FOREWORD INTRODUCTION

ACETANILIDE

CAS N°: 103-84-4

SIDS Initial Assessment Report for 13th SIAM

(Bern, 6-9 November 2001)

Chemical Name : Acetanilide

CAS No : 103-84-4

Sponsor Country : Republic of Korea

National SIDS Contact Point in Sponsor Country :

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History :

This chemical was assigned to Korea in 1999 and first discussed at SIAM10, March 2000. At the meeting, it was agreed that results of a repeated dose toxicity study with the reproduction/developmental toxicity screening test, acute toxicity to algae and daphnia were necessary for the finalization. Korea performed those toxicity tests and a few more tests for the clarification of the initial assessment. The SIAR was then revised.

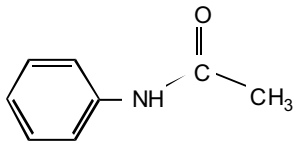
Testing : **N**o testing ( )
Testing (x) : Melting point, Boiling point, Partition coefficient, Stability in water, Toxicity to algae, Acute Toxicity to Daphnia, Combined repeated dose toxicity study with the reproduction / developmental toxicity screening test, Mutagenic toxicity in vivo

Comments :

Deadline for circulation :
Date of Circulation :

Revised : September 2001

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	103-84-4
Chemical Name	Acetanilide
Structural Formula	$CH_3CONHC_6H_5$ 

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acute toxicity of acetanilide is low since the LD_{50} of oral exposure in rats is 1,959 mg/kg bw.

For repeated dose toxicity, acetanilide was given by gavage at doses of 22, 67, 200, and 600 mg/kg/day to male rats for 30 days and to female rats for 39-50 days in accordance with an OECD TG 422 (combined repeated dose toxicity study with reproduction/developmental toxicity screening test). The adverse effects were red pulp hyperplasia of spleen, bone marrow hyperplasia of femur and decreased hemoglobin, hematocrit and mean corpuscular hemoglobin concentration. The LOAEL for repeated dose toxicity in rats was 22 mg/kg/day for both sexes.

Most of the *in vitro* mutagenic toxicity studies including the Ames assay, mammalian chromosomal aberration test, *Bacillus subtilis* recombination assay and SCE assay showed negative results. Regarding *in vivo* studies, a mammalian erythrocytes micronucleus test performed by OECD TG 474 showed negative results. Therefore acetanilide is not considered to be genotoxic. There is some evidence that this chemical is not carcinogenic in rats, mice and hamsters.

In a reproductive/developmental toxicity study performed according to OECD TG 422, no treatment-related changes in precoital time and rate of copulation, impregnation, pregnancy were shown in any treated group. However, viability of offsprings at 600 mg/kg bw/day and body weight of pups at 200 mg/kg/day were significantly reduced. At 600 mg/kg bw/day, four dams died and body weight was decreased at day 0 and 4 of lactation. At 200 mg/kg bw/day, there were signs of maternal toxicity (cf. repeated dose toxicity). The NOAELs for reproduction and developmental toxicity (offspring toxicity) are considered to be 200 mg/kg bw/day and 67 mg/kg bw/day, respectively.

This chemical is not irritating to skin, but slightly irritating to the eyes of rabbits. There is no information available on skin sensitization.

Environment

Physical-chemical properties of acetanilide are as follows: melting point 113.7 ºC, boiling point 304 ºC at 760 mmHg, water solubility 4 g/L at 20 ºC, Log Pow 1.16 at 23 ºC. EQC model of fugacity level I shows that the chemical will be distributed mainly to water. Acetanilide is readily biodegradable (MITI test : 68.7 % after 14 days as BOD) and an estimated BCF of 1.56 by BCFWIN model based on log Pow (1.16) implies that bioaccumulation of acetanilide is low.

Ecotoxicity data has been generated in a limited number of aquatic species of algae (72 hr-E_bC_{50} ; 13.5 mg/L), daphnid (48 hr-EC_{50} ; > 100 mg/L) and fish (96 hr-LC_{50} ; 100 mg/L). No data on prolonged fish toxicity and toxicity to terrestrial organisms are available. From the acute toxicity values, the predicted no effect concentration (PNEC) of 0.135 mg/L was derived using an assessment factor of 100.

Exposure

The total production of acetanilide was about 2,300 tonnes/year in Korea in 1998, and 196 tonnes in the USA in 1998. Acetanilide is mainly used as an intermediates for the synthesis of pharmaceuticals and as an additive in hydrogen peroxide, varnishes, polymers and rubber. The most probable human exposure would be occupational exposure through dermal contact or inhalation at workplaces where acetanilide is produced or used.

In Korea, 2,320 tonnes of the chemical was used as an intermediate for the synthesis of pharmaceuticals. Only a small amount of 120 kg was used as a stabilizer for hydrogen peroxide solutions for hair colouring agents in 1998 and based on general information the content of the substance in such preparations would be very low and the human exposure is insignificant. Readily available environmental or human exposure data do not exist in Korea at the present time. And potential exposure from drinking water, food, ambient water and in the workplace is expected to be negligible because this chemical is produced in a closed system in only one company in Korea.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

FULL SIDS SUMMARY

CAS NO: 103-84-4		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		OECD TG 102	113.7 °C
2.2	Boiling Point		OECD TG 103	304 °C (at 760 mmHg)
2.3	Density		NA	1,219 kg/m^3
2.4	Vapour Pressure		NA	0.002 hPa at 20 °C
2.5	Partition Coefficient (Log P_{OW})		OECD TG 107	1.16 at 23 °C
2.6 A.	Water Solubility		NA	4 g/L at 20 °C
B.	pH		NA	6.5 at 20 °C
	pKa		NA	0.5 at 25 °C
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Estimated (AOPwin)	In T1/2 =31 hour in air
3.1.2	Stability in Water		OECD TG 111	In T1/2 > 1 year
3.2	Monitoring Data			No data
3.3	Transport and Distribution		Estimated (EQC model : fugacity Level I)	In Air 0.13 % In Water 98.57 % In Sediment 1.26 % In Soil 0.02 % In biota/suspended sediment: 0.02 %
3.5	Biodegradation		Other (MITI, Japan)	Readily biodegradable: 68.7 %
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	Other (Korean TG)	LC_{50} (96 hr) > 100 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates	Daphnia magna	Other (Korean TG)	EC_{50} (48 hr) > 100 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	E_bC_{50} (72 hr) = 13.5 mg/L NOEC (72 hr) < 4 mg/L
4.5.2	Chronic Toxicity to Aquatic Invertebrates			No data
4.6.1	Toxicity to Soil Dwelling Organisms			No data
4.6.2	Toxicity to Terrestrial Plants			
(4.6.3)	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			No data
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD_{50} 1959 mg/kg in male/ female LD_{50} 2033 mg/kg in male LD_{50} 1893 mg/kg in female
5.1.2	Acute Inhalation Toxicity			No data
5.1.3	Acute Dermal Toxicity			No data
5.2.1	Skin Irritation	Rabbit	OECD TG 404	Not irritating
5.2.2	Eye Irritation	Rabbit	OECD TG 405	Slightly irritating
5.3	Skin Sensitisation			No data
5.4	Repeated Dose Toxicity	Rat	OECD TG 422	LOAEL = 22 mg/kg bw/day
5.5	Genetic Toxicity *in vitro*			
A.	Bacterial Test (Gene mutation)	*S. typhimurium*	Other (Ames test)	Negative (with metabolic activation) Negative (without metabolic activation)

CAS NO: 103-84-4		SPECIES	PROTOCOL	RESULTS
B.	Non-Bacterial *in vitro* Test (Chromosomal aberrations)	Chinese hamster cell	Other (cytogenetic)	Negative (without metabolic activation)
5.6	Genetic Toxicity *in vivo*	Mouse	OECD TG 474	Negative
5.7	Carcinogenicity	Rat/mouse/hamster	Other	No tumorigenesis
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOAEL=200 mg/kg /day
5.9	Developmental Toxicity / Teratogenicity	Rat	OECD TG 422	NOAEL (offspring toxicity) = 67 mg/kg /day
5.11	Experience with Human Exposure	Human	exposure in workplace, overdosing as a drug	Cyanosis, methemoglobinemia

SIDS INITIAL ASSESSMENT REPORT

1 IDENTITY

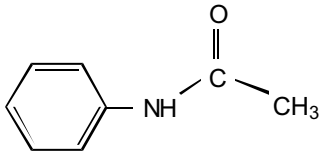
OECD Name : Acetanilide

Synonym : Acetaminobenzene ; Acetanil ; Acetanilid; Acetaminobenzene; Acetic acid anilide; Acetoanilide; Acetylaminobenzene; Acetylaminobenzol; Acetylaniline; Antifebrin; N-Acetyl aniline; N-Acetyl-benzenamine; N-Phenyl acetamide; N-Phenyl acetic acid amide; Phenalgene; Phenalgin; USAF EK-3

CAS Number : 103-84-4

Molecular Formula : C_8H_9NO

Structural Formula : $CH_3CONHC_6H_5$



Degree of Purity : > 97% (industrial grade)

Major Impurity : unknown

Essential Additives : unknown

Physical-chemical properties

Melting Point : 113.7 °C
Boiling Point : 304 °C at 760 mmHg
Vapour Pressure : 0.002 hPa at 20 °C
Water Solubility : 4 g/L at 20 °C
Partition Coefficiency (Log P_{OW}) : 1.16 at 23 °C

Classification in member countries
Not classified as a toxic chemical in the Toxic Chemicals Control Act, Republic of Korea

2. GENERAL INFORMATION ON EXPOSURE

Acetanilide is produced in a non-dispersive manner and mainly used as an intermediates in the synthesis of pharmaceuticals and dyes, as an additive for hydrogen peroxide and cellulose ester varnishes, and as a plasticizer in polymer industry as well as accelerator in the rubber industry.

Total production of acetanilide in Korea is about 2,300 tonnes/year and the import into Korea was less than 1 % of the total production in 1998 (MOE, Korea, 1998). Acetanilide is produced by only one company in Korea. Mostly it is used as an intermediate for synthesis of pharmaceuticals and dyes. Less than 0.2 ton/year is used as a stabilizer in hydrogen peroxide solution. Acetanilide is produced as a solid form with an industrial grade purity of > 97 % in Korea. The US EPA reported that 196 tonnes of acetanilide were produced in 1998 in the US.

Although acetanilide is used mainly as an intermediate in closed systems, it may be released into the environment from its production and processing sites. No monitoring data are available in Korea at the present time.

2.1 Environmental Fate

Acetanilide is not expected to undergo direct photolysis in water due to the lack of functional groups to absorb UV light (HSDB, 2000). However, in air, it is expected to degrade rapidly by reaction with photochemically-produced hydroxyl radicals. The estimated half-life is about 31 hours (NIER, Korea, 2001a).

Hydrolysis of acetanilide is less than 10 % over 5 days in a water solution of pH 4 – pH 9 at 50 °C using OECD TG 111(NIER, Korea, 2001b). Therefore, the chemical hydrolysis is not expected to be an environmentally important removal process in aquatic systems (Mabey, W., 1978).

If released into water, biodegradation of acetanilide is expected to be an important removal process. Biodegradation of acetanilide was 68.7 % after 14 days in a MITI I test. The substance is therefore considered to be readily biodegradable (MITI, Japan, 1992). An estimated BCF of 1.56 by BCFWIN Model (NIER, Korea, 2001a), based on log P_{OW} =1.16 (NIER, Korea, 2001c), implies that bioaccumulation of acetanilide in aquatic organisms is low (Franke et al., 1994).

If it is released into the soil, acetanilide is expected to exhibit very high mobility (Swann et al, 1983) based on a measured K_{OC} of 27 (Briggs et al, 1981). Acetanilide is not expected to volatilize from wet soil based on an estimated Henry's Law constant of 6.2 x 10^{-9} atm m^3/mole (NIER , Korea, 2001a).

No monitoring data of acetanilide in Korea are available.

The distribution of emitted acetanilide at equilibrium in the environmental compartments was obtained by the EQC model of fugacity level I, and it showed that the highest distribution of the chemical is in the water system (Water, 98.57 % ; Air, 0.13 % ; Soil, 1.26 % ; Sediment, 0.02 % ; biota and suspended sediment, 0.02 %) (NIER, Korea, 2001a).

2.2 Human Exposure

The most probable human exposure would be occupational exposure through dermal contact or inhalation at workplaces where acetanilide is produced or used. NIOSH (National Occupational

Exposure Survey 1981-1983) has statistically estimated that 9,000 workers (6,100 of these are female) are potentially exposed to acetanilide in USA.
No human exposure data are available in Korea at present time. However, it seems that consumer exposure does not occur. Potential exposure to this chemical from drinking water, food and ambient water is expected to be negligible because it is produced in the closed system in only one company in Korea.

3. HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics and Metabolism

Acetanilide is converted to a phenolic metabolite in the human body which gives it an analgesic effect, but some is converted to aniline (aminobenzene) which is toxic. It was found that for a single dose of 10 mg/kg of acetanilide, the half-life in blood plasma was 191.5 ± 27.8 min. of in 25 subjects (human) and the metabolic clearance rate was 14.1 ± 2.8 liter/h of (Kellerman et al., 1978).

3.1.2 Acute Toxicity

The acute effects of acetanilide exposure have been examined in mice, rats, guinea pigs, rabbits, cats and dogs. The data show a wide range of LD_{50}s depending on the species. The preferred results are shown in Table 1. The oral LD_{50} value ranges from 1,428 to 2,429 mg/kg bw for male and female rats with a combined average of 1,959 mg/kg bw. Based on this information, the acute oral toxicity of this chemical is likely to be low according to the harmonized integrated hazard classification system. The adverse effects by oral administration observed in laboratory animals are ptosis, lethargy, abnormal gait, lacrimation, sedation, narcosis, paralysis and death after administration (Higgins et al., 1993 ; Van den Heuvel et al., 1990).

Table 1. Acute toxicity of acetanilide in experimental animals

Route	Animal	Value	Type	Reference
Oral	Rat	Male/Female : 1959 (1428-2429) mg/kg Male :2033 (1368-2858) mg/kg Female:1893(1218~2459) mg/kg	LD_{50}	Van den Heuvel et al., 1990
	Mouse	1210 mg/kg bw	LD_{50}	Starmer 1971
Inhalation.	No data			
Dermal	No data			
I.P	Rat	540 mg/kg bw	LD_{50}	Argus 1959
	Mouse	715 mg/kg	LD_{50}	Argus 1959

Conclusion:

Oral LD_{50} value for male and female rats was 1,959 mg/kg bw.

3.1.3 Repeated Dose Toxicity

The study by MOE (MOE,Korea, 2001a) conducted according to GLP using OECD test guideline 422 was selected as the key study for repeated dose toxicity. Details of the study are as follows;

Acetanilide was administrated to rats (males: 12/dose, females: 12/dose) by gavage at doses of 22, 67, 200 and 600 mg/kg/day. Males were dosed for 30 days and females were dosed for 39-50 days from 14 days before mating to day 3 of lactation.

Cyanosis was observed at 600 mg/kg in males and females, and decreased locomotor activity was noted at 200 mg/kg in males as well as at 600 mg/kg in males and females. Salivation at 67, 200, 600 mg/kg and reddish tear at 600 mg/kg in males were shown as well.

Four females at 600 mg/kg died on days 21, 22, and 23 of pregnancy and day 4 of lactation, respectively.

There were significant decreases in HGB, HCT, MCHC at 22, 67, 200, 600 mg/kg and RBC at 67, 200, 600 mg/kg and increase in MCV at 67, 200, 600 mg/kg, MCH at 200, 600 mg/kg and RET at 600 mg/kg for males. Blood biochemistry revealed increases in AST, ALT, ALB, A/G ratio and total bilirubin in males at 200 and/or 600 mg/kg.

Increased weights of spleen, liver, brain, heart, kidney, and ovary and decreased thymus weights were noted in rats.
In histopathological examination, red pulp hyperplasia of spleen and bone marrow hyperplasia of femur were observed at 22, 67, 200, 600 mg/kg and extramedullary hematopoiesis of liver at 200 and 600 mg/kg in both sexes. Also significant increases of thymus atrophy were observed in females at 200 and 600 mg/kg.

The LOAEL for repeated dose toxicity of acetanilide was 22 mg/kg/day for male and female.

Conclusion:

The adverse effects in rats by oral administration were red pulp hyperplasia of spleen, bone marrow hyperplasia of femur and decreased HGB, HCT and MCHC. The LOAEL for repeated dose toxicity in rats was 22 mg/kg/day for both sexes.

3.1.4 Genetic Toxicity or Mutagenicity

Several *in vitro* studies show that acetanilide is non-mutagenic to *Salmonella typhimurium* with or without metabolic activation (Goldman et al., 1977 & 1980; Wheeler et al., 1975; Ogawa et al., 1987; Sugimura et al., 1976; Zeiger et al., 1988). Two mammalian chromosomal aberration tests, a *Bacillus subtilis* recombination assay and a SCE assay show negative results (Sasaki et. al., 1983; Yoshida, 1980; Ishidate et al., 1978; Tanooka et al., 1977).
Regarding genetic toxicity *in vivo*, a mammalian erythrocytes micronucleus test was performed by MOE using OECD TG 474. In the study 6 male ICR mice were treated by i.p up to 1500 mg/kg b.w and the result showed acetanilide did not induce micronuclei of bone marrow cells (NIER, Korea, 2001d). Another available micronucleus test showed acetanilide has a weak micronucleous-inducing potency (Sicardi, 1991). In this assay, the MNPCE rate in the control group was relatively higher than what would usually be expected. Positive results were reported in an *in vivo* study regarding chromosome aberrations, in which breaks and gaps in rat bone marrow cells were examined (Shimazu, 1976). However, this study is considered invalid since the test condition details are poorly reported. Other *in vivo* studies mostly indicated that acetanilide is not genotoxic.

Conclusion:

Acetanilide is not genotoxic because of negative results in bacterial and non-bacterial tests with and without exogenous metabolic activation system *in vitro* as well as in a micronucleus test *in vivo*.

3.1.5 Carcinogenicity

Limited information on carcinogenicity is available from studies performed in both male and female of rats, mice and hamsters. However, carcinogenicity studies showed no evidence of tumors in liver, mammary gland, etc. (Blunck, J.M., 1975; Yamamoto et al., 1970; Wright, 1967). Even a 4 generation study using mouse strains of ABC-A revealed that there was no appearance of tumors in the mammary gland (Wright, 1967). Human data are not available at present.

Conclusion:

There is some evidence that acetanilide is not carcinogenic in rats, mice and hamsters.

3.1.6 Reproduction / Developmental Toxicity

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) was conducted using Sprague-Dawley rats (MOE,Korea, 2001a). In this study, the rats were exposed to acetanilide at doses of 22, 67, 200, and 600 mg/kg/day for 30 days for male and for 39 - 50 days for females.
No treatment-related changes in precoital time, rate of copulation, impregnation and pregnancy were observed in any exposure level group.

At 200 mg/kg/day, there was a decrease in body weight gain at day 4 after birth in both male and female pups. Perinatal deaths were increased, and cyanosis and icterus in offsprings were observed in the 600 mg/kg/day dose group. The viability index on day 4 was decreased in 600 mg/kg/day dose group and the NOAEL for reproduction is 200 mg/kg /day. The body weight of pups was decreased from the dose level of 200 mg/kg/day, and the NOAEL for developmental toxicity (offspring toxicity) is considered to be 67 mg/kg /day.

Conclusion:

No treatment-related changes in precoital time, rate of copulation, impregnation and pregnancy were observed in any treated group. However, the viability of offspring at 600 mg/kg/day and the body weight of pups at 200 mg/kg/day were significantly reduced. The NOAELs for reproduction and developmental (offspring) toxicity are considered to be 200 mg/kg /day and 67 mg/kg /day, respectively.

3.1.7 Other: Irritation ; Sensitization ; Corrosivity

According to the studies performed according to OECD TG 404 (acute dermal irritation/corrosion) and TG 405 (acute eye irritation/corrosion), acetanilide was not irritating to skin but slightly irritating to the eyes of rabbits (Hoechst AG, 1991). It is described that labelling is not required. There is no information available for skin sensitization.

Conclusion:

Acetanilide is not irritating to skin but slightly irritating to the eyes in animals. There is no information available data for skin sensitization.

3.2 Initial Assessment for Human Health

Acetanilide is converted to a phenolic metabolite in the body that gives it an analgesic effect,

however some is converted to aniline (aminobenzene) which is toxic.
The LD_{50} for acute oral toxicity was 1,959 mg/kg bw for male and female rats. This chemical is not irritating to skin but slightly irritating to the eyes of rabbits. There is no information available on skin sensitization.

In accordance with OECD TG 422 (combined repeated dose with the reproduction/developmental toxicity screening test), acetanilide was given by gavage at doses of 22, 67, 200 and 600 mg/kg/day to male rats for 30 days and female rats for 39-50 days. The adverse effects were red pulp hyperplasia of spleen, bone marrow hyperplasia of femur and decreased HGB, HCT and MCHC. The LOAEL for repeated dose toxicity in rats was 22 mg/kg/day for both sexes.

In the reproduction/developmental toxicity screening study, no treatment-related changes in precoital time, rate of copulation, impregnation and pregnancy were found in any treated group. However, the viability of offspring at 600 mg/kg/day and the body weight of pups at 200 mg/kg/day were significantly reduced. The NOAELs for reproduction and developmental toxicity are considered to be 200 mg/kg /day and 67 mg/kg /day, respectively.
Most *in vitro* mutagenic toxicity studies including Ames assays, mammalian chromosomal aberration tests, a *Bacillus subtilis* recombination assay and a SCE assay showed negative results. Regarding *in vivo* studies, a mammalian erythrocytes micronucleus test performed according to OECD TG 474 also showed negative results. Therefore acetanilide is not considered to be genotoxic.
There is some evidence that this chemical is not carcinogenic in rats, mice and hamsters.

4. HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Ecotoxicity data have been generated in a limited number of aquatic species of algae, daphnids and fish. No data on prolonged fish toxicity and toxicity to terrestrial organisms are available. Results are summarized in Table 2.

Table 2. Summary of effects on aquatic organisms

Species	Exposure duration	Results (mg/L)	Reference
Algae : - *Selenastrum capricornutum*	72 hr	E_bC_{50} = 13.5 NOEC < 4	MOE, Korea, 2001c
Daphnids : - *Daphnia magna*	48 hr	EC_{50} > 100	MOE, Korea, 2001b
Fish : - *Oryzias latipes* - *Lepomis macrochirus* - *Menidia beryllina*	 96 hr 96 hr 96 hr	 LC_{50} > 100 LC_{50} = 100 LC_{50} = 115	 MOE, Korea, 1997 Dawson et al., 1975/1977 Dawson et al., 1975/1977

4.2 Terrestrial Effects

There is no available information.

4.3 Other Environmental Effects

There is no available information.

4.4 Initial Assessment for the Environment

The estimation with a fugacity level I model (EQC) reveals that the majority of acetanilide will be distributed to water (98.57 %). The chemical is readily biodegradable (68.7 %) and it has a low potential for bioaccumulation (1.56). From the lowest acute toxicity value of algae, daphnid and fish, the predicted no effect concentration (PNEC) of 0.135 was derived using an assessment factor of 100, which is based on the 72 hr - E_bC_{50} of algae, 13.5 mg/L.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Physical/Chemical property, production, use and distribution

Acetanilide is readily biodegradable (MITI I test: 68.7 % after 14 days as BOD). An estimated BCF of 1.56 by BCFWIN Model based on the log P_{OW} (1.16) implies that bioaccumulation of acetanilide is low. A fugacity level I model calculation shows that the chemical will be distributed mainly to water. The total production volume of acetanilide in Korea was about 2,300 tonnes/year in 1998. Mostly it is used as an intermediate for the synthesis of pharmaceuticals and dyes. Less than 0.5 ton is used as a stabilizer in hydrogen peroxide solutions. Although acetanilide is used mainly as an intermediate in closed systems, it may be released into the environment from its production and processing sites. No monitoring data are available in Korea at the present time.

Human Health

Acetanilide is converted to a phenolic metabolite in the body that gives it an analgesic effect, but some is converted to aniline which is toxic.
The LD_{50} for acute oral toxicity was 1,959 mg/kg bw for male and female rats. This chemical is not irritating to skin but slightly irritating to the eyes of rabbits. There is no information available on skin sensitization.
In accordance with OECD TG 422 (combined repeated dose toxicity test and reproduction/developmental toxicity screening test), acetanilide was given by gavage at doses of 22, 67, 200, and 600 mg/kg/day to male rats for 30 days and female rats for 39-50 days. The adverse effects were red pulp hyperplasia of spleen, bone marrow hyperplasia of femur and decreased HGB, HCT and MCHC. The LOAEL for repeated dose toxicity in rats was 22 mg/kg/day for both sexes. In the reproduction/developmental toxicity screening study, no treatment-related changes in precoital time, rate of copulation, impregnation and pregnancy were noted in any treated group. However, the viability of offspring at 600 mg/kg/day and the body weight of pups at 200 mg/kg/day were significantly reduced. The NOAELs for reproduction and developmental (offspring) toxicity are considered to be 200 mg/kg/day and 67 mg/kg/day, respectively.
Most *in vitro* mutagenic toxicity studies including Ames assays, mammalian chromosomal aberration tests, a *Bacillus subtilis* recombination assay and a SCE assay showed negative results. Regarding *in vivo* studies, a mammalian erythrocytes micronucleus test performed under OECD TG 474 showed negative results. Therefore acetanilide is not considered to be genotoxic.
There is some evidence that this chemical is not carcinogenic in rats, mice and hamsters.

Environment

Ecotoxicity data has been generated in a limited number of aquatic species of algae (72 hr-E_bC_{50} ; 13.5 mg/L), daphnids (48 hr-LC_{50} ; >100 mg/L) and fish (96 hr-LC_{50} ; 100 mg/L). No data on prolonged fish toxicity and toxicity to terrestrial organisms are available. From the acute toxicity values, the predicted no effect concentration (PNEC) of 0.135 was derived using an assessment factor of 100.

5.2 Recommendations

The chemical is currently of low priority for further work

6. REFERENCES

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REVISED OECD HPV FORM 1

SIDS DOSSIER
ON THE HPV CHEMICAL

Acetanilide

CAS No. 103-84-4

Sponsor Country : Republic of Korea

DATE : September 2001

Revised : September 2001

S I D S P R O F I L E

1.01 A.	**CAS No.**	103-84-4
1.01 C.	**CHEMICAL NAME (OECD Name)**	Acetanilide
1.01 D.	**CAS DESCRIPTOR**	Not applicable
1.01 G.	**STRUCTURAL FORMULA** **OTHER CHEMICAL IDENTITY INFORMATION**	$CH_3CONHC_6H_5$ Acetaminobenzene Acetanil Acetanilid Acetamidobenzene Acetic acid anilide Acetoanilide Acetylaminobenzene Acetylaminobenzol Acetylaniline Antifebrin N-Acetyl aniline N-Acetyl-benzenamine N-Phenyl acetamide N-Phenyl acetic acid amide N-phenylacetamide Phenalgene Phenalgin USAF EK-3
1.5	**QUANTITY**	2,300 tonnes/year in Korea
1.7	**USE PATTERN**	Intermediates for synthesis of pharmaceuticals and dyes in closed system
1.9	**SOURCES AND LEVELS OF EXPOSURE**	
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)		

SIDS SUMMARY

CAS NO: 103-84-4		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	Y	N	N	N	Y	N
2.2	Boiling Point	Y	Y	N	N	N	Y	N
2.3	Density	Y	N		Y	N	Y	N
2.4	Vapour Pressure	Y	N		Y	N	Y	N
2.5	Partition Coefficient	Y	Y	Y	N	N	Y	N
2.6	Water Solubility	Y	N		Y	N	Y	N
	pH and pKa values	Y	N		Y	N	Y	N
2.12	Oxidation: Reduction potential	N						N
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	Y				Y	Y	N
3.1.2	Stability in water	Y	Y	N	N	N	Y	N
3.2	Monitoring data	Y			Y	N	Y	N
3.3	Transport and Distribution	Y				Y	Y	N
3.5	Biodegradation	Y	N		Y	N	Y	N
OTHER ENV FATE STUDIES RECEIVED								
ECOTOXICITY								
4.1	Acute toxicity to Fish	Y	N	Y	Y	N	Y	N
4.2	Acute toxicity to Daphnia	Y	N	Y	Y	N	Y	N
4.3	Toxicity to Algae	Y	Y	Y	N	N	Y	N
4.5.2	Chronic toxicity to Daphnia	N						N
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	N						N
4.6.3	Toxicity to Birds	N						N
OTHER ECOTOXICITY STUDIES RECEIVED								
TOXICITY								
5.1.1	Acute Oral	Y	Y		N	N	Y	N
5.1.2	Acute Inhalation	N						N
5.1.3	Acute Dermal	N						N
5.4	Repeated Dose	Y	Y	Y	N	N	Y	N
5.5	Genetic Toxicity *in vitro*							
	. Gene mutation	Y	N		Y	N	Y	N
	. Chromosomal aberration	Y	N		Y	N	Y	N
5.6	Genetic Toxicity *in vivo*	Y	Y	Y	N	N	Y	N
5.8	Reproduction Toxicity	Y	Y	Y	N	N	Y	N
5.9	Development / Teratogenicity	Y	Y	Y	N	N	Y	N
5.11	Human experience	Y	N	N	Y	N	Y	N
OTHER TOXICITY STUDIES RECEIVED							-	

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

A. **CAS number** 103-84-4

B. **Name** *(IUPAC name)* Acetanilide

C. **Name** *(OECD name)* Acetanilide (EINECS)

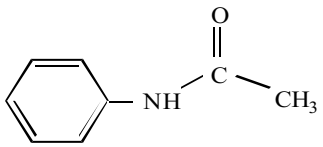
D. **CAS Descriptor** *(where applicable for complex chemicals)*
Not Applicable since acetanilide is not a complex chemical.

E. **EINECS-Number** 203-150-7

F. **Molecular Formula** C_8H_9NO

G. **Structural Formula** *(indicate the structural formula in smiles code, if available)*

$CH_3CONHC_6H_5$



H. **Substance Group** *(if possible, only for petroleum products, see HEDSET explanatory note)*
Not Applicable since acetanilide is not a petroleum product.

I. **Substance Remark** *(Indicate the substance remark as prescribed in the EINECS Inventory, if possible)*
Not Applicable since no prescription in the EINECS Inventory.

J. **Molecular Weight** 135.17

1.02 OECD INFORMATION

A. **Sponsor Country :** Republic of Korea

B. **Lead Organisation:**

Name of Lead Organisation: National Institute of Environmental Research
Contact person: Dr. Moon-Soon LEE
Address:
Street: Gyeongseo-dong, Seo-gu
Postal code : 404-170
Town: Incheon
Country: Republic of Korea
Tel: 82-32-560-7113
Fax: 82-32-568-2037
E-mail : mslee416@me.go.kr

C. **Name of responder** *(Information on a responder should be provided when companies respond to Lead Organisation or SIDS Contact Points.)*

Name : same as above
Address : same as above

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic [x];
organometallic [ ]; petroleum product [ ]

B. Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [ ]; solid [x]

C. Purity *(indicate the percentage by weight/weight)*

> 97 % (Industrial grade, Korea)
97 & 99.95+%(Aldrich Catalog Handbook of Fine Chemicals)
90 – 100 % (MSDS from Oxford Univ.)
99 – 100 % (MSDS from Mallinckrodt Baker, Inc.)

1.2 SYNONYMS

Acetaminobenzene
Acetanil
Acetanilid
Acetamidobenzene
Acetic acid anilide
Acetoanilide
Acetylaminobenzene
Acetylaminobenzol
Acetylaniline
Antifebrin
N-Acetyl aniline
N-Acetyl-benzenamine
N-Phenyl acetamide
N-Phenyl acetic acid amide
N-phenylacetamide
Phenalgene
Phenalgin
USAF EK-3

1.3 IMPURITIES *[Indicate CAS No., chemical name (IUPAC name is preferable), percentage, if possible EINECS number.]*

CAS No:
EINECS No:
Name:
Value:
Remarks:

1.4 ADDITIVES *(e.g. stabilising agents, inhibitors etc. Indicate CAS No., chemical name (IUPAC name is preferable), percentage, if possible EINECS number), the component of the UVCB (substance with no defined composition) should be indicated here.*)

CAS No:
EINECS No:
Name:
Value:
Remarks:

1.5 QUANTITY *[Information on production or import levels should be provided in figures or ranges (e.g. 1,000-5,000, 5,000-10,000 tonnes, etc.) per responder or country and the date for which those ranges apply should be given. For EU Member states, only indicate the EU import figure. Give an estimation of the global production quantity in the remarks field. Information on the number of producers in the country and the source of information should also be given in the remarks field.)*

Remarks: *(If possible, indicate if the substance was produced and/or imported during the 12 months following adoption of the EU regulation on existing chemicals.)*
The production level of acetanilide in Korea is estimated as 2,300 tons in 1998.
Less than 1% of the produced is exported.
According to a survey by US NIOSH in 1983, 716 facilities in 3 kinds of industries were reported to engage either in production or use of the chemical.
The total volume of acetanilide in the world is not available.

Reference : Ministry of Environment(MOE), Korea(1998), Survey on Circulation Volume of Chemicals in Korea

1.6 LABELLING AND CLASSIFICATION *[If possible, enter information on labelling and classification, such as labelling and classification system, existence of specific limit, symbols, nota, RPhrases and S-Phrases of EC Directive 67/548/EEC. See HEDSET Explanatory Note.]*

Labelling
Type:
Specific limits:
Symbols:
Nota:
R-phrases:
S-phrases:

Text of S-phrases:
Remarks:

Classification
Type:
Category of danger:
R-phrases:

Remarks:

* Acetanilide is not listed on the Dangerous Substance Directive (Annex I) of EC Directive 67/548/EEC
** Acetanilide is not classified as Toxic Chemicals in Korea

1.7 USE PATTERN

A. General *[Data on use pattern have to be given by assigning main types according to their exposure relevance (i.e. non-dispersive use, use in closed systems, use resulting in inclusion into or onto matrix and wide dispersive use), industrial categories (e.g. basic chemical industry, chemical industry, agricultural industry, personal and domestic use) and use categories such as colouring agents, intermediates, solvents, adhesives, cleaning/washing agents, fertilizers, impregnation agents, surface-active, etc. If available, give an estimation of different uses in percentage terms.]*

Type of Use:	**Category:**
(a) main industrial use	non-dispersive use chemical industry: used in synthesis intermediates (medicines, dyes, and camphor)
(b) main industrial use	non-dispersive use chemical industry: used as additives stabilizer(hydrogen peroxide and cellulose ester varnishes)

(c)	main industrial use	use resulting in inclusion into matrix polymer industry : as plasticizer others (plasticizer)
(d)	main industrial use	use resulting in inclusion into matrix other: rubber industry others (accelerator)
	Reference :	Ministry of Environment(MOE), Korea(1998), Survey on Circulation Volume of Chemicals in Korea
	Remark :	General use of acetanilide in the world are shown above. Among 2,300 tons consumed in Korea, Most of them are used for synthesis of pharmaceuticals and dyes, and the rest (< 1 %) are consumed as a stabilizer of hydrogen peroxide solution.

B. Uses in Consumer Products

Function	Amount present	Physical state

Remarks:
Reference:

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

None

1.9 SOURCES OF EXPOSURE

Describe sources of potential human [other than concentration of chemicals in the workplace and indoor environment (see 5.11)], or environmental exposure, including emission data (e.g. quantities per media with information such as time dimensions of release, indication of type of release (e.g. point source or diffuse), type of estimating (e.g. average or worst case), uncertainties in estimation), for all phases of the life cycle of the chemical, if available, including manufacturing and user areas.
For environmental exposure, indicate the production process briefly, number of sites of manufacture and, the basis for concluding that the process is "closed" if applicable.
Also an indication of measured exposure levels (expressed in an appropriate form, e.g. geometric mean and standard deviation) can be mentioned here Any information that will help to focus the assessment of exposure (either quantitative or quantitative in nature) can be mentioned, if available.)

Source:	Media of release Quantities per media
Remarks:	Number of workers potentially exposed to acetanilide in the U.S. : 9,000 (6,100 female) Limited monitoring data indicate that non-occupational exposure can occur from the ingestion of contaminated drinking water. However, the most probable human exposure would be occupational exposure, which may occur through dermal contact at workplaces.
Reference:	NIOSH National Occupational Exposure Survey 1983

1.10 ADDITIONAL REMARKS

A. Options for disposal *[Mode of disposal (e.g. incineration, release to sewage system, etc.) for each category and type of use, if appropriate; recycling possibility]*

Remarks:	Add to a flammable solvent (alcohol or benzene) Pour into an iron pan in an open pit

Ignite or spray into an incinerator (incineration at 1,000 °C followed by treatment of the off-gas recommended)
Oxides of nitrogen may be scrubbed out with alkaline solution.

Reference: Online Toxicology Data Network (TOXNET): Hazardous Substances Data Bank (HSDB), 2000

B. Other remarks

None

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT *(If more than one, identify the recommended value.)*

a) Preferred result

Value:	=113.7 °C
Decomposition:	Yes [ ] No [x] Ambiguous [ ]
Sublimation:	Yes [ ] No [x] Ambiguous [ ]
Method:	OECD TG 102 (melting point/melting range)
GLP:	Yes [ ] No [x] ? [ ]
Remarks:	
Reference:	National Institute of Environmental Research (NIER), Korea (2001), Test of Acetanilide melting point/melting range(tested by LGCI)

b)

Value:	= 113.6°C
Decomposition:	Yes [ ] No [ ] Ambiguous [ ]
Sublimation:	Yes [ ] No [ ] Ambiguous [ ]
Method:	
GLP:	Yes [ ] No [ ] ? [x]
Remarks:	
Reference:	Hoechst AG : EG -Sicherhetsdatenblatt Acetanilide, 26, January, 1994

c)

Value:	=114.3 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [ ]
Sublimation:	Yes [ ] No [ ] Ambiguous [ ]
Method:	
GLP:	Yes [ ] No [ ] ? [x]
Remarks:	
Reference:	Lide, D.R. (ed.): CRC Handbook of Chemistry and Physics. 71th ed. Boca Raton, FL: CRC Press Inc., p. 4-6, 1990 - 1991

2.2 BOILING POINT *(If more than one, identify the recommended value.)*

a) Preferred result

Value:	=304°C
Pressure:	at 760 mmHg
Decomposition:	Yes [ ] No [x] Ambiguous [ ]
Method:	OECD TG 103 " Boiling point–Method according to Siwoloboff"
GLP:	Yes [ ] No [x] ?[ ]
Remarks:	
Reference:	National Institute of Environmental Research (NIER), Korea(2001), Test of Acetanilide boiling point, (tested by LGCI).

b)

Value:	=305 °C
Pressure:	at 1,013 hPa
Decomposition:	Yes [ ] No [ ] Ambiguous [ ]
Method:	
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	
Reference:	Hoechst AG : EG -Sicherheitsdatenblatt Acetanilide, 26, January, 1994

2.3 DENSITY (relative density) *(Where applicable, indicate the relative density of the substance.)*

a) Preferred result

Type:	Bulk density [ ]; Density [ ]; Relative Density [x]
Value:	1.2190 g/cm^3
Temperature:	15 °C
Method:	
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	
Reference:	Lide, D.R. (ed.)., CRC Handbook of Chemistry and Physics. 71th ed. Boca Raton, F.L., CRC Press Inc., p. 4-6, 1990-1991

b)

Type:	Bulk density [ ]; Density [ ]; Relative Density [x]
Value:	1.21 g/cm^3
Temperature:	20 °C
Method:	
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	
Reference:	Hoechst AG: EG -Sicherheitsdatenblatt Acetanilide, 26, January, 1994

c)

Type:	Bulk density [ ]; Density [ ]; Relative Density [x]
Value:	1.2105 g/cm^3
Temperature:	4 °C
Method:	
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	
Reference:	Richardson, M.L. and Gangolli, S., The Dictionary of Substances and their Effects, Royal Society of Chemistry, p. 19, 1995

2.4 VAPOUR PRESSURE *(if more than one, identify the recommended value)*

a) Preferred result

Value:	0.002 hPa
Temperature:	20 °C
Method:	calculated [ ]; measured [ ]
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	
Reference:	IUCLID (International Uniform chemical Information Database) data set (Acetanilide;103-84-4), June, 1998

b)

Value:	0.2×10^{-3} mmHg
Temperature:	25 °C
Method:	calculated [ ]; measured [x]
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	
Reference:	Daubert, T.E.; Danner, R.P.; Physical and Thermodynamic Properties of Pure chemicals data compilation design institute for physical property data, American institute of chemical engineers hemisphere pub. New York, NY., 4, 1989

c)

Value:	1.22×10^{-3} mmHg
Temperature:	25 °C
Method:	calculated [ ]; measured [ ]
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	
Reference:	Online Toxicology Data Network (TOXNET): Hazardous Substances Data Bank (HSDB), 2000

d)

Value:	0.207×10^{-3} mmHg (0.26 Pa)
Temperature:	25 °C
Method:	calculated [x]; measured [ ]
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	
Reference:	National Institute of Environment Research (NIER), Korea (2001), Estimation of physical/chemical properties and environmental fate of SIDS chemical

2.5 PARTITION COEFFICIENT log P_{OW} *(if more than one, identify the recommended value)*

a) Preferred result

Log P_{ow}:	=1.16
Temperature:	23 ± 1 °C
Method:	calculated [ ]; measured [x]
GLP:	Yes [x] No [ ] ?[ ]
Remarks:	measured by OECD TG 107 (shake flask method)
Reference:	National Institute of Environmental Research (NIER), Korea (2001), Test of Acetanilide Partition Coefficient (n-octanol/water) (tested by KRICT)[c)]

b)

Log P_{ow}:	=1.16
Temperature:	25 ± 5 °C
Method:	calculated [ ]; measured [x]
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	
Reference:	1. Fujita, T., Iwasa, J. and Hansch, C., A New Substituent Constant, Derived from Partition Coefficients, J. Am. Chem. Soc. 86, 5175-5180, 1964 2. Hansch, C., Leo, A. and Hoekman, D., Exploring QSAR – Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society, p. 42, 1995

c)

Log P_{ow}:	=1.10
Temperature:	25 C
Method:	calculated [x]; measured [ ]
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	estimated by KWOWIN model.
Reference:	National Institute of Environment Research (NIER), Korea (2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

2.6 WATER SOLUBILITY *(if more than one, identify the recommended value)*

A. Solubility

a) Preferred result

Value:	4 g/l
Temperature:	20 °C
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [x]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	
GLP:	Yes [ ] No [ ] ? [x]
Remarks:	
Reference:	Hoechst AG : EG -Sicherheitsdatenblatt Acetanilide, 26, January, 1994

b)

Value:	6.390 g/l
Temperature:	25 °C
Description:	Miscible[ ]; Of very high solubility [ ];

Of high solubility [ ]; Soluble [x]; Slightly soluble [ ];
Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]

Method:
GLP: Yes [ ] No [ ] ?[x]
Remarks:
Reference: Online Toxicology Data Network (TOXNET):Hazardous Substances Data Bank (HSDB), 2000

c)
Value: 5.4 g/l
Temperature: 25 °C
Description: Miscible[ ]; Of very high solubility [ ];
Of high solubility [ ]; Soluble [x]; Slightly soluble [ ];
Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
GLP: Yes [ ] No [ ] ?[x]
Remarks:
Reference: Online Toxicology Data Network (TOXNET): Hazardous Substances Data Bank (HSDB), 2000

B. pH Value, pKa Value

a)
pH Value: =6.5, measured
Concentration: 4 g/L
Temperature: 20 °C
Method:
GLP: Yes [ ] No [ ] ?[x]
pKa value = 0.5 at 25 °C
Remarks:
Reference: 1. Hoechst AG : EG-Sicherheitsdatenblatt Acetanilide, 26, January, 1994
2. Online Toxicology Data Network (TOXNET): Hazardous Substances Data Bank (HSDB), 2000

2.7 FLASH POINT *(liquids)*

a)
Value: 169 °C
Type of test: Other
Method: Closed cup [ ]; Open cup [ ]; Other [ ]
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Online Toxicology Data Network (TOXNET): Hazardous Substances Data Bank (HSDB), 2000

b)
Value: 174 °C
Type of test: Other
Method: Closed cup [ ]; Open cup [ ]; Other [ ]
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Hoechst AG : EG -Sicherheitsdatenblatt Acetanilide, 26, January. 1994

c)
Value: 173 °C
Type of test: Other
Method: Closed cup [ ]; Open cup [ ]; Other [ ]
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Richardson, M.L. and Gangolli, S. The Dictionary of Substances and their Effects. Royal Society of Chemistry, p. 19, 1995

2.8 AUTO FLAMMABILITY *(solid/gases)*

a)
Value: 540 °C
Pressure: 1013 hPa
Method:
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: Hoechst AG : EG -Sicherheitsdatenblatt Acetanilide, 26, January, 1994

2.9 FLAMMABILITY

a)
Results: Extremely flammable [ ]; Extremely flammable - liquified gas [ ];
Highly Flammable [ ]; Flammable [ ]; Non flammable [ ];
Spontaneously flammable in air [ ]; Contact with water liberates highly flammable gases [ ]; Other [x]
Method:
GLP: Yes [ ] No [ ] ?[x]
Remarks: Brennzahl ; 1(Non combustible)
Reference: Hoechst AG : EG -Sicherheitsdatenblatt Acetanilide, 26, January, 1994

2.10 EXPLOSIVE PROPERTIES

Results: Explosive under influence of a flame[ ];
More sensitive to friction than m-dinitrobenzene [ ];
More sensitive to shock than m-dinitrobenzene [ ]; Not explosive [ ];
Other [x]
Method:
GLP: Yes [ ] No [ ] ?[x]
Remarks: Splash explosion class: ST1
Reference: Hoechst AG : EG -Sicherheitsdatenblatt Acetanilide, 26, January, 1994

2.11 OXIDIZING PROPERTIES

Results: Maximum burning rate equal or higher than reference mixture [ ];
Vigorous reaction in preliminary test [ ];
No oxidizing properties [x]; Other [ ]
Method:
GLP: Yes [ ] No [ ] ?[ ]
Remarks: No studies located, but not expected from structure to have oxidizing properties.
Reference:

2.12 OXIDATION: REDUCTION POTENTIAL

(Where applicable, indicate the redox potential and the conditions under which it was measured.)

Value: Not applicable since acetanilide is not expected to have oxidizing properties
Method:
GLP: Yes [ ] No [ ] ?[ ]
Remarks:

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (K_d)

(a)

Value:	K_{OC} : 27
Method:	measured
GLP:	Yes [ ] No [ ] ? [x]
Remarks:	Very high mobility in soil.
Reference:	1. Briggs,G.G.; Theoretical and Experimental relationships between soil adsorption, octanol-water partition coefficients water solubilities, bioconcentration factors and the parachor, J; Agric. Food Chem.; 29:1050-9 2. Online Toxicology Data Network (TOXNET): Hazardous Substances Data Bank (HSDB), 2000

(b)

Value:	K_{OC} : 38
Method:	estimated by PCKOCWIN v1. 66
GLP:	Yes [ ] No [ ] ?[x]
Remarks:	very high mobility in soil
Reference:	National Institute of Environment Research (NIER), Korea (2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

B. Other data

(e.g. Henry's Law constant, fat solubility, surface tension (of aqueous solution), adsorption/desorption on soil, particle size distribution, etc.

1. Henry's Law Constant

a)

Value :	5.57×10^{-9} atm m^3/mole at 25 °C
Method :	estimated
Remarks :	calculated by fragment constant estimation method.
Reference:	Meylan, W.M. and P.H. Howard., Bond contribution method for estimating Henry's law constants. Environ. Toxicol. Chem. 10:1283-1293, 1991

b)

Value :	5.3×10^{-8} atm m^3/mole at 25 °C
Method :	estimated
Remarks :	calculated by vapour pressure /water solubility method.
Reference:	Mackay, D. and W.J. Shiu. critical review of Henry's law constants for chemicals of environmental interest. J. Phys. Chem. Ref. Data 10:1175-1199, 1981

c)

Value :	6.17×10^{-9} atm m^3/mole at 25 °C
Method :	estimated
Remarks :	calculated by HENRYWIN Version 3.10
Reference:	National Institute of Environment Research (NIER), Korea (2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

2. Volatilization from Soil/ Water

a)

Results:	Volatilization from Moist soil surfaces is not expected to be important.(1) Volatilization from dry soil surfaces may not exist (2)
Remarks:	(1) given an estimated Henry's law constant of 6.2×10^{-9} atm m^3/mole. (2) based on the exptrapolated vapor pressure of 1.22×10^{-3} mmHg.
Reference:	Online Toxicology Data Network (TOXNET): Hazardous Substances Data Bank (HSDB), 2000

b)

Results:	Nonvolatile from water surfaces
Remarks:	based on an estimated Henry's Law constant of 6.2×10^{-9} atm m^3 /mole (by use of a fragment constant estimation method).
Reference:	Online Toxicology Data Network (TOXNET): Hazardous Substances Data Bank (HSDB), 2000

3. ENVIRONMENTAL FATE AND PATHWAYS

[Reporting of studies should give the test method, test conditions (laboratory versus field studies), test results (e.g. % degradation in specified time period) and reference information on breakdown products (transient and stable) should be provided when available.]

3.1 STABILITY

3.1.1 PHOTODEGRADATION

a) Preferred result

Type :	Air [x]; Water [ ]; Soil [ ]; Other [ ]
Light source :	Sunlight [ ]; Xenon lamp [ ]; Other [ ]
Light spectrum :	nm
Relative intensity:	*(based on intensity of sunlight)*
Spectrum of substance:	*[e.g. lambda (max.)(> 29 5nm) and epsilon (max) or epsilon (295 nm)]*nm
Concentration of Substance :	
Temperature:	25 °C
Direct photolysis:	
Half life:	
Degradation:	% (weight/weight) after (exposure time)
Quantum yield:	
Indirect Photolysis:	
Type of sensitizer:	OH radical
Concentration of sensitizer:	0.5×10^{6} molecule/ m^3
Rate constant (radical):	12.52×10^{-12} cm^3/molecule-sec
Degradation:	ca. 50 % after 1.282 days (31 hours)
Method:	calculated [x]; measured[ ]
GLP:	Yes [ ] No [ ] ?[x]
Test substance:	purity:
Remarks:	an estimated EPIWIN model
Reference:	National Institute of Environment Research (NIER), Korea (2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

*3.1.2 STABILITY IN WATER

a) Preferred result

Type:	Abiotic (hydrolysis) [x]; biotic (sediment)[ ]
Half life:	> 1 year
Degradation:	3.91 %, 1.085 % and 4.78 % at pH 4.0, pH 7.0 and pH 9.0 at 50 °C (5 days)
Method:	OECD TG 111
GLP:	Yes [ ] No [x] ?[ ]
Test substance:	Aldrich (39722-9), purity : 99.5 %
Remarks:	Since the chemical is not degradable less than 10 % in this test condition, It is presumably stable in water.
Reference:	National Institute of Environmental Research (NIER), Korea (2001), Test of Acetanilide Hydrolysis as a Function of pH, (tested by LGCI)

3.1.3 STABILITY IN SOIL

Type:	Field trial [ ]; Laboratory [ ]; Other [ ]
Radiolabel:	Yes [ ] No [ ] ? [ ]
Concentration:	mg/kg
Soil temperature:	°C
Soil humidity:	of field capacity
Soil classification:	DIN19863 [ ]; NF X31-107 [ ]; USDA [ ]; Other [ ]
	Year
Content of clay etc.:	Clay %, Silt %, Sand %
Organic Carbon:	%
Soil pH:	
Cation exchange capacity:	m mol/kg
Microbial biomass:	

Dissipation time:	DT 50:
	DT 90:
Dissipation:	% after day
Method:	*(e.g. OECD, other (with the year of publication or updated of the method used))*
GLP:	Yes [ ] No [ ] ? [ ]
Test substance:	
Remarks:	No studies located
Reference:	

3.2 MONITORING DATA (ENVIRONMENTAL)

Note that data on biological effects monitoring, including biomagnification, and biotransformation and kinetics in environmental species are to be reported in section 4.7 and 4.8, respectively. Nonetheless, concentration in various biota should be reported here. Data on concentration in the workplace or indoor environment should be reported under item 5.11.

Type of M easurement:	Background [ ]; At contaminated site [ ]; Other [ ]
Media:	
Results:	
Remarks:	No monitoring data of acetanilide were given
Reference:	

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

3.3.1 TRANSPORT

a)

Type :	Adsorption [ ]: Desorption [ ]; Volatility [x]: Other [ ]
Media :	Water-air
Method :	an estimated by WVOLWIN model.
Results :	River (Half-life) :1.465 years, LAKE (Half-life) : 16 years
Remarks :	base on an estimated Molecular Weight (135.17 g/mole), water solubility (4000 ppm), vapor pressure (0.0015 mmHg). Henry's Law Constant (5.3E-008 atm m^3/mole)
Reference:	National Institute of Environment Research (NIER), Korea (2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

a) Preferred result

Media:	Air-biota [ ]; Air-biota-sediment-soil-water [x]; Soil-biota [ ]; Water-air [ ]; Water-biota [ ]; Water-soil [ ]; Other [ ]
Method:	Fugacity level I [x]; Fugacity level II [ ]; Fugacity level III [ ]; Fugacity level IV[ ]; Other (calculation) [ ]; Other (measurement)[ ]
Results:	In air 0.13 % In water 98.57 % In soil 1.26 % In sediment 0.02 % In biota/suspended sediment : 0.02 %
Remarks:	The EQC model was used for calculation.
Reference:	National Institute of Environment Research (NIER), Korea (2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

b)

Media:	Air-biota [ ]; Air-biota-sediment-soil-water [x]; Soil-biota [ ]; Water-air [ ]; Water-biota [ ]; Water-soil [ ]; Other [ ]

Method: Fugacity level I [ ]; Fugacity level II [ ]; Fugacity level III [x];
Fugacity level IV [ ]; Other (calculation) [ ]; Other (measurement)[ ]
Results: In air 0.027 %
In water 47.20 %
In soil 52.7 %
In sediment 0.108 %
Remarks: The EQC model was used for calculation.
Reference: National Institute of Environment Research (NIER), Korea (2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Results: No data available
Remarks:
Reference:

3.5 BIODEGRADATION

a) Preferred result

Type: aerobic [x]; anaerobic [ ]
Inoculum: adapted [ ]; non-adapted [x]; Activated sludge
Concentration of the chemical: related to COD [ ]; DOC [ ]; test substance [x]
100 mg/L
Medium: water [x]; water-sediment [ ]; soil [ ]; sewage treatment [ ]
Degradation: *(percentage reduction/exposure time)*
68.7 % after 14 days incubation
Results: *(see OECD Guidelines)* readily biodeg. [x]; inherently biodeg. [ ]; under test condition no biodegradation observed [ ], other [ ]
Kinetic (e.g. Zahn-Wellens-Test) % in (time)
Method: MITI Test, Japan
GLP: Yes [ ] No [ ] ? [x]
Test substance: purity:
Remarks: Sludge 30 mg/L
Reference: MITI, Japan, Biodegradation and Bioaccumulation Data of Existing Chemicals based on the CSCL Japan: Published by Japan Chemical Industry Ecology-Toxicity & Information Center, p.3-21, October, 1992

b)
Type: aerobic [x]; anaerobic [ ]
Inoculum: adapted [ ]; non-adapted [x]; .
Predominantly domestic sewage
Concentration of the chemical: 2.4 mg/L related to COD [ ]; DOC [ ]; test substance [x]
Medium: water [x]; water-sediment [ ]; soil [ ]; sewage treatment [ ]
Degradation: > 90 % after 20 days as BOD
Results: readily biodeg. [x]; inherently biodeg. [ ];
under test condition no biodegradation observed [ ], other [ ]
Kinetic (e.g. Zahn-Wellens-Test) % in (time)
Method: OECD Guideline 301 D 'Ready Biodegradability: Closed Bottle Test.
GLP: Yes [ ] No [ ] ? [x]
Test substance: purity:
Remarks: *[In the case of poorly soluble chemicals, treatment given (nature, concentration, CAS number, name and percentage of degradation products etc.)]:*
Reference: IUCLID (International Uniform chemical Information Database) data set (Acetanilide;103-84-4), June, 1998

c)
Type: aerobic [x]; anaerobic [ ]
Inoculum: adapted [x]; non-adapted [ ]; Activated sludge
Concentration of the chemical: 200mg/L related to COD [x]; DOC [ ]; test substance [ ]
Medium: water [x]; water-sediment [ ]; soil [ ]; sewage treatment [ ]
Degradation: *(percentage reduction/exposure time)*
94.5 % after 5 days as COD
Results: readily biodeg. [x]; inherently biodeg. [ ];
under test condition no biodegradation observed [ ], other [ ]
Kinetic (e.g. Zahn-Wellens-Test) % in (time)
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*.
GLP: Yes [ ] No [ ] ? [x]
Test substance: purity:
Remarks: *[In the case of poorly soluble chemicals, treatment given (nature, concentration, CAS number, name and percentage of degradation products etc.)]:*
Reference: Pitter, P. Determination of Biological degradability of Organic Substances. Water Research.10, 231-235, 1976

d)
Type: aerobic [x]; anaerobic [ ]
Inoculum: adapted [ ]; non-adapted [x]; River Water and sludge
Concentration of the chemical: 6-7 mg/L related to COD [ ]; DOC [ ]; test substance [x]
Medium: water [x]; water-sediment [ ]; soil [ ]; sewage treatment [ ]
Degradation: *(percentage reduction/exposure time)*
100 % after 43 days incubation
Results: readily biodeg. [x]; inherently biodeg. [ ];
under test condition no biodegradation observed [ ], other [ ]
Kinetic (e.g. Zahn-Wellens-Test) % in (time)
Method: River Die-Away
GLP: Yes [ ] No [ ] ? [x]
Test substance: purity:
Remarks: *[In the case of poorly soluble chemicals, treatment given (nature, concentration, CAS number, name and percentage of degradation products etc.)]:*
Reference: El-Dib, M.A. and O.A. Aly. Persistence of some Phenylamide Pesticides in the Aquatic Environment-III. Biological Degradation. Water Res. 10, 1055-9, 1976

3.6 BOD_5, COD OR RATIO BOD_5/COD

BOD_5
Method:
Concentration: related to COD [ ]; DOC [ ]; Test substance [ ]
Value: mg O_2/l
GLP: Yes [ ] No [ ] ? [ ]

COD
Method:
Value: mg O_2/g
GLP: Yes [ ] No [ ] ? [ ]

Ratio BOD_5/COD:
Remarks: No data available
Reference:

3.7 BIOACCUMULATION

a)Preferred result
Species:
Exposure period:
Temperature(°C): °C
Concentration:

BCF:	1.56
Elimination:	Yes [ ] No [ ] ? [ ]
Method:	Calculated from experimental P_{ow} (1.16).
Type of test:	calculated [x]; measured [ ] static [ ]; semi-static [ ]; flow-through [ ]; other *(e.g. field test)* [ ]
GLP:	Yes [ ] No [ ] ? [ ]
Test substance:	purity:
Remarks:	BCFWIN Model Version 2.14
Reference:	National Institute of Environment Research(NIER), Korea(2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

b)

Species:	*Carassius auratus* (goldfish)
Exposure period:	
Temperature(°C):	℃
Concentration:	
BCF:	1.23
Elimination:	Yes [ ] No [ ] ? [x]
Method:	
Type of test:	calculated [x]; measured [ ] static [ ]; semi-static [ ]; flow-through [ ]; other *(e.g. field test)* [ ]
GLP:	Yes [ ] No [ ] ? [x]
Test substance:	purity:
Remarks:	
Reference:	Nakatsugawa, T. and P. A., Nelson. Studies on insecticide detoxication in invertebrates; an enzymological approach to the problem of biological magnification, in "Environmental Toxicological of Pesticides", edited by Matsumura, F. et al., Academic Press, New York and London, pp. 501-524, 1972.

3.8 ADDITIONAL REMARKS

A. **Sewage treatment** *(information on treatability of the substance)*

Results:	
Remarks:	No data available
Reference:	

B. **Other information** *[information that will help to focus the exposure assessment (either qualitative or quantitative)]*

No data available

4. ECOTOXICITY

4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a) Preferred Result

Type of test:	static [x];semi-static[ ];flow-through[ ]; other (e.g.field test) [ ] open system[ ]; closed system [ ]
Species:	*Oryzias latipes* (medaka, Fresh water)
Exposure period:	96 hr
Results:	LC_{50} (96 h) >100 mg/L
Analytical monitoring:	Yes[ ] No[x] ? [ ]
Method:	other: Testing of industrial chemicals (Ministry of Environment), Korea
GLP:	Yes[x] No[ ] ? [ ]
Test substance:	Purity > 99.9 %
Remarks:	Limit test at 100 mg/L showed no mortality.
Reference:	Ministry of Environment (MOE), Korea (1997), Toxicity evaluation of existing chemicals (X)(ES-010)

(b)

Type of test:	static [x]; semi-static[ ];flow-through[ ]; other (e.g. field test) [ ] open system[ ]; closed system [ ]
Species:	*Lepomis macrochirus* (Bluegill sunfish, fresh water)
Exposure period:	96 hr
Results:	LC_{50} (96 h) = 100 mg/L
Analytical monitoring:	Yes[ ] No[x] ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]*
GLP:	Yes[ ] No[ ] ? [x]
Test substance:	97 % acetanilide
Remarks:	
Reference :	Dawson, G.W., A.L. Jennings, D.Drozdowski, E.Rider. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. J. Hazard. Mater. 1, 303-318, 1975/ 1977

(c)

Type of test:	static [x]; semi-static[ ]; flow-through[ ]; other (e.g. field test) [ ] open system[ ]; closed system [ ]
Species:	*Leuciscus idus* (Ide, fresh water)
Exposure period:	48 hr
Results:	LC_{50} (48 h) = 200 mg/L
Analytical monitoring:	Yes[ ] No[x] ? [ ]
Method:	*[e.g. OECD, other(with the year of publication or updating of the method used)]*
GLP:	Yes[ ] No[ ] ? [x]
Test substance:	purity
Remarks:	
Reference:	IUCLID (International Uniform chemical Information Database) data set (Acetanilide;103-84-4), June, 1998

(d)

Type of test:	static [x]; semi-static[ ];flow-through[ ]; other (e.g. field test) [ ] open system[ ]; closed system [ ]
Species:	*Menidia beryllina* (tidewater silverside, sea water)
Exposure period:	96 hr
Results:	LC_{50} (96 h) = 115 mg/L
Analytical monitoring:	Yes[ ] No[x] ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]*
GLP:	Yes[ ] No[ ] ? [x]
Test substance:	purity
Remarks:	
Reference :	Dawson, G.W., A.L. Jennings, D. Drozdowski, E. Rider. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. J. Hazard. Mater. 1, 303-318, 1975/ 1977.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

(a) Preferred Result

Type of test:	static [x]; semi-static[ ];flow -through[ ]; other (e.g. field test) [ ] open system[ ]; closed system [ ]
Species:	*Daphnia magna*
Exposure period:	48 hr
Results:	EC_{50} (48 h) > 100 mg/L
Analytical monitoring:	Yes[x] No[ ] ? [ ]
Method:	Other: Testing of industrial chemicals (Ministry of Environment), Korea
GLP:	Yes[x] No[ ] ? [ ]
Test substance:	Purity > 99.95 %
Remarks:	
Reference :	Ministry of Environment (MOE), Korea(2001), The Acute toxicity of Acetanilide to Aquatic Invertebrate (tested by KRICT)

B. Other aquatic organisms

Type of test:	static [ ]; semi-static[ ];flow-through[ ]; other (e.g. field test) [ ] open system[ ]; closed system [ ]
Species:	
Exposure period:	
Results:	
Analytical monitoring:	Yes[ ] No[ ] ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]*
GLP:	Yes[ ] No[ ] ? [ ]
Test substance:	
Remarks:	No data available
Reference :	

4.3 TOXICITY TO AQUATIC PLANTS

Algae

(a) Preferred Result

Species:	*Selenastrum capricornutum*
End point:	Biomass[x] ; Growth rate [ ]; Other[ ]
Exposure period:	72 hr
Results:	EC_{50} (72 h) = 13.5 mg/L , NOEC < 4 mg/L
Analytical monitoring:	Yes[x] No[ ]
Method:	OECD Guideline 201
GLP:	Yes[x] No[ ] ? [ ]
Test substance:	Purity > 99.95 %
Remarks:	open-system[ ] ; closed-system[ ]
Reference :	Ministry of Environment (MOE), Korea(2001), The toxicity of Acetanilide to Aquatic plant s (algae) (tested by KRICT)

4.4 TOXICITY TO BACTERIA

A. Bacteria

(a)

Type of test:	Aquatic [x]; Field[ ]; Soil [ ]; Other[ ]
Species:	*A*ctivated sludge
Exposure period:	3 hr
Results:	EC_{50} (3 h)= 2589 mg/L
Analytical monitoring:	Yes[ ] No[ ] ? [x]
Method:	Test for Inhibition of Oxygen Consumption by Activated Sludge, ISO 8192

GLP:	Yes[ ] No[ ] ? [x]
Test substance:	purity
Remarks:	
Reference:	IUCLID (International Uniform chemical Information Database) data set (Acetanilide;103-84-4), June, 1998

(b)

Type of test:	Aquatic [x]; Field [ ] Soil [ ]; Other [ ]
Species:	*Photobacterium phosphoreum* (Bacteria)
Exposure period:	30 min
Results:	EC_{50} (30 min) = 282.4 mg/L
Analytical monitoring:	Yes[ ] No[ ] ? [x]
Method:	other: no description
GLP:	Yes[ ] No[ ] ? [x]
Test substance:	purity
Remarks:	
Reference:	IUCLID (International Uniform chemical Information Database) data set (Acetanilide; 103-84-4), June, 1998

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

No data available

4.6.3 TOXICITY TO OTHER NON-MAMMALIAN TERRESTRIAL SPECIES

No data available

4.7 BIOLOGICAL EFFECTS MONITORING

No data available

4.8 BIOTRANSFORMATION AND KINETICS

No data available

4.9 ADDITIONAL REMARKS

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a) Preferred Result

Type:	LD_0[ ]; LD_{50}[x]; LD_{100}[ ]; LDLo[ ]; Other [ ]
Species/strain	Rat
Value:	2033 mg/kg for male 1893 mg/kg for female 1959 mg/kg for male/female
Discriminating dose :	maximum dose limit 2000 mg/kg bw
Method:	OECD Guideline 401
GLP:	Yes[ ] No[ ] ? [x]
Test substance:	commercial available purity : unknown
Remark:	Symptoms: ptosis, respiratory effects, lethargy, abnormal gait, lacrimation
Reference:	Van den Heuvel, M.J., D.G Clark, R.J. Fielder, P.P. Koundakjian, G.J.A. Oliver, D. Pelling, N.J. TomLinson, A.P. Walker. The International validation of a fixed-dose procedure as an alternative to the classical LD_{50} test. Food Chem. Tox. 28 (7), 469-482 (1990)

(b)

Type:	LD_0[ ]; LD_{50}[ ]; LD_{100}[ ]; LDLo[ ]; Other [x]
Species/strain	Rat
Value:	Harmful (4 lab), Unclassified (21 lab) : EC classification
Discriminating dose :	5, 50, 500, 2000 mg/kg bw
Method:	Fixed-dose method (OECD TG 420)
GLP:	Yes[x] No[ ] ?[ ]
Test substance:	Commercial purity : unknown
Remark:	
Reference:	Van den Heuvel, M.J., D.G Clark, R.J. Fielder, P.P. Koundakjian, G.J.A. Oliver, D. Pelling, N.J. TomLinson, A.P. Walker. The International validation of a fixed-dose procedure as an alternative to the classical LD_{50} test. Food Chem. Tox. 28 (7), 469-482 (1990)

(c)

Type:	LD_0[ ]; LD_{50}[x]; LD_{100}[ ]; LDLo[ ]; Other [ ]
Species/strain	Rat/Wistar
Value:	980 mg/kg bw for male 1350 mg/kg bw for female
Discriminating dose :	unknown
Method:	Other
GLP:	Yes[ ] No[ ] ?[x]
Test substance:	Commercial purity: highest purity available
Remark:	
Reference:	Hasegawa, R., Nakaji, Y., Kurokawa, Y. and Tobe, M. Acute toxicity on 113 environmental chemicals. Sci. Rep. Res. Inst. Tohoku Univ., C, 36, 10-16,1989

(d)

Type:	LD_0[ ]; LD_{50}[x]; LD_{100}[ ]; LDLo[ ]; Other [ ]
Species/strain	Rat/Sprague-Dawley (female)
Value:	1107 (mg/kg)
Discriminating dose :	the dose for next animal was increased or decreased by a factor of 1.3
Method:	Up and Down method (OECD TG 425)
GLP:	Yes[ ] No[ ] ?[x]
Test substance:	Commercial purity : unknown
Remark:	

Reference: Yam, J., Reer, P. J. and Bruce, R.D. Comparison of the up and down method and the fixed-dose procedure for acute oral toxicity testing. Food. Chem. Toxicol. 29, 259-263, 1991

(e)
Type: LD_0[ ]; LD_{50}[ ]; LD_{100}[ ]; LDLo[ ]; Other [x]
Species/strain Rat/Sprague-Dawley (female)
Value: unclassified (EC classification)
Discriminating dose : 5, 50, 500, 2000 mg/kg bw
Method: Fixed-dose method (OECD TG 420)
GLP: Yes[ ] No[ ] ?[x]
Test substance: Commercial purity : unknown
Remark:
Reference: Yam, J., Reer, P. J. and Bruce, R.D. Comparison of the up and down method and the fixed-dose procedure for acute oral toxicity testing. Food. Chem. Toxicol. 29, 259-263, 1991

(f)
Type: LD_0[ ]; LD_{50}[x]; LD_{100}[ ]; LDLo[ ]; Other [ ]
Species/strain Rat
Value: 1700 (mg/kg)
Discriminating dose : unknown
Method: Other
GLP: Yes[ ] No[x] ? [ ]
Test substance: Acetanilide purity : unknown
Remark:
Reference: Hart, E.R. The toxicity and analgetic potency of salicylamide and certain of its derivatives as compared with established analgetic-antipyretic drugs. J. Pharm. Exp. Ther. 89, 205-209 (1947)

(g)
Type: LD_0[ ]; LD_{50}[x]; LD_{100}[ ]; LDLo[ ]; Other [ ]
Species/strain Rat
Value: 800 (mg/kg)
Discriminating dose : Unknown
Method: Unknown
GLP: Yes[ ] No[x] ? [ ]
Test substance: Acetanilide
Remark:
Reference: Smith, P.K. and W.E Hambourger. The ratio of the toxicity of acetanilide to its antipyretic activity in rats. J. Pharm. Exp. Ther. 54, 159-161 (1935)

(h)
Type: LD_0[ ]; LD_{50}[x]; LD_{100}[ ]; LDLo[ ]; Other [ ]
Species/strain Mouse/Albino (QS strain)
Value: 1210 (mg/kg)
Discriminating dose : Unknown
Method: Other
GLP: Yes[ ] No[x] ? [ ]
Test substance: Prepared by standard method or Commercially obtained, purity : unknown
Remark:
Reference: Starmer, G.A. S. McLean, J. Thomas. Analgesic potency and acute toxicity of substituted anilides and benzamides. Tox. Appl. Pharm. 19, 20-28 (1971)

(i)
Type: LD_0[ ]; LD_{50}[ ]; LD_{100}[ ]; LDLo:[x]; Other [ ]
Species/strain Rabbit
Value: 1500 (mg/kg)
Discriminating dose : 550, 600, 700, 1200, 1500, 1600 mg/kg bw
Method: Other
GLP: Yes[ ] No[x] ? [ ]
Test substance: Test substance dissolved in ethanol, in mucilage of acacia
Remark: Symptoms: paralysis; death 4 days after application

Reference: Higgins, J.A. & H.A McGuigan. The influence of caffeine on the effects of acetanilide. J. Pharm. Exp. Ther. 49, 466-478, 1933

(j)
Type: LD_0[ ]; LD_{50}[ ]; LD_{100}[ ]; LDLo [x]; Other [ ]
Species/strain Guinea pig
Value: about 1400 (mg/kg)
Discriminating dose : Unknown
Method: Other
GLP: Yes[ ] No[x] ? [ ]
Test substance: Acetanilide purity : unknown
Remark:
Reference: Munch, J.C. H.J. Pratt, L.M. Acetanilide studies I. Acute toxicity. J. Am. Pharm. Assoc., Sci. Ed. 30, 91-98 (1941)

5.1.2 ACUTE INHALATION TOXICITY

No data available

5.1.3 ACUTE DERMAL TOXICITY

No data available

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a)
Type: LC_0[ ]; LC_{50}[ ]; LC_{100}[ ]; LCLo [ ]; Other [ ]
LD_0[ ]; LD_{50}[x]; LD_{100}[ ]; LDLo [ ]; Other [ ]
Species/strain Rat/Sprague-Dawley (4 female rats/group)
Route of Administration: i.m.[ ]; i.p [x]; i.v. [ ]; infusion [ ]; s.c. [ ]; Other [ ]
Exposure time:
Value: 540 (mg/kg)
Method: Other
GLP: Yes[ ] No[x] ?[ ]
Test substance: Merk acetanilide (recrystallized from water)
Remarks:
Reference: Argus, M.F. M.P. Newell, J.T. Henderson, F.E. Ray. Antipyretic and toxicity studies with acetanilide and o-,m-, and p-chloroacetanilide. J. Am. Pharm. Assoc. 48, 204-207 (1959)

(b)
Type: LC_0[ ]; LC_{50}[ ]; LC_{100}[ ]; LCLo [ ]; Other [ ]
LD_0[ ]; LD_{50}[x]; LD_{100}[ ]; LDLo [ ]; Other [ ]
Species/strain Mouse/C57b1/6
Route of Administration: i.m.[ ]; i.p [x]; i.v. [ ]; infusion [ ]; s.c. [ ]; Other [ ]
Exposure time:
Value: 715 (mg/kg)
Method: Other
GLP: Yes[ ] No[x] ?[ ]
Test substance: Merk acetanilide (recrystallized from water)
Remarks:
Reference: Argus, M.F. M.P. Newell, J.T. Henderson, F.E. Ray. Antipyretic and toxicity studies with acetanilide and o-,m-, and p-chloroacetanilide. J. Am. Pharm. Assoc. 48, 204-207 (1959)

(c)
Type: LC_0[ ]; LC_{50}[ ]; LC_{100}[ ]; LCLo [ ]; Other [ ]
LD_0[ ]; LD_{50}[ ]; LD_{100}[ ]; LDLo [x]; Other [ ]
Species/strain Cat
Route of Administration: i.m.[ ]; i.p [ ]; i.v. [x]; infusion [ ]; s.c. [ ]; Other [ ]
Exposure time:
Value: 8 mg/kg
Method:

GLP: Yes[ ] No[x] ?[ ]
Test substance:
Remarks:
Reference: Munch, J.C. H.J. Pratt, L.M. Acetanilide studies I. Acute toxicity. J. Am. Pharm. Assoc. Sci. Ed. 30, 91-98 (1941)

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION

(a) Preferred Result

Species/strain: Rabbit
Results: Highly corrosive [ ] ; corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [x]
Classification: Highly corrosive (cause severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [ ]; Not irritating [x]
Method: OECD Guideline 404 "Acute Dermal Irritation /Corrosion" , 1990
GLP: Yes[x] No[ ] ?[ ]
Test substance: Purity 97.8 %
Remarks: Labeling not required
Reference: Hoechst AG, Unpublished reports. Ber. 90,1295 (1991)

5.2.2 EYE IRRITATION/CORROSION

(a) Preferred Result

Species/strain: Rabbit
Results: Highly corrosive [ ] ; corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [x]; Not irritating [ ]
Classification: Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes [ ]
Method: OECD Guide line 405 "Acute Eye Irritation/Corrosion" , 1990
GLP: Yes [x] No [ ] ? [ ]
Test substance: Purity 97.8 %
Remarks: Labelling not required
Reference: Hoechst AG, Unpublished reports. Ber. 90, 1336 (1990)

5.3 SKIN SENSITIZATION

no data available

5.4 REPEATED DOSE TOXICITY

(a) Preferred Result

Species/strains: Rat / Sprague-Dawley
Sex: Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of administration: Oral (gavage)
Exposure period: male : 30 days, female : from 2 weeks before mating to the day 3 of lactation
Frequency of treatment: Once a day
Post exposure observation period: 1 day
Dose: 0, 22, 67, 200, 600 mg/kg/day
Control group: Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [x]; Historical [ ]
NOAEL: < 22 mg/kg bw/day for both sexes
LOAEL: 22 mg/kg bw/day for both sexes
Results: Male : The mean body weight gains at day 0 and 4 of lactation of 600 mg/kg females were significantly lower than those of controls. The mean food consumption of 67, 200, and 600 mg/kg males and females was significantly reduced at day 1. The incidence rate of decreased locomotor activity (600, 200 mg/kg), reddish tear (600 mg/kg), salivation (600, 200 mg/kg) and cyanosis (600, 67 mg/kg) were significantly increased in male rats. In female, cyanosis and decreasing locomotor

activity were found during premating period and cyanosis were found during pregnancy and lactation period at 600 mg/kg exposure group. In males there was significant decrease in HGB, HCT and MCHC value at all dose group hyperplasia of spleen and bone marrow, hematological changes. At 600 mg/kg, those values of AST, ALT, BUN, T-BIL, ALB, Calcium and A/G ratio in males were increased significantly. There was also significant increase in BUN, T-BIL and decrease in Na at 200 mg/kg. Four females at 600 mg/kg died at the day 21, 22 and 23 of pregnancy and the day 4 of lactation. Increased absolute/relative spleen weight (at 67, 200, 600 mg/kg), relative liver weight (at 200, 600 mg/kg) and absolute/relative spleen weight (at 600 mg/kg) were noted in males. Decreased thymus weight at 200 mg/kg (absolute) and 600 mg/kg (absolute and relative), increase in relative brain wt (at 200, 600 mg/kg), kidney (200 mg/kg), absolute/relative ovary and spleen wt (at 600 mg/kg), relative heart wt (600 mg/kg) were noted in females. There was increase in hyperplasia/red pulp of spleen and hyperplasia/bone marrow of fumer at 22, 67, 200 and 600 mg/kg in both sexes.

Method: OECD TG 422
GLP: Yes [x]; No [ ]; ? [ ]
Test substance: Source : Aldrich Chemical Co. purity ; 97 %
Reference: Ministry of Environment (MOE), Korea (2001), Combined Repeated Dose Toxicity with the Reproduction /Developmental Toxicity Screening Testing of Acetanilide in Rats (test No.G00154, tested by KRICT)

(b)
Species/strains: Rat / Sprague-Dawley
Sex: Female [ ]; Male [x]; Male/Female [ ]; No data [ ]
Route of administration: Oral feed
Exposure period: application of acetanilide in food for 16 consecutive weeks, then basal food for 8 weeks, then returning to experimental diet for several 4-week periods, with a week between each period during which rats were fed basal diet; the study was terminated after 27 or 41 weeks
Frequency of treatment: Daily
Post exposure observation period:
Dose: 0.8 % in food = about 533 mg/kg b.w
Control group: Yes [x]; No [ ]; No data [ ]
Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL: < 0.8 % (533 mg/kg b.w)
LOAEL:
Results: Anemia splenomegaly; dark discoloration of livers
Method: Other
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Not detailed
Remarks: A significant correlation showed between the spleen size and the HGB (r= -0.833, P < 0.01). Acetanilide inhibits azo dye carcinogenesis in the liver of the rat.
Reference: Blunck, J. M. and Crowther, C. E. Enhancement of azo dye carcinogenesis by ietary sodium sulphate. Europ. J. Cancer. 11, 23-31, 1975

(c)
Species/strains: Rat/Albino
Sex: Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of administration: oral (gavage)
Exposure period: 4 weeks
Frequency of treatment: Once a day, 6 days/week
Post exposure observation period: One week
Dose: 0, 135, 540 mg/kg /day
Control group: Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL: 540 mg/kg/day
LOAEL: > 540 mg/kg/day
Results: No change in blood
Method: Other
GLP: Yes [ ]; No [x]; ? [ ]

Test substance: U.S.P quality
Remarks: One week after dosing was discontinued, the amounts of methemoglobin and sulfhemoglobin were almost the same as in controls. Small amount of sulfhemoglobin remained in most cases.
Reference: Smith, P.K. Change in blood pigments associated with the prolonged administration of large doses of acetanilide and related compounds. J. Pharm. Exp. Ther. 70, 171-178 (1940)

(d)
Species/strains: Monkey / Mangabey
Sex: Female [ ]; Male [ ]; Male/Female [ ]; No data [x]
Route of administration: oral
Exposure period: I: 108 days; II: 95 days; III: 104 days
Frequency of treatment: Once daily, 6 days/week
Post exposure observation period:
Dose: I: 50 mg/kg bw; II: 135 mg/kg bw; III: 540 mg/kg bw/day
Control group: Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL: 50 mg/kg bw/day
LOAEL: 135 mg/kg bw/day
Results: Moderate amount of methemoglobin and sulfhemoglobin were formed.
Method: 2 animals/group were tested
GLP: Yes [ ]; No [x]; ? [ ]
Test substance:
Reference: Smith, P.K. Change in blood pigments associated with the prolonged administration of large doses of acetanilide and related compounds. J. Pharm. Exp. Ther. 70, 171-178 (1940)

(e)
Species/strains: Cat
Sex: Female [ ]; Male [ ]; Male/Female [ ]; No data [x]
Route of administration: Not specified
Exposure period: 3 weeks/ another 5 weeks/34 days
Frequency of treatment: Once a day
Post exposure observation period:
Dose: 30 mg/kg /day were applied for 3 weeks, then the dose was doubled (60 mg/kg) for another 5 weeks and then raised to 125 mg/kg/day for 34 days (death of the cat) (no further information available)
Control group: Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL: 30 mg/kg/day
LOAEL:
Results: 30 mg/kg /day: no toxic effect;
60 mg/kg/day: slight weight loss;
125 mg/kg bw/day: decline in weight;
extensive hemorrhage in the kidneys, mottled livers, death at d 34 of the application
Method:
GLP: Yes [ ]; No [x]; ? [ ]
Test substance:
Reference: Dunker, M.F.W. & Thompson, M.R. Toxicity and antipyretic properties of some halogenated acetanilids. J. Am. Pharm. Assoc. 28, 70-73 (1939)

5. 5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

(a) Preferred Result
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 97, TA 98, TA 100, TA 1535
Concentration: 5 doses (max. dose of 10 mg/plate)
Metabolic activation: With [ ]; Without [ ]; With and Without [x]; No data [ ]

Results:
Cytotoxicity conc: With metabolic activation : no data
Without metabolic activation : no data
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation :	[ ]	[ ]	[x]
Without metabolic activation :	[ ]	[ ]	[x]

Method: Other(preincubation method)
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Source : Aldirch Chem. Purity : 97 %
Remarks:
Reference: Zeiger, E. B. Anderson, S. Haworth, T. Lawlor, K. Mortelmans. Salmonella mutagenicity tests:IV. Results form the testing of 300 chemicals. Env. Mol. Mutag. Vol.11/12, 1-19 (1988)

(b)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA100, TA98
Concentration: 0.1 mg/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [x]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : not observed
Without metabolic activation : not observed
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation :	[ ]	[ ]	[x]
Without metabolic activation :	[ ]	[ ]	[x]

Method: Other (Ames 1975)
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Source : Wako Pure Chemical Ind.
Remarks: preincubation metaboloic incubation : Rat liver, S-9, PCB
Reference: Kuboyama, N. and A. Fujii. Mutagenicity of analgesics, their derivatives, and anti-inflammatory drugs with S-9 mix of several animal species; J. Nihon Univ. Sch. Dent. 34 (3):183-195, 1992

(c)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 98
Concentration: 536.9 nmoles/plate
Metabolic activation: With [x]; Without [ ]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: not specified
Precipitation conc: not stated
Genotoxic effects:

	+	?	-
With metabolic activation :	[ ]	[ ]	[x]
Without metabolic activation :	[ ]	[ ]	[ ]

Method: Other (Ames 1983)
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Source : Nakarai Chemical Co. Ltd. (guaranteed grade)
Remarks: Preincubation method according to Maron, D.M. & Ames, B.N., Mutat. Res. 113, 173-215 (1983)
Reference: Ogawa, S. T. Hirayama, Y. Fujioka, S. Ozasa, M. Tokuda, K Hirai, S. Fukui. Mutagenicity modulating effect of quercetin on aromatic amines and acetamides. Mutation Research 192, 37-46 (1987)

(d)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 1538
Concentration: 10 mg/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [x]; No data [ ]
Results:
Cytotoxicity conc: No data
Precipitation conc: Not specified

Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [x]
Without metabolic activation : [ ] [ ] [x]
Method: Other(Ames 1973)
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Source : Aldrich Chemical Co.
Remarks: Method : According to Ames, B.N. et al., Proc. Nat. Acad. Sci. USA 70, 782-786, 1973
Reference:
1. Goldman, P. L.A. Wheeler, J.H. Carter, J.A. Ingelfinger, F.B. Soderberg. Properties of the Ames salmonella mutants lodged in the gastrointestinal tract of gnotobiotic rats. Am. J. Clin. Nutr. 30, 1921-1926 (1977)
2. Wheeler, L.A., J. H. Carter, F.B. Soderberg, and P. Goldman. Association of salmonella mutants with germfree rats: Site specific model to detect carcinogens as mutagens. Proc. Natl. Acad. Sci. USA 72(11), 4607-4611, 1975

(e)
Type: Bacterial reverse mutation assay
System of testing: *Bacillus subtilis* TKJ5211
Concentration: 50, 500 ug/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [x]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : not observed
Without metabolic activation : not observed
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [x]
Without metabolic activation : [ ] [ ] [x]
Method: Backward mutation of histidin auxotrophic mutants
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: source : commercial
Remarks:
Reference: Tanooka, H. Development and Applications of *Bacillus subtilis* Test Systems for Mutagens, involving DNA-Repair Deficiency and Suppressible Auxotrophic Mutations. Mutation Research. 42, 19-32, 1977

(f)
Type: *Bacillus subtilis* recombination assay
System of testing: *Bacillus subtilis* HLL 3 g (wild), HJ-15
Concentration: 50, 500 µg/plate
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : not observed
Without metabolic activation : not observed
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [ ] [ ] [x]
Method: Other (Kada 1972)
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: source : commercial
Remarks: The difference in width of the inhibition zones produced with HLL 3g and HJ–15 was taken as an indication of the excision and/or recombination repair dependent DNA damage by the chemical
Reference: Tanooka, H. Development and Applications of *Bacillus Subtilis* Test Systems for utagens, involving DNA-Repair Deficiency and Suppressible Auxotrophic Mutations. Mutation Research. 42, 19-32, 1977

B. NON-BACTERIAL TEST

(a)
Type: Mammalian Chromosomal aberration test
System of testing: Species/Strains: Chinese hamster fibroblast cells
Concentration: The max. effective dose 1.60 mg/mL

Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : not observed
Without metabolic activation : not observed
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation :	[ ]	[ ]	[ ]
Without metabolic activation :	[ ]	[ ]	[x]

Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: supplied from the project team supported by Ministry of Health & Welfare, Japan.
Remarks: Different doses were exposed directly to the cells and chromosome preparation was made 24h and 48h after treatment.
Reference: Ishidate, M. & Odashima, S. Chromosome tests with 134 compounds on Chinese hamster fibroblast cells *in vitro* – A screening for chemical carcinogenes. Mutation Research. 48, 337-354 (1977)

(b)
Type: Mammalian Chromosomal aberration test
System of testing: Chinese hamster ovary cells (CHO-K1)
Concentration: 0, 10, 50, 100 µg/mL
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : not specified
Without metabolic activation : not specified
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation :	[ ]	[ ]	[ ]
Without metabolic activation :	[ ]	[ ]	[x]

Method: other
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: source : commercial
Remarks:
Reference: Sasaki M., Yoshida, S. and Hiraga K. Additional effect of acetaminophen on the mutagenicity and clastogenicity of *N*-methyl-*N*' -nitro-*N*-nitrosoguanidine in cultured Chinese hamster CHO-Kl cells. Mutation Research. 122, 367-372, 1983 (1980)

(c)
Type: Sister-chromatid-exchange
System of testing: Chinese hamster cells (CHO-K1)
Concentration: 25, 50, 75, 100, 200, 400, 800, 1600 µg/mL
Metabolic activation: With [ ]; Without [ ]; With and Without [x]; No data [ ]
Results:
Cytotoxicity conc: not specified
Precipitation conc: not stated
Genotoxic effects:

	+	?	-
With metabolic activation :	[ ]	[ ]	[x]
Without metabolic activation :	[ ]	[ ]	[x]

Method: Other
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Source : commercial
Remarks:
Reference: Yoshida, S., S. Nawai, and K. Hiraga. Cytogenetic Studies of Acetaminophen and Its Related Compounds. Ann. Rep. Tokyo Metr. Res. Lab. Pub. Health 31(2), 102-108, 1980

5. 6 GENETIC TOXICITY IN VIVO

(a) Preferred Result

Type: Micronucleus test
Species/Strains: Mouse / ICR
Sex: Female [ ]; Male [x]; Male/Female [ ]; No data [ ]
Route of Administration: i.p.
Exposure period: single dose
Doses: 0, 500, 1000, 1500 mg/kg bw
Results: Negative
Method: OECD TG 474
GLP: Yes [x]; No [ ]; ? [ ]
Test substance: Source : Aldrich Chemical Co. purity : > 99.90 %
Remarks:
Reference: Ministry of Environment (MOE), Korea (2001) Micronucleus test of acetanilide in Mouse (Test No.257, tested by LGCI toxicology center)

(b)
Type: Cytogenetic assay
Species/Strains: Mouse / CD-1
Sex: Female [ ]; Male [ ]; Male/Female [ ]; No data [x]
Route of Administration: i.p. and oral
Exposure period: One application
Doses: 300, 600, 1200 mg/kg to i.p./ 600, 1200, 1800 mg/kg to oral
Results: Negative (no significant increase of aberration in the cells analyzed)
Method: Duration of treatment: 6 or 24 hours (animals were killed for chromosome examination 6 or 24 hours after substance application)
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Commercial
Remarks:
Reference: Yoshida, S., Nawai S., Hirage K. Cytogenetic studies of acetaminophen and its related compounds. Ann. Rep. Tokyo Metr. Res. Lab. P. H. 31-32, 102-108 (1980)

(c)
Type: Micronucleus test
Species/Strains: Mouse / Swiss SJL
Sex: Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration: i.p.
Exposure period: single dose
Doses: 0, 5, 50, 100, 200 and 400 mg/kg
Results: Positive
Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Source : commercial (purified by recrystallization)
Remarks: micronucleated polychromatic erythrocyte (MNPCE) frequency in bone marrow cells

Dose, mg/kg	MNPCE % ± SEM	% increase over control	Micronucleus inducing potency
0	2.75 ± 0.41		
5	2.00 ± 0.57		
50	5.38 ± 0.48	95.6	258.5
100	8.63 ± 0.51	213.8	292.9
200	3.75 ± 0.28	36.4	24.9
400	4.00 ± 0.41	45.5	15.6

Reference: Sicardi, S. M., Martiarena J.L., Iglesias M.T. Mutagenic and analgesic activities of aniline derivatives. J. Pharm. Sci. 80 (8),761-764 (1991)

(d)

Type:	Cytogenetic assay
Species/Strains:	Rat / strain: LE
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No data [x]
Route of Administration:	i.p.
Exposure period:	One application
Doses:	0.01-10 mM/kg = 1.35-1351.6 mg/kg (no other information)
Results:	Positive (significantly increased number of chromosomal aberrations in bone marrow cells)
Method:	
GLP:	Yes [ ]; No [ ]; ? [x]
Test substance:	
Remarks:	Duration of treatment: 6 hours (animals were killed for chromosome examination 6 hours after substance application); Acetanilide was suspended in saline containing pluronic F68; 175 metaphase bone marrow cells were examined for occurrence of breaks and gaps.
Reference:	Shimazu, H., Shiraishi N., Akematsu T., Ueda N., Sugiyama T. Carcinogenicity screening tests on induction of chromosomal aberrations in rat bone marrow cell in vivo. Mutation Research. 38, 347a (1976)

(e)

Type:	Host-mediated-assay
Species/Strains:	Rat / Sprague-Dawley
Sex:	Female [ ]; Male [x]; Male/Female [ ]; No data [ ]
Route of Administration:	Oral
Exposure period:	5 days
Doses:	10 mg/day
Results:	Negative (no increase of the number of revertants in the feces)
Method:	
GLP:	Yes [ ]; No [ ]; ? [x]
Test substance:	
Remarks:	Indicator organism: *Salmonella typhimurium* TA 1538, lodged into the gastrointestinal tract of otherwise germ-free rats
Reference:	Goldman, P. L.A. Wheeler, J.H. Carter, J.A. Ingelfinger, F.B. Soderberg. Properties of the Ames salmonella mutants lodged in the gastrointestinal tract of gnotobiotic rats. Am. J. Clin. Nutr. 30, 1921-1926 (1977)

5. 7 CARCINOGENICITY

(a)

Species/Strains:	Mouse / ABC-A
Sex:	Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration:	Oral feed
Exposure period:	rd (0.5, 1.0 %) and 4th (0.1 %) generation study
Frequency of treatment:	Daily
Post exposure observation period:	
Doses:	0.1, 0.5, 1.0 % in food = ca. 125, 625, 2000 mg/kg /bw
Control group:	Yes [ ]; No [ ]; No dat a [x]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	No induction of mammary carcinoma
Method:	
GLP:	Yes [ ]; No [x]; ? [ ]
Test substance:	
Remarks:	4 generation study with strain of ABC-A; no analysis of tumor types besides the mammary gland.
Reference:	Wright, H.N. Chronic Toxicity Studies of Analgesic and Antipyretic Drugs and Congeners. Tox. and Applied Pharmacology. 11, 280-292, 1967

(b)

Species/Strains:	Rat / Sprague-Dawley
Sex:	Female [ ]; Male [x]; Male/Female [ ]; No data [ ]
Route of Administration:	Oral feed

Exposure period: see method
Frequency of treatment: Daily
Post exposure observation period:
Doses: 0.8 % in food = ca. 533 mg/kg/day
Control group: Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results: No hyperplasic or dysplastic changes were observed
Method: Application of acetanilide in food for 16 consecutive weeks, then basal food for 8 weeks, then returning to experimental diet for several 4-week periods, with a week between each period with basal diet feeding; the study was terminated after 27 or 41 weeks.
GLP: Yes [ ]; No [ ]; ? [x]
Test substance:
Remarks: The aim of the study was to investigate the influence of acetanilide or sodium sulphate on 3-methyl-4-dimethylamino- azobenzene carcinogenicity; acetanilide group served as one control group
Reference: Blunck, J. M. and Crowther, C. E. Enhancement of azo dye carcinogenesis by dietary sodium sulphate. Europ. J. Cancer 11, 23-31, 1975

(c)
Species/Strains: Rat / Fischer F344
Sex: Female [ ]; Male [x]; Male/Female [ ]; No data [ ]
Route of Administration: Oral feed
Exposure period: 16 weeks
Frequency of treatment: Daily
Post exposure observation period: 10 weeks
Doses: 8000 ppm = 400 mg/kg /bw in food
Control group: Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results: No induction of liver tumors
Method:
GLP: Yes [ ]; No [x]; ? [ ]
Test substance:
Remarks: The aim of the study was to investigate the influence of acetanilide and other substances on *N*-2-fluorenylacetamide carcinogenicity. The addition of acetanilide in 44 times molar excess to diet protested rats against liver tumor induction by *N*-2-fluorenylacetamide.
Reference: Yamamoto, R.S., Frenkel H.H, Weisburger. Effects of isomers of acetotoluidide and aminobenzoic acid on the toxicity and carcinogenicity of *N*-2-fluorenylacetamide. Tox. Appl. Pharm., 17, 98-106 (1970)

5. 8 TOXICITY TO REPRODUCTION

(a) Preferred Result
Type: Fertility [ ]; One generation study [x]; Two generation study [ ]; Other [ ]
Species/Strains: Rat / Sprague-Dawley
Sex: Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration: Oral (gavage)
Exposure period: 30 days for male, 39-50 days for female
Frequency of treatment: once a day
Post exposure observation period: 1 day
Premating exposure period: 2 weeks for Male and female
Duration of test: 51 days
Doses: 0, 22, 67, 200, 600 mg/kg/day
Control group: Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [x]; Historical [ ]
NOAEL parental : = 600 mg/kg/day
NOAEL F1 Offspring: = 200 mg/kg/day
Results: No significant differences appeared between the treatment groups and control group in precoital time, copulation rate, impregnation rate and pregnancy rate. Both sexes of F1 showed significant decrease in survival rate at 600 mg/kg.
Method: OECD TG 422

GLP: Yes [x]; No [ ]; ? [ ]
Test substance: Source : Aldrich Chemical Co, purity 97 %
Remarks:
Reference: Ministry of Environment (MOE), Korea (2001), Combined Repeated Dose Toxicity with the Reproduction /Developmental Toxicity Screening Testing of Acetanilide in Rats (test No.G00154, tested by KRICT)

(b)
Type: Fertility [ ]; One generation study [ ]; Two generation study [ ]; Other [x]
Species/Strains: Mouse / strain ABC-A (inbred)
Sex: Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration: Oral feed
Exposure period: Not specified
Frequency of treatment: continuously in diet
Post exposure observation period:
Premating exposure period: Not specified
Duration of test:
Doses: 0.1, 0.5, 1.0 % in diet = ca. 125, 625, 2000 mg/kg bw/day
Control group: Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOEL parental : =
NOEL F1 Offspring: =
NOEL F2 Offspring:
Results: Depressant effect on reproduction and litter raising; 0.1 %: Significant reduction of survival in the 3rd and 4th generation (insufficient number of offsprings were born to continue the 5th generation); 0.5; 1 %: Reduction of survival (significant only in the 2nd generation); retardation of growth; deterioration of condition; methemoglobin formation; cyanosis; it was only possible to carry the 0.5 and 1.0 % concentration through 3 generations because of the reduced reproductive capacity and the small number of pups raised (0.5 %: 53.6 % and 1.0 %: 20 % of the litters born were raised); at 1.0 % only 15 pups raised in the fourth generation (60 % of the females had no litters), so it was not possible to continue the study through the 5th generation.
Method:
GLP: Yes [ ]; No [x]; ? [ ]
Test substance:
Remarks:
Reference: Wright, H.N. Chronic Toxicity Studies of Analgesic and Antipyretic Drugs and Congeners. Tox. and Applied Pharmacology. 11, 280-292, 1967

5. 9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a) Preferred Result
Species/Strains: Rat / Sprague-Dawley
Sex: Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration: Oral (gavage)
Exposure period: 30 days for male, 39-50 days for female
Frequency of treatment: once a day
Post exposure observation period: 1 days
Premating exposure period:2 weeks for Male and female
Duration of test: 51 days
Doses: 0, 22, 67, 200, 600 mg/kg/day
Control group: Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [x]; Historical [ ]
NOAEL For developmental: 67 mg/kg/day
Results: In the 600 mg/kg exposure group the survivals at birth showed increase in cyanosis and icterus. The body weight of pups gain on the day 4 after birth decreased at 200 mg/kg. No significant differences appeared between the treatment and control group in any other observation.
Method: OECD TG 422
GLP: Yes [ ]; No [x]; ? [ ]
Test substance: Source : Aldrich Chemical Co, purity: 97 %

Remarks:
Reference: Ministry of Environment (MOE), Korea (2001), Combined Repeated Dose Toxicity with the Reproduction /Developmental Toxicity Screening Testing of Acetanilide in Rats (test No.G00154, tested by, KRICT)

(b)
Species/strain: *Drosophila* / Oregon R, Canton S_{109} and Canton S.
Sex: Female [ ]; male [ ]; Male/Female [ ]; No data [ ]
Route of administration:
Duration of the test:
Exposure period: 24 hrs
Frequency of treatment:
Doses: 1 mM
Control group: Yes [ ]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOEL Maternal Toxicity:
NOEL Teratogenecity
Results: Non teratogen
GLP: Yes [ ]; No [ ]; ?[x]
Test substance:
Remarks: The possible teratogenic effect of acetanilide was tested *in vitro* using Drosophila embryonic cell cultures. Acetanilide showed no teratogenic effect in this assay
Reference: Vardiabasis, N.B., Teplitz, R.L., Chernoff, G.F. and Seecof, R.L.; Detection of Teratogens in the *Drosophila* Embryonic Cell Culture Test. Teratology 28, 109-122, 1983

5. 10 OTHER RELEVANT INFORMATION

A. Specific toxicity, Neurotoxicity, immunotoxicity etc.

(a)
Type: Neurotoxicity
Results: Acetanilide (500, 700, 900, 1100 mg/kg) was tested in a modified acute toxicity test in female Sprague-Dawley rats (6 rats/ dose). General indices of toxicity, i.e. body weight gain, food and water consumption and body temperature were recorded at regular intervals, motor activity was monitored; neurobehavioral dysfunctions were assessed; routine hematology was done on 4th day after application. All measured toxic signs were scored in relation to the control group. Combined calculation of dose and item specific individual scores results in the so called Tox-score classification. Acetanilide was classified 3 in a classification scheme ranging from 1 (highly toxic) to 5 (low toxicity).
Remarks:
Reference: Tamborini, P. H. Sigg, G. Zbinden. Quantitative analysis of rat activity in the home cage by infrared monitoring. Application to the acute toxicity of acetanilide and phenylmercuric acetate. Arch. Tox. 63, 85-96 (1989)

(b)
Type: Toxicity in Blood
Results: Acetanilide was administered to various experimental animal species by stomach tube and to human subjects in tablets. The rabbit and the monkey form virtually no hemoglobin after acetanilide application. With regard to sensitivity to hemoglobin formation from the substance, man is slightly more than half as sensitive as the cat, the dog half as sensitive as man, and the rat one-sixth as sensitive as the dog. The curve obtained by plotting methemoglobin against dose of acetanilide is S-shaped. Methemoglobin is formed only when a certain minimal dose is exceeded and there is an upper limit to the formation irrespective of dose. Administration of amounts beyond that producing maximum concentration of methemoglobin only increases the length of time the methemoglobin persists.
Remarks:
Reference: Lester, D., J. Formation of methemoglobin. I. Species differences with acetanilide and acetophenetidine. Pharm. Exp. Ther. 77, 154-159 (1943)

(c)

Type: *in vitro* Hepatotoxicity

Results: Hepatocytes from adult male Wistar rats were incubated with acetanilide. The dose that caused 50% inhibition of protein synthesis after 1 hour was 6.5 mM (878.5 mg/L).

Remarks:

Reference: Gwynn, J., Fry J.R, Bridges J.W. The effect of paracetamol and other foreign compounds on protein synthesis in isolated adult rat hepatocytes. Biochemical Society Transactions - 579th Meeting, London, Vol. 7, 117-119 (1979)

(d)

Type: Effects on blood, circulation and respiration in dogs

Results: Dogs were treated with solvents (2 % acetic acid; 80 %, 50 %, 35 % ethanol) and increasing doses of acetanilide (35 and 50 ccm of 0.2 % acetanilide; 25 and 50 ccm of 0.8 % acetanilide; 12 and 25 ccm of 10 % acetanilide). Formation of Met-Hb could not be observed. Low doses resulted in a reversible drop of blood pressure without pathological electrocardiographic findings. High doses caused a marked drop of blood pressure as a result of cardiac insufficiency. The conduction system of auricles and ventricles was impaired, primarily right and left bundle branch blocks were described, followed by lethal ventricular fibrillation in the highest dose. Aqueous solutions (0.5 %) of acetanilide up to 90 cc did not show any influence on the respiration (a total of 4 dogs was used). Effects of higher doses tested in ethanol could not be discriminated from results seen after ethanol alone: respiratory stimulation was followed by periods of apnea, respiratory depression and death (dose dependent)

Remarks:

Reference: Young, A.G. & Wilson, J.A. Toxicological studies of anilin and anilin compounds. III. Toxicological and hematological studies of acetanilide poisoning. J. Pharm. Exp. Ther. 27, 133-148 (1926)

(e)

Type: Glutathione depeletion

Results: Liver microsomes glutathione depletion was not observed

Remarks: Mouse/CRJ:ICR, Rat/Wistar, Guinea pig/Hartley and Rabbit /New Zealand

Reference: Aikawa K., Satoh T., Kobayashi K., Kitagawa H. Glutathione depletion by aniline analogs in vitro associated with liver microsomal cytochrome P-450; Jpn. J. Pharmacol. 28 (5), 699, 1978.

B. Toxicodynamics, toxicokinetics

(a)

Type: Excretion

Results: Plasma elimination rates of phenacetin, acetanilide & theophylline have been determined in 32 healthy subjects. The plasma half-lives and metabolic clearance rates of the three drugs were correlated with the inducibilities of aryl hydrocarbon hydroxylase (AHH) in mitogen-stimulated lymphocytes. Plasma half-lives of acetanilide in 25 subjects is 191±27.8 min. Metabolic clearance rate is 14.1 ± 2.8 liter/h.

Remarks: 10 mg/kg, single dose. Blood Sample.

Reference: Kellermann, G., M.L. Kellermann. Benzo (a) pyrene Metabolism and Plasma Elimination Rates of Phenacetin, Acetanilide and Theophylline in Man. Pharmacology (Basel) 17 (4), 191, 1978

(b)

Type: Metabolism in rabbits

Results: Acetanilide (oral or i.v. administration of 300 mg) is mainly converted to 4-hydroxyacetanilide which is excreted as conjugates with glucuronic acid and sulfuric acid.

Remarks: Formation of 4-hydroxyacetanilide was found to be not a simple first order process but it could be well expressed by Michaelis-Menten equation

Reference: Shibasaki, J., T. Koizumi, T. Tanaka. Drug Absorption, Metabolism, and Excretion. I. Some pharmacokinetic Aspect of Metabolism of Acetanilide and 4-Hydroxyacetanilide. Chem. Pharm. Bull. 16, 1661-1673,1968

(c)
Type: Metabolism
Results: Beside the glucuronic acid and sulphuric acid conjugates of p-hydroxyacetanilide, two other metabolites were excreted in urine: 3-(5-acetamido-2-hydroxyphenyl)thio-N-acetylalanine (7-10 % of applied dose) and 3-(5-acetamidophenyl)thio)-N-acetylalanine (1-3 % of applied dose). Their mode of formation may involve an intermediate epoxide.
Remarks:
Reference: Grantham, P.H., L.C. Weisburger, H.M. Fales, E.A. Sokoloski, J.H. Weisburger. Identification of New Water-Soluble Metabolites of Acetanilide. Xenobiotica 4, 69-76,1974

(d)
Type: Metabolism *in vitro*
Results: The metabolism of acetanilide with hepatic microsomal preparations was investigated in Sprague-Dawley male rats. The major biotransformation yielded 4 hydroxyacetanilide (> 94 % of total phenols) with 2-hydroxy- and 3-hydroxy-acetanilide as minor products.
Remarks:
Reference: Selander, H.G., D.M.Jerina, J.W.Daly. Metabolism of Acetanilide with Hepatic Microsomes and Reconstituted cytochrome Monoxygenase systems. Arch. Biochem. Biophys. 164, 241-246,1974

(e)
Type: Metabolism
Results: In a rat metabolism study with labelled acetanilide chronic intake (0.8 % in food, 4 weeks), one day feeding (0.8 %) and single injection (i.p. 200 mg/kg) were compared. There was an increase in the excretion of glucuronic acid conjugates in urine (4.6 % of single i.p. dose and 6 % of dose after 1 day feeding) and a concominant decrease or levelling off of sulphuric acid ester conjugates (70 % of dose at 24 h, 40 % of dose after 1 week feeding). Blood levels of radioactivity were 11-fold higher after 1 week feeding than after single dose and the live contained 15 times more radioactivity after 4 weeks feeding than after single dose. After 4 weeks feeding there was a greater binding in the liver to DNA (180-fold), RNA (15-fold) and proteins (33-fold) than after a single i.p. injection. Radioactivity from labelled acetanilide was also bound to serum and erythrocyte proteins.
Remarks :
Remarks: Grantham, P.H., T. Matsushima, L. Mohan, E.K. Weisburger, J.T. Weisburger. Changes in the Metabolism of Labelled Acetanilide and Binding of Isotope to Serum and Liver Macromolecules during Chronic Administration. Xenobiotica 2, 551-565,1972

(f)
Type: Metabolism *in vitro*
Results: In rat liver microsomes, oxidative metabolism of acetanilide is accompanied by NADPH-dependent lipid peroxidation and the breakdown of cytochrome P-450. The addition of EDTA to the incubations blocked lipid peroxidation, as measured by malondialdehyde formation, and the destruction of cytochrome P-450.
Remarks:
Reference: Jacobson, M., W. Levin, A.Y.H. Lu, A.H. Conney, R. Kuntzman. The rate of pentobarbital and Acetanilide metabolism by liver microsomes: A Function of Lipid Peroxidation and degradation of cytochrome p-410 Heme. Drug Metab. Dispos. 1, 766-774,1973

(g)
Type: Metabolism *in vitro*
Results: The metabolism of acetanilide was investigated in vitro in microsomes, which were prepared from the livers of mice pretreated without or with an inducer

(sodium phenobarbital, 3-methylcholanthrene, isosafrole or n-butylbenzodioxole for 3 days). The use of radiolabelled acetanilide was combined with an extraction procedure that selectively separates the parent compound from the phenolic compounds. Beside 4-hydroxy-acetanilide as the primary metabolite also the 3-hydroxy- and the 2-hydroxyacetanilide were detected.

Remarks:

Reference: Lewandowski, M., Y.C. Chui, P. Levi, E. Hodson. Acetanilide 4-hydroxylase and acetanilide 2-hydroxylase activity in hepatic microsomes from induced mice. Tox. Lett. 55, 223-231,1991

(h)

Type: Metabolism *in vitro*

Results: An in vitro study was conducted to characterize the enzymes involved in the hydrolysis of acetanilide in rat liver microsomes. The optimum pH ranged between 8 and 9.5. The activities of enzymes hydrolyzing acetanilide were found to be unaffected by Mg++, Ca++ and EDTA. However, by employing high concentrations of metals ($CuSO_4$, $AgNO_3$) and selective inhibitors (p-CMB, SKF-525A), it was possible to dissociate the enzymes. The activities of acetanilide N-deacetylase were evaluated in the homogenates of various rat organs. The results show a distinct organ distribution of the hydrolases. There were also species variations in the rate of hydrolysis at acetanilide when investigated in the liver homogenates of rat, mouse, cat, and dog.

Remarks:

Reference: Ali, B, E.C. James, S. Kaur, S.J. BrumLeve, S.S. Parmar. Evidence for distinct Carboxylesterases/amidases for hydrolytic metabolism of procaine, acetanilide and 2-acetylaminofluoren.Proc. West. Pharmacol. Soc. 27, 259-263,1984

(i)

Type: Metabolism, pharmacokinetics

Results: In rabbits, the elimination of acetanilide from the blood was compared, after i.v. injection of acetanilide (300 mg) alone, with the elimination after giving 200 mg N-phenylurea and 3 hours later 200 mg acetanilide. The elimination rate of acetanilide from the blood was affected and reduced by the simultaneous administration of N-phenylurea. The hydroxylation process of these drugs was mutually inhibited.

Remarks:

Reference: Koizumi, T., M. Ueda, M. Kakemi, J. Shibasaki, S. Matsumoto, R. Shinagawa. Mutual Inhibition in hydroxylation of Acetanilide and N-Phenylurea in Rabbits. Chem. Pharm. Bull. 22, 988-1002 ,1974

(j)

Type: Metabolism, toxicokinetics

Results: It could be demonstrated that in rabbits, receiving 50 and 250 mg/kg of acetaminophen and acetanilide, the hydroxylation process of acetanilide is saturable.

Remarks:

Reference: Koizumi, T., M. Ueda, S. Asami, J. Shibasaki, T. Tanaka, K. Yamanaka. Drugs known to be metabolized in man et al. Chem. Pharm. Bull. 24, 1439-1450 ,1976

(k)

Type: Metabolism *in vitro*

Results: The p-hydroxylation of acetanilide was measured in three different incubation systems containing either hemoglobin, rat liver microsomes, or microsomes plus hemoglobin. While only low p-hydroxylation activity was found in the tissue-free system, the microsomal activity was enhanced by addition of hemoglobin to 135 % in the case of acetanilide hydroxylation.

Remarks:

Reference: Jonen, H.G., R. Kahl, G.F. Kahl. Enhancement of Microsomal Aniline and Acetanilide Hydrosylation by Haemoglibin. Xenobiotica 6, 307-320 ,1976

(l)

Type: Metabolism *in vitro*

Results: The metabolism of acetanilide was studied with 3-methylcholanthrene-induced rat liver microsomes. 25 µg/mol of acetanilide were added to the incubation medium, and incubations were carried out at 37°C for 15 min. The major metabolite was the p-hydroxylation product (2.6 µg/mol). No m-hydroxylation took place and the o-hydroxylation product was identified only in traces (< 0.2 µg/mol).

Remarks:

Reference: Daly, J. Metabolism of Acetanilides and Anisoles with Rat Liver Microsomes. Biochem. Pharmacol. 19, 2979-2993,1970.

(m)

Type: Metabolism, toxicokinetics

Results: oral dose of 10 and 100 mg/kg trideuteroacetanilide were given by gastric tube to Sprague-Dawley rats. In urine samples collected at 4, 8, 12, 24, and 48 h post administration it was determined whether the major metabolite was deuterated paracetamol or a mixture of this compound with unlabelled paracetamol produced by deacetylation followed by subsequent reacetylation. Acetyl group exchange of the parent compound was also studied. Paracetamol containing no deuterated acetyl group was detected together with the labelled metabolite. The acetyl group exchange was time-dependent and higher than in man (see above), the mean ratios of deuterated to unlabelled paracetamol in urine were: 2 : 1 (urine samples collected 0-4 h) and 4 : 1 (urine samples collected 24-48 h).
However, adjustment of the dose for the mean body weight indicates that the amount administered to humans was approximately 130-fold lower than the low dose in rats. The authors stated that the different extents of acetyl group exchange in the two species could be dose-related. A high dose of trideuteroacetanilide could be sufficient to saturate the oxidation of the chemical to trideuteroparacetamol and therefore to increase metabolism by deacetylation-reacetylation.

Remarks:

Reference: Baty, J.D., R.M. Lindsay, W.R. Fox, R.G. Willis. Stable Isotopes as Probes for the Metabolism of Acetanilide in Man and the Rat. Biomed. Environ. Mass Spect. 16, 183-189,1988

(n)

Type: Metabolism *in vitro*

Results: The role of cytochrome P450 /A2 in acetanilide.
4-Hydroxylation was studied in vitro with cDNA expression and monoclonal antibodies. The results strongly suggest that P450 / A2 is the major and perhaps the only enzyme responsible for the metabolism of acetanilide.

Remarks:

Reference: Liu, G., H.V. Gelboin, M.J. Myers. Role of Cytochrome P450 IA2 in Acetanilide 4-Hydroxylation as Determined with c DNA Expression and Monoclonal Antibodies. Arch. Biochem. Biophys. 284, 400-406,1991

(o)

Type: Metabolism

Results: The Metabolism of ^{3}h-acetanilide was studied in rats after single i.p. dose (200 mg/kg), 1-5 days of continuous feeding of 0.8% in diet and at weekly intervals during 4 wk of such feeding. 3 groups excreted 56, 62 & 86% of dose, respectively, in 24 hr samples of urine. 4-Hydroxyacetanilide, the major metabolite, was found free, as well as conjugated with glucuronic and sulphuric acids in all groups.

Remarks:

Reference: Grantham. P.H. Changes in the Metabolism of Labelled Acetanilide and Binding of Isotope to Serum and Liver Macromolecules during Chronic Administration. Xenobiotica. 2 (6), 551-565, 1972

(p)

Type: Distribution

Results: Blood levels of radioactivity at one week was 11 fold higher than after single dose (200 mg/kg i.p.). The liver contained 15 times more isotope at 4 week (0.8 %

of diet) & binding to RNA, DNA & liver proteins 180, 15 & 33 fold higher than the values found after 1 dose.

Remarks:

Reference: Grantham. P.H. Changes in the Metabolism of Labelled Acetanilide and Binding of Isotope to Serum and Liver Macromolecules during Chronic Administration. Xenobiotica. 2 (6), 551-565, 1972

(q)

Type: Metabolism

Results: Female Wistar rats were orally admin ^{14}C labeled acetanilide and nitrobenzene. Tissue concentration of nitrobenzene were significantly higher than acetanilide. Within 24 hr, 78 % of the acetanilide dose, but only 50 % of the nitrobenzene dose appeared in the urine. Only 33% of the acetanilide dose was excreted in the feces, versus 15.5 % of nitrobenzene. More nitrobenzene than acetanilide metabolites were bound to hemoglobin and plasma proteins. Binding occurred through the reaction of nitrobenzene with sulfhydryl groups of cysteine as a sulfinic acid amide. Results indicate that both aniline and nitrobenzene yield hemoglobin binding metabolites in rats.

Remarks:

Reference: Albrecht, W. and Neumann H.G. Biomonitoring of aniline and nitrobenzene (Hemoglobin binding in rats and analysis of adducts. Arch. Toxicol. 57 (1), 1-5, 1985

(r)

Type: Excretion

Results: The effects of single doses (25 g and 50 g) oral ethanol on the disposition of acetanilide (50 mg/kg metabolic active mass) were studied in 10 healthy adults and in 10 patients with chronic nonalcoholic liver disease. In healthy adults, ethanol produced a dose-dependent increase in acetanilide half-life, and a decrease in acetanilide clearance. In patients with liver disease, ethanol produced a similar proportional change in acetanilide half-life and clearance, but these were less consistent. Liver disease itself was associated with a reduction in clearance. It was concluded that single oral doses of ethanol, comparable to those consumed during social drinking, may inhibit some forms of microsomal oxidation and may have important clinical implications.

Remarks:

Reference: McKay. J., M.D. Rawlings, I. Cobden, O.F.W. James. The Acute Effects of Ethanol on Acetanilide Disposition in Normal Subjects, and In Patients with Liver Disease. Br. J. Clin. Pharmacol. 14, 501-4, 1982

5. 11 EXPERIENCE WITH HUMAN EXPOSURE

(a)

Type: occupational exposure

Results: No significant adverse effects

Remarks: Experience with human exposure in a retrospective cohort study of 342 employees engaged in the manufacture of organic dyes, no deaths due to the bladder cancer were observed and no statistically significant increases in mortality by duration of exposure were found based on comparison with the US white male population: 48/342 workers exposed to acetanilide have been reported with 25 having been exposed for < 1 year, 18 for 1-4 years and 5 for 5 years.

Reference: Ott, M.G. & Langner, R.R. A mortality survey of men engaged in the manufacture of organic dyes. J. Occ. Med. 25, 763-768 (1983)

(b)

Type: occupational exposure

Results: A medical officer in a chemical factory which produced acetanilide in India wrote for consultation advice regarding the reaction of workers who fill bags of acetanilide. After duty hours most of the workers complained of chest pain, giddiness, epigastric pain and highly colored urine. Clinically, there were no signs, but occasionally there was a tinge of cyanosis. The hemoglobin values of these process workers were between 70 and 85 %. When there was cyanosis the workers

were admitted to a hospital and received injections of methylene blue plus vit C iv.

Remarks:

Reference: Clayton, G. D. and Clayton F. E., (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982. p. 2432

(c)

Type: metabolism

Results: No significant change in hepatic oxidation

Remarks:

Reference: Playfer, J.R. J.D. Baty, J. Lamb, C. Powell, D.A. Price-Evans, Age related differences in the disposition of acetanilide, Br. J. Clin. Pharm. 6, 529-533 (1978)

(d)

Type: Human poisoning

Results: Cases of human poisoning from the therapeutic use and abuse of acetanilide are reported. The picture of acute poisoning is characterized by cyanosis, fatigue, vertigo, somnolence, oppression and palpitation. Nausea, gastric pain, vomiting, diarrhea, twitchings, visual disturbances, trismus, rigor and delirium are reported. Also coma and death were observed. In many cases these toxic effects are accompanied by urticaria and eczema. The continued use of acetanilide leads to chronic poisoning characterized by gastroenteric disturbances, cardiac disfunctioning, drowsiness, hemolytic anemia, methemoglobinemia, reticulocytosis, cyanosis, antipyresis, acute renal failure and collapse. Advanced degenerative changes of the kidneys were the most prominent postmortem findings.

Remarks: Hanzlik, P.J. Health hazards in acetanilide-containing nostrums and mixtures. J. Am. Dent. Ass. 27, 1505-1513 (1940)

(e)

Type: Human toxicity in blood

Results: It is well known to produce cyanosis in some humans when taken repeatedly, which is possible due to formation of sulfhemoglobin. Large doses in acute poisoning produce methemoglobin.

Remarks:

Reference: Patty, F. (ed.). Industrial Hygiene and Toxicology: Volume II: Toxicology. 2nd ed. New York: Interscience Publishers, 1963

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ROBUST STUDY SUMMARIES
Acetanilide (CAS No. 103-84-4)

1) MELTING POINT

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks : Source :Aldrich product No.39722-9, purity 99.9 %

METHOD

- Method : OECD TG 102 " Melting Point/Melting range "
- GLP : No
- Year : 2001

⇒ Remarks :

? Test condition
. Differential scanning calorimetry
. Temperature range : 173 ~ 1273 K
. Heating rate : 5.0 ℃ / min
. Estimated accuracy : ± 0.5~2.0 K

RESULTS

- Melting point value in °C:

	Chemical weight (mg)	Temperature range (℃)	Heating rate (°C / min)	Melting range(℃)	
				Initial	Final
1	3.5	25 ~ 300	5	113.7	116.5
2	3.6	25 ~ 300	5	113.6	116.4
mean	-	-	-	113.7	116.4

- Decomposition : No
- Sublimation : No

⇒ Remarks

CONCLUSIONS

- Melting point : 113.7°C.

DATA QUALITY

- Reliabilities : Reliable with restriction.

⇒ Remarks :

REFERENCES (Free Text)

National Institute of Environmental Research (NIER), Korea(2001), Test of Acetanilide melting point/melting range, (tested by LGCI)

OTHER

- Last changed : August 2001
- Order number for sorting

⇒ Remarks

2) BOILING POINT

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks : Source : Aldrich chemical company Inc. Rot. No. 20615CO, purity 99.90 %

METHOD

- Method : OECD TG 103 "Boiling point –Method according to Siwoloboff"
- GLP : No
- Year : 2001

⇒ Remarks :

? Test condition
. Siwoloboff
. Temperature range : ~ 600 K
. Heating rate : 1 ± 0.5 °C / min
. Estimated accuracy : ± 2.0 K

RESULTS

- Boiling point value in °C:

	Chemical weight (mg)	Heating rate (℃/min)	Boiling point (℃)
Preliminary test	~ 70	10	~ 304
First test	66.2	25℃ ~ 290℃ : 10 290℃ ~ : 1 ± 0.5	304
Second test	97.6	25℃ ~ 290℃ : 10 290℃ ~ : 1 ± 0.5	304
Mean	-	-	304

- Pressure : 760
- Pressure unit : mmHg
- Decomposition : No

⇒ Remarks

CONCLUSIONS

- Boiling point : 304°C at 760 mmHg.

DATA QUALITY

- Reliabilities : Reliable with restriction.

⇒ Remarks :

REFERENCES (Free Text)

National Institute of Environmental Research (NIER), Korea(2001), Test of Acetanilide boiling point, (tested by LGCI).

OTHER

- Last changed : August 2001
- Order number for sorting

⇒ Remarks

3) VAPOUR PRESSURE

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks

METHOD

- Method / guideline followed : Not stated
- GLP : No details
- Year : 1994

⇒ Remarks

RESULTS

- Vapour pressure value : 0.002 hPa
- Temperature °C: 20°C

⇒ Remarks

CONCLUSIONS

⇒ Remarks
Vapour pressure value : 0.002 hPa at 20°C

DATA QUALITY

- Reliabilities : Reliable with restriction

⇒ Remarks

REFERENCES (Free Text)

IUCLID (International Uniform chemical Information Database) data set (Acetanilide;103-84-4), June, 1998

OTHER

- Last changed : August 2001
- Order number for sorting

4) PARTITION COEFFICIENT

TEST SUBSTANCE

• Identity : Acetanilide (CAS No. 103-84-4)
⇒ Remarks : Source : Sigma Aldrich Korea, Lot No. 02910EU
Purity : 97 %, White crystalline powder, Stability during use confirmed by FT-IR spectrometry.

METHOD

• Method : OECD TG 107 (Shake Flask Method)
• GLP : Yes
• Year : 2001
⇒ Remarks :

RESULTS

• Log POW : 1.16 ± 0.06
• Temperature : 23°C
⇒ Remarks :
– Test condition was conducted in triple under the following conditions. Test chemical was analyzed by HPLC(HP 1100 HPLC).
· Detector : HP 1100, DAD, G1315A
· Column : Luna 5u, C - 18 column
· Mobil phase : Acetonitrile / Water(90/10, v/v)
· Flow rate : 0.8 ml/min
· Wavelength : 254 nm
· Injection volume : 20

– **Test condition**

	Condition-1	Condition-2	Condition-3
Test chemical in 1-octanol saturated with water (0.001M)	1 mL	2 mL	4 mL
Water saturated with 1-octanol	30 mL	30 mL	30 mL

– **Test results**

Sample	Log Pow	Avg. Log Kow ± S.D	Total Avg. Log Pow ± S.D
1ml-1	1.11	1.13 ± 0.02	1.16 ± 0.06
1ml-2	1.12		
1ml-3	1.15		
2ml-1	1.13	1.14 ± 0.03	
2ml-2	1.17		
2ml-3	1.12		
4ml-1	1.19	1.23 ± 0.06	
4ml-2	1.20		
4ml-3	1.29		

CONCLUSIONS

• Log Pow : 1.16.
⇒ Remarks

DATA QUALITY

- Reliabilities : Reliable without restriction

⇒ Remarks

REFERENCES (Free Text)

National Institute of Environmental Research (NIER), Korea (2001), Test of Acetanilide Partition Coefficient (n-octanol/water), (tested by KRICT)

OTHER

- Last changed : August 2001
- Order number for sorting

⇒ Remarks

5) WATER SOLUBILITY

TES T SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks

METHOD

- Method / guideline followed : Not stated
- GLP : No details
- Year : 1994

⇒ Remarks

RESULTS

- 4 g/l at 20°C
- Description of solubility : Soluble
- pH value and concentration at temperature : 6.5 at 20°C
- pKa value at 25°C: 0.5

⇒ Remarks

CONCLUSIONS

- Acetanilde is soluble in water at 20°C

⇒ Remarks

DATA QUALITY

- Reliabilities : reliable with restriction

⇒ Remarks

REFERENCES (Free Text)

1. Hoechst AG : EG-Sicherheitsdatenblatt Acetanilid, 26, January, 1994
2. Online Toxicology Data Network (TOXNET) : Hazardous Substances Data Bank(HSDB), 2001

OTHER

- Last changed : August 2001
- Order number for sorting

⇒ Remarks

ENVIRONMENTAL FATE AND PATHWAY

6) PHOTODEGRADATION (INDIRECT-IN AIR)

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks : Source : unavailable.

METHOD

- Method/guideline followed : Other
- Type (test type) : Estimated by the AOPWIN Not stated (using a structure estimation method)
- GLP : No details
- Year : 2001

⇒ Remarks

The estimation by the AOPWIN (v1.90) model is base on the Atkinson model recommended in the OECD Guidance.

RESULTS

- Concentration of substance: Not stated
- Temperature ?: 25?
- Direct photoylsis : Not stated
- Indirect photoylsis
  - Type of Sensitizer : OH
  - Concentration of Sensitizer : 0.5 x 106 OH/cm^3
  - Rate Contant (Radical) : 12.52 x 10^{-12} cm^3 /molecule sec
  - Degradation 50 % after1.282 (31 hours)
- Breakdown products : Not stated

⇒ Remarks :

CONCLUSIONS

A half-life of 31 hours was measured for Acetanilide due to indirect photolysis.

DATA QUALITY

- Reliabilities : reliable with restriction

⇒ Remarks

REFERENCES (Free Text)

National Institute of Environmental Research (NIER), Korea(2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

OTHER

- Last changed : August 2001
- Order number for sorting

⇒ Remarks

7) STABILITY IN WATER

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks : source : Aldrich product No.39722-9, purity 99.9 %

METHOD

- Method/guideline followed : OECD TG 111 " Hydrolysis as a Function of pH"
- Type : Preliminary test-hydrolysis at 50°C for 5 days at pH 4, pH 7 and pH 9.0
- GLP : No
- Year : 2001

⇒ Remarks

RESULTS

- Nominal

	pH 4.0	pH 7.0	pH 9.0
Experiment I	136 mg/L	136.4 mg/L	136.4 mg/L
Experiment II	133 mg/L	136 mg/L	136 mg/L

- Measured value(at 50°C)

	pH 4.0		pH 7.0		pH 9.0	
	0 day	5 day	0 day	5 day	0 day	5 day
Experiment I	146.6 mg/L	140.8 mg/L	144.5 mg/L	142.3 mg/L	149 mg/L	140.8 mg/L
Experiment II	137.6 mg/L	143.2 mg/L	138.7 mg/L	137.8 mg/L	145.8 mg/L	139.9 mg/L

- Degradation 3.91 %, 1.085 % and 4.78 % at a pH 4.0, pH 7.0 and p H 9.0 and 50 °C after 5 days.

	pH 4.0	pH 7.0	pH 9.0
Experiment I	3.96 %	1.51 %	5.51 %
Experiment II	3.89 %	0.66 %	4.05 %
Average (±S.D)	3.93 % (± 0.0495)	1.09 % (±0.601)	4.78 % (±1.03)

- Half-life (t1/2) : > 1 year
- Breakdown products : Not stated

⇒ Remarks

CONCLUSIONS

- Acetanilide is relatively stable in water

⇒ Remarks

DATA QUALITY

- Reliabilities : Reliable with restriction

⇒ Remarks

REFERENCES (Free Text)

National Institute of Environmental Research (NIER), Korea(2001), Test of Acetanilide Hydrolysis as a Function of pH, (tested by LGCI)

OTHER

- Last changed : August 2001
- Order number for sorting

⇒ Remarks

8) TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENT(FUGACITY)

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks

METHOD

- Test(test type) : Calculation
- Method : Fugacity level I(EQC model)
- Year : 2001

⇒ Remarks : The parameter used are shown in the Appendix I

RESULTS

- Media : Air-sediment-soil-water
- Estimation Distribution and Media concentration (Level I)

Compartment	Mass Amount(%)
Air	0.13
Water	98.57
Soil	1.26
Sediment	0.02
Biota/suspended sediment	0.02

⇒ Remarks

CONCLUSIONS

- Most of test substance distributed into water phase.

⇒ Remarks

DATA QUALITY

- Reliabilities : reliable without restriction.

⇒ Remarks :

REFERENCES (Free Text)

National Institute of Environmental Research (NIER), Korea (2001), Estimation of physical/chemical properties and environmental fate of SIDS chemicals

OTHER

- Last changed : August 2001
- Order number for sorting

⇒ Remarks

Appendix I: Parameters used in the Fugacity Calculations

Input parameter

- Molecular weight : 135
- Melting point (°c) : 113.7
- Vapor pressure[pa] : 0.2
- Water solubility[g/m^3] : 4000
- Log POW : 1.16
- Half lives(h)- (Note 1)
  - In air : 31(estimated)
  - In water : 8760 (measured)
  - In soil : default value (1E+11)
  - In sediment : default value (1E+11)
- Temperature : 20°c

NOTE 1

The estimation of half-live in air and water were generated through EPIWIN model and OECD TG 111.

9) BIODEGRADATION

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks for Test Substance
Source : unavailable

METHOD

- Method : MITI test, JAPAN
- GLP : No details
- Test type : aerobic
- Year : 1992 (printed year)
- Contact Time : 14 days
- Innoculum : activated sludge

Remarks field for test conditions

- Innoculum (concentration and source)
  ·Activated sludge
- Concentration of test chemical, vehicle used, pre-acclimation conditions
  ·Concentration of chemical : 100 mg/L
  ·100 mg of the test substance or aniline (reference) and 30 mg of activated sludge were added to 300 ml of the test medium.
- Temperature of incubation : 25 ±1°C
- Dosing procedure :
- Sampling frequency : 17 (duplicate)
- Appropriate controls and blank system used ? yes
- Analytical methods used to measure biodegradation :
  ·Automatic electrolytic biochemical oxygen demand meter for BOD, total organic carbon meter for TOC, gas chromatograph, ult ra violet absorption spectrometer were used
- Methods of calculating measured concentrations (i.e., arithmetic mean, geometric mean, etc.)
  Not stated.

RESULTS

- Degradation % after time : 68.7 % after 14 days (BOD), 80.1mg (TOD)
- Results : readily biodegradable
- Kinetics :

	Flask	BOD(mg) after time (days)								
		1day	2	3	3.12	3.24	3.36	3.48	3.64	4
Test substance + Sludge	A	0.0	2.3	14.2	18.1	20.9	27.3	33.7	37.6	41.2
	B	0.0	0.2	8.2	13.6	17.9	25.3	28.7	35.1	40.7

	Flask	BOD(mg) after time (days)						
		5day	6	7	8	9	11	14
Test substance + Sludge	A	46.2	50.6	52.5	53.2	54.5	54.3	55.9
	B	44.7	49.0	51.0	51.7	53.0	53.5	55.3

- Breakdown products (yes/no): not stated

Remarks field for results

CONCLUSIONS

- The substance is readily biodegradable.

⇒ Remarks :

DATA QUALITY

- Reliabilities : reliable with restriction

⇒ Remarks :

REFERENCES (Free Text)

MITI, Japan, Biodegradation and Bioaccumulation Data of Existing Chemicals Based On the CSCL JAPAN, Published by Japan Chemical Industry Ecology-Toxicology & Information Center, p.3-21, October 1992.

OTHER

- Last changed : August, 2001
- Order number for sorting

⇒ Remarks :

ECOTOXICITY ELEMENT

10) ACUTE TOXICITY TO FISH

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks : Source – Lot No. TQ-09415PQ (Sigma Chemical Co. St. Louis, USA), purity > 99.9 %

METHOD

- Method / guideline followed: other: Testing of industrial chemicals (Ministry of Environment), Korea
- Type : Static
- GLP : Yes
- Year : 1997 (study performed)
- Species / Strain / Supplier : *Oryzias latipes* (medaka)
- Analytical monitoring : No
- Exposure period : 96 hours
- Statistical methods : Not relevant (limit test)

⇒ Remarks :

- **Test fish :**
  - · Age : 8 months
  - · Length : 2.9 ± 0.10 cm
  - · Weight : 0.2 ± 0.0 g

- **Test conditions :**
  - · Details of test : Static
  - · Dilution water source : Underground water by passing through activated carbon and the membrane filter(1u)
  - · Dilution water chemistry : not stated
  - · Stock and test solution and how they are prepared : Dilution water was used to prepare the stock solution.
  - · Concentrations dosing rate : Control, 100 mg/L
  - · Vehicle/solvent and concentrations : Not used
  - · Stability of the test chemical solutions : Not measured
  - · Exposure vessel type : 5 L glass aquarium, light/dark=16/8 hr, Light intensity=1640-1650 Lux
  - · Number of replicates, fish per replicate : No replicate, 7 fish/vessel
  - · Water chemistry in test(O2, pH) in the control and one concentration where effects were observed: pH : 7.51 ~8.03, DO : 2.6 ~ 8.2 mg/L

- Test temperature range : 24.5 ~ 25.3°C
- Method of calculating mean measured concentrations : Not relevant (limit test)

RESULTS

- Nominal concentrations (as mg/L) : 100 mg/L
- Measured concentrations (as mg/L) : not determined
- Unit : mg/ L
- Element value : 96 hr-LC50 > 100 mg/L based on nominal concentration
- Statistical results, as appropriate : Not relevant (limit test)

⇒ Remarks :

- Biological observations :
  ·Observable symptoms of intoxication : All normal
- Table showing cumulative mortality : no death was observed
- Lowest test substance concentration causing 100 % mortality: not obtained under the test conditions studied
- Mortality of controls : 0 %
- Abnormal responses : No
- Reference substances : No
- Any observations, such as precipitation that might cause a difference between measured and nominal values : No

⇒ Remarks:

CONCLUSIONS

• For acetanilide, the 96 hours LC50 of the fish, *Oryzias latipes* (medaka), was > 100 mg/ L.
⇒ Remarks :

DATA QUALITY

• Reliabilities : Reliable without restrictions
⇒ Remarks :

REFERENCES (Free Text)

Ministry of Environment (MOE), Korea (1997), Toxicology Evaluation of Synthetic Chemicals (X)

OTHER

• Last changed : August 2001
• Order number for sorting
⇒ Remarks :

11) TOXICITY TO AQUATIC PLANTS (ALGAE)

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks : Source – Lot No. 13325BU (Aldrich Co.), purity > 99.95 %

METHOD

- Method : OECD TG 201, "Alga, Growth Inhibition Test"(1984)
- Type : Static
- GLP : Yes
- Year : 2001 (study performed)
- Species / Strain / Supplier : Green algae (*Selenastrum capricornutum*), Strain No. ATCC 22662 obtained from American Type Culture Collection (12301 Park lawn Drive, Rockville, Maryland 20852, USA), and subcutured at the testing facility.
- Analytical monitoring : Yes, measured by HPLC at 0 and 72 hr.
- Exposure period/Endpoint : 72 hours
- Element basis : Area under the growth curve
- Statistical methods : Non-linear regression analysis was employed to determine EC50 by Comprehensive Toxicity Data Analysis and Database Software (Version 5.0). For the determination of NOEC, Dennett's test was used ($p < 0.05$).

⇒ Remarks :

- **Test organisms**
  - ·Laboratory culture : OECD medium
  - ·Method of cultivation : shaking at 100 rpm in the shaking incubator
  - ·Controls : OECD medium

- **Test conditions**
  - ·Test temperature range : 22-24°C
  - ·Growth/test medium : OECD medium
  - ·Dilution water source : OECD medium
  - ·Exposure vessel type : 100 ml- medium in a Erlenmeyer flask , 3 per treatment
  - ·Water chemistry in test (pH) in at least one replicate of each concentration (at start and end of the test): pH=7.55 - 8.51 at start, pH=7.45 - 8.00 at end of the test (72 hr)
  - ·Stock solutions preparation : stock solution was prepared with OECD medium and sterilized through 0.45 μm acrodisc filter
  - ·Light levels : 8,220 - 8,312 Lux, continuous

- **Test design**
  - · Number of replicates ; Triplicate
  - · Concentration :
    - Nominal concentration : 3, 6, 13, 25, 50, 100 (mg/L)
    - Measured concentration : 4, 8, 18, 29, 58, 105 (mg/L)
  - · Initial cell number: 1×10^4 (cells/ml)

- Method of calculating mean measured concentrations : Geometric mean

RESULTS

- Nominal concentrations (as mg/L) : 3, 6, 13, 25, 50, 100
- Measured concentrations (as mg/L) : 4, 8, 18, 29, 58, 105
- Unit : mg/L
- Element value : 72 hr-EC50 =13.5 mg/L, NOEC < 4mg/L
- Was control response satisfactory : Yes, Cell density in control increased by 120 times at the termination of experiment (72 hr).

• Statistical results, as appropriate : Not described
⇒ Remarks:

- Biological observations : cell density measured during the experiment

Nominal concentration (mg/L)	Measured Concentration (mg/L)	Cell concentration for each exposure($\times 10^4$ cells/ml)			
		0 hr	24 hr	48 hr	72 hr
0	0	1.0 ± 0.2	2.4 ± 0.5	21.0 ± 3.2	120.0 ± 17.3
3	4	1.0 ± 0.3	1.7 ± 0.7	14.0 ± 2.6	105.0 ± 8.7
6	8	1.1 ± 0.3	1.5 ± 0.5	14.0 ± 1.7	72.0 ± 11.5
13	18	1.1 ± 0.2	1.4 ± 0.2	11.0 ± 3.1	53.0 ± 13.3
25	29	0.92 ± 0.1	1.5 ± 0.2	8.3 ± 3.7	41.0 ± 11.5
50	58	0.96 ± 0.1	1.4 ± 0.1	3.9 ± 0.7	17.0 ± 1.7
100	105	0.88 ± 0.1	1.1 ± 0.5	2.9 ± 0.5	5.9 ± 0.8

CONCLUSIONS

• For acetanilide, the 72 hours EC50 of Algae, S*elenastrum capricornutum,* is 13.5 mg/L.
⇒ Remarks :

DATA QUALITY

• Reliabilities : Reliable without restrictions
• Remarks field : Experimental design and analytical procedure were well documented.
⇒ Remarks :

REFERENCES (Free Text)

Ministry of Environment (MOE), Korea (2001), The Toxicity of Acetanilide to Aquatic Plants(*Algae*) (tested by KRICT)

OTHER

• Last changed : August 2001
• Order number for sorting
⇒ Remarks :

12) ACUTE TOXICITY TO AQUATIC INVERTEBRATE (Daphnia)

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks : Source – Lot No. 13325BU (Aldrich Chemical Co.), purity > 99.95 %

METHOD

- Method / guideline followed: Acute toxicity test to Daphnia, Testing of industrial chemicals, Ministry of Environment, Korea
- Test type : 24 and 48 hrs immobilization test
- GLP : Yes
- Year : 2001 (study performed)
- Species / Strain: Daphnia (*Daphnia magna*)
- Details of test : Static
- Analytical monitoring : Yes, Measured by HPLC (3 replicates) at 0 and 48 hr
- Statistical methods : Not relevant (limit test)

⇒ Remarks :

- **Test organisms :**
  - · source, supplier, any pre-treatment , breeding methods : From GSF Institute of Ecological Chemistry, Germany
  - · Age at study initiation < 24-hr-old

- **Test conditions**
  - · Stock solutions preparation and stability: stock solution was prepared with dilution water (M4 medium)
  - · Test temperature range : 19.9-21.9°c
  - · Exposure vessel type : 100 ml test solution in a 150 ml crystallizing dish; 3 per treatment
  - · Dilution water source : M4 medium (OECD TG 1998)
  - · Dilution water chemistry : hardness=224 mg/L ;alkalinity=39 mg/L; pH= 8.0
  - · Water chemistry in test : pH=7.92-8.03 ; DO= 8.4-9.2 mg/L
  - · Lightning: light intensity=563-634 Lux; light periocity light/dark=16/8 hr
- Element (unit) basis : immobilization

- **Test design:**
  - ·30 Daphnia (3 replicates ; 10 organisms in each replicate)

- Method of calculating mean measured concentration : not stated
- Exposure period : 24 and 48 hrs
- Analytical monitoring : Yes, Measured by HPLC (3 replicates) at 0 and 48 hr

RESULTS

- Nominal concentrations (as mg/L) : 0, 100 mg/L
- Measured concentrations (as mg/L) :
- Unit (results expressed in what unit) : mg/L
- EC50 (24 hr) : >100 mg/L, EC50 (48 hr) : >100 mg/L
- Statistical results, as appropriate : Not relevant (limit test)

⇒ Remarks :

- Measured concentration in the test solution

Time(hr)	Target Concentration (mg/L)	Mean Concentration ±S.D
0	100	104.7 ±1.1
48	100	103.5 ±3.0

- Biological observations
  ·Number immobilized as compared to the number exposed: no immobilisation was observed
  ·Concentration response with 95 % confidence limits :
  ·Cumulative immobilization : no immobilisation was observed
  ·Was control response satisfactory : yes, normal

CONCLUSIONS

• For acetanilide, the 48 hours EC50 of the *Daphnia magna* was > 100 mg/L.
⇒ Remarks :

DATA QUALITY

• Reliabilities : Reliable without restrictions.
⇒ Remarks : Experimental designs and analytical procedure were well documented.

REFERENCES (Free Text)

Ministry of Environment (MOE), Korea (2001), The Acute Toxicity of Acetanilide to Aquatic Invertebrate (*Daphnia*), (tested by KRICT)

OTHER

• Last changed : August, 2001
• Order number for sorting
⇒ Remarks :

13) ACUTE TOXICITY

TEST SUBSTANCE

• **Identity** : Acetanilide (CAS No. 103-84-4)
⇒ **Remarks** : Source – commercial

METHOD

• **Method / guideline followed** : OECD TG 401(1981)
• **Type** : Acute oral toxicity test
• **GLP** : No details
• **Year** : 1988
• **Species** : Rat
• **Strain** : Sprague-Dawley
• **Route of administration** : Oral
• **Duration of test** : Not specified
• **Sex** : Male/Female
• **No. of animals per sex per dose** : 30 animals used
• **Vehicle** : Not specified

REMARKS FIELD FOR TEST CONDITIONS

- ***Age*** : Unknown
- ***Doses*** : not specified
- ***Doses per time period*** : Single
- ***Volume administered or concentration*** : 1-2 ml/100 g(b.w)
- ***Post dose observation period*** : 14 day

RESULTS

• **Value with confidence limits if calculated** :
LD50 : 1959(1428~2429) mg/kg b.w for male/female, 2033(1368~2858)mg/kg b.w for male,1893 (1218~2459) mg/kg b.w for female(95 % confidence limit)
• **Number of deaths at each dose level** : Not stated

REMARKS FIELD FOR RESULTS

- ***Time of death*** : Not stated
- ***Description, severity, time of onset and duration of clinical signs at each dose level***
  ·Signs of toxicity reported in LD50 : Ptosis, posture, respiratory effect, lethargy, abnormal gait, prostrate coma, lacrimation.
  ·Time to onset of signs : LD50 1 day
  ·Duration of signs : 4 days
- ***Necropsy findings, included doses affected, severity and number of animals affected***
  ·Autopsy finding : None
  ·Number of rats found dead : 15

- ***Potential target organs*** : Not reported
- ***If both sexes tested, results should be compared*** :

Sex	LD50 (mg/kg b.w.)	95 %confidence limit	Slope
M	2,033	1,368 ~ 2,858	7.0
F	1,893	1,218 ~ 2,459	
M/F	1,959	1,428 ~ 2,429	

(* M = male; F =female)

CONCLUSIONS

Acute oral toxicity (LD50) was 2033 mg/kg bw in male and 1893 mg/kg bw in female. Acetanilide was harmful as EC classification.

DATA QUALITY

- Reliabilities : Reliable with restrictions.

⇒ *Remarks field for Data quality*

Well conducted study, carried out by a laboratory from 11 OECD countries volunteered to participate in the study. The LD50 test was conducted 'blind' (no information on the identity of the distributed chemical) and in accordance with the 1981 OECD test guideline.

REFERENCES (Free Text)

Van den Heuvel, M.J., D.G Clark, R.J. Fielder, P.P. Koundakjian, G.J.A. Oliver, D. Pelling, N.J. Tomlinson, A.P. Walker. The International validation of a fixed-dose procedure as an alternative to the classical LD50 test. Food Chem. Tox. 28(7), 469-482 (1990)

OTHER

- Last changed : August 2001
- Order number for sorting

14) GENETIC TOXICITY IN VIVO (CHROMOSOME ABERRATIONS)

TEST SUBSTANCE

- **Identity** : Acetanilide (CAS No. 103-84-4)

⇒ **Remarks** : Source – Aldrich chemical Co. Purity – 99.90 % up

METHOD

- **Method / guideline followed**: OECD TG 474
- **Type** : mammalian erythrocyte micronucleus test in vivo
- **GLP** : Yes
- **Year** : 2001
- **Species/Strain** : Mouse/ICR
- **Sex** : Male and female
- **Route of administration** : i.p.
- **Doses/concentration levels** : 0, 500, 1000, 1500 mg/kg (bw)
- **Exposure period**: 2 days
- **Statistical methods** : Chi-square test

REMARKS FIELD FOR TEST CONDITIONS

- ***Age at study initiation*** : 8 weeks
- ***Weight of study initiation*** **:** 30 - 40 g
- ***No. of animals per dose*** : 6 males per dose group
- ***Vehicle***: Pluronic F68 solution (5 %)
- ***Duration of test*** : 2 days.
- ***Frequency of treatment*** : 2 times consecutive dose (24 hours interval)
- ***Sampling times and number of samples*** : 24 hours after last administration and 6 samples/dose
- ***Control groups and dose groups for the test substance*** *:*
  - Negative control group: concurrent vehicle (5 % Pluronic F68 sol.)
  - Positive control group: administrated 2 mg/kg dose of Mitomycin C
- ***Clinical observations performed*** : mortality, body weight, general clinical observation
- ***Organs examined at necropsy*** : Not examined
- ***Criteria for evaluating results*** :

  statistical analysis between control and treated animals were carried out and p values < 0.05 were considered to be significant: more than 0.1 of PCE/(PCE+NCE) rate, dose-related increase in the number of micronucleated cell and reproducible increase in the number of micronucleated cells

RESULTS

- **Genotoxic effects** : Negative
- **NOAEL(NOEL) (C)/LOAEL(LOEL) (C)** : None
- **Effect on mitotic index or PCE/NCE ratio by dose level** :

Dose (mg/kg)	Group mean PCE/(PCE+NCE)	Group mean frequency of MNPCE (per 1000)
0	0.63	1.42
500	0.64	1.67
1000	0.70	1.58
1500	0.67	1.08
Positive	0.61	58.08

- **Statistical results, as appropriate** : Only positive control group showed statistical significance ($p < 0.05$)

REMARKS FIELD FOR RESULTS

- ***Mortality at each dose level by sex*** : No animal died during the test.
- ***Description, severity, time of onset and duration of clinical signs at each dose level and sex*** :
  All animals showed significant clinical observation including recumbent, paralysis, convulsion, ataxia, dyspnea at all dose level.
- ***Body weight changes by dose and sex*** : Only at 1000 mg/kg, significant decrease in body weight showed.
- ***Food/water consumption changes by dose and sex*** : Not examined

CONCLUSIONS

This chemical showed negative result in micronucleus test *in vivo*.

DATA QUALITY

- Reliabilities : Reliable without restriction

⇒ *Remarks field for Data Reliability*
Well conducted study, carried out by Institute of LG biotech in Korea

REFERENCES (Free Text)

Ministry of Environment (MOE), Korea(2001), Micronucleus test of acetanilide in Mouse(Test No.257, tested by LGCI toxicology center)

OTHER

- Last changed : July 2001
- Order number for sorting

15) GENETIC TOXICITY IN VITRO (GENE MUTATION)

TEST SUBSTANCE

- Identity : Acetanilide (CAS No. 103-84-4)

⇒ Remarks : Source : Aldrich Chemical purity : 97 %

METHOD

- **Method / guideline Followed**: Other(Haworth et al, 1983)
- **Type** : Reverse mutation assay (preincubation assay)
- **System of testing** : Bacterial
- **GLP** : No details
- **Year** : 1988
- **Species/strain**: Bacterial, *Salmonella typhimurium* TA 100, TA 1535, TA 97, TA 98
- **Metabolic activation**
  - ***Species and cell type*** : Syrian hamster and S-D rat
  - ***Quantity*** : 10 % S-9, 30 % S-9/S-9 mix
  - ***Induced or not induced*** : Aroclor-1254-induced
- **Concentrations tested** : a half log dose intervals up to elicited toxicity dose, five doses and max. dose of 10 mg/plate applied.
- **Statistical methods** : no details

REMARKS FIELF FOR TES T CONDITIONS

—**Test Design**

- ***Number of replicates*** : 2
- ***Plate per test*** : 3 plates/dose
- ***Positive and negative control groups and treatment*** :
  ·Negative : Concurrent solvent
  ·Positive (-S9 mix.) : Sodium azid (TA1535,100), 9-aminoacridine (TA97,1537), 4-nitro-o-
  ·phenylenediamine (TA98)
  Positive (+ S9 mix.) : 2-aminoanthracene (all strains)
- **Solvent** : not specified
- **Description of follow up repeat study** :
  First test : without S9 and with 10 % S9; TA98,100 without and with 30 % S9
  Second test : without S9 and with 30 % S9; the other strain with 30 % and 10 % S9
- **Criteria for evaluating results** : Dose-dependent increase/reproducibility (2-fold of control was not necessarily requested)

RESULTS

- **Cytotoxic concentration** : Judged by a preliminary test, but no data
- **Genotoxic effects** :
  - With metabolic activation : Negative
  - Without metabolic activation : Negative

REMARKS FIELD FOR RESULTS

- **Frequency of reversions** : No difference from control groups
- **Precipitation concentration if applicable** : Not mentioned.
- **Mitotic index :** Not applicable

CONCLUSIONS

Acetanilide did not induce mutation in the *S. typhimurium* with and without metabolic activation.

DATA QUALITY

- Reliabilities : Reliable with restriction.

REFERENCES (Free Text)

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. salmonella Mutagenicity Tests : IV. Results from the Testing of 300 Chemicals. Env. Mol. Mutag. 11/12, l-158 (1988)

OTHER

- Last Changed : August 200l
- Order number for sorting

16) REPEATED DOSE TOXICITY

TEST SUBSTANCE

- **Identity** : Acetanilide (CAS No. 103-84-4)

⇒ **Remarks** : Source – Aldrich Chemical Co.

METHOD

- **Method / guideline followed** : OECD TG 422
- **Type** : Combined Repeat Dose and Reproduction/Developmental Toxicity Screening Test
- **GLP** : Yes
- **Year** : 2001
- **Species** : Rat
- **Strain** : Sprague-Dawley
- **Route of administration** : Oral (gavage)
- **Duration of test** : male: for 31 days, female: for 51 days
- **Doses/concentration levels** : 0, 22, 67, 200, 600 mg/kg/day
- **Sex** : Male/Female
- **Exposure period** : male : 30 days, female : from 2 weeks before mating to the day 3 of lactation
- **Frequency of treatment** : once a day
- **Control group and treatment** : Concurrent vehicle(1 % CMC)
- **Post exposure observation period** : 1 day
- **Statistical methods** : Dunnett's or Scheffe's test and Chi square test

REMARKS FIELD FOR TEST CONDITIONS

— **Test Subjects**

·***Age*** : 8 week old for male and female

·***No. of animals per sex per dose*** : 12 animals/sex/dose

— **Study Design**

·***Vehicle*** **:** 1 % Carboxylmethyl cellulose (CMC) solution

·***Satellite groups and reasons they were added*** **:** None

·***Clinical observations performed and frequency*** **:**

General condition and body wt. were observed once a day and once a week respectively. For pregnant females, body wt. was determined on the day 0, 7, 14, and 20 of gestation and 0 and 4 of lactation. Food consumption was determined on the next day when food was supplied as residual food weight. Haematology and biochemistry for males only at time of necropsy after 30 days of chemical exposure.

·***Organs examined at necropsy :***

Organ weight : liver, kidney, adrenal gland, testis, epididymis, thymus, spleen, brain, heart, ovary, uterus, thyroid gland, spermary, prostrate gland

Microscopic : brain, spinal cord, stomach, pancreas, jejunum, ileum, cecum, colon, rectum, liver, kidney, adrenal gland, spleen, heart, thymus, thyroid, bronchus, lung, pituitary gland, ovary, uterus, vagina, testis, epididymis, spermary, prostrate gland, mammary gland, bladder, nodi lymphatici mesenterici, nodi lymphatici, nervus ischiadicus, femoral marrow and all gross lesion.

RESULTS

- **NOAEL** : less than 22 mg/kg/day
- **LOAEL :** 22 mg/kg/day

- **Toxic response/effects by dose level :** There was significant decrease in hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration and also significant increase in red pulp hyperplasia of spleen, bone marrow hyperplasia of femur at all dose group.

REMARKS FIELD FOR RESULTS

— ***Body weight*** : The mean body weight gains at day 0 and 4 of lactation of 600 mg/kg females were significantly lower than those of controls($p < 0.05$).

— ***Food/water consumption*** : The mean food consumption of 67, 200 and 600 mg/kg was significantly reduced at day 1 males and females

— ***Description, severity, time of onset and duration of clinical signs***

·Male : The incidence rate of decreased locomotor activity(600, 200 mg/kg), reddish tear(600 mg/kg), salivation(600, 200 mg/kg) and cyanosis(600, 67 mg/kg) were significantly higher than those of control group.

· Female : cyanosis and decreased locomotor activity were found during premating period and cyanosis were found during pregnancy and lactation period at 600 mg/kg exposure group.

— ***Hematological and biochemical findings incidence and severity***

· Hematological findings: In males there was significant decrease in HGB, HCT and MCHC value at all dose group

TEST(s):	WBC	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	RET.#	MET-HB
UNITS:	thousand	millions	g/dl	%	fl	pg	g/dl	thousand	second	/1000	g/dl
Group: V.CONTROL : 0 (mg/kg)											
MEAN	9.47	8.06	15.4	46.5	57.7	19.1	33.0	933	15.3	2.5	0.262
Group: T1 : 22 (mg/kg)											
MEAN	9.79	7.64	14.4**	44.4*	58.2	18.9	32.4*	1050	15.6	5.9	0.286
Group: T2 : 67 (mg/kg)											
MEAN	9.28	7.03**	14.3**	44.4*	63.2**	20.4	32.2**	1090*	15.4	6.4	0.536
Group: T3 : 200 (mg/kg)											
MEAN	18.63	6.29**	14.4**	44.2**	70.8**	23.0**	32.5	957	15.1	8.8	0.198
Group: T4 : 600 (mg/kg)											
MEAN	54.45**	5.23**	13.7**	43.0**	82.5**	26.4**	32.0**	897	15.8	15.0**	0.326

* : Significant difference from v.control group ($p<0.05$)
** : Significant difference from v.control group ($p<0.01$)

· Biochemical findings : At 600 mg/kg, those values of AST, ALT, BUN, T-BIL, ALB, Calcium and A/G ratio were increased significantly. There was significant increase in BUN, T-BIL and decrease in Na at 200 mg/kg

— ***Mortality and time to death*** : 0/11 (control); 0/12 (22 mg/kg); 0/12 (67 mg/kg); 0/10 (200 mg/kg); 4/11(600 mg/kg). Four females at 600 mg/kg died at the day 21, 22 and 23 of pregnancy and the day 4 of lactation.

— **Ophthalmologic findings** : Not examined

— **Organ weight changes**

· ***male*** : increase in spleen, liver, and kidney weight as follow; spleen - 67, 200, 600 mg/kg (absolute and relative); liver-200 mg/kg(relative), 600 mg/kg(absolute and relative); kidney -600 mg/kg(relative)

· ***female*** : decrease in thymus weight at 200 mg/kg(absolute) and 600mg/kg(absolute and relative); increase in brain, kidney, ovary, spleen, heart weight as follows; brain-200, 600 mg/kg(relative); kidney -200mg./kg(relative), 600 mg/kg(absolute and relative); spleen-600mg/kg(absolute and relative); ovary- 600 mg/kg(absolute and relative); heart-600 mg/kg(relative)

— **Histopathology incidence and severity**

· ***male :***

- Liver : increase of extramedullary hematopoiesis at 200, 600 mg/kg ($p < 0.01$)
- Spleen : increase of hyperplasia/red pulp at 22, 67, 200 and 600 mg/kg ($p < 0.01$)
- Femur : increase of hyperplasia/bone marrow at 22, 67, 200 and 600 mg/kg ($p < 0.01$)

· ***female :***

- Liver : increase of extramedullary hematopoiesis at 200, 600 mg/kg ($p < 0.01$)

- Spleen : increase of hyperplasia/red pulp at 22, 67, 200 and 600 mg/kg ($p < 0.01$)
- Femur : increase of hyperplasia/bone marrow at 22, 67, 200 and 600 mg/kg ($p < 0.01$)
- Thymus : atrophy at 200, 600 mg/kg($p < 0.01$)

CONCLUSIONS

All treatment group showed the LOAEL associated with red pulp hyperplasia of spleen, bone marrow hyperplasia of femur and significant decrease in HGB, HCT and MCH. This result indicated the LOAEL is 22 mg/kg to both male and female.

DATA QUALITY

• Reliabilities : Reliable without restrictions.

⇒ *Remarks field for Data quality*

Well conducted study, carried out by Korea Research Institute of Chemical Technology.

REFERENCES (Free Text)

Ministry of Environment (MOE), Korea(2001), Combined Repeated Dose Toxicity with the Reproduction /Developmental Toxicity Screening Testing of Acetanilide in Rats(test No.G00154, tested by KRICT)

OTHER

• Last changed : August 2001
• Order number for sorting

17) REPRODUCTION/DEVELOPMENTAL TOXICITY

TEST SUBSTANCE

- **Identity** : Acetanilide (CAS No. 103-84-4)

⇒ **Remarks** : Source – Aldrich Chemical Co.

METHOD

- **Method / guideline followed** : OECD TG 422
- **Type** : Combined Repeat Dose and Reproduction/Developmental Toxicity Screening Test
- **GLP** : Yes
- **Year** : 2001
- **Species** : Rat
- **Strain** : Sprague-Dawley
- **Route of administration** : Oral (by gavage)
- **Duration of test** : male: for 31 days, female: for 51 days
- **Doses/concentration levels** : 0, 22, 67, 200, 600 mg/kg/day
- **Sex** : Male/Female
- **Exposure period** : male : 30 days, female : from 2 weeks before mating to the day 3 of lactation
- **Frequency of treatment** : once a day
- **Control group and treatment** : Concurrent vehicle (1 % CMC)
- **Premating exposure period for males and females** : 2 weeks for both sexes
- **Statistical methods** : Dunnett's or Scheffe's test and Chi square test

REMARKS FIELD FOR TEST CONDITIONS

- **Test Subjects**
  - ***Age*** : 8 week old for male and female
  - ***Weight at study initiation*** **:** 255.9~326.0 g for males, 185.5~231.2 g for females
  - ***No. of animals per sex per dose*** : 12 animals/sex/dose

- **Study Design**
  - Vehicle : Carboxylmethyl cellulose(CMC) solution 1%
  - ***Dosing schedule*** **:**
    males - premating period(2 weeks) and mating period ; 30 days
    females -premating period(2 weeks), mating, pregnant and lactation period ; 39~50 days
  - ***Mating procedures*** **:** M/F ratios per cage ; 1/1, proof of pregnancy; sperm detection in vagina
  - ***Clinical observations performed and frequency*** :
    General condition was observed once a day. Body weight and food consumption of pregnant animals were determined on the day 0, 7, 14, 20 of pregnancy and the day 0, 4 of lactation. Haematology and biochemistry for males only at the time of necropsy after 30 days of chemical exposure.
  - ***Organ examined at necropsy*** :
    Organ weight : liver, kidney, adrenal gland, testis, epididymis, thymus, spleen, brain, heart, ovary, uterus, thyroid gland, spermary, prostrate gland.
    Microscopic : brain, spinal cord, stomach, pancreas, jejunum, ileum, cecum, colon, rectum, liver, kidney, adrenal gland, spleen, heart, thymus, thyroid, bronchus, lung, pituitary gland, ovary, uterus, vagina, testis, epididymis, spermary, prostrate gland, mammary gland, bladder, nodi lymphatici mesenterici, nodi lymphatici, nervus ischiadicus, femoral marrow and all gross lesion.
  - ***Parameters assessed during study***
    Body wt.(once a week), food consumption(once a week), copulation index (No. of animals with successful copulation/No. of mated animals ×100), fertility index (No. of impregnating animals/ No. of animals with successful copulation ×100), pregnancy index (No. of pregnant animals/ No. of pairs with successful copulation ×100), gestation index (No. of females with live pups/No. of living

pregnant females x 100), viability index (No. of live offspring at day 4 / No. of live offspring at birth×100), body weight of live pups(on day 0 and 4), No. of corpora lutea, No. of female mated, abortion, premature birth, gestation period, sex ratio(Total No.of male pups/Total No. of female pups)

RESULTS

- **NOAEL and LOAEL for reproduction toxicity:**
  NOAEL : 200 mg/kg/day
  LOAEL : 600 mg/kg/day
- **NOAEL for developmental toxicity:**
  NOAEL : 67 mg/kg/day
  LOAEL : 200 mg/kg/day

- **Reproduction/developmental data**
  No significant differences appeared between the treatment group and control groups in precoital time, copulation rate, impregnation rate and pregnancy rate. At 600 mg/kg, both sexes of F1 showed significant decrease in viability index on the day 4 after birth and in body weight gain on the day 0, 4 after birth. At 200 mg/kg dose, there are significant decrease in body weight of the both sexes on the day 4 after birth. No. of neonates with clinical signs (icterus, cyanosis) were significant increase in 600 mg/kg dose group. No significant differences appeared between the treatment and control group in any other observation.

DOSE : (mg/kg)	0	22	67	200	600
No. of mated males	12	12	12	12	12
Copulation index(%)	12/12(100)	12/12(100)	12/12(100)	11/12/(92)	11/12(92)
Fertility index (%)	11/12(92)	12/12(100)	12/12(100)	10/11/(91)	11/11(100)
No. of mated females	12	12	12	12	12
Copulation index (%)	12/12(100)	12/12(100)	12/12(100)	11/12/(92)	11/12(92)
Pregnancy index (%)	11/12(92)	12/12(100)	12/12(100)	10/11/(91)	11/11(100)
No. of dams	11	12	12	10	8
No. of corpora lutea	196	168	204	156	142
Mean±S.D	17.8±1.25	14.0±4.97	17.0±2.34	15.6±2.59	17.8±1.98
No. of implantations	171	164	189	147	136
Mean±S.D	15.5±3.05	13.7±5.05	15.8±1.91	14.7±2.58	17.0±1.07
No. of neonates with clinical signs (%)	0	0	0	0	10(9.3)**
No. of perinatal deaths	2	0	3	3	11*
% to implantation: Mean±S.D	1.1±2.48	0	1.7±3.11	1.9±4.22	8.1±9.86*
No. of live young at birth Mean±S.D	14.5±2.84	13.3±5.26	14.9±1.88	13.7±2.75	13.5±2.73
% to implantation: Mean±S.D	93.9±6.50	95.0±9.90	94.8±5.61	93.0±6.82	79.6±16.2
Pregnancy period (Mean±S.D)	21.6±0.30	21.8±0.44	21.7±0.26	21.8±0.35	19.9±7.26
Viability index (Mean±S.D)	98.3±2.89	90.0±28.5	97.9±4.11	98.6±2.91	65.1±41.12*
Body weights of pups (g)					
Male 0 DAY	7.2±0.78	7.2±0.43	7.0±0.55	6.4±0.77	5.7±0.8*
4 DAY	11.7±1.45	11.7±0.94	11.1±1.18	9.9±1.34*	9.1±0.54*
Female 0 DAY	6.8±0.81	6.9±0.71	6.5±0.37	6.0±0.73	5.2±0.66*
4 DAY	11.1±1.68	10.5±1.08	10.5±1.14	9.3±1.30*	8.7±0.86*

* Statistically significant difference from control group($p<0.05$)

REMARKS FIELD FOR RESULTS

- ***Mortality and day of death*** : At 600 mg/kg, four females died on day 21, 22 and 23 of pregnancy and day 4 of lactation.
- ***Body weight*** : Body weight significantly decreased at day 0 and 4 of lactation in females in 600 mg/kg dose group. Low body weight of pups showed in 200 and 600 mg/kg dose.
- ***Food/water consumption*** : Significantly low food consumption was indicated at day of treatment in males and females

DOSE : (mg/kg)	0	22	67	200	600
No. of females paired	12	12	12	12	12
No. of females mated	12	12	12	11	11
Days (Mean±S.D.)	2.8 ±3.04	2.6 ±1.16	2.6 ±2.47	2.9 ±1.22	2.1 ±0.94

- ***Precoital time of parent animals(No. of day taken to mate)***
- ***Grossly visible abnormalities, external, soft tissue and skeletal abnormalities***

No statistically significant effects were observed.

CONCLUSIONS

Significant toxic effect were found in pups at 200 mg/kg. The reproduction/developmental oral toxicity test in rats indicates that the NOAEL is 67 mg/kg bw/day.

DATA QUALITY

- Reliabilities : Reliable without restrictions.

⇒ *Remarks field for Data quality*

Well conducted study, carried out by Korea Research Institute of Chemical Technology.

REFERENCES (Free Text)

Combined Repeated Dose Toxicity with the Reproduction /Developmental Toxicity Screening Testing of Acetanilide in Rats(test No.G00154, May 2001, KRICT, sponsored by Ministry of Environment, Korea)

OTHER

- Last changed : August 2001
- Order number for sorting