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HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM

TEST PLAN

FOR

ACETOACET-0-ANISIDIDE
CAS NO. 92-15-9

PREPARED BY:

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TABLE OF CONTENTS

OVERVIEW	3
TEST PLAN FOR ACETOACET-0-ANISIDIDE	4
I. Background	4
II. Rationalization for Use of Surrogate Data	4
III. Description of the Test Plan for Each SIDS Endpoint.. ..	.5
IV. Evaluation of Data for Quality and Acceptability	7
ROBUST SUMMARIES	8
I. General Information	8
II. Physical-Chemical Data.....	9
A. Melting Point.....	9
B. Boiling Point.. ..	9
C. Vapor Pressure.....	10
D. Partition Coefficient.....	11
E. Water Solubility.....	12
III. Environmental Fate Endpoints.....	13
A. Photodegradation	13
B. Stability in Water.....	14
C. Biodegradation	16
D. Transport between Environmental Compartments (Fugacity).....	.20
IV. Ecotoxicity.....	21
A. Acute Toxicity to Fish.....	21
B. Acute Toxicity to Aquatic Invertebrates.....	22
C. Toxicity to Aquatic Plants.....	.23
V. Toxicological Data.....	25
A. Acute Toxicity.. ..	25
B. Repeated Dose Toxicity.....	26
C. Genetic Toxicity - Mutation.....	32
D. Genetic Toxicity - Chromosomal Aberration.....	34
E. Genetic Toxicity - Primary DNA Damage.. ..	.36
F. Developmental Toxicity.....	38
G. Reproductive Toxicity.....	41

OVERVIEW

The Diarylide Intermediates Task Force (DITF) of the Color Pigment Manufacturers Association (CPMA) and its member companies hereby submit for review and public comment the test plan for acetoacet-o-anisidide (AAoA) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of the DITF and its member companies to use either existing **data, data** from structurally similar compounds, and predictive computer models to adequately fulfill the Screening Information Data Set (SIDS) for **physicochemical** endpoints, environmental fate endpoints, ecotoxicity test, and human health effects. The DITF believes that adequate data exist to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

CAS No. 92-15-9	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y		Y		N	Y	N
Boiling Point	Y			Y	N	Y	N
Vapor Pressure	Y			Y	N	Y	N
Partition Coefficient	Y		Y		N	Y	N
Water Solubility	Y		Y		N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y			Y	N	Y	N
Stability in Water	Y		Y		N	Y	N
Biodegradation	Y					Y	N
Transport between Environmental Compartments (Fugacity)	Y			Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	Y			Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y		Y		N	Y	N
Toxicity to Aquatic Plants	Y			Y	N	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y		Y		Y	Y	N
Repeated Dose Toxicity	Y ¹		Y		N	Y	N
Genetic Toxicity - Mutation	Y		Y		Y	Y	N
Genetic Toxicity - Chromosomal Aberrations	Y ²	Y			Y	Y	N
Developmental Toxicity	Y ²	Y			Y	Y	N
Toxicity to Reproduction	Y ²	Y			Y	Y	N
OTHER TOXICITY DATA							
Genetic Toxicity - Primary DNA Damage	Y		Y		Y	Y	N

1. A 14-day repeated dose dietary study on AAoA is supported by 28-day OECD guideline study conducted under GLP assurances using the surrogate chemicals AAA and AAoT.
2. An assessment of these end-points is accomplished through the use of surrogate data from AAA and AAoT.

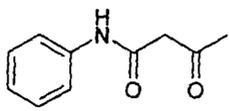
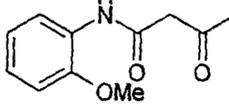
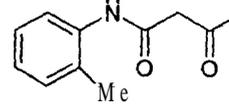
TEST PLAN FOR ACETOACET-O-ANISIDIDE

I. Background

Acetoacet-o-anisidide (**AAoA**) is an off-white solid (powder) chemical of very high purity. It is a chemically stable material. It is manufactured and transported in closed-systems and sold to a limited number of customers who also handle it in closed-systems. Its sole use is as a chemical intermediate in the production of pigments. There is no known direct or consumer use of this chemical where exposure to the general population may occur. Exposure to **AAoA** by employees is minimized through its manufacture within closed systems and by good industrial hygiene practices. Exposure to the environment is unlikely except under conditions of an accident during manufacture or transport.

II. Rationalization for Use of Surrogate Data

As a means to reduce the number of tests that may be conducted the EPA allows for the use of data from **structurally** similar compounds to characterize specific SIDS endpoints (US EPA 1999a). Accordingly, the DITF believes that data from the compounds **acetoacetanilide** (AAA) and acetoacet-o-toluidide (**AAoT**) meet the needed criteria for use as surrogates in the completion of some SIDS endpoints. As is readily seen by their structures below, AAA, **AAoA** and **AAoT** only differ by the presence of a methyl or a methoxy group in the ortho position. This single substitution does not significantly alter the basic **physicochemical** properties or its basic biological effects. **All** three compounds have a similar acute toxicity value. Furthermore, results from repeat exposure studies on the three compounds show that they all target the red-blood-cell inducing a methemoglobinemia and a subsequent anemia. Accordingly, data from AAA and **AAoT** have been used to fulfill the endpoints for developmental and reproductive toxicity and chromosomal aberration potential. In addition, data from these two compounds were used to supplement repeat exposure endpoints where current data on **AAoA** was of insufficient duration (**14-days**). Data from AAA were also utilized to supplement computer model estimations on toxicity to aquatic plants and experimental data on stability in water,

CAS Number	102-01-2	92-15-9	93-68-5
Structure			
Common Name	Acetoanilide (AAA)	Acetoacet-o-Anisidide (AAoA)	Acetoacet-o-Toluidide (AAoT)
Physical Chemical			
Melting Point	83-85 C	83-85 C	106 C
Boiling Point	Solid	Solid	Solid
Density/Sp. G	1.26	1.13	1.062
Vapor Press. (kPa)	0.001 @ 20 c	0.00002 @ 25 c	0.133 @ 20 c
Partition Coeff.	Kow log P = 0.76	Kow log P = 1.01	Kow log P = 0.99
Water Solubility	7.3 g/L	3 g/L	2 g/L
Acute Toxicity (Rat LD ₅₀) ^a	1131-1600 mg/kg	1600-1903 mg/kg	1600 mg/kg
Repeat Toxicity ^b (Target organ)	Erythron • Methemoglobinemia	Erythron • Methemoglobinemia	Erythron • Methemoglobinemia

a) Data are from Eastman Chemical Company MSDS's.

b) Data from **AAoA** were from a 14-day study, while data from AAA and **AAoT** were from 28-day exposures.

III. Description of the Test Plan for Each SIDS Endpoint

A. Physicochemical

- Melting point ▪ A value for this endpoint was obtained from reputable textbook.
- Boiling Point - A value for this endpoint was obtained using MPBPWIN, a computer estimation program (1). Technically, data are not required as material is a solid (2).
- Vapor Pressure - A value for this endpoint was obtained using MPBPWM, a computer estimation program (1).
- Partition Coefficient ▪ Two values were obtained for this end point. One was by a laboratory procedure using HPLC and the other was by KOWIN, a computer estimation program (1).
- Water Solubility ▪ Two values were obtained for this end point. One was by a laboratory procedure and the other was by WSKOW, a computer estimation program (1).

Conclusion: All end points haven been satisfied by, either actual data or accepted estimation models, and are of sufficient quality to conclude that no additional testing are needed.

B. Environmental Fate

- Photodegradation ▪ A value for this endpoint was obtained using AOPWIN, a computer estimation program (1).
- Stability in Water - Data for this endpoint are from a study assessing its hydrolysis in a simulated gastric fluid preparation. While this study is not as robust as an OECD TG- 111 study, the data should be deemed acceptable to fulfill an understanding of this property. In addition, the data are consistent with that of the OECD TG- 111 study conducted on the structurally similar compound AAA (2).
- Biodegradation - This endpoint was satisfied through the use of existing data that included an evaluation of chemical and biological oxygen demand (similar to OECD TG-30 1 C), a 2 1 -day biodegradation assessment, as well as an OECD TG-302B **Zahn-Wellens** Test.
- Fugacity ▪ Transport between environmental compartments was determined by using **EPIWIN:EQC**, a Level III fugacity computer model (1).

Conclusion: All endpoints have been satisfied using data or estimation models that are of sufficient quality to conclude that no additional testing is needed. The sole use of this substance is as a chemical intermediate and because it is handled in closed-systems it is very unlikely to enter into the environment.

C. Ecotoxicity Data

- Acute Toxicity to Fish ▪ This endpoint is **filled** by data from an OECD TG-203 study.
- Acute Toxicity to Aquatic invertebrates - This endpoint is filled by data from a study that followed a protocol similar to OECD TG-202.
- Toxicity to Aquatic Plants - This endpoint is filled by data developed by ECOSAR, a computer simulation model (1), along with data from an OECD TG-20 1 study on AAA, a structural surrogate (3).

Conclusion: All endpoints have been satisfied with data, on **AAoA** or through the use of estimations models and structural surrogates, which are of sufficient quality to conclude that no additional testing is needed. The sole use of this substance is as a chemical intermediate and because it is handled in closed-systems it is very unlikely to enter into the environment.

D. Toxicological Data

- Acute Toxicity • This endpoint is filled by data from a study conducted in 1990 using an established protocol [EEC Directive **84/449/EEC** (OJ No. **L25 1, 19.09.84**), Part B, Method **B1** Acute toxicity (oral)] with GLP assurances.
- Repeat Dose Toxicity • This endpoint is filled with data that exist on **AAoA** and by data on two **structurally** similar compounds, AAA and **AAoT**. The study with **AAoA** is of only a **14-day** duration. However, the target organ in this study is identical to that of the two surrogate chemicals whose studies lasted **28-days**, followed OECD protocols, and were conducted under GLP assurances.
- Genetic Toxicity Mutation • This endpoint is filled with two studies conducted under GLP assurances. One study looked for mutations in *Salmonella typhimurium* (Ames Assay) while the other study assessed the induction of forward mutations in Chinese hamster ovary cells (**CHO/HGPRT**).
- Aberration • This endpoint is filled with data on two structurally similar compounds, AAA and **AAoT**. Both studies followed OECD protocol TG-473 and were conducted under GLP assurances.
- Primary DNA Damage • While not a HPV SIDS endpoint, a robust summary has been prepared to determine the potential ability of **AAoA** to induce unscheduled DNA synthesis in rat hepatocytes. This study was conducted under GLP assurances. This **study** was included to further demonstrate a lack of potential for **AAoA** to adversely affect DNA.
- Developmental Toxicity • This endpoint is filled with data on two structurally similar compounds, AAA and **AAoT**. Both studies followed OECD protocols (TG-42 1 and 422 respectively) and were conducted under GLP assurances.
- Reproductive Toxicity • Since **AAoA** is in industrial intermediate with controlled transport this endpoint is technically not needed (1). Nevertheless, **data to** fulfill this endpoint has been presented. Data on two structurally similar compounds, acetacetanilide and acetoacet-o-toluidide have been used as surrogates. Both studies followed OECD protocols (TG-42 1 and 422) and were conducted under GLP assurances.

Conclusion: All endpoints have been satisfied with data, on **AAoA** or through the use of structural surrogates, which are of **sufficient** quality to conclude that no additional testing is needed. Given that the sole use of this substance is as a chemical intermediate there is essentially no exposure to the general population and, because it is handled in closed-systems, employee exposure is minimized through good industrial hygiene practices.

IV. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance (4) **and the** systematic approach described by Klimisch *et al.* (1997). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (4). The codification described by Klimisch specifies four categories of reliability for describing **data** adequacy. These are:

- (1) **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
- (2) **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
- (3) **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
- (4) **Not Assignable:** Includes studies or **data** in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or **secondary** literature.

References:

1. EPIWIN, Version 1.2, Syracuse Research Corporation, Syracuse, New York.
2. OECD SIDS Document: Section 3. Data Evaluation, Preparation of SIDS Dossiers and Testing Plans
3. US EPA. 1999a. The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.
4. USEPA. 1999b. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.
5. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25: 1-5.