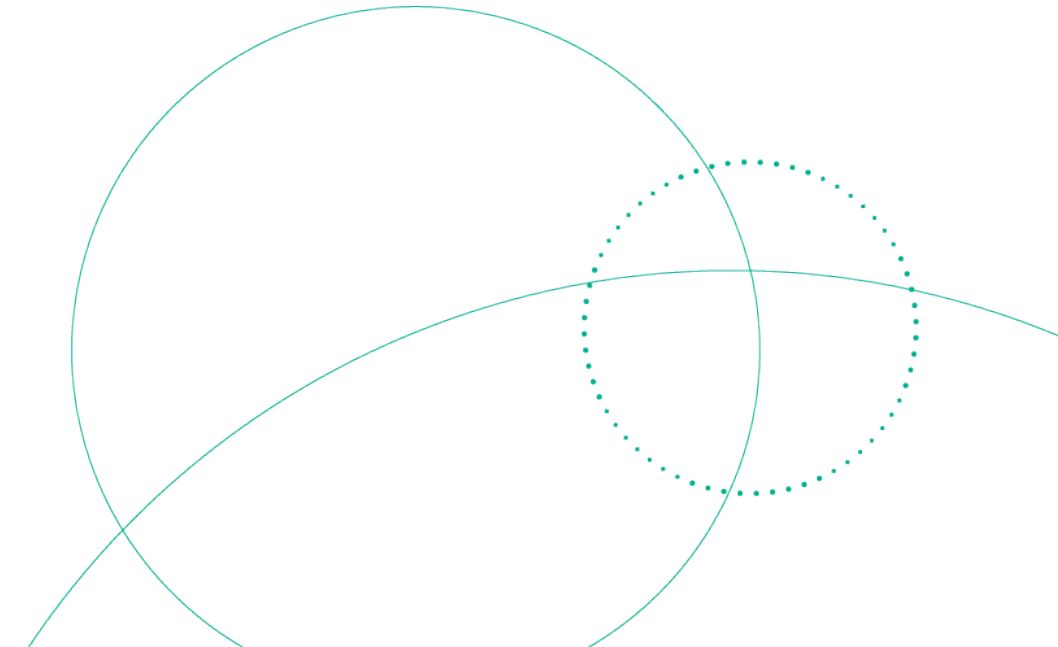
World Health Organization

WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: WHOPAR Part 3

Axient 440EW (Tagros Chemicals India Private Limited) 004-017

Quality Assessment



Contents

1. Chemical and physical data

1.1 Chemical and physical properties

Data on the chemical and physical properties of the active ingredient and the product Axient 440EW were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP) and are considered complete. Product specific properties are summarized in Table 1. The WHO Specification 12/EW is available for use in support of QA/QC testing. These summary results are based on the analysis of batches: 066F2018, 074J2019, 078J2019, 083J2019.

Table 1. Chemical and physical properties for Axient 440EW

Data requirement	Study number	Test method ID	Result
Identification of Malathion	RCC Study number 7975	12/EW/(M)/2,CIPAC Handbook K, p. 92, 2003	The active ingredient complies with an identity test
Malathion content (test item stored at room temperature)	RCC Study number 7975	12/EW/(M)/3,CIPAC Handbook K, p. 92, 2003	Malathion mean content: 44.63 % w/v
Malathion content (after accelerated storage stability, 14 days at 54 ± 2 °C)	RCC Study number 7975	CIPAC MT 46.3 Handbook J. p.128. 2000	Malathion mean content: 44.31 % w/v (99.3% of the initial content)
Relevant impurities	RCC Study number 7975 ^{31}P-NMR analysis for malathion EW samples GLP Study SP-334	Fully validated GC-FID method Fully validated GC-FID method Fully validated HPLC-PDA method Fully validated NMR method for malaoxon impurity in malathion	Impurity I (MeOOOPS-triester): 0.145 % w/w Impurity II (MeOOSPS-triester): 0.490 % w/w Impurity III (isomalathion): 0.165 % w/w Impurity IV (malaoxon): <0.0 % w/w
pH (1% aqueous dilution)	RCC Study number 7970	CIPAC MT 75.3 , Handbook J. p.131. 2000	Measured mean value (from three replications): 3.76
Pourability	RCC Study number 7971	CIPAC MT 148.1, Handbook J. p.133. 2000	Measured mean value (from 2 replications): 2.74 %
Emulsion stability and re-emulsification	RCC Study number 7972	CIPAC MT 36.3, Handbook K. p.137. 2003	Measured mean value (2 replications per time interval measured): 0 h Initial emulsification complete 0.5 h Cream: none 2.0 h Cream: none 24 h Re-emulsification complete 24.5 h Cream: none Free oil: none
Persistent foam	RCC Study number 7973	CIPAC MT 47.3, Handbook O, p.177, 2017	Measured mean value (from two replications): 0.0 ml after 1 minute Measured mean value (from two replications): 0.0 ml after 12 minutes
Storage stability at 0°C	RCC Study Number 7974	CIPAC MT 39.3 Handbook J. p.126. 2000	No significant chemical and physical changes were observed after storage at 0°C for 7 days, no layer separation was observed.

No significant differences were recorded among the properties of the product kept at ambient temperature and after accelerated storage stability test conditions.

Note: In supplement to the GLP study, Quality Control data generated by the applicant was submitted on 10 additional batches. All batches complied with the presented limits, including after accelerated storage.

1.2 Manufacturing, composition and formulant information

Data on the manufacturing process and product composition for Axient 440EW have been provided and are adequate. A summary is presented in Table 2. Detailed information on the manufacturing process and product formulation is considered Confidential Business Information (CBI).

Table 2. Manufacturing process and product composition data submitted for Axient 440EW

Description of Starting Material	Malathion TC formulated as part of the production process as an emulsion, oil in water (EW). The source of active ingredient is supported by a current evaluation report confirming compliance of the material with the established WHO specification.
Declaration of product formulation	Included in the confidential business information.
Production / Formulation Process	Axient 440EW is an emulsion, oil in water (EW), formulation containing malathion (CAS No. 121-75-5; 440g/l; 44.63%). Malathion is the ISO common name for diethyl (dimethoxythiophosphorylthio)succinate or S-1,2-bis(ethoxycarbonyl)ethyl O,O-dimethyl phosphorodithioate (IUPAC). The technical material is a racemic mixture of R-malathion [butanedioic acid, [(dimethoxyphosphinothioyl)thio]-, diethyl ester (2R)-(9Cl)] and S-malathion [butanedioic acid, [(dimethoxyphos-phinothioyl)thio]-, diethyl ester (2S)-(9Cl)].
Packaging	Unit packaging HDPE, CO-ex and PET bottles packed in carton box. The sizes of the unit packaging are 20 x 500ml, 10 x 1 liter and 4 x 5liter. A label is printed/pasted on bottles. Printed labels are pasted on Carton Boxes.
Discussion of Impurities	Four impurities of toxicological concern were checked in the formulated product (Impurity I (MeOOOPS-triester), Impurity II (MeOOSPS-triester), Impurity III (isomalathion), Impurity IV (malaoxon)). All impurities were below the specification limits: Impurity I (MeOOOPS-triester): 0.145 % w/w Maximum: 0.5 % of the malathion content, 0.22 % w/v Impurity II (MeOOSPS-triester): 0.490 % w/w Maximum: 1.6 % of the malathion content, 0.71 % w/v Impurity III (isomalathion): 0.165 % w/w Maximum: 0.6 % of the malathion content, 0.27 % w/v Impurity IV (malaoxon): <0.0 % w/w Maximum: 0.8 % of the malathion content, 0.36 % w/v
Certification of Limits	Malathion: 44 % w/v, acceptable limits 41.8 % w/v – 46.2 % w/v

1.3 Enforcement analytical method

Table 3. Details of the analytical method used to determine Malathion in Axient 440EW

Quantification of Malathion	Malathion 12/EW/(M)/3, CIPAC Handbook K, p. 92, 2003

This method is appropriate for the determination of the active ingredient content of the product.

2. Overall quality conclusions

Based on the studies and information provided, all data requirements for the prequalification assessment of product quality have been satisfied. These data have been relied upon to assess the formulation, manufacturing process and physical/chemical characteristics for the purpose of establishing the identity of the product and assuring that the product can be produced consistently.

The methods for assessing the physical/chemical properties of the product were CIPAC methods and/or validated methods.

The quality component of the dossier is considered complete, and the assessment of the submitted information on quality supports prequalification of the product.

Table 4. List of studies related to quality submitted to WHO as part of the prequalification dossier

Studies that were relied upon for decision making	
Study number	Study title
MLT/MXN/38K19	Determination of Malaoxon content in three batches of Malathion 44% EW
7975	Accelerated Storage Stability of Malathion 44% EW
7972	Determination of Emulsion Stability of Malathion 44% EW
7973	Determination of Foam Persistence of Malathion 44% EW
7974	Low temperature stability of Malathion 44% EW
7970	Determination of pH of Malathion 44% EW
7971	Determination of Pourability of Malathion 44% EW
GLP Study SP-334	^{31}P-NMR analysis for malathion EW samples
Studies that were not used to inform decision making	
	None

3. Manufacturing release specifications

3.1 Summary of manufacturing release specifications

Table 5. Summary of manufacturing release specifications

Description: The formulation shall consist of an emulsion of technical malathion, complying with the requirements of WHO specification 12/TC, in an aqueous phase together with suitable formulants*. After gentle agitation, the formulation shall be homogeneous and suitable for dilution in water.

ID	Property	Method	Declared value
1	Identity test	12/EW/(M)/2, CIPAC Handbook K, p.92, 2003	
2*	Malathion content	12/EW/(M)/3, CIPAC Handbook K, p. 92, 2003	44 % w/v ±5%
3*	Relevant impurities	Impurity I (MeOOOPS-triester) Impurity II (MeOOSPS-triester) Impurity III (isomalathion) Impurity IV (malaoxon)	Maximum: 0.5 % of the malathion content, 0.22 % w/v Maximum: 1.6 % of the malathion content, 0.71 % w/v Maximum: 0.6 % of the malathion content, 0.27 % w/v Maximum: 0.8 % of the malathion content, 0.36 % w/v
4	pH range	CIPAC MT 75.3 , Handbook J. p.131. 2000	2 to 5
5	Pourability	CIPAC MT 148.1, Handbook J. p.133. 2000	Maximum residue: 5%
6*	Emulsion stability and re-emulsification	CIPAC MT 36.3, Handbook K. p.137. 2003	The formulation, when diluted at 30 ± 2°C with CIPAC Standard Waters A and D, shall comply with the following: 0 h Initial emulsification complete 0.5 h Cream: maximum 2ml 2.0 h Cream: maximum 4ml Free oil: none 24 h Re-emulsification complete 24.5 h Cream: maximum 2ml Free oil: none Note: tests after 24 h are required only where results at 2 h are in doubt.
7*	Persistent foam	CIPAC MT 47.3, Handbook O, p.177, 2017	Maximum: 50 ml after 1 minute

*Indicates that additional information is available in Appendix 2.

Manufacturers are expected to rely on the information above as part of a QC management plan and for validation of product quality when released. To the extent required, Certificates of Analysis to support the release of products should present results for the attributes identified in the above table.

3.2 Storage

Accelerated storage stability data were generated as per CIPAC MT 46.3. Test samples were stored for 8 weeks at 40°C. No significant differences were recorded among the properties of the product kept at ambient temperature and after accelerated storage stability test conditions.

Products should be stored and transported in appropriate conditions in accordance with the recommendations of the manufacturer.

Where products have been subjected to prolonged storage or adverse conditions during storage, analysis and testing are recommended to assess changes in characteristics and their suitability for use.

Appendix 1. Summary of available data considered in Module 3

Batches used to generate the physical/chemical data

Batch number	Date	Formulation	Uses
074J2019	10/2019	White color liquid	Malaoxon content
078J2019	10/2019	White color liquid	Malaoxon content
083J2019	10/2019	White color liquid	Malaoxon content
066F2018	06/2018	Off- white to white colored liquid	Storage stability, Malaoxon content

Appendix 2. Manufacturing release specifications: Methods and notes

Description

Odour modifying agents may be included so that the odour is not objectionable, if required for specific uses.

Attribute 2: Malathion content

If the buyer requires both g/kg and g/l at 20ºC, then in case of dispute the analytical results shall be calculated as g/kg.

Attribute 3: Relevant impurities

Methods for determination of the relevant impurities are described in Appendices 1, 3 and 5 in Part 2 of the WHO Malathion Specification. The methods correspond to Cheminova Analytical Method numbers: VAM 202-01 for malaoxon; VAM 005-03 for isomalathion; and VAM 206-01 for MeOOSPS-triester and MeOOOPS-triester.

Attribute 6: Emulsion stability and re-emulsification

As outlined in CIPAC MT 36.3, the test concentrations should be based on those in the recommended directions for use supplied with the product. Where several concentrations are recommended, the highest and lowest concentrations within the scope of the method should be used.

Attribute 7: Persistent foam

The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.