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ACETOACETANILIDE
CAS N°:102-01-2

SIDS Initial Assessment Report
for
SIAM 7

(Sydney, Australia, 25-27 March 1998)

Chemical Name : Acetoacetanilide
(3-Oxo-N-phenyl butamide)

CAS No.: 102-01-2

Sponsor Country: USA
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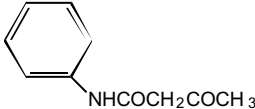
History: SIDS Dossier and Testing Plan were reviewed at the SIDS Review Meeting on September 20-24, 1993, the following SIDS Testing Plan was agreed:

no testing ()
testing (✓)

Acute Toxicity Test with the Freshwater Alga
Reproductive/Developmental Toxicity Screen

Comments: The results of toxicity tests on algae and the reproductive/developmental screening study have been incorporated into this revised SIAR.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	102-01-2
Chemical Name	Acetoacetanilide
Structural Formula	
CONCLUSIONS AND RECOMMENDATIONS	
<p>Environment</p> <p>The chemical is of low concern to aquatic organisms and is considered inherently biodegradable. The predicted environmental concentration is lower than the predicted no effect concentration. It is therefore currently considered of low potential risk and low priority for further work.</p> <p>Health</p> <p>The critical effect of this chemical is methemoglobinemia. This chemical is used as an intermediate and is produced in a closed system. Exposures at production sites are well controlled. It is therefore currently considered of low potential risk and low priority for further work.</p>	
SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS	
<p>Acetoacetanilide (AAA) is a chemical intermediate used in the production of pigments. Approximately 10 000 metric tonnes are manufactured each year in a closed system. This substance is then isolated and transported under closed conditions to pigment manufacturing facilities. There is no known direct or consumer use. Non-aqueous wastes from manufacture are incinerated, and aqueous wastes are sent to a wastewater treatment facility for treatment.</p> <p>Following environmental release AAA is expected to distribute in the aquatic environment, biodegradation is expected to be rapid. The predicted environmental concentration from the manufacture of AAA has been estimated to be 16 µg/L and 46 µg/L based on two different production sites. The predicted environmental concentration from pigment manufacture is estimated to be 8.6 µg/L.</p> <p>The acute toxicity of AAA has been evaluated in a number of aquatic species including the fathead minnow, and several invertebrate species including <i>Daphnia</i>. In all cases the LC₅₀ concentration was greater than 100 mg/L (the highest concentration tested) for the 96-hour exposure. The EC₅₀ for algae of 318 mg/L was used to calculate a predicted no effect concentration of 0.32 mg/l using an assessment factor of 1000. Comparing the hypothetical PEC_{initial} in water to the PNEC for algal toxicity, the ratio is less than one and therefore it may be concluded that AAA has a low potential risk to the environment.</p> <p>Acetoacetanilide is manufactured in closed systems. Based on the results of air monitoring of bagging and drumming areas, airborne concentrations in the workplace which are at or below 0.3 mg/m³ would be expected to result in an EHE of 0.04 mg/kg. There is no direct consumer exposure to AAA because the substance is used as an intermediate in other manufacturing processes. The EHE for indirect exposure is orders of magnitude lower.</p> <p>Repeated oral exposure in rats to dose levels of >30 mg/kg/day may result in methemoglobinemia. Daily doses of >100 mg/kg/day for 28 days result in reduced weight gains and feed consumption, possible cyanosis, methemoglobinemia, haemolytic anaemia, and extramedullary hematopoiesis in the spleen and liver. Animals</p>	

allowed to recover for 14 days had hematologic parameters that were near normal with no evidence of anaemia or methemoglobinemia. The no-observable-effect level (NOEL) for 14 days of treatment was 102.4 mg/kg/day, but the NOEL for 28 days of treatment was 12 mg/kg/day with evidence that a dose level of 30 mg/kg for 6-8 weeks result in minimal methemoglobinemia (<5% MetHB) which is not clinically significant (NOAEL was 30 mg/kg/day). The NOEL for reproductive toxicity and developmental toxicity was 100 mg/kg. Mating and fertility were unaffected by treatment, and there were no microscopic lesions in the sex organs. There were no effects on gestation, implantation or viability, and no effects were observed in the pups.

Considering the effect on methemoglobinemia, the Estimated Dose of Low Concern (EDLC) is 0.3 mg/kg based on a NOAEL of 30 mg/kg from repeated dose studies and an Uncertainty Factor of 100. Based on the results of air monitoring of bagging and drumming areas, airborne concentrations in the workplace which are at or below 0.3 mg/m³ would be expected to result in an EHE of 0.04 mg/kg. The EHE for indirect exposure is orders of magnitude lower. Using the occupational EHE, the ratio of EHE to the EDLC is less than 1, alternatively the margin of safety is 750, indicating that AAA is a chemical of low potential risk to man.

NATURE OF FURTHER WORK RECOMMENDED

SIDS FULL SUMMARY

CAS NO: 102-01-2		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point	NA	?	83-85°C
2.2	Boiling Point	NA	?	>400 °C
2.3	Density	NA	?	1.26 g/cc at 20°C
2.4	Vapour Pressure	NA	?	0.001 kPa at 20°C
2.5	Partition Coefficient (log P _{ow})	NA	Calculated Measured	0.76 0.70 at 25°C
2.6 A	Water Solubility	NA	?	8,375 - 10,000 mg/L
2.6B	pH	NA	?	Neutral
	pKa	NA	?	-
2.12	Oxidation:Reduction Potential			-
ENVIRONMENTAL FATE/BIODEGRADATION				
3.1.1	Photodegradation	NA	Calculated	Residence time = 192 hours
3.1.2	Stability in water	NA	OECD 111	T _½ = 131.4 d at pH 1.5
3.2	Monitoring data	NA	NA	In air = ND In surface water = ND In soil/sediment = ND In biota = ND
3.3	Transport and Distribution	NA	Calculated (Fugacity level I)	In Air 1.36% In Water 97.29 % In Sediment 1.09 % In Soil 0.23 % In Biota 0.02 %
3.5	Biodegradation	NA	Similar to OECD 301E DIN 38412	51.6% over 21 days 85% after 5 days
3.6	BOD ₅		Similar to OECD 301D	0.04 g/g

SIDS FULL SUMMARY

CAS NO: 102-01-2		SPECIES	PROTOCOL	RESULTS
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	<i>Pimephales promelas</i> <i>Brachydanio rerio</i>	Similar to OECD 203 OECD 203	LC ₅₀ (96 hr) = > 100 mg/L LC ₅₀ (96 hr) between 242 and 332 mg/L
4.2	Acute/Prolonged Toxicity to Aquatic Invertebrates	<i>Daphnia magna</i> <i>Gammarus fasciatus</i> <i>Dugesia dorocephalo</i> <i>Planorbis trivolvis</i> <i>Lumbriculus variegatus</i> <i>Caecidota intermedia</i>	DIN 34812, Part II Similar to OECD 202 Similar to OECD 202 Similar to OECD 202 Similar to OECD 202 Similar to OECD 202 Similar to OECD 202	EC ₅₀ (24 hr) = 70-200 mg/L EC ₅₀ (96 hr) = > 100 mg/L LC ₅₀ (96 hr) = > 100 mg/L LC ₅₀ (96 hr) = > 100 mg/L LC ₅₀ (96 hr) = > 100 mg/L LC ₅₀ (96 hr) = > 100 mg/L LC ₅₀ (96 hr) = > 100 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	<i>Selenastrum capricornutum</i>	OECD 201	EC ₅₀ (72 hr) = 318 mg/L NOEC (72 hr) = 180 mg/L
4.4	Toxicity to Bacteria	Activated sludge	Similar to OECD 209	IC ₅₀ = >2000 mg/L
4.5.1	Chronic Toxicity to Fish	-	-	-
4.5.2	Chronic Toxicity to Aquatic Invertebrates (Daphnia)	-	-	-
4.6.1	Toxicity to Soil Dwelling Organisms	-	-	-
4.6.2	Toxicity to Terrestrial Plants	Ryegrass Radish Lettuce Corn Marigold Lettuce Radish	ASTM STP 1091 NA	NOEC = 100 mg/L NOEC = 100 mg/L NOEC = 100 mg/L NOEC = 100 mg/L NOEC = 10 mg/L NOEC = 10 mg/L NOEC = 10 mg/L
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)	-	-	-

SIDS FULL SUMMARY

CAS NO: 102-01-2	SPECIES	PROTOCOL	RESULTS
TOXICOLOGY			
5.1.1 Acute Oral Toxicity	Rat	Similar to OECD 401	LD ₅₀ = 5400 mg/kg (f) - 6500 mg/kg (m) (in propylene glycol)
	Rat		LD ₅₀ = 2450 mg/kg (in 2% starch)
	Mouse		LD ₅₀ between 800 and 1600 mg/kg (in 0.5% guar gum)
	Rat	-	LD ₅₀ between 1600 and 3200 mg/kg (in 0.5% guar gum)
5.1.2 Acute Inhalation Toxicity	Rat		LD ₅₀ = 1131 mg/kg (f) - 1600 mg/kg (m)
5.1.3 Acute Dermal Toxicity	-		(in 0.5% guar gum)
	Guinea pig (Duncan/Hartley)		- LD ₅₀ between 500 and 1000 mg/kg
	Guinea pig (Duncan/Hartley)		LD ₅₀ = > 1000 mg/kg
5.4 Repeated Dose Toxicity	Rat (Sprague-Dawley)	other	NOEL (oral) = 102.4 mg/kg (14 d)
	Rat (Sprague-Dawley)	OECD 407	NOEL (oral) = 12 mg/kg (28 d)
	Rat (Sprague-Dawley)	other	NOEL (oral) = <30 mg/kg (7 d)
5.5 Genetic Toxicity in Vitro	Salmonella typhimurium	Similar to OECD 471	Negative (with metabolic activation) Negative (without metabolic activation)
A Bacterial Test (Gene Mutation)			
B Non-Bacterial in Vitro Test (Chromosomal aberrations)	Human Lymphocytes	OECD 473	Negative (with metabolic activation) Negative (without metabolic activation)
5.6 Genetic Toxicity in Vivo	-	-	-
5.8 Toxicity to Reproduction	Rat (Sprague-Dawley)	OECD 421	NOEL = 3 mg/kg (General toxicity) NOEL = 100 mg/kg (Repro. Tox. parental) NOEL = 100 mg/kg (Repro. Tox. F1)
5.9 Developmental Toxicity/ Teratogenicity	Rat (Sprague-Dawley)	OECD 421	NOEL = 3 mg/kg (General toxicity) NOEL = 100 mg/kg (Pregnancy/litter) NOEL = 100 mg/kg (Foetal data)
5.11 Experience with Human Exposure	NA	NA	Air emissions during drumming: ≤0.34 mg/m ³ Air emissions during bagging: ≤0.01 mg/m ³

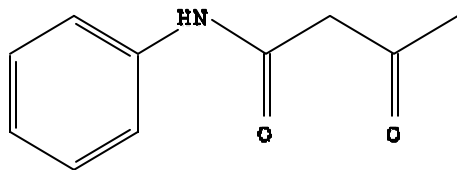
SIDS Initial Assessment Report

1. IDENTITY

Chemical Name: 3-Oxo-N-phenyl butamide
(Acetoacetanilide)

CAS No.: 102-01-2

Molecular formula: C₁₀H₁₁NO₂



Structural formula:

Molecular Weight: 177.20

Acetoacetanilide (AAA) is a white solid that is 99% pure. Impurities have not been identified, and there are no additives. AAA is soluble in water (8,375-10,000 mg/L) and has a low octanol/water partition coefficient (a measured log K_{ow} of 0.70). The vapor pressure is very low (< 0.01 mm Hg). Although the pH in water has not been determined precisely, AAA is stated to have a pH of near a value of 7. No data were found that describe the oxidation potential of AAA, but it is considered to be not reactive by the National Fire Prevention Association.

AAA is manufactured by reacting aniline and a diketene.

2. GENERAL INFORMATION ON EXPOSURE

Acetoacetanilide is used in the manufacture of pigments. Approximately 5,000 to 10,000 metric tonnes are manufactured in the U.S. each year in a closed system (1990 data). The substance is then isolated and transported under closed conditions to user facilities. Release of the pure solid substance to the environment is unlikely except as an accidental release in handling or transport. Non-aqueous wastes from manufacture are incinerated, and aqueous wastes at production and pigment manufacturing facilities are sent to wastewater treatment plants for biodegradation. A survey of pigment manufacturers that use AAA indicated that the majority of users discharge wastes into publicly owned wastewater treatment plants, and that the remaining users dispose of wastewater in lined onsite facilities. In addition, sludge from private wastewater facilities is either placed into off-site lined industrial or municipal landfills, or incinerated (Color Pigments Manufacturers Association, 1995). The USEPA has reported that AAA was detected in untreated wastewater streams at pigment manufacturing sites. EPA has suggested that AAA from wastewater or from sludge that is stored in private unlined monofill treatment facilities could contaminate air, groundwater, and terrestrial plants.

Occupational exposure to AAA is minimized during manufacture through the use of good industrial hygiene practices. Air monitoring data indicate that airborne concentrations of AAA during bagging and drumming operations are below $\sim 0.3 \text{ mg/m}^3$.

There is no known direct or consumer use of AAA.

2.1. Environmental Exposure and Fate

2.1.1 Environmental Exposure

Air

Environmental releases of AAA during manufacture are unlikely because the chemical is synthesized in a closed system. Environmental releases may occur, however, during bagging or drumming operations, prior to transport to user facilities. Even so, because AAA is a solid with a relatively low vapor pressure, substantial airborne concentrations are not likely.

Wastewater

Releases of AAA to the environment are expected to be primarily in wastewater and wastewater sludge from AAA production sites and from pigment manufacturing facilities. Estimates of AAA in wastewater and the amount that is discharged into surface water vary based on the source and facility.

Estimated Releases from Manufacturing Facilities. Based on the annual production volume of 10,000 tonnes, the AAA manufacturers have estimated the AAA concentration in wastewater entering a treatment facility would be no greater than 5 g/L. It is assumed that the wastewater contains both dissolved AAA and suspended solids. Wastewater entering the treatment facility is diluted approximately 1:1000 resulting in a concentration of 5 mg/L in the facility.

Assuming 86-90% TOC removal, the effluent from wastewater treatment plants associated with AAA production facilities is estimated to be 0.5 mg/L. This assumption is based on data from Matsui *et al.* (1988) who demonstrated that TOC removal efficiency was 86% in 10 days. Using a discharge dilution rate of 12:1, the concentration of AAA in the

receiving waters can be estimated to be 46 µg/L for wastewaters associated with AAA manufacture. A similar environmental concentration of AAA has been estimated for the receiving waters at a German production site. Based on the maximum production volume and site-specific data for the flow -rate of the river receiving the effluent, the AAA concentration in the river was predicted to be 16 µg/L (J. Ahlers, pers. com.). In summary, the Predicted Environmental Concentrations (PECs) resulting from the manufacture of AAA are 16 and 46 µg/L.

Estimated Releases from Pigment Production Facilities. Based on the highest concentration found in wastewater from a manufacturing facility, the AAA concentration in wastewater generated at a pigment production site has been estimated to be 1.03 mg/L (Color Pigments Manufacturers Association, 1995). Because the concentration may be further reduced through dilution in an equalization tank prior to entering the wastewater treatment facility, 1.03 mg/L is considered an upper limit.

Assuming the same percent TOC removal (86-90%) as for treatment plants associated with manufacturing facilities, wastewater treatment plant effluents associated with pigment production is estimated to be 0.103 mg/L. Using a discharge dilution rate of 12:1, the PEC of AAA in the receiving waters can be estimated to be 8.6 µg/L for wastewaters associated with pigment manufacture.

Sludge

Based on an annual production of 10,000 tonnes, AAA manufacturers have estimated that 4275 kg of AAA are released annually to lined landfills as wastewater sludge or from off-spec production. Based on data in the EPA's support document for the Hazardous Waste Identification Project (1994, *Fed Reg* 59: 66088), the concentration of AAA in wastewater sludge is expected to be 64.23 mg/kg. In another study it was estimated that sludge generated from azo pigment production would have a maximum AAA concentration of 0.9 mg/kg, and that the AAA concentration in a landfill in which the sludge was deposited would be 0.009 mg/kg. Using a MULTIMED model, it was calculated that a landfill concentration of 0.009 mg/kg might yield a hypothetical concentration of 2×10^{-8} mg/L in wellwater at a location 200 feet from the landfill (comments Hoechst Corporation, 1995, Color Pigments Manufacturers Association Comments, 1995).

2.1.2 Environmental Fate

AAA is soluble in water and its octanol-water partition coefficient is moderately low, which suggests that AAA preferentially partitions into water. These conclusions are supported by Level I Fugacity modeling which indicates that, following release to the environment, equilibrium partitioning of AAA will result in the following pattern of distribution:

In air	1.361%
In soil	0.234%
In water	97.291%
In biota	0.021%
In suspended solids	0.002%
In sediment	1.092%

Photodegradation

Acetoacetanilide does not absorb wavelengths of light above 290 nm and thus will not be susceptible to direct (uncatalyzed) photodegradation.

The reaction of acetoacetanilide with hydroxide [OH⁻] will be the only significant process by which this material will be removed from the atmosphere. Atmospheric residence time is estimated to be 192 hours (Lyman et al., 1982).

Stability in Water

AAA has a neutral pH in water, and does not readily hydrolyze. Only 3.5% decomposition occurred after 167.5 days (Appel and Muhlberger, 1990).

Biodegradation

In tests conducted with activated sludge, biodegradation rates of 85% in 5 days and 51.6% in 21 days (based on carbon dioxide evolution) have been reported (Wellens, 1988; Watson, 1984). AAA is considered inherently biodegradable.

Although AAA is inherently biodegradable, high concentrations may inhibit microbial activity. In tests with activated sludge, an AAA concentration of 2000 mg/L inhibited glucose metabolism by 40%; however, lower concentrations of 20 and 200 mg/L had no adverse effects.

Bioaccumulation

The octanol/water partition coefficient is low ($\log K_{ow} = 0.70$), suggesting that AAA is not lipophilic and is not likely to bioaccumulate.

2.2 Human Exposure

2.2.1 Occupational Exposure

Employee exposure to AAA is minimized during manufacture through good industrial hygiene practices. It is estimated that no more than 50-100 individuals in the USA are exposed during the manufacturing and handling process. A survey conducted by NIOSH estimated that there are a total of 1108 employees in the pigment industry that are potentially exposed to AAA (NIOSH, 1983).

At present, there are no published occupational exposure values (e.g., OEL, TLV, or MAK) developed by regulatory agencies. Eastman Chemical Company has established an internal OEL of 2 mg AAA/m³. Air monitoring of bagging and drumming areas at manufacturing sites (≤ 0.3 mg/m³) indicate that actual AAA concentrations are well below this limit. Assuming a maximum airborne concentration of 0.3 mg/m³ (worst case) and a total tidal volume of 10 m³ during an 8-hour period, a 70 kg person would receive an inhaled dose of 0.04 mg/kg (assuming 100% absorption).

2.2.2 Consumer Exposure

There is no direct consumer exposure to AAA because the test substance is used as an intermediate in other manufacturing processes and is completely consumed in the process.

2.2.3 Indirect Exposure via the Environment

The US EPA has assumed that human populations living near wastewater treatment facilities of the pigment manufacturing industry may be indirectly exposed to AAA (US EPA, 1994). The most likely source of exposure is considered to be from groundwater contaminated with AAA that leaches or accidentally spills from an unlined onsite monofill

treatment facility. Exposure via air was considered by the EPA to be possible, but not likely to be substantial because of the very low vapor pressure. Likewise, exposure from contaminated soil is also likely to be low given the low K_{ow} for AAA. Therefore, as predicted by the fugacity model calculations, exposure via contaminated groundwater was considered by EPA to be the greatest concern.

However, the concentrations of AAA in wastewater, which if improperly managed could subsequently contaminate groundwater, may be much lower than the EPA estimates would suggest (Color Pigments Manufacturers Association, 1995). Analyses of wastewater from pigment manufacturing plants indicate the presence of at least 3 similarly-structured substances (one being AAA) that co-elute. Thus, there is no certainty that the concentration cited by EPA is only AAA. Instead, it is likely that the actual environmental exposure concentrations are low. Matsui *et al.* (1975) found the concentration of AAA in wastewater sludge from an industrial complex in Japan to be 0.67 gTOC/g. A recent risk analysis of a representative pigment manufacturing plant wastewater treatment system estimated that worst case groundwater contamination from untreated wastewater from the pigment manufacturing facility is likely to be $<1.0 \times 10^{-6}$ $\mu\text{g/L}$ AAA and that the chronic daily intake would be predicted to be comparable to 1.0×10^{-9} mg/kg/day (Comments, Hoechst Corporation, 1995).

3. EFFECTS ON HUMAN HEALTH

3.1 Acute Toxicity

There are no data available evaluating the effects of AAA on humans. However, there are several studies on experimental animals. Depending on the vehicle used, oral LD₅₀ values for rats range from greater than 800 to 6500 mg/kg. In tests in which propylene glycol was the vehicle, the LD₅₀ values were >5000 mg/kg (Wallace, 1975). In tests in which starch (2%) or guar gum (0.5%) was used, the LD₅₀ values were between 800 and 3200 mg/kg (Scholz and Weigand, 1965; Fassett, 1962; Bernard, 1982). In one dermal test, application of 1000 mg/kg of AAA to the skin of guinea pigs for 24 hr resulted in no systemic toxicity (Bernard, 1982). Another study resulted in deaths of guinea pigs at the highest dose of 1000 mg/kg, resulting in an LD₅₀ between 500 and 1000 mg/kg (Fassett, 1962).

AAA caused little or no irritation to the skin of rabbits exposed for 4 hours (Prate, 1974; Kreiling and Jung, 1988) or to the skin of guinea pigs exposed for 24 hours (Fassett, 1962; Bernard, 1982). Ocular irritation in the rabbit is characterized as moderate; irritation of the conjunctiva occurred immediately after exposure but abated to slight or minimal within 24 hours (Kreiling and Jung, 1988). Irrigation of the eye immediately after exposure reduced the severity of the reaction (Bernard, 1982). AAA was not found to be a dermal sensitizer (Bernard, 1982).

3.2 Repeated-Dose Toxicity

The subchronic toxicity of AAA has been investigated in several 14- and 28-day oral toxicity studies in rats. Repeated oral exposure of rats to dose levels of ≥ 30 mg/kg/day may result in methemoglobinemia. Bernard (1982) reported that rats treated with 0.1 or 1.0 % AAA in the diet (102.4 and 1001.7 mg/kg bw) for 14 days had signs of cyanosis at the high-dose, but no signs of toxicity were observed at the low-dose. The NOEL was 102.4 mg/kg/d. Scholz and Weigand (1965) treated rats with 250 mg/kg by gavage 14 times over a 21-day period and found no evidence of toxicity. Edwards *et al.* (1991) reported that animals treated with 12, 100, or 850 mg/kg AAA by gavage for 28 days demonstrated evidence of systemic toxicity and neurotoxicity. Dose-dependent changes in hematology and serum chemistry occurred that were indicative of hemolytic anemia and methemoglobinemia, and these were statistically significant in the high and mid-dose groups. Compensatory erythropoiesis was confirmed in the evaluation of bone marrow smears. By the end of the 14-day recovery period, hematologic parameters were near normal with no evidence of anemia or methemoglobinemia. Spleen weights after 4 weeks of treatment were significantly greater in the high- and mid-dose animals compared with controls. Higher spleen weights were also evident after recovery. Microscopic evaluation of tissues indicated extramedullary hematopoiesis in the liver with siderosis in the spleen. Evidence of renal excretion of heme was also present. The NOEL was 12 mg/kg/day.

Foss (1996) treated rats with 30, 100, or 300 mg/kg for 7 days in a range-finding study. No signs of toxicity were observed. Body weights and feed consumption were comparable. Methemoglobin levels were higher for all treated groups compared with the controls (Table 1).

Table 1. Methemoglobin values for animals treated with AAA for 7 days

Sex	Control	30 mg/kg	100 mg/kg	300 mg/kg
Males	1.7 ± 0.2%	2.7 ± 0.4%	3.8 ± 0.6%	6.6 ± 1.2%
Females	1.7 ± 0.3%	2.6 ± 0.2%	5.7 ± 4.1%	5.3 ± 0.9%

Spleen weights (absolute and relative to body weight) for the 30 mg/kg group were comparable with controls, but higher for the 100 and 300 mg/kg groups. In the subsequent reproductive/developmental toxicity screening study, animals received 3, 30, or 100 mg/kg for 6-8 weeks (Foss, 1996). Methemoglobinemia was seen in the 30 and 100 mg/kg groups (Table 2).

Table 2. Hematologic parameters for animals treated with AAA for 6-8 weeks

Parameter (units)	Sex	Control	3 mg/kg	30 mg/kg	100 mg/kg
MetHb (%)	Males	1.0 ± 0.8	1.4 ± 0.8	2.3 ± 0.6*	4.4 ± 2.1*
	Females	0.3 ± 0.4	0.6 ± 0.6	1.6 ± 0.7*	3.0 ± 1.4*
RBC (10⁶/μl)	Males	7.76 ± 0.39	7.70 ± 0.86	7.44 ± 0.59	6.35 ± 0.35*
	Females	5.94 ± 0.55	6.01 ± 0.47	5.85 ± 0.53	4.87 ± 0.42*
Hct (%)	Males	44.4 ± 2.4	43.7 ± 4.9	44.0 ± 2.2	40.7 ± 2.4
	Females	37.4 ± 2.3	38.4 ± 2.5	38.2 ± 3.1	34.7 ± 2.1*
Hgb (g/dl)	Males	15.8 ± 0.8	15.5 ± 1.6	15.4 ± 0.7	14.3 ± 0.8*
	Females	13.2 ± 0.7	13.7 ± 1.0	13.5 ± 1.0	12.2 ± 0.7*

* = Significantly different from control group, $p \leq 0.05$.

Since methemoglobinemia was minimal (< 5% MetHB) at 30 mg/kg and not clinically significant (Gossel and Bricker, 1994) and there were no other effects on hematology at that dose level, 30 mg/kg may represent a no-observable-adverse-effect level (NOAEL).

3.3 Reproductive and Developmental Toxicity

The reproductive and developmental toxicities of AAA were evaluated in an OECD Reproductive/Developmental Toxicity Screening Study (TG 421). Dose levels of 3, 30, and 100 mg/kg were used with the highest dose level expected to result in methemoglobinemia (Foss, 1996). Mating and fertility were unaffected by treatment, and there were no microscopic lesions in the sex organs. There were no effects on gestation, implantation, or viability, and no effects were observed in the pups. The NOEL for reproductive toxicity and developmental toxicity was 100 mg/kg. There is no reproductive or developmental health hazard from exposure to AAA.

3.4 Genotoxicity

AAA was found to be not mutagenic in *Salmonella typhimurium* strains TA-97, TA-98, TA-100, or TA-1535 when tested with or without metabolic activation (Zeiger *et al.*, 1988). In addition, no mutations were observed in human lymphocytes when tested *in vitro* in a standard OECD 473 study both with and without metabolic activation (Brooker *et al.*, 1990).

The genetic toxicity of AAA has not been tested *in vivo*; however, a micronucleus test may not be appropriate because background levels of bone marrow micronuclei may increase in

animals dosed with AAA due to compensatory responses to the hematologic effects of AAA.

3.5 Carcinogenicity

Long-term carcinogenicity studies have not been conducted with AAA.

3.6 Mechanism of Toxicity

It is possible that the reversible hematotoxicity of AAA is a result of its metabolic conversion to aniline or a related metabolite. The EPA has suggested that aniline is the primary chemical of concern from AAA metabolism, and the Agency has suggested that the toxicity of AAA parallels that of aniline. Both substances cause methemoglobinemia. Both substances were found not to be teratogenic at dose levels that result in maternal toxicity. The dissimilarity between AAA and aniline is the total dose necessary to cause effects. Aniline is considered by the US EPA to be highly acutely toxic, while AAA is only slightly acutely toxic. A single oral dose of 50 mg aniline/kg bw to dogs can result in methemoglobinemia. By contrast, rats that consumed feed with 0.1% AAA (100 mg/kg) for 14 days had no adverse effects, and repeated treatment with 30 mg/kg for 68 weeks resulted in only minimal methemoglobinemia (< 5%) which is not considered to be clinically important. Therefore, while the biological effect may be similar, it is not reasonable to assume that the hazard of AAA to human health is equivalent to that of aniline.

3.7 Initial Assessment for Human Health

The primary effect of oral ingestion of AAA is methemoglobinemia. Dose levels of 100 mg/kg/day for more than 14 days result in methemoglobin levels in rats that are considered to be toxicologically adverse. Using this effect, the Estimated Dose of Low Concern (EDLC) is 0.3 mg/kg based on a NOAEL of 30 mg/kg from repeated dose studies and an Uncertainty Factor of 100.

$$\text{EDLC} = \frac{30 \text{ mg/kg}}{100} = 0.3 \text{ mg/kg}$$

Using a more conservative approach to the EDLC, a NOEL of 12 mg/kg from the 28-day study may be used to calculate an EDLC of 0.12 mg/kg.

The Estimated Human Exposure (EHE) values are low. Airborne concentrations in the workplace, which are at or below 0.3 mg/m³, would be expected to result in an EHE of 0.04 mg/kg. The EHE for indirect exposure is orders of magnitude lower.

Using the occupational EHE of 0.04 mg/kg and the conservative EDLC of 0.12 mg/kg, the ratio of EHE to EDLC is less than 1, indicating that AAA is a chemical of low potential risk to man.

4. EFFECTS ON THE ENVIRONMENT

4.1 Aquatic Effects

The acute toxicity of AAA has been evaluated in a number of aquatic species using standard test methods. The fathead minnow, Zebrafish, and several invertebrate species including *Daphnia* have been tested. Zebrafish were exposed to 177, 235, 242, or 332 mg/L for 96 hours with mortality occurring only at 332 mg/L (Markert and Jung, 1988). Signs of toxicity, including abnormal swimming behavior and tremors or convulsions were observed in fish exposed to 242 mg/L, and reduced activity was observed in fish exposed to the two lowest concentrations. The 96-hr LC₅₀ for fathead minnows was reported to be greater than 100 mg/L (Watson, 1984).

Two acute toxicity studies have been conducted on daphnids. A 24 hr EC₅₀ of 70-200 mg/L has been reported by Völskow, (1988). However, there is insufficient information to determine the reliability of the study results. A 96-hr daphnid study resulted in an EC₅₀ > 100 mg/L (Watson, 1984). The results of the Watson study are considered more reliable because they more closely follow OECD Guidelines requiring that daphnid studies be conducted using a 48 hr or 96 hr exposure duration.

Other invertebrates have also been exposed to a concentration of 100 mg/L without evidence of adverse effects (Watson, 1984). In all cases, the EC₅₀ or LC₅₀ concentration was greater than 100 mg/L for a 96-hour exposure.

The majority of results suggest that AAA is of low toxicity to aquatic organisms and is of low concern for environmental effects to these species even though the expected distribution in the environment favors partitioning into water.

Although a chronic test in *Daphnia* is not available, there is no reason to expect that chronic effects of AAA would differ markedly from acute effects. AAA hydrolyzes only very slowly to the more toxic compound aniline. Studies by Appel and Mühlberger (1990), indicate that under abiotic conditions only 3.6% of AAA is hydrolyzed to aniline after 167.5 days.

Acute toxicity tests (OECD TG 201) have also been conducted on the alga, *Selenastrum capricornutum*. Exposures for 72 hr to AAA concentrations of 11.3, 22.5, 45, 90, 180, 360, or 720 mg/L resulted in an EC₅₀ value of 318 mg/L (Roberts and Swigart, 1995). A no-observable-effect concentration (NOEC) of 180 mg/L was also determined.

Predicted No Effect Concentration (PNEC):

An estimate of the PNEC is based on the reported EC₅₀ of 318 mg/L for the algal species *Selenastrum capricornutum*. This study is one of the more recent ones conducted on AAA, follows OECD test guidelines, has a more robust data set than the other entries, and clearly defines a NOEC and a 72 hr EC₅₀. Almost all other available studies do not adequately define a NOEC or an EC₅₀. As noted above, although a 24-hr EC₅₀ of 70-200 mg/L for daphnids was reported by Voelskow (1988), these data do not agree with the 96 hr EC₅₀ of >100 mg/L reported by Watson, (1984).

Basing the PNEC on the algal EC₅₀ of 318 mg/L is consistent with the results of the acute toxicity study with Zebrafish in which 90% mortality occurred at a concentration of 332 mg/L and no mortality occurred at 242 mg/L.

Because only acute toxicity studies are available, the PNEC for AAA was calculated from the algal EC₅₀ of 318 mg/L using an assessment factor of 1000.

$$\text{PNEC} = \frac{318 \text{ mg/L}}{1000} = 0.32 \text{ mg/L}$$

It may also be appropriate to use an estimated NOEC of 100 mg/L for fish, or the reported NOEC of 180 mg/L for algae to derive the PNEC. Using these values, a PNEC of 0.1 - 0.18 mg/L is obtained if the same Assessment Factor of 1000 is used.

4.2 Terrestrial Effects

The toxicity of AAA has been tested in a variety of terrestrial plants (ryegrass, radish, lettuce, corn, and marigold). The effect of 10 or 100 mg/L was evaluated on both germination and root and seedling growth. Germination of ryegrass, radish and lettuce was not affected by 100 mg/L. A concentration of 100 mg/L had no effect on germination of ryegrass, radish or lettuce, but did inhibit root growth of marigold and lettuce and seedling growth of marigold, lettuce and radish (Watson, 1984). A concentration of 10 mg/L had no effect on plant growth. There are no data available on other species such as birds or terrestrial organisms such as earthworms.

4.3 Other Effects

Other ecotoxicological effects of AAA are not anticipated. Tests on bacteria demonstrate that AAA adversely affects bacterial respiration only at a very high concentration (2000 mg/L) and that a concentration of 200 mg/L has no adverse effect (Watson, 1984). Secondary poisoning of mammalian or avian species due to bioaccumulated AAA or its metabolites does not appear to be likely since the K_{ow} is low and bioaccumulation is not likely.

4.4 Initial Assessment for the Environment

The available data on the toxicity to aquatic and terrestrial organisms indicate that AAA is relatively non-toxic to these organisms (most reported EC₅₀ and LC₅₀ values > 100 mg/L). A PNEC value of 0.32 mg/L for aquatic toxicity was calculated based on toxicity to *Selenastrum capricornutum*. This species was considered to represent the most sensitive species.

The hypothetical PEC_{initial} resulting from the release of AAA in wastewaters at pigment manufacturing facilities was estimated to be 0.0086 mg/L, and the PNEC for algal toxicity was calculated to be 0.32 mg/L; therefore the PEC/PNEC ratio is less than 1.

$$\text{PEC/PNEC ratio for algal toxicity} = \frac{0.0086 \text{ mg/L}}{0.32 \text{ mg/L}}$$

The hypothetical PEC_{initial} resulting from the release of AAA in wastewaters at AAA production sites was estimated to be 0.046 mg/L or 0.016 mg/L, and the PNEC for algal toxicity was calculated to be 0.32 mg/L; therefore the PEC/PNEC ratio is also less than 1.

$$\text{PEC/PNEC ratio for algal toxicity} = \frac{0.046 \text{ or } 0.016 \text{ mg/L}}{0.32 \text{ mg/L}}$$

Because the PEC/PNEC ratios are less than 1, AAA is considered to be of low potential concern for the environment. It should be noted that the PEC/PNEC ratio remains less than 1 even if the more conservative PNEC values of 0.10 or 0.18 mg/L are used.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

AAA is a chemical intermediate used in the production of pigments and seed coatings. Human health concerns center around methemoglobinemia, an effect that has been observed in experimental animals exposed for prolonged periods to dose levels ≥ 30 mg/kg/day. However, direct occupational exposure or indirect general exposure to AAA is minimal and the ratio of human exposure levels to dose levels of concern indicates a low level of concern for human health.

Data from environmental toxicity studies indicate that AAA is of low concern for aquatic or plant species. Solubility studies indicate that AAA in the environment will partition into water, where biodegradation then occurs. Estimates of environmental concentrations are low with comparison to no effect concentrations, indicating a low level of concern for the environment.

5.2 Recommendations

Low priority for further work. No recommendation.

6. REFERENCES

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SIDS DOSSIER
FOR
ACETOACETANILIDE
(3-OXO-N-PHENYL BUTAMIDE)
CAS No. 102-01-2

1. GENERAL INFORMATION**1.01 SUBSTANCE INFORMATION**

A. CAS number

102-01-2

B. Name

3-Oxo-N-phenyl butamide

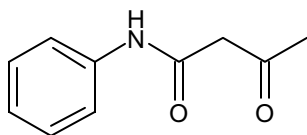
C. CAS Descriptor

Not applicable

D. Molecular formula

 $C_{10}H_{11}NO_2$

E. Structural formula



F. Molecular Weight

177.20

1.02 OECD INFORMATION

A. Sponsor country

United States of America

B. Lead Organization

U S EPA

Contact point

Oscar Hernandez, Division Director
Office of Pollution Prevention and Toxics
U.S. EPA (7403M)
1200 Pennsylvania Ave, N.W.
Washington, DC 20460
phone: 202-564-7641
e-mail: hernandez.oscar@epa.gov

C. Name of Responder

Dr. James Deyo
Eastman Chemical Company
100 North Eastman Road
Kingsport, TN 37662

Telephone: (423) 229-5208
Fax: (423) 224-0208
Email: deyo@eastman.com

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

organic

B. Physical State

solid

C. Purity

99% by weight

1.2 SYNONYMS

((Acetoacetyl)amino)benzene
a-Acetyl-N-phenylacetamide
a-Acetylacetanilide
β-Ketobutyranilide
1-(Phenylcarbamoyl)-2-propanone
Acetessiganilid
Acetoacetamidobenzene
Acetoacetanilide
Acetoacetic acid anilide
Acetoacetic anilide
Acetoacetylaniline
Butanoic acid, 3-oxo-, amide, N-phenyl-
Butansaeureamid, 3-oxo-N-phenyl
N-(Acetylacetyl)aniline
N-Acetoacetylaminobenzol
N-Phenylacetoacetamide

1.3 IMPURITIES

Trace impurities not identified

1.4 ADDITIVES

No additives typically present

1.5 QUANTITY

5,000 to 10,000 tonnes per year in US (1990 data)

1.6 LABELLING AND CLASSIFICATION

Not applicable

1.7 USE PATTERN**A. General**

Acetoacetanilide is classified as a chemical intermediate. The test substance is isolated and transported in a controlled environment to second parties.

<u>Type of Use</u>	<u>Category</u>
type	Use in a closed system
industry	Chemical industry: intermediate for paint
use	Intermediate for colouring agent
type	Non-dispersive use
industry	Agriculture industry
use	Seed coating ¹

There is no known public use of the substance.

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

Not established

1.9 SOURCES OF EXPOSURE

Exposure to employees is minimized during manufacture by using good industrial hygiene practices. It is estimated that no more than 50-100 individuals in the USA are exposed during the manufacturing and handling process. NIOSH has estimated that there are a total of 1108 employees in the pigment industry that are exposed to AAA (NIOSH, 1983). There is no direct consumer exposure.

Processes: Acetoacetanilide is formed from the reaction of diketene and aniline in the presence of a solvent. The resulting product is then recovered via crystallization/filtration followed by drying. The reaction step is completely enclosed and dust collection systems are used to minimize employee exposure in the solids handling equipment. Equipment used to manufacture acetoacetanilide is operated continuously 24 hours a day, 365 days per year.

¹ AAA exported to Canada for seed coatings use.

1.10 ADDITIONAL REMARKS

A. Options for disposal:

Non-aqueous wastes are incinerated, and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

2. PHYSICAL-CHEMICAL DATA**2.1 MELTING POINT:**

Method:
GLP: YES [] NO [X]
Results: 83-85°C
Comments:
Reference: MSDS Hoechst AG, 28.12.88

2.2 BOILING POINT:

Method :
GLP: YES [] NO [X]
Results: >400°C
Comments:
Reference: MSDS Hoechst AG, 28.12.88

2.3 DENSITY:

Method :
GLP: YES [] NO [X]
Results: 1.26 g/cc at 20°C
Comments:
Reference: MSDS Hoechst AG, 28.12.88

2.4 VAPOR PRESSURE

Method :
GLP: YES [] NO [X]
Results: 0.001 kPa at 20°C
Comments:
Reference: MSDS Hoechst AG, 28.12.88

2.5a PARTITION COEFFICIENT N-OCTANOL/WATER

Method: calculated [X] measured []
GLP: YES [] NO [X]
Results: $\log P_{ow} = 0.76$ at 25°C
Analytical Method:
Comments: Calculation by Med Chem Software Release 3.42 (1986)
Reference: Medicinal Chemistry Project, Pomona College Claremont, CA

2.5b Method: calculated [] measured [X]
GLP: YES [] NO [X]
Results: $\log P_{ow} = 0.70$ at 25°C
Analytical Method: HPLC

Comments: Data collected prior to codification of Good Laboratory Practice regulations.
Reference: Watson, H.M. (1984). Basic Environmental Profile For Acetoacetanilide (Unpublished Report). Health and Environment Laboratories, Eastman Kodak Company.

2.6 WATER SOLUBILITY:

A. Solubility

Method
GLP: YES [] NO [X]
Analytical Method:
Results: 10,000 mg/L at 25°C
Comments
Reference: MSDS Hoechst AG 28.12.88

Method : Similar to preliminary method in OECD Guideline 105. 100 mg dissolved in varying amounts of water and the absorbance at 238 nm measured. Conducted at room temperature.

GLP: YES [] NO [X]
Analytical Method: Ultraviolet absorption at 238 nm
Results: 8375 mg/L
Comments: Data collected prior to codification of Good Laboratory Practice regulations.
Reference: Watson, H.M. (1984). Basic Environmental Profile For Acetoacetanilide (Unpublished Report). Health and Environment Laboratories, Eastman Kodak Company.

B. pH Value, pKa Value

pH Value
Method : Not provided
GLP: YES [] NO []
Results: Neutral at 10 g/L and 25°C
Comments: Substance only slightly soluble in water.
Reference: LONZA, Inc. Safety Data Sheet/ECDIN

pKa Value
No Data Available

2.7 FLASH POINT (LIQUIDS)

Method: Cleveland Open Cup ASTM D92
GLP: YES [] NO [X]
Results: 185°C
Comments: Substance is a solid.
Reference: LONZA, Inc. Safety Data Sheet/ECDIN

2.8 AUTO FLAMMABILITY

Method:
GLP: YES [] NO [X]
Results: Auto Ignition Temperature 360°C
Comments: Substance is a solid.
Reference: MSDS Hoechst AG 28.12.88

2.9 FLAMMABILITY

Method:
GLP: YES []
NO [X]
Results: Ignition Temperature 452°C
Comments: Substance is a solid.
Reference: MSDS Hoechst AG 28.12.88

2.10 EXPLOSIVE PROPERTIES

No Data Available.
Substance is a solid.

2.11 OXIDIZING PROPERTIES

Results: No Data Available
Comments: Considered to be Not Reactive (R0) by National Fire Protection Association

2.12 OXIDATION:REDUCTION POTENTIAL

No Data Available

2.13 ADDITIONAL DATA

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Type: Air
 Substance: Acetoacetanilide
 Method: Handbook of Chemical Property Estimation Methods
 GLP: YES [] NO [X]
 Results: Acetoacetanilide does not absorb wavelengths of light above 290 nm and thus will not be susceptible to direct (uncatalyzed) photodegradation.
 The reaction of Acetoacetanilide with hydroxide [OH⁻] in water vapor will be the only significant process by which this material will be removed from the atmosphere.
 Percentage of degradation after certain period: Atmospheric residence time t = 192 hours
 Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 10. McGraw-Hill, New York.

3.1.2 STABILITY IN WATER

Type: Abiotic hydrolysis
 Substance: Acetoacetanilide >99% pure
 Method: OECD Guideline 111
 GLP: YES [X] NO []
 Results: The primary product of hydrolysis was aniline based on HPLC analysis.

Time (days)	% Aniline	% Decomposition of Acetoacetanilide
28	0.6	< 0.5
52	1.1	< 0.5
95.5	2.1	0.7
167.5	3.6	3.5

Percentage of degradation after certain period:
 $t_{1/2} = 131.4$ days at pH 1.5 and 37°C.
 Reference: Appel, M., and Mühlberger, B. (1990). Abiotischer Abbau Hydrolyse als Funktion des pH-Wertes (Unpublished report). Analytisches Laboratorium, Hoechst AG.

3.1.3 STABILITY IN SOIL

No Data Available

3.2 MONITORING DATA (ENVIRONMENT)

No Data Available

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT

Transport and distribution into environmental compartments are not likely because acetoacetanilide is a chemical intermediate that is manufactured in a closed system and transported under controlled conditions to second parties for further processing.

3.3.2 THEORETICAL DISTRIBUTION

Level I Fugacity:

The equilibrium partitioning of AAA in the environment following release is expected to be:

In air	1.361%
In soil	0.234%
In water	97.291%
In biota	0.021%
In suspended solids	0.002%
In sediment	1.092%

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Based on a survey of manufacturers, AAA in wastewater is treated in on-site treatment facilities or publicly-owned treatment facilities (POTW). Treatment facilities can remove 90% TOC and 95-98% BOD. Residual solids are incinerated or released to lined landfills.

3.5 BIODEGRADATION

Substance:	Acetoacetanilide, assumed 99% pure
Type:	aerobic [X], anaerobic []
Medium:	Activated sludge
Method:	Eastman Kodak Company, Health and Environment Laboratories Protocol as cited in Boatman, R.J., Cunningham, S.L., and Ziegler, D.A. (A Method for Measuring the Biodegradation of Organic Chemicals, <i>Environ. Toxicol. Chem.</i> 5, 233-243, 1986). Similar to OECD Guideline 301E except that sludge is acclimated and is from several sources.
GLP:	YES [] NO [X]
Results:	Degradation was 51.6% based on the carbon dioxide evolution.
Comments:	Test conducted over 21 days. Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.
Substance:	Acetoacetanilide, assumed 99% pure
Type:	aerobic [X], anaerobic []

Medium: Activated sludge
 Method: Static test; DIN 38412 (Zahn-Wellens Test)
 GLP: YES [] NO [X]
 Results: Degradation was 85% after 5 days.
 Comments:
 Reference: Wellens (1988). Ergebnis der abwasserbiologischen Untersuchungen: Acetessiganilid TTR (unpublished report). Hoechst AG.

3.6 BOD₅, COD OR RATIO BOD/COD

BOD₅

Medium: Activated sludge
 Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Similar to OECD Guideline 301D.
 Concentration: 3 to 70 mg/L
 GLP: YES [] NO [X]
 Results: BOD₅ = 0.04 g/g (at 70 mg/L)
 BOD₂₀ = 1.3 g/g (at 3 mg/L).

COD

Medium: Activated sludge
 Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Similar to OECD Guideline 301D.
 Concentration: 3 to 70 mg/L
 GLP: YES [] NO [X]
 Results: COD = 1.99 g/g and TOD = 2.0 g/g.
 Comments: The test substance is considered biodegradable because it meets the 60% criterion (BOD is 60% of COD at 20 days). Test conducted over 20 days rather than 28 days although no indication of plateau. Range of concentrations used were broader than recommended by OECD. No indication of biodegradability was noted within 5 days. Data collected prior to codification of Good Laboratory Practice regulations.
 Reference: Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.

COD

Medium: Activated sludge
 Method: Biodegradability was measured using a "fill-and-draw" type unit described by Nambu (*Water Res.* 5, 1127-1134, 1971). TOC and COD_{Mn} (as determined by the Japanese Industrial Standard - JIS K0102) were measured 2, 4, and 24 hours after incubation with activated sludge.
 GLP: YES [] NO [X]
 Results: COD_{Mn} removal efficiency = 18% after 24 hours. TOC removal efficiency = 50% after 24 hours.
 Comments: Test not within OECD Guidelines. Predates GLP regulations.
 Reference: Matsui, S., Murakami, T., Sasaki, T., Hirose, Y., and Iguma, Y. (1975). Activated Sludge Degradability of Organic Substances in the Waste Water of the Kashima Petroleum and Petrochemical Industrial Complex, *Prog. Water Tech.* 7, 645-659.

COD:	
Medium:	Activated sludge
Method:	TOC and COD _{Mn} (as determined by the Japanese Industrial Standard - JIS K0102) were measured after 10 days incubation with activated sludge. Initial Acetoacetanilide concentration was 100 mg/L.
GLP:	YES [] NO [X]
Results:	COD _{Mn} removal efficiency = 87% after 10 days. TOC removal efficiency = 86% after 10 days.
Comments:	Test not within OECD Guidelines.
Reference:	Matsui, S., Okawa, Y., and Ota, R. (1988). Experience of 16 Years' Operation and Maintenance of the Fukushima Industrial Wastewater Treatment Plant of the Kashima Petrochemical Complex - II. Biodegradability of 37 Organic Substances and 28 Process Wastewaters, <i>Water Sci. Tech.</i> 20, 201-210.

3.7 BIOACCUMULATION

No Data Available. However, the low K_{ow} suggests that bioaccumulation is not likely.

3.8 ADDITIONAL REMARKS

A. Sewage Treatment

Substance:	Acetoacetanilide, assumed 99% pure
Species:	Activated sludge
Method:	Eastman Kodak Company, Health and Environment Laboratories Protocol. Similar to OECD Guideline 209. ¹⁴ C-Glucose metabolism measured.
Type of test:	IC50; Secondary Waste Treatment [X] Other (e.g., field observation) []
GLP:	YES [] NO [X]
Results:	IC50 = > 2000 mg/L Bacteria were incubated with concentrations of 20, 200, or 2000 mg/L. After 5 hours, the 2000 mg/L concentration inhibited glucose metabolism by 40% while lower concentrations had no effect.
Comments:	¹⁴ C-Carbon dioxide evolution measured rather than oxygen consumption. Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.

4. ECOTOXICOLOGICAL DATA

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Substance:	Acetoacetanilide, >99% pure
Species:	<i>Brachydanio rerio</i> (Zebra fish)
Method:	OECD Guideline 203
Exposure period:	48 and 96 hours
Type of test:	static <input checked="" type="checkbox"/> , semi-static <input type="checkbox"/> , flow -through <input type="checkbox"/> Other (e.g., field observation) <input type="checkbox"/>
GLP:	YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
Results:	LC ₅₀ >242 mg/L Fish were exposed to concentrations of either 0, 177, 235, 242, or 332 mg/L for 96 hours. At the two high concentrations, fish alternated between swimming followed by resting at the surface or bottom, nose-heavy or tail-heavy swimming. They had increased respiration, or irregular or abrupt respiration. The covers of the gills were open. Body surface (scales) was discolored. Fright-reaction was diminished. Staggering to turning, spinning, reduced activity, laying on the side or on the back at the bottom of the tank and tremors or convulsions were observed. At the two lower concentrations, activity was decreased. During the first day of exposure, the cover of the gills was open; tail fin motionless; fish were sitting on the bottom of the tank, and body surfaces (scales) was discolored dark. Mortality occurred only at the 332 mg/L concentration and increased from 6 of 10 fish at 48 hours to 9 of 10 fish at 96 hours. The LC ₅₀ was between 242 and 332 mg/L.
Comments:	Additional concentrations were not tested because HPLC analysis indicated loss of material as nominal concentration increased such that analytical concentrations were increased by the square-root of the change in nominal concentration.
Reference:	Markert and Jung (1988). Acetessiganilid Prüfung der akuten Toxizität am Fisch Zebrabärbling (<i>Brachydanio rerio</i>) über 96 Stunden (Unpublished report). Pharma Forschung Toxikologie und Pathologie, Hoechst AG.
Substance:	Acetoacetanilide, assumed 99% pure
Species:	<i>Pimephales promelas</i> (Fathead minnow)
Method:	Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell, W.S., Gorsuch, J.W., Kringle, R.O., Robillard, K.A., and Spiegel, R.C. (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, <i>Environ. Toxicol. Chem.</i> 5, 831-840, 1986). Similar to OECD Guideline 203. Only two concentrations used: 10 and 100 mg/L.
Exposure period:	96 hours
Type of test:	static <input checked="" type="checkbox"/> , semi-static <input type="checkbox"/> , flow -through <input type="checkbox"/> Other (e.g., field observation) <input type="checkbox"/>
GLP:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
Results:	LC ₅₀ = > 100 mg/L at 96 hours.
Comments:	No analysis of test solution. However, hydrolysis is known to be minimal. Data collected prior to codification of Good Laboratory Practice regulations.

Reference: Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.

4.2 ACUTE/PROLONGED TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Substance: Acetoacetanilide TTR, assumed 99% pure
 Species: *Daphnia magna*
 Method: DIN 38412 Part II
 Exposure period: 24 hours
 GLP: YES [] NO [X]
 Results: $EC_{50} = 70-200$ mg/L (24 hours)
 Comments:

Reference: Voelskow (1988). Untersuchung von Produktproben auf Daphnientoxizität (Unpublished report). Hoechst AG.

Substance: Acetoacetanilide, assumed 99% pure
 Species: *Daphnia magna*
 Method: Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell, W.S., Gorsuch, J.W., Kringle, R.O., Robillard, K.A., and Spiegel, R.C. (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, *Environ. Toxicol. Chem.* 5, 831-840, 1986). *Daphnia* exposed to either 10 or 100 mg/L for 96 hours.

Exposure period: 96 hour
 GLP: YES [] NO [X]
 Results: $EC_{50} = > 100$ mg/L
 Comments: No analysis of test solution. However, hydrolysis is known to be minimal. Data collected prior to codification of Good Laboratory Practice regulations.

Reference: Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.

B. Other aquatic organisms

Substance: Acetoacetanilide, assumed 99% pure
 Species: *Gammarus fasciatus* (sideswimmer)
 Method: Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell, W.S., Gorsuch, J.W., Kringle, R.O., Robillard, K.A., and Spiegel, R.C. (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, *Environ. Toxicol. Chem.* 5, 831-840, 1986). Similar to OECD Guideline 202.

Exposure period: 96 hours
 Type of test: static [X], semi-static [], flow-through []
 Other (e.g., field observation) []
 GLP: YES [] NO [X]
 Results: LC50 value (acute): > 100 mg/L at 96 hours

Comments:	No analysis of test solution for test substance. However, hydrolysis is known to be minimal (see Section 4.1.3). Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.
Substance:	Acetoacetanilide, assumed 99% pure
Species:	<i>Dugesia tigrina</i> (current taxonomy: <i>Dugesia dorotocephalo</i> ; flatworm)
Method:	Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell, W.S., Gorsuch, J.W., Kringle, R.O., Robillard, K.A., and Spiegel, R.C. (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, <i>Environ. Toxicol. Chem.</i> 5, 831-840, 1986). Similar to OECD Guideline 202.
Exposure period:	96 hours
Type of test:	static <input checked="" type="checkbox"/> , semi-static <input type="checkbox"/> , flow -through <input type="checkbox"/> Other (e.g., field observation) <input type="checkbox"/>
GLP:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
Results:	LC50 or EC50 values (acute): > 100 mg/L at 96 hours
Comments:	No analysis of test solution. However, hydrolysis is known to be minimal. Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.
Substance:	Acetoacetanilide, assumed 99% pure
Species:	<i>Helisoma trivolvis</i> (current taxonomy: <i>Planorbis trivolvis</i> ; snail)
Method:	Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell, W.S., Gorsuch, J.W., Kringle, R.O., Robillard, K.A., and Spiegel, R.C. (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, <i>Environ. Toxicol. Chem.</i> 5, 831-840, 1986). Similar to OECD Guideline 202.
Exposure period:	96 hours
Type of test:	static <input checked="" type="checkbox"/> , semi-static <input type="checkbox"/> , flow -through <input type="checkbox"/> Other (e.g., field observation) <input type="checkbox"/>
GLP:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
Results:	LC50 or EC50 values (acute): > 100 mg/L at 96 hours
Comments:	No analysis of test solution. However, hydrolysis is known to be minimal. Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.
Substance:	Acetoacetanilide, assumed 99% pure
Species:	<i>Lumbriculus variegatus</i> (aquatic earthworm)
Method:	Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell, W.S., Gorsuch, J.W., Kringle, R.O., Robillard, K.A., and Spiegel, R.C. (Simultaneous Evaluation of the

	Acute Effects of Chemicals on Seven Species, <i>Environ. Toxicol. Chem.</i> 5, 831-840, 1986). Similar to OECD Guideline 202.
Exposure period:	96 hours
Type of test:	static <input checked="" type="checkbox"/> , semi-static <input type="checkbox"/> , flow -through <input type="checkbox"/> Other (e.g., field observation) <input type="checkbox"/>
GLP:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
Results:	LC50 or EC50 values (acute): > 100 mg/L at 96 hours
Comments:	No analysis of test solution. However, hydrolysis is known to be minimal. Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.
Substance:	Acetoacetanilide, assumed 99% pure
Species:	<i>Asellus intermedius</i> (current taxonomy: <i>Caecidota intermedia</i> ; pillbug)
Method:	Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell, W.S., Gorsuch, J.W., Kringle, R.O., Robillard, K.A., and Spiegel, R.C. (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, <i>Environ. Toxicol. Chem.</i> 5, 831-840, 1986). Similar to OECD Guideline 202.
Exposure period:	96 hours
Type of test:	static <input checked="" type="checkbox"/> , semi-static <input type="checkbox"/> , flow -through <input type="checkbox"/> Other (e.g., field observation) <input type="checkbox"/>
GLP:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
Test results:	LC50 or EC50 values (acute): > 100 mg/L at 96 hours
Comments:	No analysis of test solution. However, hydrolysis is known to be minimal. Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.

4.3 TOXICITY TO AQUATIC PLANTS eg. algae

Substance:	Acetoacetanilide 99.8%
Species:	<i>Selenastrum capricornutum</i>
Method :	OECD TG 201(Growth)
Exposure period:	72 hours
GLP:	YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
Results:	EC ₅₀ (24h)= >720 mg/L EC ₅₀ (48h)= 362 mg/L EC ₅₀ (72h)= 318 mg/L NOEC (72h)=180 mg/L
Comments:	Concentrations tested were 11.3, 22.5, 45, 90, 180, 360, and 720 mg/L
Reference:	LONZA, Inc. Report 1000-0005. Roberts, C.A. and Swigart, J.P. (1995). An Evaluation of Acetoacetanilide in a 72-Hour Toxicity Test with the Freshwater Alga <i>Selenastrum capricornutum</i> (Unpublished report). Wildlife International Ltd.

4.4 TOXICITY TO BACTERIA

Substance:	Acetoacetanilide, assumed 99% pure
Species:	Activated sludge
Method :	Eastman Kodak Company, Health and Environment Laboratories Protocol. Similar to OECD Guideline 209.
Type of test:	IC50; Secondary Waste Treatment [X] Other (e.g., field observation) []
GLP:	YES []NO [X]
Results:	IC50 = > 2000 mg/L Bacteria were incubated with concentrations of 20, 200, or 2000 mg/L. After 5 hours, the 2000 mg/L concentration inhibited glucose metabolism by 40% while lower concentrations had no effect.
Comments:	Previously reported under Section 3.8. No analysis of the test solution. However, hydrolysis is known to be minimal. Does not meet OECD criteria for a valid microbial inhibition test because no positive control (known inhibitor such as 3,5-dichlorophenol) was used, although was valid by Health and Environment Laboratories Protocol. Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS**4.5.1 CHRONIC TOXICITY TO FISH**

No Data Available

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

No Data Available

4.6 TOXICITY TO TERRESTRIAL ORGANISMS**4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS**

No Data Available

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Substance:	Acetoacetanilide, assumed 99% pure
Species:	Ryegrass Radish Lettuce
Method:	Eastman Kodak Company, Health and Environment Laboratories Protocol according to Gorsuch, J.W., Kringle, R.O., and Robillard, K.A. (Chemical Effects on the Germination and Early Growth of Terrestrial Plants, Plants for Toxicity Assessment, ASTM STP 1091, 1990).

	Approximately 80 seeds of each species were exposed to a concentration of 10 or 100 mg/L for 7 days and germination compared to control shoots.
GLP:	YES [] NO [X]
Results:	Maximum concentration at which no effect was observed within the period of the test: 100 mg/L (NOEC = 100 mg/L) Minimum concentration at which effect was observed within the period of the test: Not determined.
Comments:	Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.
Substance:	Acetoacetanilide, assumed 99% pure
Species:	Corn Marigold Lettuce Radish
Method:	Eastman Kodak Company, Health and Environment Laboratories Protocol. Ten to twenty seedlings of each species were exposed to a concentration of 100 mg/L (or 10 mg/L if effects at 100 mg/L were observed) for 7 days and growth of shoots and roots compared with control seedlings.
GLP:	YES [] NO [X]
Results:	At 100 mg/L, acetoacetanilide caused root inhibition of marigold and lettuce seedlings (11 and 15%, respectively). Growth of marigold, lettuce, and radish seedlings was inhibited 33, 22, and 20%, respectively. Corn was unaffected at 100 mg/L, and other species were unaffected at 10 mg/L. Maximum concentration at which no effect was observed within the period of the test: 10 mg/L for Marigold, Lettuce, and Radish. 100 mg/L for Corn. Minimum concentration at which effect was observed within the period of the test: 100 mg/L for Marigold, Lettuce, and Radish.
Comments:	Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Watson, H.M. (1984). Basic Environmental Profile for Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report ES-84-67, Health and Environment Laboratories, Eastman Kodak Company.

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No Data Available

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No Data Available. However, the low K_{ow} suggests that biomagnification is not likely.

4.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES

No Data Available

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Substance: Acetoacetanilide in Propylene glycol
 Species/strain: Rat/strain not identified
 Method : Similar to OECD Guideline 401
 GLP: YES [] NO [X]
 Results: Male and female rats were given doses of between 4000 and 16000 mg/kg. At a dose of 4000 mg/kg, animals were lethargic and unkempt. Male rats had tremors for 2-3 days post-dosing, but all animals survived. Tremors, cyanosis, and mortality occurred at a dose of 5000 mg/kg and higher.
 LD₅₀: 6500 mg/kg in male and 5400 mg/kg in female rats.
 Comments: Report predates GLP regulations. No indication was made of whether dosages were administered by equal volume or concentration. No analysis of dosing solutions. The vehicle used may have confounded the results.
 Reference: LONZA, Inc. report 0061. Wallace, J.M. (1975). Toxicity Studies for LONZA Ltd. (Unpublished report). Bio-Toxicology Laboratories, Inc.

Substance: Acetoacetanilide (10% in 2% starch)
 Species/strain: Rat/strain not identified
 Method : 10 fasted animals per group were treated and observed for 7 days post-dosing.
 GLP: YES [] NO [X]
 Results: Ten female rats per group were treated with either 1600, 2500, or 4000 mg/kg and observed for mortality for 7 days. Mortality occurred at the two higher dosage levels.
 LD₅₀: 2450 mg/kg
 Comments: Report predates GLP regulations. No clinical observations cited. No analysis of dosing solutions.
 Reference: Scholz and Weigand (1965). Unpublished report, Laboratorie für Gewerbe- und Arzneimitteltoxikologie, Farbwerke Hoechst AG.

Substance: Acetoacetanilide (10% in 0.5% guar gum)
 Species/strain: Mouse/strain not identified
 Method : Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two males per group were treated with either 200, 400, 800, 1600, or 3200 mg/kg and observed for 14 days.
 GLP: YES [] NO [X]
 Results: Animals were moderate to very weak and cyanotic. Respiration was irregular with gasping. Animals had rough hair coats and were prostrate. Mortality occurred at the three highest dosage levels.
 LD₅₀: 800-1600 mg/kg
 Comments: Report predates GLP regulations.

Reference:	Fassett, D.W. (1962). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.
Substance:	Acetoacetanilide (10% in 0.5% guar gum)
Species/strain:	Rat/strain not identified
Method :	Eastman Kodak Company, Laboratory of Industrial Medicine
Protocol.	Two males per group were treated with either 200, 400, 800, 1600, or 3200 mg/kg and observed for 14 days.
GLP:	YES [] NO [X]
Results:	Animals were moderate to very weak and cyanotic. They had rough hair coats and were prostrate. Mortality occurred at the two highest dosage levels.
LD ₅₀ :	1600-3200 mg/kg
Comments:	Report predates GLP regulations. No analysis of dosing solutions.
Reference:	Fassett, D.W. (1962). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.
Substance:	Acetoacetanilide (10% in 0.5% guar gum)
Species/strain:	Rat/strain not identified
Method :	Eastman Kodak Company, Health, Safety, and Human Factors Laboratory Protocol. Two males per group were treated with either 200, 400, 800, 1600, or 3200 mg/kg and observed for 14 days.
GLP:	YES [] NO [X]
Results:	Animals receiving 800 mg/kg or greater exhibited transient slight to moderate weakness with slight cyanosis. At higher dose levels, animals were prostrate, and had tremors, convulsions and tachycardia. Mortality occurred at the two highest dosage levels.
LD ₅₀ :	1600 mg/kg in male rats and 1131 mg/kg in female rats.
Comments:	No analysis of dosing solutions. Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Bernard, L.G. (1982). Basic Toxicity of Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report TX-82-12, Health, Safety, and Human Factors Laboratory, Eastman Kodak Company.

5.1.2 ACUTE INHALATION TOXICITY

No Data Available

5.1.3 ACUTE DERMAL TOXICITY

Substance:	Acetoacetanilide (99%)
Species/strain:	Guinea Pig/Duncan-Hartley
Method:	Eastman Kodak Company, Health, Safety, and Human Factors Laboratory Protocol. Five animals per dosage level were treated with 250, 500, or 1000 mg/kg by occlusive patch for 24 hours. Animals were observed for 14 days.
GLP:	YES [] NO [X]
Results:	Administration of the test material at these doses did not cause systemic toxicity or death.

LD₅₀: > 1000 mg/kg
 Comments: Data collected prior to codification of Good Laboratory Practice regulations.
 Reference: Bernard, L.G. (1982). Basic Toxicity of Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report TX-82-12, Health, Safety, and Human Factors Laboratory, Eastman Kodak Company.

Substance: Acetoacetanilide (99%)
 Species/strain: Guinea Pig/Duncan-Hartley
 Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Five animals per dosage level were treated with 250, 500, or 1000 mg/kg by occlusive patch for 24 hours.

GLP: YES [] NO [X]
 Results: LD50 = < 1000 mg/kg. Animals at the highest dose died within one week of treatment.
 Comments: Report predates GLP regulations.
 Reference: Fassett, D.W. (1962). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION

Substance: Acetoacetanilide
 Species/strain: Rabbit/No strain designated
 Method: Department of Transportation
 GLP: YES [] NO [X]
 Results: Minimal erythema was observed after 4 hours, but no irritation was observed thereafter. Considered slight irritant.
 Comments: Report predates GLP regulations.
 Reference: LONZA, Inc. Report 0062. Prate, M.P. (1974). Primary Irritation Studies for LONZA, Inc. (Unpublished report). Bio-Toxicology Laboratories, Inc.

Substance: Acetoacetanilide TTR, 99% pure
 Species/strain: Rabbit/New Zealand White
 Method: OECD Guideline 404
 GLP: YES [X] NO []
 Results: No irritation was observed.
 Comments:
 Reference: Kreiling and Jung (1988). Acetessiganilid TTR Prüfung auf Hautreizung am Kaninchen (Unpublished report). Pharma Forschung Toxikologie und Pathologie, Hoechst AG.

Substance: Acetoacetanilide
 Species/strain: Guinea Pig/Duncan-Hartley
 Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Four animals treated with 250-1000 mg/kg by occluded patch for 24 hours.
 GLP: YES [] NO [X]

- Results: Slight irritation
 Comments: Report predates GLP regulations.
 Reference: Fassett, D.W. (1962). Toxicity Report (Unpublished report).
 Laboratory of Industrial Medicine, Eastman Kodak Company.
- Substance: Acetoacetanilide, assumed 99% pure
 Species/Strain: Guinea Pig/Duncan-Hartley
 Method: Eastman Kodak Company, Health, Safety, and Human Factors
 Laboratory Protocol. Four animals treated with 250-1000 mg/kg by
 occluded patch for 24 hours.
- GLP: YES [] NO [X]
 Results: Slight irritation
 Comments: Data collected prior to codification of Good Laboratory Practice
 regulations.
- Reference: Bernard, L.G. (1982). Basic Toxicity of Acetoacetanilide
 (Unpublished report). Eastman Kodak Internal Report TX-82-12,
 Health, Safety, and Human Factors Laboratory, Eastman Kodak
 Company.
- Substance: Acetoacetanilide (50% solution of the test chemical in 10%
 alcohol/90% glycerol)
 Species/strain: Guinea Pig/Duncan-Hartley
 Method: Eastman Kodak Company, Health, Safety and Human Factors
 Laboratory Protocol. A group of five animals were repeatedly
 administered 0.5 mL of a 50% solution of the test chemical in 10%
 alcohol/90% glycerol topically to the clipped skin of the back for a
 total of nine doses over an eleven-day period. Both primary
 irritation and exacerbation of effects were measured.
- GLP: YES [] NO [X]
 Results: Repeated application produced slight exacerbation of initial irritation.
 Comments: Data collected prior to codification of Good Laboratory Practice
 regulations.
- Reference: Bernard, L.G. (1982). Basic Toxicity of Acetoacetanilide
 (Unpublished report). Eastman Kodak Internal Report TX-82-12,
 Health, Safety, and Human Factors Laboratory, Eastman Kodak
 Company.

5.2.2 EYE IRRITATION

- Substance: Acetoacetanilide, >99% pure
 Species/strain: Rabbit/New Zealand White
 Method: OECD Guideline 405.
 GLP: YES [X] NO []
 Results: Moderate erythema and edema of the conjunctiva with minimal
 erythema of the iris occurred at 1 hour post application, but by 24
 hours, the conjunctival irritation was reduced to minimal with one
 animal demonstrating minimal corneal opacity. All animals were
 normal by 72 hours post-application.
- Comments:

Reference:	Kreiling and Jung (1988). Acetessiganilid TTR Prüfung auf Augenreizung am Kaninchen (Unpublished report). Pharma Forschung Toxikologie und Pathologie, Hoechst AG.
Substance:	Acetoacetanilide, assumed 99% pure
Species/strain:	Rabbit/No strain designated
Method:	Eastman Kodak Company, Health, Safety, and Human Factors Laboratory Protocol. Six rabbits instilled in one eye with a few crystals of test material. The eyes of three animals were immediately washed.
GLP:	YES [] NO [X]
Results:	Slight erythema of the conjunctiva occurred at 1 hour post application, but by 48 hours, all animals were normal. Irrigation reduced the irritation to erythema only or limited the response to only one hour.
Comments:	Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Bernard, L.G. (1982). Basic Toxicity of Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report TX-82-12, Health, Safety, and Human Factors Laboratory, Eastman Kodak Company.

5.3 SKIN SENSITISATION

Substance:	Acetoacetanilide (10% in 0.5% guar gum)
Method:	Eastman Kodak Company, Health, Safety, and Human Factors Laboratory Protocol.
GLP:	YES [] NO [X]
Results:	Negative for sensitization Number of animals with skin reaction at challenge: 0 Number of animals with skin reaction in control group at challenge: 0
Comments:	No analysis of dosing solutions. Data collected prior to codification of Good Laboratory Practice regulations.
Reference:	Bernard, L.G. (1982). Basic Toxicity of Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report TX-82-12, Health, Safety, and Human Factors Laboratory, Eastman Kodak Company.

5.4 REPEATED DOSE TOXICITY

Substance:	Acetoacetanilide (1.0 or 0.1% in diet)
Species/strain:	Rat/Sprague-Dawley
Method:	Eastman Kodak Company, Health, Safety, and Human Factors Laboratory Protocol. Groups of five male and five female rats were administered the test material in the diet at concentrations of 1.0%, 0.1%, or 0% (corn oil/feed) over a period of 14 days. Parameters evaluated included clinical observations, body weights, feed consumption, hematology, clinical chemistry, and gross and histopathology examinations.
GLP:	YES [] NO [X]
Results:	Daily doses were 1001.7 and 102.4 mg/kg/day based on feed consumption and body weight. Weight gains and feed consumption

were reduced in the high-dose group. High-dose animals had dark eyes and a slight blue tone to the skin (possible cyanosis), but no signs of toxicity were observed in low-dose animals. High-dose animals had lower erythrocyte counts, but higher hematocrit, mean corpuscular volumes, and mean corpuscular hemoglobin.

Polychromasia, anisocytosis, poikilocytosis, macrocytosis, Howell-Jolly bodies, and spherocytosis were observed in the blood of high-dose animals. Alkaline phosphatase and blood urea nitrogen were also increased. Low-dose animals were not affected. Dark and enlarged spleens were observed in two of the five high-dose animals. Spleens had minimal congestion, extramedullary hematopoiesis and minor lymphoid hyperplasia of the lymphatic follicles. Based on these results, the no-observable-effect level (NOEL) was 102.4 mg/kg/day.

Comments: No analysis of dosing solutions. Data collected prior to codification of Good Laboratory Practice regulations.

Reference: Bernard, L.G. (1982). Basic Toxicity of Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report TX-82-12, Health, Safety, and Human Factors Laboratory, Eastman Kodak Company.

Substance: Acetoacetanilide in 2% starch

Species/strain: Rat/No strain designated

Method: Groups of five male and five female rats were administered 250 mg/kg of the test material in 2% starch by gavage 14 times over a 21-day period. Animals were euthanized 3 days after the last dose. Parameters evaluated included clinical observations, body weights, hematology (erythrocyte counts, absolute and differential leukocyte counts, hemoglobin), urinalysis, and gross and histopathology examinations.

GLP: YES [] NO [X]

Results: Body weights of treated animals were lower than controls by the end of the study. No signs of toxicity were observed. Hematology and urinalysis were normal. No gross or microscopic pathology was noted in the heart, lungs, liver, kidneys, or spleen.

Comments: Report predates GLP regulations. No analysis of dosing solutions. No information about dose-responses. No data provided.

Reference: Scholz and Weigand (1965). Unpublished report, Laboratorie für Gewerbe- und Arzneimitteltoxikologie, Farbwerke Hoechst AG.

Substance: Acetoacetanilide >99% pure (8.5, 1.0 or 0.12% in 1% methylcellulose)

Species/strain: Rat/Sprague-Dawley

Method: OECD Guideline 407. Treatment with 12, 100, or 850 mg/kg/day of test substance in 1% methylcellulose by daily gavage for 28 days. Additional animals from the high-dose and control groups allowed to recover for 14 days after the last treatment. Bone marrow smears were also evaluated.

GLP: YES [X] NO []

Results: Evidence of systemic and neurotoxicity occurred in the high- and mid-dose groups. The incidence increased after dosing. Signs of neurotoxicity were ameliorated during recovery, but some evidence

of systemic toxicity remained. Body weights and feed consumption in treated animals, especially male rats, were significantly decreased compared to controls. Body weight gains and feed consumption during recovery were comparable for treated and controls animals. Water consumption measured during week 3 after observation of excessive amounts of urine was substantially (32-57%) increased in the high-dose animals compared to other groups. Water consumption during recovery was only slightly (15-22%) increased in animals that had been previously treated compared to controls. After 4 weeks of treatment, dose-dependent changes in hematology and serum chemistry occurred indicative of hemolytic anemia and methemoglobinemia with the high and mid-dose groups showing significant effects. Compensatory erythropoiesis was confirmed in the evaluation of bone marrow smears. By the end of the recovery period, hematologic parameters were near normal with no evidence of anemia or methemoglobinemia. Spleen weights after 4 weeks of treatment were significantly greater in the high- and mid-dose animals compared with controls. Higher spleen weights were also evident after recovery. Microscopic evaluation of tissues indicated extramedullary hematopoiesis in the liver with siderosis in the spleen. Evidence of renal excretion of heme was also present. Based on the results of this study, the NOEL was 12 mg/kg/day.

Comments:

Reference: LONZA, Inc. Report 1663. Edwards, J.A., Verma, C., Allan, S.A., Crook, D., Gibson, W.A., Suttie, A., Gopinath, C., Anderson, A., Dawe, I.S. (1991). Twenty-Eight Day Oral Toxicity Study in Rats with Acetoacetanilide (P0003) (Unpublished report). Huntingdon Research Centre Ltd.

Substance: Acetoacetanilide 99% pure in 1% methylcellulose

Species/strain: Rat/Sprague-Dawley

Method: Five animals per group were treated with 0, 30, 100, or 300 mg/kg/day of test substance in 1% methylcellulose by daily gavage for 7 days to establish dose levels for a Development Toxicity Screen. Animals were observed twice daily for signs of toxicity. Blood was taken at termination for hematology. A gross necropsy was performed and the spleen weighed.

GLP: YES [] NO []

Results: No signs of toxicity were observed. Body weights and feed consumption were comparable. Methemoglobin levels were higher for all treated groups compared with the controls. The increase was 59% for males and 53% for females in the 30 mg/kg group compared with controls. Spleen weights (absolute and relative to body weight) for the 30 mg/kg group were comparable with controls, but higher for the 100 and 300 mg/kg groups.

Comments:

Reference: LONZA, Inc. Report 1000-0006. Foss, J.A. (1996). A Seven Day Oral (Gavage) Dose Range-Finding Study with Acetoacetanilide in Rats (Unpublished report). Argus Research Laboratories, Inc.

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Substance: Acetoacetanilide, assumed 99% pure in DMSO
 Species/strain: Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.
 Method: Modified from Haworth et al., 1983. *Environ. Mutagen* 5 (Suppl 1):3-142.

 Procedure: Pre incubation
 Plates/test: Not stated
 Activation: Concentrations of liver S9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.
 Media: Histidine Selective
 No. replicates: Not stated
 GLP: YES [] NO [X]
 Results:
 Cytotoxicity conc:
 with metabolic activation: 10 mg/plate
 without metabolic activation: 10 mg/plate
 Precipitation conc: not stated
 Genotoxic effects: + ? -
 with metabolic activation: [] [] [X]
 without metabolic activation: [] [] [X]
 Comments: Conducted as part of Government contract. Not under GLP regulations.
 Reference: Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, *Environ. Mol. Mutagen.* 11 (Suppl 12), 1-158.

B. NON-BACTERIAL IN VITRO TEST

Substance: Acetoacetanilide, 99% pure in DMSO
 Species/strain: Human lymphocytes
 Method: OECD Guideline 473
 Procedure: Cytogenetics test: Human Lymphocytes cultured *in vitro*
 Fixation time: 48 hrs.
 Dose levels: 7.3, 14.5, 29, 58, 116, 232, 464, 929, 1860, and 3710 µg/mL
 Plates/test: 1
 Activation system: Liver S9 from rats treated with Aroclor 1254
 Medium: RPMI 1640
 No. replicates: 2
 GLP: YES [X] NO []
 Results:
 Cytotoxicity conc:
 with metabolic activation: 3710 µg/mL
 without metabolic activation: 1860 µg/mL
 Precipitation conc: 3710 µg/mL
 Genotoxic effects: + ? -
 with metabolic activation: [] [] [X]
 without metabolic activation: [] [] [X]
 Comments:

Reference: LONZA, Inc. Report 1530. Brooker, P.C., Paterson, K.M.A., and King, J.D. (1990). Metaphase Chromosome Analysis of Human Lymphocytes Cultured In Vitro (Unpublished report). Huntingdon Research Centre Ltd.

5.6 GENETIC TOXICITY IN VIVO

No Data Available.

5.7 CARCINOGENICITY

No Data Available

5.8 TOXICITY TO REPRODUCTION

Substance: Acetoacetanilid
 Species/strain: Mice/ABC-A Strain
 Method: Two males and three females were allowed to cohabit in groups of 20 per dosage level. Animals were fed the test material mixed in the diet at concentrations of 0.1, 0.5, and 1.0%. Food consumption was measured twice per week and body weights measured weekly. Animals were maintained for 50 weeks and allowed to breed through 5 generations.

GLP: YES [] NO [X]
 Administration: Oral in feed. Animals treated for 50 weeks.
 Doses: Mean doses consumed were 130, 605, and 1230 mg/kg/day.

Results: "So few young were born it was not possible to continue beyond the first generation." (data not shown).
 General parental toxicity: Survival decreased by 25% at 130 mg/kg dose level, 33% at 605 mg/kg dose level, and 40% at 1230 mg/kg dose level. Few survivors beyond 60 weeks. Condition of animals deteriorated after 30 weeks on test.
 NOEL: Not determined
 Reproductive toxicity: 75-83% of females had no litters (offspring). Could not be determined.
 NOEL F1: Not applicable
 NOEL F2: Not applicable

Comments: Study predates GLP regulations. No specific clinical signs of toxicity cited. No additional testing is recommended due to the Chemical Intermediate Status of this substance.

Reference: Wright, H.N. (1967). Chronic Toxicity Studies of Analgesic and Antipyretic Drugs and Congeners, *Toxicol. Appl. Pharmacol.* 11: 280-292.

Substance: Acetoacetanilide, 99% pure
 Species/strain: Rats/Sprague-Dawley
 Method: OECD Guideline 421.
 GLP: YES [X] NO []

Administration: Oral gavage. Males treated for 2 weeks prior to breeding, 2 weeks during breeding, and 2-4 weeks post breeding. Females treated for 2 weeks prior to breeding, gestation, lactation, and 5 days postlactation.

Doses: 0, 3, 30, and 100 mg/kg/day

Results: General parental toxicity: Excess salivation occurred in 5 of 10 males from the 100 mg/kg group. Body weight gains and feed consumption were reduced in this group. Females were unaffected except during pregnancy. Methemoglobinemia was seen for the 30 and 100 mg/kg groups. Signs of hemolytic anemia occurred in the 100 mg/kg group (males and females). There were no microscopic lesions in the testes, epididymides, or ovaries.
 NOEL: 3 mg/kg/day
 Reproductive toxicity: Mating and fertility were unaffected by treatment.
 NOEL F1: Not applicable
 NOEL F2: Not applicable

Comments:

Reference: LONZA, Inc. Report 1000-0007. Foss, J.A. (1996). Oral (Gavage) Reproductive/Developmental Toxicity Screen of Acetoacetanilide in Rats (Unpublished report). Argus Research Laboratories, Inc.

5.9 TERATOGENICITY/DEVELOPMENTAL TOXICITY

Substance: Acetoacetanilide, 99% pure

Species/strain: Rats/Sprague-Dawley

Method: OECD Guideline 421. Dose levels of 0, 3, 30, and 100 mg/kg/day administered by oral gavage.

GLP: YES [] NO []

Results: Maternal general tox: Excess salivation occurred in 5 of 10 males from the 100 mg/kg group. Body weight gains and feed consumption were reduced in this group. Females were unaffected except during pregnancy. Methemoglobinemia was seen for the 30 and 100 mg/kg groups. Signs of hemolytic anemia occurred in the 100 mg/kg group (males and females). There were no microscopic lesions in the testes, epididymides, or ovaries.
 NOEL: 3 mg/kg/day
 Pregnancy/litter data: Mating was unaffected by treatment. Body weight gains were reduced for the 100 mg/kg females. There were no effects on gestation, implantation, or viability.
 NOEL: 100 mg/kg/day
 Fetal data: No effects were observed in the pups.
 NOEL: 100 mg/kg/day

Comments:

Reference: LONZA, Inc. Report 1000-0007. Foss, J.A. (1996). Oral (Gavage) Reproductive/Developmental Toxicity Screen of Acetoacetanilide in Rats (unpublished report). Argus Research Laboratories, Inc.

5.10 OTHER RELEVANT INFORMATION

A. TOXICITY TO BLOOD

- Substance: Acetoacetanilide (10% in 0.5% guar gum)
 Species/strain: Rat/No strain designated
 Method: Eastman Kodak Company, Health, Safety, and Human Factors Laboratory Protocol. Three animals per group were treated by gavage with 1600 mg/kg of test substance. Other groups received either a positive control (Dinitrobenzene) or a negative control (water). Blood was collected and analyzed for methemoglobin.
- GLP: YES [] NO [X]
 Results: Substantial (26-38%) levels of methemoglobin were detected in animals treated with the test substance.
- Comments: No analysis of dosing solutions. Data collected prior to codification of Good Laboratory Practice regulations.
- Reference: Bernard, L.G. (1982). Basic Toxicity of Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report TX-82-12, Health, Safety, and Human Factors Laboratory, Eastman Kodak Company.
- Substance: Acetoacetanilide in 10% starch
 Species/strain: Cat/No strain designated
 Method: Two male cats per dose level were treated with a single oral dose of either 100 or 500 mg/kg. Blood was collected after 1, 3, 7, 24 and 30 hours for methemoglobin determination.
- GLP: YES [] NO [X]
 Results: Substantial (7.0-10.7%) levels of methemoglobin were observed at both dosage levels even after 1 hour with peak concentrations of 11.9-14.0% achieved after 3 or 7 hours. Methemoglobinemia persisted longer in animals receiving 500 mg/kg, although both cats treated with 500 mg/kg died prior to the end of the study.
- Comments: Report predates GLP regulations. No analysis of dosing solutions.
- Reference: Scholz and Weigand (1965). Unpublished report, Laboratorie für Gewerbe- und Arzneimitteltoxikologie, Farbwerke Hoechst AG.
- Substance: Acetoacetanilide TTR in 2% starch
 Species/strain: Cat/No strain designated
 Method: Two female cats were treated with a single oral dose of 100 mg/kg. Blood was collected after 1, 3, 7, 24, 48, 72, and 96 hours, and 7, 14, 21, and 28 days after treatment for hematologic determination.
- GLP: YES [] NO [X]
 Results: Animals exhibited an immediate increase in salivation and after 1 hour showed signs of increased respiration, cyanosis, and imbalance. One cat vomited after 1 and 4.5 hours following treatment. Both animals lost weight. The highest methemoglobin concentrations were 9.7 and 8.9% after 3 hours with 93.5 to 90.5% Heinz-body forms after 1 day. Heinz bodies were greater than 40% for as long as 14 days after treatment. No other changes in hematology were apparent.
- Comments: Report predates GLP regulations. Adequate presentation of methodology and results. No analysis of dosing solutions.

Reference: Leist and Weigand (1978). Wirkung von Acetessiganilid TTR auf das Blutbild weiblicher Katzen (Unpublished report). Pharma Forschung Toxikologie der Hoechst AG.

B. TOXICODYNAMICS, TOXICOKINETICS

No Data Available

5.11 EXPERIENCE WITH HUMAN EXPOSURE

Information:

Source	Number of Workers Exposed	Frequency & duration of exposure	Emission (mg/m ³)	Date
Drumming	1.5	Daily, up to 8 hours/day	0.084-0.343	1995
Bagging	1.5	Daily, up to 8 hours/day	<0.002 - 0.01	1995
Drumming	1.5	Daily, up to 8 hours/day	<0.01	1991
Drumming	2	Daily, up to 7 hours/day	0.02 – 0.17	1995

Comment:

Reference: Eastman Chemical Company and LONZA Inc. data.

APPENDIX OF REPORTS NOT CITED IN THE LITERATURE

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections, only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)Watson, H.M. (1984). Basic Environmental Profile For Acetoacetanilide (Unpublished Report). Health and Environment Laboratories, Eastman Kodak Company.

LONZA, Inc. Report 1000-0005. Roberts, C.A. and Swigart, J.P. (1995). An Evaluation of Acetoacetanilide in a 72-Hour Toxicity Test with the Freshwater Alga *Selenastrum capricornutum* (Unpublished report). Wildlife International Ltd.

Appel, M., and Mühlberger, B. (1990). Abiotischer Abbau Hydrolyse als Funktion des pH-Wertes (Unpublished report). Analytisches Laboratorium, Hoechst AG.

Markert and Jung (1988). Acetessiganilid Prüfung der akuten Toxizität am Fisch Zebraäbrbling (*Brachydanio rerio*) über 96 Stunden (Unpublished report). Pharma Forschung Toxikologie und Pathologie, Hoechst AG.

Voelskow (1988). Untersuchung von Produktproben auf Daphnientoxizität (Unpublished report). Hoechst AG.

LONZA, Inc. report 0061. Wallace, J.M. (1975). Toxicity Studies for LONZA Ltd. (Unpublished report). Bio-Toxicology Laboratories, Inc.

(*)Scholz and Weigand (1965). Unpublished report, Laboratorie für Gewerbe- und Arzneimitteltoxikologie, Farbwerke Hoechst AG.

(*)Fassett, D.W. (1962). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(*)Bernard, L.G. (1982). Basic Toxicity of Acetoacetanilide (Unpublished report). Eastman Kodak Internal Report TX-82-12, Health, Safety, and Human Factors Laboratory, Eastman Kodak Company.

LONZA, Inc. Report 0062. Prate, M.P. (1974). Primary Irritation Studies for LONZA, Inc. (Unpublished report). Bio-Toxicology Laboratories, Inc.

Kreiling and Jung (1988). Acetessiganilid TTR Prüfung auf Hautreizung am Kaninchen (Unpublished report). Pharma Forschung Toxikologie und Pathologie, Hoechst AG.

Kreiling and Jung (1988). Acetessiganilid TTR Prüfung auf Augenreizung am Kaninchen (Unpublished report). Pharma Forschung Toxikologie und Pathologie, Hoechst AG.

LONZA, Inc. Report 1663. Edwards, J.A., Verma, C., Allan, S.A., Crook, D., Gibson, W.A., Suttie, A., Gopinath, C., Anderson, A., Dawe, I.S. (1991). Twenty-Eight Day Oral Toxicity Study in Rats with Acetoacetanilide (P0003) (Unpublished report). Huntingdon Research Centre Ltd.

LONZA, Inc. Report 1530. Brooker, P.C., Paterson, K.M.A., and King, J.D. (1990). Metaphase Chromosome Analysis of Human Lymphocytes Cultured In Vitro (Unpublished report). Huntingdon Research Centre Ltd.

LONZA, Inc. Report 1000-0006. Foss, J.A. (1996). A Seven Day Oral (Gavage) Dose Range-Finding Study with Acetoacetanilide in Rats (Unpublished report). Argus Research Laboratories, Inc.

LONZA, Inc. Report 1000-0007. Foss, J.A. (1996). Oral (Gavage) Reproductive/Developmental Toxicity Screen of Acetoacetanilide in Rats (Unpublished report). Argus Research Laboratories, Inc.

Leist and Weigand (1978). Wirkung von Acetessiganilid TTR auf das Blutbild weiblicher Katzen (Unpublished report). Pharma Forschung Toxikologie der Hoechst AG.