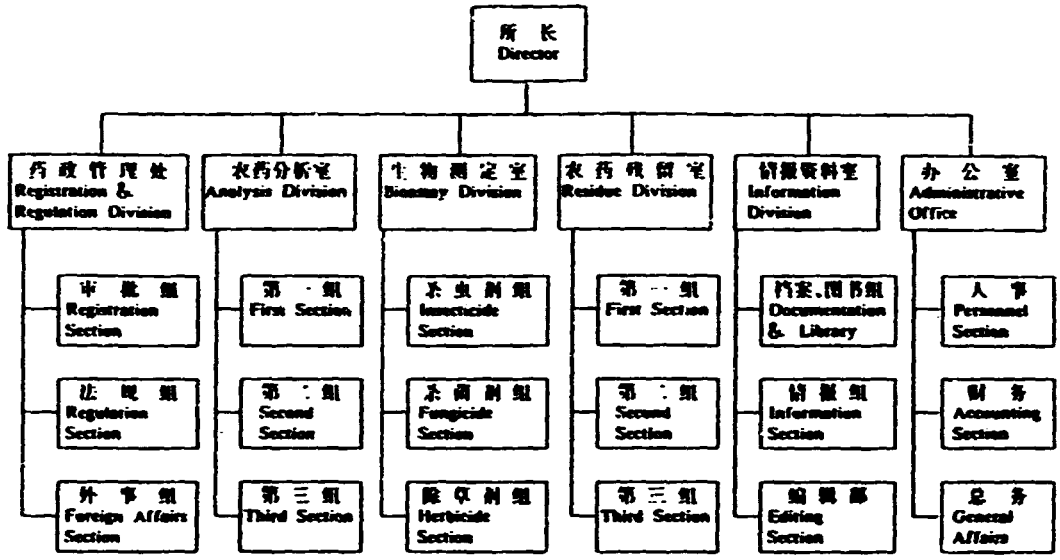
JOB DESCRIPTION
DP/RAS/88/031/11-60

1.	Post title	Procedure for the preparation of Pesticide Standard Sample.
2.	Duration	One month.
3.	Date required	A soon as possible.
4.	Duty station	Beijing, Peoples Republic of China.
5.	Purpose of project	Setting up of Bank for Pesticide Reference standard samples in Asia-Pacific in order to meet requirement of the region.
6.	Duties	i) Preparation of pesticide standard. ii) Procedure for the preparation of different kind of pesticide standards such as CRYSTALLIZATION, LIQUID- LIQUID PARTITION & COLUMN CHROMATOGRAPHY ETC. iii) Determination of purity using GC, HPLC, GC-Mass. etc. iv) Preparation and characterisation of primary standards as per international regulations. v) Storage: Pesticides Reference Standards to be stored properly to maintain its shelf life. vi) Packing, handling and forwarding: Suitable methods and guidlines for handling, packing and forwarding of of samples.

ORGANIZATIONS APPENDIX 2

农药检定所组织机构

Organizational Chart of ICAMA



ORGANIZATION OF PESTICIDES ANALYSIS DIVISION

Mr Zhang Bai Zhen
(director)

Mr Ye Ji Ming (deputy director)	Mme Jiang Shuxiu (deputy director)	Mme Tian Qiu Lan (deputy director)

Group 1 Chemical Analysis	Group 2 Hplc Analysis	Group 3 Glc Analysis	Group4 GC/MS Analysis
Mme Li Ping Mr Zhang Zhi Y Mr Zhen Kuei	Mme Yang Yi Yan Mr Sun Bai Zhong Mr Wu Di Mme Sun Qi Li	Miss Ren Wei Jun Mme Lui Ping	Miss Ji Ying Mr Lui Shao Yen

NOTES USED FOR LECTURES ON STANDARDS. APPENDIX 4.

P1 THE PREPARATION OF PESTICIDE STANDARDS

WHAT IS A STANDARD?

When we are talking about pesticide analysis, it is a materials that we are confident that we know sufficient about it's composition, that we may use it to calibrate the analysis of similar material of unknown composition.

BAKER AND PAVEL Defined two types of pesticide standard (Ref 1), briefly they may be described as:

1. A Primary Standard - highly purified and thoroughly characterised.

2. A Working Standard - of consistent quality and strength to be suitable for calibration in routine analysis.

P2. WHY DO WE NEED STANDARDS FOR PESTICIDE ANALYSES?

Because chromatography methods, which are mainly used now to determine pesticides, separate the components of raw materials and formulations. The peak area of a component is proportional to the amount of material creating it. It is therefore necessary to have materials of known strength, to determine the correct ratio of area to mass, to calibrate the analysis.

WHERE DO THEY COME FROM?

They are prepared in laboratories of regulatory authorities and manufacturers.

P3.HOW DO WE START?

1. Research the literature.
   - Pesticide Manual (Ref 2)
   - CIPAC Handbooks (Ref 3)
   - (Some contain methods)
   - Manufacturers' data sheets

   To find:
   - Solubility
   - Stability
   - Melting point
   - Hazards & toxicity
   - Methods of analysis
   - Possible impurities
   - And any other useful properties.

2. Acquire a reasonable quantity of raw material to purify - say 500g. And check the identity to ensure that you are not working on the wrong material.

An infrared spectrum is sufficient.

P4. WHY PURIFY THE RAW MATERIAL?

To remove:
- Insoluble impurities
- Soluble impurities
- Solvents
- Water

To have a standard of:
- High purity
- Consistent quality
- (it must be homogeneous)
- Improved stability

HOW DO WE PURIFY A PESTICIDE?

There are many techniques for purifying materials, some requiring specialised skills or expensive equipment, but for the majority of pesticides we use:

RECRYSTALLIZATION.

A useful book on the subject of purification has been written by Perrin & Armarego (Ref 4).

P5. WHAT APPARATUS DO WE NEED?
- Large beakers & Flasks (1-4L)
- Large filter funnels (15cm diameter)
- Buchner filter flasks (1-2L)
- Buchner funnels (10, 15 & 20cm diameter)
- A range of filter papers and glass-fibre filter discs to fit the filter funnels.
- Petri-dishes, tall sided, (12cm diameter)
- Large watch-glasses to cover beakers and Petri-dishes.
- Large vacuum desiccators (30cm diameter)
- Safety cages for Buchner funnels and vacuum desiccators.
- Large mortars & pestles (15 & 30cm diameter)
- Magnetic stirrer
- Rotary evaporator
- Electric vacuum pump
- Normal analytical laboratory apparatus
- Screw-capped, 100ml glass bottles
- Screw-capped, 5ml glass vials

WHAT REAGENTS DO WE NEED?
- Activated charcoal powder
- Silica gel (self-indicating)
- A range of Laboratory Quality solvents
- Filter aid

P6 SAFETY

Larger scale laboratory work with solvent solutions of pesticides present a greater hazard to the worker than normal analytical work. You must minimise hazards from:

Toxic solvents
Toxic pesticides in concentrated solutions
Highly flammable solvents

By wearing:
Suitable protective gloves
Safety spectacles & face shields
Laboratory coats & plastic aprons

By working:
In fumecupboards

By disposing of waste solvents and chemicals in recognized waste containers.

By checking the exposure of operators to solvent vapours by regular air monitoring.

Glassware under vacuum presents a hazard.
Use only sound glassware.
Enclose glassware in a mesh cage when evacuating it and when it is standing under vacuum.
Label apparatus under vacuum.

P7. THE RECRYSTALLIZATION

1. Small scale tests (1-2g) to find a suitable solvent. You want:

a. Limited solubility at room temperature leading to crystallization from concentrated solutions at room temperature, or colder.

b. Liquid pesticides to crystallize on freezing from raw material or solution..

2. Large scale crystallization (300-500g)

Dissolve.

Use good quality solvents
Do you need to warm the solution?
Do you need to use carbon to decolorize the solution?

Filter to remove insoluble material and carbon.

Crystallize by cooling
Does it need to be helped by the evaporation of some of the solvent?
Does it need to be helped by chilling in a freezer?
Is there a good yield of material?

P8. FILTRATION & DRYING.

Remove the crystals by filtering on a Buchner funnel.
Wash the crystals with chilled solvent.
Draw air through the crystals for about 10 minutes to remove most of the solvent.

Examine the crystals to try to assess whether they need more crystallizations to purify them. If they do, use fresh solvent.
When satisfactory crystals are obtained, dry them.

Usually in a vacuum desiccator, using silica gel as desiccant.
To help drying spread the crystals in large dishes to a depth of 1cm.
Periodically mix the contents of the dishes.
When the crystals appear to be dry, grind and mix them thoroughly in a mortar, continue drying.

Once drying is judged to be complete homogenize the material again and fill into 100g stock bottles to await validation.

P9. CHECK THE QUALITY OF YOUR MATERIAL BY:

Infrared spectrum - identity
Melting points/boiling points/solubility in different solvents - these tests will indicate whether the sample has a reasonable purity.

If these tests, or the strength determinations outlined on the next page, are unsatisfactory, you must review the whole process to discover which stage may have caused the problem.
Was it:
Drying?
Mixing?
Analysis?

P10.
If the tests are satisfactory and a suitable calibration material is already available, determine the purity of the material using:

The recommended standard method for the compound. Ideally an autosampler should be used to perform injections.

Use 3 weights of calibration and sample.

5 Alternating injections of 1st reference and sample solutions, then repeat for the second and third set of weighings.

Calculate the strength of the new material for each pair of injections to give 15 results.

Calculate the mean: $\bar{x} = \frac{\Sigma x}{15}$

The standard deviation: $\sigma = \sqrt{\frac{\Sigma (x - \bar{x})^2}{n - 1}}$

The coefficient of variation: $CV = \frac{100\sigma}{\bar{x}}$

If the CV $\leq$0.8% the results are acceptable, the mean strength, to three significant figures , is assigned to the new material, which becomes a new working standard.

If the statistics of the analysis are unsatisfactory the results must be subjected to further testing as shown in the examples in ref 1.

P11. THE PRIMARY REFERENCE STANDARD

A reminder of the definition:

"A highly purified and extremely well characterised, certified reference material used for the calibration of working standards."

If the recrystallized material is of high purity (>99%), then it may be characterised further for use as a primary standard. If it is not of adequate purity it should be subjected to further purification before characterisation.

If recrystallization does not improve the purity of the material intended as a primary standard then other techniques may have to be used, e.g. Prep' LC.

P12. CHARACTERISATION OF PRIMARY MATERIAL

Potential primary standards should be analysed by a wide variety of methods in order to put a high degree of certainty on the strength of the material. Such tests may include:

Melting & setting points
Boiling points
Infrared & uv spectroscopy
NMR
Capillary gc (more than one column)

Capillary gc/mass spectrometry
Hplc (more than one column)
Loss on drying
Water by Karl Fischer
Solvent determinations
Titrimetry
TLC
Ashing

An example of a validation process is shown on pages 17 & 18.

P13.

The analyst must choose the tests that will be used to assess the primary standard, based on experience in purifying the material and knowledge of the chemistry of the compound.

The analyst must make the final decision in assigning a strength to the primary reference material.

They must ask:

Do the facts of the analysis confirm a strength for the material?
Do the facts add up? For example:

GC/MS observations
Normalised chromatography results
Solvent and moisture contents

When the testing has been completed to the satisfaction of the analyst, and a strength assigned to the primary standard material, the tests used to assess it must be listed on the analytical certificate.

P14.

When a new standard has been produced it essential to preserve its integrity by:

1. Filling the standard into 1 gramme vials, sufficient for two years use.

2. Filling the remaining stock into 100g bottles.

3. Sealing all vials and bottles with a suitable stretch tape.

4. Clearly labelling all bottles and vials with the name of the pesticide, identity number and production and expiry dates.

5. Storing all stock at 5 degrees C.

6. Forbidding the use of material from stock bottles.

7. Allowing all containers to reach room temperature before opening them.

8. Maintaining good records.

9. Encouraging the reporting of any change in appearance or quality

P15.

To operate an analytical standards system successfully it is necessary to have good records. These should include:

1. Details of the process used for purification, together with any useful information collected from publications.

2. A unique batch number for each standard.

3. Date the standard was characterised.

4. All analytical data collected during the characterisation, including chromatograms etc.

5. An expiry date, when the standard will be re-characterised, usually after 5 years.

6. A standard certificate of analysis.

7. Stock records.

8. Records of distribution.

9. Record of the hazards of the pesticide.

P16. REFERENCES.

1. CIPAC Handbook D, Pure pesticides, pages 186-196.

2. Pesticide Manual, A World Compendium, published by the British Crop Protection Council.

3. CIPAC Handbooks, 1,1B,1C & 1D, pages 1640-,1928-, 2307-, and 197-, respectively.

4. Purification of Laboratory Chemicals, 3rd edition, by D.D.PERRIN & W.L.F.ARMAREGO, Published Pergamon.

P17. VALIDATION

Hypothetical Example

We have a newly purified material 'ICAMA' to test.

1. Melting point quoted 96 ^{o} C
found 95.6 - 96.2^{o} C

2. Infrared spectrum confirmed that the identity was that of icama. No abnormal peaks detected.

3. Fortunately we have a small amount of standard icama, and a standard method of analysis by glc, so we determine the strength following the recommended scheme.

The mean strength is 99.1% m/m, with a coefficient of variation of ± 0.7%.

Our new material may now be used as a working standard.

The sample of icama is needed as a primary standard so it is subjected to further testing.

4. As the material is suitable for glc analysis using fid, it is analysed twice using two types of capillary columns.

a. Non-polar
b. Polar

On column (a) we have good separation of five peaks which give on normalization:

Peak A = 0.1%
Peak B = 0.2%
Peak C = 0.15%
Peak D = 99.35%
Peak E = 0.2%

On column (b) the peaks are not retained very well but no other components are noted.

5. The separation is repeated using column (a) in the gc/ms.

The major peak 'D' is confirmed to be solely icama.

Peaks 'A', 'B' and 'C' are closely related compounds

Peak E is a compound with a mass twice that of icama, with a probable carbon content twice that of icama.

It is therefore decided to adjust the normalization to allow for the fact that 'E' may have twice the response factor of the other separated components.

The adjusted normalization is Peak A = 0.1%
Peak B = 0.2%
Peak C = 0.15%
Peak D = 99.45%
Peak E = 0.1%

The capillary gc analysis is repeated twice more to get a better estimate of the impurities. The values do not change.

We now do analysis by hplc but despite using different columns and solvent systems we do not find any evidence of any other components.

A moisture analysis by Karl Fischer shows that the water content is well below 0.1%.

But a loss on drying gives a result of 0.2% , a repeat analysis gives 0.3%.

As icama was recrystallized from hexane, the sample is analysed for hexane.
The hexane content is 0.3%

We can now take stock of our analyses

Working standard strength	Primary standard analysis
99.1% m/m	Strength by normalized gc
	99.4%
	Impurity A 0.1%
	Impurity B 0.2%
	Impurity C 0.15%
	Impurity E 0.1%
	Hexane 0.3%
	Water < 0.1%
	Total 0.85%
	Strength by deduction
	99.1%

Strength assigned to primary standard 99.1% m/m*

*This standard would need more drying to remove the hexane, followed by further validation.

This is a simplified example and much more work may be needed on some primary standards, particularly if the strength has to be solely determined by subtracting the total percentage of impurities from 100%.

P19. EXAMPLE

ICAMA

CERTIFICATE OF ANALYSIS

NAME: Phoxim PURITY: 98.5%

REFERENCES, IDENTITY: IAB/1 DATA FILE: Notebook 1

DATES, VALIDATED : 18th Dec 92 EXPIRY: 17th Dec 97

METHODS OF VALIDATION

hplc

ADDITIONAL INFORMATION

Working standard

STORAGE: Store in a refrigerator (5° C)

SAFETY & HANDLING

Organo-phosphorus compound. Wear laboratory coat, safety spectacles and gloves.

CERTIFIED BY: (Signed)

ISSUED BY: (Signed) DATE:

ADDRESS: TELEPHONE:
FAX:

UNIDO COMMENTS

The report deals with an important topic of quality control especially preparation of standards and maintaining a bank of standard samples. This is one of the major problems faced by many developing countries and the quality control system becomes less reliable due to lack of proper standard or reference materials. Despite having sophisticated analytical equipment, lack of reference materials givesunreliable results.

The author has shown as to how one could prepare standard samples needed for analysis from technical materials by simple crystallization, IR techniques and other methods.

The report will go a long way in following basic requirements for running a quality control laboratory with adequate provision of standard samples as and when needed.

The regional project is putting more and more emphasis on quality control which is the nerve centre of any chemical industry and more to those laboratories dealing with pesticides.