Overview information for

1-Aminonaphthalene

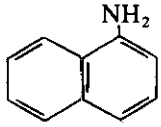
OCCUPATIONAL SAFETY AND HEALTH GUIDELINE FOR alpha-NAPHTHYLAMINE POTENTIAL HUMAN CARCINOGEN

INTRODUCTION

This guideline summarizes pertinent information about alpha-naphthylamine for workers, employers, and occupational safety and health professionals who may need such information to conduct effective occupational safety and health programs. Recommendations may be superseded by new developments in these fields; therefore, readers are advised to regard these recommendations as general guidelines.

SUBSTANCE IDENTIFICATION

- **Formula:** $C_{10}H_9N$
- **Structure:**



- **Synonyms:** 1-Naphthylamine; 1-aminonaphthalene; naphthalidam; naphthalidine
- **Identifiers:** CAS 134-32-7; RTECS QM1400000; DOT 2077, label required: "St. Andrew's Cross (X)"
- **Appearance and odor:** Colorless to yellow crystals which darken in air to a reddish purple color with a weak ammonia-like odor

CHEMICAL AND PHYSICAL PROPERTIES

- **Physical data**

1. Molecular weight: 143.20
2. Boiling point (at 760 mmHg): 301°C (573.8°F)
3. Specific gravity (water = 1): 1.2
4. Vapor density (air = 1 at boiling point of alpha-naphthylamine): 4.93
5. Melting point: 50°C (122°F)
6. Vapor pressure at 104°C (219°F): 1 mmHg
7. Solubility in water, g/100 g water at 25°C (77°F): 0.17

- **Reactivity**

1. Incompatibilities: alpha-naphthylamine oxidizes in air
2. Hazardous decomposition products: Toxic vapors and gases (e.g., oxides of nitrogen and carbon monoxide) may be released in a fire involving alpha-naphthylamine.

- **Flammability**

1. Flash point: 157°C (315°F) (closed cup)
2. Extinguishant: Water, dry chemical, carbon dioxide, or alcohol foam
3. Combustible solid, Flammability Rating 1 (NFPA)

- **Warning properties**

Evaluation of warning properties for respirator selection: Warning properties are not considered in recommending respirators for use with carcinogens.

EXPOSURE LIMITS

The Occupational Safety and Health Administration (OSHA) does not have a specific permissible exposure limit (PEL) for alpha-naphthylamine; however, the OSHA standard requires implementation of stringent controls wherever alpha-naphthylamine or solid or liquid mixtures containing at least 0.1% by weight or volume of alpha-naphthylamine are manufactured, processed, repackaged, released, handled, or stored (see "General Control Procedure"). Details of this standard can be found in the Code of Federal Regulations, 29 CFR 1910.1004, alpha-Naphthylamine. The National Institute for Occupational Safety and Health (NIOSH) concurs with the OSHA standard. The American Conference of Governmental Industrial Hygienists (ACGIH) does not have an assigned threshold limit value (TLV®) for alpha-naphthylamine.

HEALTH HAZARD INFORMATION

- **Routes of exposure**

alpha-Naphthylamine may cause adverse health effects following exposure via inhalation, ingestion, or dermal contact.

- **Summary of toxicology**

1. *Effects on animals:* In mice and dogs, chronic oral administration or subcutaneous injection of alpha-naphthylamine produced inconclusive evidence of liver, bladder, lung, or lymphatic cancer; however, beta-naphthylamine, which is a contaminant in commercial grade alpha-naphthylamine, is a recognized animal carcinogen. In addition, certain metabolites of alpha-naphthylamine have been shown to be carcinogenic in animals (e.g., N-(1-naphthyl)-hydroxylamine induces bladder cancer in mice, and 1-nitrosonaphthalene induces tumors in rats).

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Public Health Service Centers for Disease Control
National Institute for Occupational Safety and Health
Division of Standards Development and Technology Transfer

2. *Effects on humans:* Long-term exposure of workers to commercial alpha-naphthylamine (which contains 4%-10% beta-naphthylamine) has been associated with an increased incidence of bladder cancer.

• **Signs and symptoms of exposure**

1. *Short-term (acute):* Exposure to alpha-naphthylamine can cause mild skin and eye irritation.

2. *Long-term (chronic):* Exposure to alpha-naphthylamine can cause headache, dizziness, a feeling of euphoria, weakness, impaired muscular coordination (ataxia), bluish discoloration of skin and mucous membranes (due to methemoglobinemia), breathing difficulty (dyspnea), blood in the urine, and painful, difficult, or frequent urination.

RECOMMENDED MEDICAL PRACTICES

• **Medical surveillance program**

Workers with potential exposures to chemical hazards should be monitored in a systematic program of medical surveillance intended to prevent or control occupational injury and disease. The program should include education of employers and workers about work-related hazards, placement of workers in jobs that do not jeopardize their safety and health, earliest possible detection of adverse health effects, and referral of workers for diagnostic confirmation and treatment. The occurrence of disease (a "sentinel health event," SHE) or other work-related adverse health effects should prompt immediate evaluation of primary preventive measures (e.g., industrial hygiene monitoring, engineering controls, and personal protective equipment). A medical surveillance program is intended to supplement, not replace, such measures.

A medical surveillance program should include systematic collection and epidemiologic analysis of relevant environmental and biologic monitoring, medical screening, morbidity, and mortality data. This analysis may provide information about the relatedness of adverse health effects and occupational exposure that cannot be discerned from results in individual workers. Sensitivity, specificity, and predictive values of biologic monitoring and medical screening tests should be evaluated on an industry-wide basis prior to application in any given worker group. Intrinsic to a surveillance program is the dissemination of summary data to those who need to know, including employers, occupational health professionals, potentially exposed workers, and regulatory and public health agencies.

• **Preplacement medical evaluation**

Prior to placing a worker in a job with a potential for exposure to alpha-naphthylamine, the physician should evaluate and document the worker's baseline health status with thorough medical, environmental, and occupational histories, a physical examination, and physiologic and laboratory tests appropriate for the anticipated occupational risks. These should concentrate on the function and integrity of the skin, liver, lymphatic system, and urinary tract.

A preplacement medical evaluation is recommended in order to detect and assess preexisting or concurrent conditions which may be aggravated or result in increased risk when a worker is exposed to alpha-naphthylamine. The examining physician should consider the probable frequency, intensity, and duration of exposure, as well as the nature and degree of the condition, in placing such a worker. Such conditions, which should not be regarded as absolute contraindications to job placement, include a history of chronic skin disease or concurrent dermatitis.

• **Periodic medical screening and/or biologic monitoring**

Occupational health interviews and physical examinations should be performed at regular intervals. Additional examinations may be necessary should a worker develop symptoms that may be attributed to exposure to alpha-naphthylamine. The interviews, examinations, and appropriate medical screening and/or biologic monitoring tests should be directed at identifying an excessive decrease or adverse trend in the physiologic function of the skin, liver, lymphatic system, and urinary tract as compared to the baseline status of the individual worker or to expected values for a suitable reference population.

• **Medical practices recommended at the time of job transfer or termination**

The medical, environmental, and occupational history interviews, the physical examination, and selected physiologic and laboratory tests which were conducted at the time of placement should be repeated at the time of job transfer or termination. Any changes in the worker's health status should be compared to those expected for a suitable reference population. Because occupational exposure to alpha-naphthylamine may cause diseases of prolonged induction-latency, the need for medical surveillance may extend well beyond termination of employment.

• **Sentinel health events**

1. Acute SHE's include: Contact and/or allergic dermatitis.
2. Delayed-onset SHE's include: Bladder cancer.

MONITORING AND MEASUREMENT PROCEDURES

• **Method**

Sampling and analysis may be performed by collecting alpha-naphthylamine dust with glass-fiber filters and silica gel tubes followed by elution with acetic acid in 2-propanol and analysis by gas chromatography. Direct-reading devices calibrated to measure alpha-naphthylamine may also be used if available. A detailed sampling and analytical method for alpha-naphthylamine may be found in the *NIOSH Manual of Analytical Methods* (method number 264).

PERSONAL PROTECTIVE EQUIPMENT

Chemical protective clothing (CPC) should be selected after utilizing available performance data, consulting with the manufacturer, and then evaluating the clothing under actual use conditions.

In operations involving "laboratory-type hoods" or in locations where alpha-naphthylamine is contained in an otherwise "closed system" but is transferred, charged, or discharged into other normally closed containers, OSHA requires that workers: (1) be provided with and required to use clean, full-body

CPC (smocks, coveralls, or long-sleeved shirts and long pants), shoe covers, and gloves prior to entering a regulated area; (2) be provided with and required to use approved respirators (a respirator affording higher levels of protection may be substituted); and (3) remove the protective clothing and equipment prior to exiting a regulated area, and at the last exit of the day, place used clothing and equipment in impervious containers for decontamination or disposal.

SANITATION

For closed system operations or in locations where alpha-naphthylamine is contained in an otherwise "closed system" but is transferred, charged, or discharged into other normally closed containers, OSHA requires that workers: (1) wash their hands, forearms, faces, and necks prior to exiting the regulated area and before engaging in other activities, and (2) shower in designated facilities after the last exit of the day.

In isolated systems, such as a "glove box," OSHA requires that workers wash their hands and arms with soap and water upon completion of the assigned task and before engaging in other activities not associated with the isolated system.

If it is necessary for workers to wear protective clothing, OSHA requires that a clean change room be provided and equipped with showers and washing facilities. NIOSH recommends that lockers that permit separation of street and work clothes be provided for the worker.

Clothing which is contaminated with alpha-naphthylamine should be removed immediately and placed in sealed containers for storage until it can be discarded or until provision is made for the removal of alpha-naphthylamine from the clothing. If the clothing is to be laundered or cleaned, the person performing the operation should be informed of alpha-naphthylamine's hazardous properties. Reusable clothing and equipment should be checked for residual contamination before reuse or storage.

Decontamination and disposal procedures should be established and implemented to remove alpha-naphthylamine from materials and equipment. Contaminated material should be removed from regulated areas without further contamination of the facility.

OSHA requires that workers wash their faces, necks, hands, and forearms thoroughly with soap and water before eating, smoking, or using toilet facilities.

In regulated areas, OSHA prohibits the storage or consumption of food or beverages, the storage or application of cosmetics, the storage or smoking of tobacco or other smoking materials, or the storage or use of products for chewing.

OSHA prohibits the location of drinking fountains in regulated areas.

GENERAL CONTROL PROCEDURES

The following control procedures are derived from OSHA requirements as stated in 29 CFR 1910.1004:

Areas where alpha-naphthylamine is manufactured, processed, used, repackaged, released, handled, or stored shall be designated as regulated areas, and entry into and exit from these areas shall be restricted and controlled. Only authorized workers shall be permitted access to regulated areas.

Workers authorized to enter regulated areas shall receive a training and indoctrination program including but not limited to the nature of the carcinogenic hazards of alpha-naphthylamine, local and systemic toxicity, the specific nature of the operation which could result in exposure, and the purpose for and the significance of decontamination and emergency practices and procedures.

Entrances to regulated areas shall be posted with signs indicating that a cancer-suspect agent is present and that only authorized workers wearing appropriate protective clothing and equipment shall be admitted.

Appropriate signs and instructions shall be posted at the entrance to and exit from regulated areas to inform workers of the procedures that must be followed when entering or leaving a regulated area.

Open vessel system operations involving alpha-naphthylamine which are not in an isolated system, laboratory-type hood, or other system affording equivalent protection against the entry of alpha-naphthylamine into regulated areas, nonregulated areas, or the external environment are prohibited.

In operations involving "laboratory-type hoods" or in locations where alpha-naphthylamine is contained in an otherwise "closed system" but is transferred, charged, or discharged into other normally closed containers, each operation shall be provided with continuous local exhaust ventilation so that air movement is always from ordinary work areas to the operation. Exhaust air shall not be discharged to regulated areas, nonregulated areas, or the external environment unless decontaminated. Clean makeup air shall be introduced in sufficient volume to maintain the correct operation of the local exhaust system.

Containers of alpha-naphthylamine shall be identified as to contents and shall contain a hazard warning.

Regulated areas (with the exception of outdoor operations) shall be operated under negative pressure with respect to nonregulated areas. Local exhaust ventilation may be used to satisfy this requirement. Clean makeup air in equal volume shall replace air that is removed.

The introduction or removal of any equipment, materials, or other items to or from a regulated area shall be done in a manner that does not cause contamination of nonregulated areas or the external environment.

Decontamination procedures shall be established and implemented to remove alpha-naphthylamine from the materials, equipment, and decontamination facility.

COMMON OPERATIONS AND CONTROLS

Common operations in which exposure to alpha-naphthylamine may occur and control methods which may be effective in each case are listed in Table 1.

Table 1.—Operations and methods of control for alpha-naphthylamine

Operations	Controls
During use in the manufacture of dyes, herbicides, and rubber antioxidants; during use in research facilities and laboratories	Process enclosure, restricted access, local exhaust ventilation where appropriate, personal protective equipment, good housekeeping and personal hygiene practices, substitution with less toxic substances

EMERGENCY FIRST AID PROCEDURES

In the event of an emergency, remove the victim from further exposure, send for medical assistance, and initiate emergency procedures. If a worker comes in contact with alpha-naphthylamine, OSHA requires that the worker shower as soon as possible, unless contraindicated by physical injuries.

- **Eye exposure**

Where there is any possibility of a worker's eyes being exposed to alpha-naphthylamine, an eye-wash fountain should be provided within the immediate work area for emergency use.

If alpha-naphthylamine gets into the eyes, flush them immediately with large amounts of water for 15 minutes, lifting the lower and upper lids occasionally. Get medical attention as soon as possible. Contact lenses should not be worn when working with this chemical.

- **Skin exposure**

Where there is any possibility of a worker's body being exposed to alpha-naphthylamine, facilities for quick drenching of the body should be provided within the immediate work area for emergency use.

If alpha-naphthylamine gets on the skin, wash it immediately with soap and water. If alpha-naphthylamine penetrates the clothing, remove the clothing immediately and wash the skin with soap and water. Get medical attention promptly.

- **Rescue**

If a worker has been incapacitated, move the affected worker from the hazardous exposure. Put into effect the established emergency rescue procedures. Do not become a casualty. Understand the facility's emergency rescue procedures and know the locations of rescue equipment before the need arises.

SPILLS AND LEAKS

OSHA requires that hazardous conditions created by spills or leaks be eliminated and that potentially affected areas be decontaminated prior to the resumption of normal operations.

OSHA requires that affected areas of spills or leaks be evacuated as soon as an emergency has been determined.

OSHA requires that only authorized workers provided with and wearing clean, impervious garments (including gloves, boots, and supplied-air respirators) enter areas of spills or leaks.

OSHA requires that workers authorized to enter areas of spills or leaks be decontaminated before removing the protective garments and hoods and showering.

If alpha-naphthylamine is spilled or leaked, the following steps should be taken:

1. Remove all ignition sources.
2. Ventilate area of spill or leak.
3. If in solid form, alpha-naphthylamine may be collected and placed in an appropriate container.
4. alpha-Naphthylamine solid or liquid may be collected by vacuuming with an appropriate high-efficiency filtration system or by using wet methods; it may then be placed in an appropriate container. Dry sweeping and dry mopping of alpha-naphthylamine are prohibited by OSHA. If a vacuum system is used, there should be no sources of ignition in the vicinity of the spill, and flashback prevention devices should be provided.
5. For small quantities of liquids containing alpha-naphthylamine, absorb on paper towels and place in an appropriate container.
6. Large quantities of liquids containing alpha-naphthylamine may be absorbed in vermiculite, dry sand, earth, or a similar material and placed in an appropriate container.

WASTE REMOVAL AND DISPOSAL

U.S. Environmental Protection Agency, Department of Transportation, and/or state and local regulations shall be followed to assure that removal, transport, and disposal are in accordance with existing regulations.

RESPIRATORY PROTECTION

It must be stressed that the use of respirators is the least preferred method of controlling worker exposure and should not normally be used as the only means of preventing or minimizing exposure during routine operations. However, there are some exceptions for which respirators may be used to control exposure: when engineering and work practice controls are not technically feasible, when engineering controls are in the process of being installed, or during emergencies and certain maintenance operations including those requiring confined-space entry (Table 2).

In addition to respirator selection, a complete respiratory protection program should be instituted which as a minimum complies with the requirements found in the OSHA Safety and Health Standards, 29 CFR 1910.134. A respiratory protection program should include as a minimum an evaluation of the worker's ability to perform the work while wearing a respirator, the regular training of personnel, fit testing, periodic environmental monitoring, maintenance, inspection, and

cleaning. The implementation of an adequate respiratory protection program, including selection of the correct respirators, requires that a knowledgeable person be in charge of the program and that the program be evaluated regularly.

Only respirators that have been approved by the Mine Safety and Health Administration (MSHA, formerly Mining Enforcement and Safety Administration) and by NIOSH should be used. **Remember! Air-purifying respirators will not protect from oxygen-deficient atmospheres.**

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Table 2.—Respiratory protection for alpha-naphthylamine

Condition	Minimum respiratory protection*
Any detectable concentration	Any self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive pressure mode
	Any supplied-air respirator with a full facepiece and operated in a pressure-demand or other positive pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive pressure mode
Planned or emergency entry into environments containing unknown or any detectable concentration	Any self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive pressure mode
	Any supplied-air respirator with a full facepiece and operated in a pressure-demand or other positive pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive pressure mode
Firefighting	Any self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive pressure mode
Escape only	Any air-purifying full facepiece respirator with a high-efficiency particulate filter
	Any appropriate escape-type self-contained breathing apparatus

* Only NIOSH/MSHA-approved equipment should be used.

1-NAPHTHYLAMINE
(Group 3)

For definition of Groups, see Preamble Evaluation.

Supplement 7: (1987) (p. 260)

CAS No.: 134-32-7

A. Evidence for carcinogenicity to humans (*inadequate*)

An excess occurrence of bladder cancer was observed in workers who had been exposed to commercial 1-naphthylamine for five or more years who had not also been engaged in the production of 2-naphthylamine or benzidine. However, commercial 1-naphthylamine made at that time may have contained 4-10% 2-naphthylamine [ref: 1]. Among a cohort of 906 men employed for at least one year between 1922 and 1970 in a dyestuffs plant in Italy, a considerable excess of bladder cancer deaths (27 observed, 0.19 expected) was observed among 151 workers involved in the manufacture of 1- and 2-naphthylamine and benzidine [ref: 2]. A case-control study of bladder cancer in the UK showed a significant, exposure-related increased risk for dyestuffs workers. 1-Naphthylamine was plausibly concerned, but it was not possible to single out any compound from the combined exposure to arylamines [ref: 3].

In view of the contamination of the commercial product and the mixed nature of the exposures investigated, it is not possible to assess the carcinogenicity of 1-naphthylamine alone.

B. Evidence for carcinogenicity to animals (*inadequate*)

1-Naphthylamine was tested for carcinogenicity mice, hamsters and dogs by oral administration and in newborn mice by subcutaneous injection. No carcinogenic effect was observed following oral administration to hamsters [ref: 1] or dogs [ref: 1,4,5] or in a lung adenoma bioassay in mice [ref: 6]. Inconclusive results were obtained after oral administration to adult mice and subcutaneous injection of newborn mice [ref: 1].

C. Other relevant data

No data were available on the genetic and related effects of 1-naphthylamine in humans.

1-Naphthylamine did not induce micronuclei in bone-marrow cells of mice treated *in vivo*; it induced DNA strand breaks in mice, but not in rats. 1-Naphthylamine increased the incidence of chromosomal aberrations in cultured rodent cells, but the results for sister chromatid exchanges, mutation and DNA damage were inconclusive; no cell transformation was induced in Syrian hamster embryo cells. It did not induce sex-linked recessive lethal mutations in *Drosophila*. It induced aneuploidy but not mutation in yeast; results for mitotic recombination were conflicting. It was mutagenic to bacteria [ref: 7].

Overall evaluation

1-Naphthylamine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Also see previous evaluation: Vol. 4 (1974)

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Synonyms

- 1-Aminonaphthalene
- Azoic diazo component 114
- Fast garnet B base
- Fast garnet base B
- Naphthalidam
- Naphthalidine
- α-Naphthylamine

Last updated: 11 March 1998

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 134–32–7
CAS No.	134–32–7
EINECS Name	1–naphthylamine
EINECS No.	205–138–7
Molecular Formula	C10H9N

Dataset created by: EUROPEAN COMMISSION – European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non–confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

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1.0.1 OECD and Company Information

-

1.0.2 Location of Production Site

-

1.0.3 Identity of Recipients

-

1.1 General Substance Information

Substance type: organic
Physical status: solid

1.1.1 Spectra

-

1.2 Synonyms

1-AMINONAPHTHALIN
Source: Bayer AG Leverkusen

1-NAPHTHALENAMINE
Source: Bayer AG Leverkusen

1-NAPHTHALINAMIN
Source: Bayer AG Leverkusen

1-NAPHTHYLAMIN
Source: Bayer AG Leverkusen

ALPHA-AMINONAPHTHALIN
Source: Bayer AG Leverkusen

ALPHA-NAPHTHAMIN
Source: Bayer AG Leverkusen

ALPHA-NAPHTHYLAMIN
Source: Bayer AG Leverkusen

1.3 Impurities

-

1.4 Additives

-

1.5 Quantity

-

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: Xn
N
other RM: H
Specific limits: no data
R–Phrases: (22) Harmful if swallowed
(51/53) Toxic to aquatic organisms, may cause long–term adverse effects in the aquatic environment
S–Phrases: (2) Keep out of reach of children
(24) Avoid contact with skin
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

1.6.2 Classification

Classification: as in Directive 67/548/EEC
Class of danger: corrosive
R–Phrases: (22) Harmful if swallowed

Classification: as in Directive 67/548/EEC
Class of danger: dangerous for the environment
R–Phrases: (51) Toxic to aquatic organisms
(53) May cause long–term adverse effects in the aquatic environment

1.7 Use Pattern
–

1.7.1 Technology Production/Use
–

1.8 Occupational Exposure Limit Values
–

1.9 Source of Exposure
–

1.10.1 Recommendations/Precautionary Measures
–

1.10.2 Emergency Measures
–

1.11 Packaging
–

1.12 Possib. of Rendering Subst. Harmless

-

1.13 Statements Concerning Waste

-

1.14.1 Water Pollution

Classified by: KBwS (DE)
Labelled by: KBwS (DE)
Class of danger: 2 (water polluting)
Source: Bayer AG Leverkusen

1.14.2 Major Accident Hazards

Legislation:
Substance listed: no
Source: Bayer AG Leverkusen

1.14.3 Air Pollution

Classified by: other: Bay
Labelled by: other: Bay
Number: 3.1.7 (organic substances)
Class of danger: I
Source: Bayer AG Leverkusen

1.15 Additional Remarks

-

1.16 Last Literature Search

-

1.17 Reviews

-

1.18 Listings e.g. Chemical Inventories

-

2.1 Melting Point

Value: 48 degree C
Method: other: DIN 51556
Source: Bayer AG Leverkusen
(1)

2.2 Boiling Point

Value: 301 degree C at 1013 hPa
Source: Bayer AG Leverkusen
(1)

2.3 Density

Type: density
Value: 1.15 g/cm3 at 20 degree C
Source: Bayer AG Leverkusen
(1)

Type: density
Value: 1.1 g/cm3 at 60 degree C
Source: Bayer AG Leverkusen
(1)

2.3.1 Granulometry

-

2.4 Vapour Pressure

Value: .003 hPa at 20 degree C
Remark: calculated
Source: Bayer AG Leverkusen
(1)

Value: .071 hPa at 50 degree C
Remark: calculated
Source: Bayer AG Leverkusen
(1)

Value: 1.33 hPa at 104 degree C
Source: Bayer AG Leverkusen
(2)

Value: 13.3 hPa at 154 degree C
Source: Bayer AG Leverkusen
(2)

2.5 Partition Coefficient

log Pow: 2.1
Method: other (calculated): Leo, Hansch: Leo, A.: CLOGP–3.54 MedChem Software 1989. Daylight, Chemical Information Systems, Claremont, CA 91711, USA
Year:
Source: Bayer AG Leverkusen

(3)

log Pow: 2.25
Method:
Year:
Remark: experimentally determined
Source: Bayer AG Leverkusen

(4)

2.6.1 Water Solubility

Value: 1.7 g/l at 20 degree C
Source: Bayer AG Leverkusen

(5)

2.6.2 Surface Tension

–

2.7 Flash Point

Value: 157 degree C
Type: closed cup
Method: other: DIN 51758
Year:
Source: Bayer AG Leverkusen

(1)

2.8 Auto Flammability

Value:
Remark: Ignition temperature approx. 460 degree C DIN 51794
Source: Bayer AG Leverkusen

(1)

2.9 Flammability

–

2.10 Explosive Properties

–

2.11 Oxidizing Properties

–

2.12 Additional Remarks

–

3.1.1 Photodegradation

-

3.1.2 Stability in Water

-

3.1.3 Stability in Soil

-

3.2 Monitoring Data (Environment)

-

3.3.1 Transport between Environmental Compartments

-

3.3.2 Distribution

-

3.4 Mode of Degradation in Actual Use

-

3.5 Biodegradation

Type: aerobic
Inoculum: predominantly domestic sewage, adapted
Concentration: 2.4 mg/l related to Test substance
Degradation: > 80 % after 20 day
Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year: 1977 **GLP:** no
Test substance:
Remark: related to BOD
Source: Bayer AG Leverkusen

(1)

Type: aerobic
Inoculum: other: activated sludge from laboratory treament unit fed with domestic sewage
Concentration: 3.2 mg/l related to Test substance
Degradation: 6 % after 28 day
Method: other: Directive 79/831 EEC, Annex V, C.4-E Closed bottle test
Year: 1993 **GLP:** yes
Test substance: other TS: 99.65 %
Source: Bayer AG Leverkusen

(1)

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg/l related to Test substance
Degradation: 0 % after 28 day
Method: other: see remark
Year: **GLP:** no data
Test substance:
Remark: Method:
"Biodegradation test of chemical substance by micro–organisms etc." stipulated in the Order Prescribing the Items of the Test Relating to the New Chemical Substance (1974, Order of the Prime Minister, the Minister of Health and Welfare, the MITI No. 1). This guideline corresponds to "301C, Ready Biodegradability: Modified MITI Test I" stipulated in the OECD Guidelines for Testing of Chemicals (May 12, 1981).
Sludge conc.: 30 mg/l
related to BOD
Source: Bayer AG Leverkusen

(6)

Type: aerobic
Inoculum: activated sludge
Concentration: 20 mg/l related to COD (Chemical Oxygen Demand)
Degradation: after 5 day
Result: other: no degradation
Method:
Year: **GLP:** no
Test substance:
Source: Bayer AG Leverkusen

(7)

3.6 BOD5, COD or BOD5/COD Ratio

C O D

COD: 2410 mg/g substance

Source: Bayer AG Leverkusen

(1)

3.7 Bioaccumulation

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 56 day
Concentration: .2 mg/l
BCF: 13 – 54
Elimination:
Method: other: see remark
Year: **GLP:** no data
Test substance:
Remark: % lipid, average: 6.5
Method: "Bioaccumulation test of chemical substance in fish and shellfish" stipulated in the Order Prescribing the Items of the Test Relating to the New Chemical Substance (1974, Order of the Prime Minister, the Minister of Health and Welfare, the MITI No. 1). This guideline corresponds to "305C, Bioaccumulation: Degree of Bioconcentration in Fish" stipulated in the OECD Guidelines for Testing of Chemicals (May 12, 1981).
Source: Bayer AG Leverkusen

(6)

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 56 day
Concentration: .02 mg/l
BCF: 9.1 – 27
Elimination:
Method:
Year: **GLP:** no data
Test substance:
Remark: % lipid, average: 6.5
Method: "Bioaccumulation test of chemical substance in fish and shellfish" stipulated in the Order Prescribing the Items of the Test Relating to the New Chemical Substance (1974, Order of the Prime Minister, the Minister of Health and Welfare, the MITI No. 1). This guideline corresponds to "305C, Bioaccumulation: Degree of Bioconcentration in Fish" stipulated in the OECD Guidelines for Testing of Chemicals (May 12, 1981).
Source: Bayer AG Leverkusen

(6)

3.8 Additional Remarks

-

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC0: 10
LC100: 20
Method: other: Bestimmung der akuten Wirkung von Stoffen auf Fische. Arbeitskreis "Fischtest" im Hauptausschuss "Detergentien" (15.10.73)
Year: 1973 **GLP:** no
Test substance:
Remark: range finding test
Source: Bayer AG Leverkusen

(1)

Type:
Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 70 hour(s)
Unit: **Analytical monitoring:**
LD0 : 91 – 109
Method:
Year: **GLP:** no
Test substance:
Remark: oral toxicity; unit: mg/kg
Source: Bayer AG Leverkusen

(8)

Type:
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period:
Unit: **Analytical monitoring:**
Method: other: static
Year: **GLP:**
Test substance:
Remark: Fingerlings
after 30 min at 5 mg/l stress
only concentration tested
Source: Bayer AG Leverkusen

(9)

Type:
Species: Oncorhynchus mykiss (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC0: 3
LC100: 6 – 8
Method: other: semi-static
Year: **GLP:**
Test substance:
Remark: age: 2 years old
Source: Bayer AG Leverkusen

(10)

Type:
Species: Oncorhynchus mykiss (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
LC0: >= 5
Method: other: static
Year: **GLP:**
Test substance:
Remark: Fingerlings; only conc. tested
Source: Bayer AG Leverkusen

(9)

Type:
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC50: 25
Method: other: Japanese Industrial Standard (JIS K 0102–1986–71) "Testing methods for industrial waste water"
Year: **GLP:** no data
Test substance:
Remark: water solubility: 640 mg/l
Source: Bayer AG Leverkusen

(6)

Type:
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 15
Method: other: static
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(11)

Type:
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 7
Method: other: static
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(11)

Type:
Species: Petromyzon marinus
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
LC0: >= 5
Method: other: static
Year: **GLP:**
Test substance:
Remark: Larvae; only concentration tested
Source: Bayer AG Leverkusen

(9)

4.2 Acute Toxicity to Aquatic Invertebrates

-

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Anacystis aeruginosa (Algae)
Endpoint: other: inhibition of photosynthesis
Exposure period: 4 hour(s)
Unit: mg/l **Analytical monitoring:**
EC20 : .22
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(12)

Species: Selenastrum capricornutum (Algae)
Endpoint: other: inhibition of photosynthesis
Exposure period: 4 hour(s)
Unit: mg/l **Analytical monitoring:**
EC20 : 1.7
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(12)

Species: other algae: Phytoplankton
Endpoint: other: inhibition of photosynthesis
Exposure period: 4 hour(s)
Unit: mg/l **Analytical monitoring:**
EC20 : .23
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(12)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas fluorescens (Bacteria)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: 100
Method: other: Bestimmung der biologischen Schadwirkung toxischer Abwaesser gegen Bakterien. DEV, L 8 (1968) modifiziert
Year: 1973 **GLP:** no
Test substance:
Source: Bayer AG Leverkusen

(1)

Type:
Species: Nitrosomonas sp. (Bacteria)
Exposure period:
Unit: mg/l **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: % inhibition of NH3-oxidation: 75 - 100 at 100 mg/l
45 at 10 mg/l
Source: Bayer AG Leverkusen

(13)

Type:
Species: Tetrahymena pyriformis (Protozoa)
Exposure period: 60 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: 86.53
Method: other: static
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(14)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

–

4.5.2 Chronic Toxicity to Aquatic Invertebrates

–

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

–

4.6.2 Toxicity to Terrestrial Plants

–

4.6.3 Toxicity to other Non–Mamm. Terrestrial Species

–

4.7 Biological Effects Monitoring

–

4.8 Biotransformation and Kinetics

–

4.9 Additional Remarks

Remark: Growth reduction compared to control:
Test conc.: 2 mg/l
Cylindrospermum licheniforme: reduced after 7 d,
no reduction after 3, 14, 21 d
Microcystis aeruginosa : no growth after 3, 7,
14, 21 d
Scenedesmus obliquus : reduced after 3 and 7 d,
no reduction after 14, 21 d
Chlorella variegata : no growth after 3 d,
reduced after 7 d,
no reduction after 14, 21 d
Nitzschia palea : no growth after 3 d,
reduced after 7 d,
no reduction after 14, 21 d
Gomphonema parvulum : no growth after 3, 7 d,
reduced growth after 14, 21 d

Source: Bayer AG Leverkusen

(15)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 680 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(16)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 779 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(17)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 300 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Wild Norway rats were used
Source: Bayer AG Leverkusen

(18)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > .056 mg/l
Method:
Year: **GLP:**
Test substance:
Remark: No toxicological symptoms at the highest concentration that could be produced as an aerosol. No animal died.
NOEL: 0.056 mg/l/4h.
Source: Bayer AG Leverkusen

(19)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 200 – 1000 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: sex: male
Source: Bayer AG Leverkusen

(20)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 447 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: sex: female
Source: Bayer AG Leverkusen

(20)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: = 620 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(21)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: = 96 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(22)

Type: other: LDLO
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: = 300 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(23)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method: other: (see remarks)
Year: **GLP:**
Test substance:
Remark: Exposure time: 24 h, ear, 500 mg/animal, semi–occlusive, observation time: 7 d.
Source: Bayer AG Leverkusen

(24)

5.2.2 Eye Irritation

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: slightly irritating
EC classificat.:
Method: other: other (see remarks)
Year: **GLP:**
Test substance:
Remark: 50 mg/animal, observation time: 7 d.
Source: Bayer AG Leverkusen

(24)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Number of Animals:
Vehicle:
Result: sensitizing
Classification:
Method: OECD Guide–line 406 "Skin Sensitization"
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(25)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: i.p.
Exposure period: 90 d
Frequency of treatment:
Post. obs. period: no data
Doses: 50 mg/kg bw/d
Control Group: other: no data
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 12/group
Result: 11/12 animals died probably after 2 years. The primary cause of death appeared to be methemoglobinemia. 1 case of leukemia was observed.
Source: Bayer AG Leverkusen

(26)

Species: mouse **Sex:** male
Strain: other: DVA
Route of admin.: oral unspecified
Exposure period: 4, 15, 30, 60, 100, 300, 360 d
Frequency of treatment: daily
Post. obs. period: keine
Doses: 2 mg/animal/d = ca. 100 mg/kg bw/d
Control Group: no
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 10–15/group
Result: 1–NA induced only a focal adiposity of the liver. No adenome could be detected.
Source: Bayer AG Leverkusen

(27) (28)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(29)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1538
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(30) (31) (32)

Type: Ames test
System of testing: S. typhimurium TA 92, TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(33)

Type: Ames test
System of testing: S. typhimurium TA 92, TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 100.
Source: Bayer AG Leverkusen
(33)

Type: Ames test
System of testing: S. typhimurium TA 1535, TA 1538
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(34)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(35)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive in strains TA 98, TA 100, TA 1538.
Source: Bayer AG Leverkusen
(35)

Type: Ames test
System of testing: S. typhimurium TA 98
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(36)

Type: Ames test
System of testing: S. typhimurium TA 1538, TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(37)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(38)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: S–9 mix: male S.–D. rats and male Syrian hamsters.
Source: Bayer AG Leverkusen

(39)

Type: Ames test
System of testing: S. typhimurium TA 100, TA 1535, TA 1538
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 100.
Source: Bayer AG Leverkusen

(40)

Type: Ames test
System of testing: S. typhimurium TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(41)

Type: Ames test
System of testing: S. typhimurium TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Superior activation by hamster liver homogenate. The mutagenic activity is lost in the presence of Amaranth.
Source: Bayer AG Leverkusen

(42) (43)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1536, TA 1537, TA 1538
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strains TA 98 and TA 100.
Source: Bayer AG Leverkusen

(44)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: S–9 mix from liver and bladder urothelial cells.
Source: Bayer AG Leverkusen

(45)

Type: Ames test
System of testing: S. typhimurium TA 98
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Irradiation did not produce mutagenic derivatives in S. typhimurium.
Source: Bayer AG Leverkusen

(46)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 1000, TA 1535, TA 1537, TA 1538, C 3076, D 3052, G 46
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(47)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(48)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strains TA 100 and TA 1538.
Source: Bayer AG Leverkusen

(48)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 100.
Source: Bayer AG Leverkusen

(21)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(49)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Weakly mutagenic only after metabolic activation.
Source: Bayer AG Leverkusen
(50)

Type: Ames test
System of testing: S. typhimurium TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive before and after purification of the compound.
Source: Bayer AG Leverkusen
(51)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(52)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 100.
Source: Bayer AG Leverkusen

(53)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 100.
Source: Bayer AG Leverkusen

(54)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1537
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 100 after metabolic activation.
Source: Bayer AG Leverkusen

(55)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 98 after metabolic activation.
Source: Bayer AG Leverkusen

(56)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1537
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(57)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1537
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(57)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(58)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive in strains TA 100, TA 1537, TA 1538.
Source: Bayer AG Leverkusen
(58)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 1535
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 98 after metabolic activation.
Source: Bayer AG Leverkusen

(59)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 1537
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 98 after metabolic activation.
Source: Bayer AG Leverkusen

(60)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Bovine bladder urothelial cells were used as activating system.
Source: Bayer AG Leverkusen

(61)

Type: Ames test
System of testing: S. typhimurium TA 100, TA 1538
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: The 24 h urine of male Wistar rats injected i.p. with 0.25 mmol/ kg = 36 mg/kg was examined.
Source: Bayer AG Leverkusen

(62)

Type: Ames test
System of testing: S. typhimurium TM 677
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Forward mutation assay.
Source: Bayer AG Leverkusen
(63)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Fluctuation Test:
With freshly prepared rat hepatocytes as an alternative metabolizing system, the test was negative.
Source: Bayer AG Leverkusen
(64)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(65)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(66)

Type: Ames test
System of testing: S. typhimurium TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Small genetic differences between B6 and D2 mice.
Source: Bayer AG Leverkusen
(67)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1538
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(30)

Type: Ames test
System of testing: S. typhimurium TA 98
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Bovine bladder and liver cells were used as metabolizing systems.
Source: Bayer AG Leverkusen
(68)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1538, C3076, D3052, G46
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(69)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 100 after metabolic activation.
Source: Bayer AG Leverkusen
(70)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 1535
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Weakly positive only in strain TA 98.
Source: Bayer AG Leverkusen
(71) (72)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 1535
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: The microsomal fraction of ram seminal vesicles, a rich source of prostaglandin endoperoxide synthetase, was used as activating system.
2–NA was mutagenic under similar conditions.
Source: Bayer AG Leverkusen
(71) (72)

Type: Ames test
System of testing: S. typhimurium TA 1538
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Porcine hepatocyte microsomal fraction and porcine hepatocyte nuclei were used as activating systems.
Source: Bayer AG Leverkusen

(73)

Type: Ames test
System of testing: S. typhimurium TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(70)

Type: Ames test
System of testing: s. thyphimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration:
Metabolic activation:
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: TA 98 and TA 1538 after induction with Aroclor 1254, and TA 100 after induction with phenobarbital showed positive results.
Source: Bayer AG Leverkusen

(74)

Type: Ames test
System of testing: S. thyphimurium TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(70)

Type: Ames test
System of testing: S. typhimurium TA 100
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Liver S–9 mix from female B6 and D2 mice was used. 1–NA showed only very small differences between the two strains of mice.
Source: Bayer AG Leverkusen

(75)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 1535
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Weakly positive in strain TA 98. When the microsomal fraction from ram seminal vesicles was used as the activation system, 1–NA showed no mutagenic activity.
Source: Bayer AG Leverkusen

(76)

Type: Ames test
System of testing: S. typhimurium TA 1538
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(77)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: 1-NA was treated with 4 equivalent amounts of nitrite at ph 3 and 37 C for 4 h, the conditions recommended by the WHO (1978).
Source: Bayer AG Leverkusen

(78)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only in strain TA 100 after metabolic activation
Source: Bayer AG Leverkusen

(79)

Type: Unscheduled DNA synthesis
System of testing: Mouse testicular cells
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(80) (81)

Type: Unscheduled DNA synthesis
System of testing: Rat hepatocytes
Concentration:
Metabolic activation:
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(82)

Type: Unscheduled DNA synthesis
System of testing: Rat hepatocytes
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(47)

Type: Unscheduled DNA synthesis
System of testing: Mouse hepatocytes
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(83)

Type: Unscheduled DNA synthesis
System of testing: Hamster hepatocytes
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(83)

Type: Unscheduled DNA synthesis
System of testing: Hamster hepatocytes
Concentration:
Metabolic activation:
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(84) (85) (86)

Type: Unscheduled DNA synthesis
System of testing: Rat hepatocytes
Concentration:
Metabolic activation:
Result: ambiguous
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(84) (85)

Type: Unscheduled DNA synthesis
System of testing: HeLa cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(87)

Type: Unscheduled DNA synthesis
System of testing: HeLa cells
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(87)

Type: Unscheduled DNA synthesis
System of testing: Human fibroblasts (WI–38 cells)
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive after metabolic activation.
Source: Bayer AG Leverkusen
(88)

Type: Unscheduled DNA synthesis
System of testing: Human fibroblasts
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(89) (90)

Type: Unscheduled DNA synthesis
System of testing: Rat hepatocytes
Concentration:
Metabolic activation: without
Result: ambiguous
Method:
Year: **GLP:**
Test substance:
Remark: Purity of the compound: 90 %.
Source: Bayer AG Leverkusen
(91)

Type: Unscheduled DNA synthesis
System of testing: Hamster hepatocytes
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Purity of the compound: 90 %.
Source: Bayer AG Leverkusen
(91)

Type: Unscheduled DNA synthesis
System of testing: Rat hepatocytes
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(92)

Type: Unscheduled DNA synthesis
System of testing: Human fibroblastes (WI–38 cells)
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(93)

Type: other: 6TG–Resistance Mutation
System of testing: L5178Y mouse lymphoma cells
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(94)

Type: other: Anchorage Independent Growth
System of testing: Human neonatal foreskin fibroblast cells
Concentration:
Metabolic activation: with and without
Result: ambiguous
Method:
Year: **GLP:**
Test substance:
Remark: Human liver S–9 mix was used.
Source: Bayer AG Leverkusen
(95) (96)

Type: other: Arabi dopsis–Test
System of testing: Columbia wild type of Arabi dopsis
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(97)

Type: other: Cell Transformation
System of testing: Syrian Hamster Kidney Cells = BHK-21
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(98)

Type: other: Cell Transformation
System of testing: Baby Hamster Kidney Cells = BHK-21C13/HRC 1
Concentration:
Metabolic activation: with and without
Result: ambiguous
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(99)

Type: other: Cell Transformation
System of testing: Syrian Hamster Kidney Cells = BHK 21/cl 13
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(31) (32)

Type: other: Cell Transformation
System of testing: Syrian Golden Hamster Embryo Cells
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(100) (101) (102)

Type: other: Cell Transformation
System of testing: Mouse mammary glands
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: The transforming activity was only moderate.
Source: Bayer AG Leverkusen
(103)

Type: other: Cell Transformation
System of testing: Human neonatal foreskin
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(104)

Type: other: Chromosome Aberrations
System of testing: CHL cells
Concentration:
Metabolic activation: without
Result: ambiguous
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(105)

Type: other: Chromosome Aberrations
System of testing: Rat liver RL1 cells
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(106)

Type: other: Chromosome Aberrations
System of testing: CHO cells
Concentration:
Metabolic activation:
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(107)

Type: other: Chromosome Aberrations
System of testing: CHO cells
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive after metabolic activation.
Source: Bayer AG Leverkusen
(108)

Type: other: Chromosome Aberrations
System of testing: Bloom syndrome B–lymphoblastoid cell lines type I, II, III
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(109)

Type: other: DNA Amplification
System of testing: SV40–transformed Chinese Hamster embryo cell lines
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(110)

Type: other: DNA Damage
System of testing: Rat hepatocytes
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Alkaline elution assay:
Positive only at cytotoxic doses.
Source: Bayer AG Leverkusen
(111)

Type: other: DNA Damage
System of testing: B. subtilis H17, M45
Concentration:
Metabolic activation: with and without
Result: ambiguous
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(112)

Type: other: DNA Damage
System of testing: E. coli WP2, WP2uvrA, WP67, CM611, WP100, W3110, p3478
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(113)

Type: other: DNA Damage
System of testing: B. subtilis H17/M45, HLL3g/HJ-15 E. coli AB1157, JC5547, JC2921, JC2926, JC5519
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(114)

Type: other: DNA Damage
System of testing: V79 cells
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Alkaline elution assay:
Rat liver S-9 mix was used.
Source: Bayer AG Leverkusen

(115)

Type: other: DNA Damage
System of testing: Human lung fibroblasts CCD-18Lu, A 549
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: The cells were activated by ozone
Source: Bayer AG Leverkusen

(116)

Type: other: DNA Damage
System of testing: Human lung fibroblastes CCD-18 Lu
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: The cells were activated by hypochlorous acid. Hypochlorous acid can be produced during an inflammatory response.
Source: Bayer AG Leverkusen

(117)

Type: other: DNA Repair Test
System of testing: E. coli WP2, WP67 uvrA polA, CM871 uvrA recA lexA
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen

(118)

Type: other: DNA Repair Test
System of testing: E. coli WP2, WP67 uvrA polA, CM871 uvrA recA lexA
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: The compound gave a questionable effect without S9.
Source: Bayer AG Leverkusen
(119)

Type: other: DNA Repair Test
System of testing: E. coli WP2, WP67, CM871
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: The compound showed only a weak mutagenic reaction.
Source: Bayer AG Leverkusen
(66)

Type: other: DNA Repair Test
System of testing: Hepatocytes
Concentration:
Metabolic activation:
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: The "nuclei procedure" was used.
Source: Bayer AG Leverkusen
(120)

Type: other: DNA Repair Test
System of testing: E. coli P3478
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(121)

Type: other: DNA Repair Test
System of testing: E. coli pol A1–
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(122)

Type: other: DNA Repair Test
System of testing: Hepatocytes
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(123)

Type: other: Degranulation Assay (Rabin Test)
System of testing: Rat liver postmitochondrial supernatant
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(124)

Type: other: Degranulation Assay (Rabin Test)
System of testing: Rat liver rough endoplasmic reticulum
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(31) (32)

Type: other: Enhancement of Adeno Virus Transform.
System of testing: Syrian hamster embryo cells
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(125)

Type: other: Enhancement of MLV Infection
System of testing: Contact inhibited C3H2K cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: MSV–MLV = Moloney mouse sarcoma leukemia complex.
Source: Bayer AG Leverkusen
(126)

Type: other: Gene–Mutation
System of testing: CHL V79 cells
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Bovine bladder urothelial cells were used as activating system.
Source: Bayer AG Leverkusen
(61)

Type: other: Induction of Diphtheria Toxin Resistance
System of testing: Human lung fibroblast cells (HSC172)
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(127)

Type: other: Induction of Petite Mutants
System of testing: S. cerevisiae D273–10B
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Udenfriend hydroxylation medium was used.
Source: Bayer AG Leverkusen
(128)

Type: other: L–Arabinose Resistance Test
System of testing: S. typhimurium BA 13
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(129)

Type: other: Micronucleus Test
System of testing: Tradescantia paludosa Sax clone 03
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(130)

Type: other: Mitotic Aneuploidy Assay
System of testing: S. cerevisiae D6
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive after metabolic activation.
Source: Bayer AG Leverkusen
(131) (132)

Type: other: Mitotic Crossing Over
System of testing: S. cerevisiae D3
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Udenfriend hydroxylation medium was used.
Source: Bayer AG Leverkusen
(133)

Type: other: Mitotic Gene Conversion
System of testing: S. cerevisiae D7
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive after metabolic activation.
Source: Bayer AG Leverkusen
(134)

Type: other: Mitotic Gene Conversion
System of testing: S. cerevisiae JD1
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(135)

Type: other: Mitotic Recombination
System of testing: S. cerevisiae D3
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(136)

Type: other: Mitotic Recombination
System of testing: S. cerevisiae T1, T2
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(137)

Type: other: Mitotic Recombination
System of testing: S. cerevisiae T4, T5
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Rep–Test.
Source: Bayer AG Leverkusen
(137)

Type: other: Mutations of Mitochondrial DNA
System of testing: S. cerevisiae
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: No induction of mitochondrial petite mutations could be observed
Source: Bayer AG Leverkusen
(138)

Type: other: Point–Mutation
System of testing: B. subtilis TKJ5211
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(139)

Type: other: Point–Mutation
System of testing: E. coli WP2, WP2 uvrA–
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(140)

Type: other: Point–Mutation
System of testing: CHO–AT3–2 cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(141)

Type: other: Point–Mutation
System of testing: CHO–AT3–2 cells
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(141)

Type: other: Point–Mutation
System of testing: L5178Y mouse lymphoma cells
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(142)

Type: other: Point-Mutation
System of testing: E. coli WP2
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only after metabolic activation.
Source: Bayer AG Leverkusen
(35)

Type: other: Point-Mutation
System of testing: Chinese hamster V79 cells
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Positive only after metabolic activation.
Source: Bayer AG Leverkusen
(143) (144)

Type: other: Point-Mutation
System of testing: E. coli A11, A12, A23, A53, B6, B14, B36
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(26)

Type: other: Point-Mutation
System of testing: E. coli WP2 uvrA
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(60)

Type: other: Point–Mutation
System of testing: E. coli 343/113/uvrB, 343/113/uvrB/leu8 (pKM101)
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(145)

Type: other: Point–Mutation
System of testing: E. coli WP2, WP2uvrA
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(65)

Type: other: Point–Mutation
System of testing: E. coli WP2 uvrA, WP2 uvrA/pKM101, WP2 B/r
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(146)

Type: other: Point–Mutation
System of testing: N. crassa 74–OR60–29A, 74–OR31–16A
Concentration:
Metabolic activation:
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Weakly positive only in vegetative cells.
Source: Bayer AG Leverkusen
(147)

Type: other: Point–Mutation
System of testing: E. coli WP2, WP2 uvrA–
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(69)

Type: other: Pol–Assay
System of testing: E. coli
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(34)

Type: other: Pol–Assay
System of testing: E. coli W3110, P3478
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Liquid Suspension Assay:
Weakly positive only after metabolic activation.
Source: Bayer AG Leverkusen
(148)

Type: other: Prophage Induction Test
System of testing: E. coli K12 envA uvrB
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(149)

Type: other: Prophage Induction Test
System of testing: E. coli 58–161 envA, C600
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(150)

Type: other: Rec–Assay
System of testing: B. subtilis HLL3g (wild), HJ–15
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(139)

Type: other: Rec–Assay
System of testing: Spores of B. subtilis H17, M45
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(151) (152)

Type: other: Rec–Assay
System of testing: E. coli JC 2921, JC 9238, JC 8471, JC 5519, JC 7689, JC 7623
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(153)

Type: other: Rec–Assay
System of testing: B. subtilis
Concentration:
Metabolic activation: without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(154)

Type: other: SCE–Test
System of testing: CHO cells
Concentration:
Metabolic activation:
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(107)

Type: other: SCE–Test
System of testing: CHO cells
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Remark: Weakly positive after metabolic activation.
Source: Bayer AG Leverkusen
(108)

Type: other: SCE–Test
System of testing: CHO cells
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(155)

Type: other: SCE–Test
System of testing: Bloom syndrome B–lymphoblastoid cell lines type I, II, III
Concentration:
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(109)

Type: other: SOS Chromotest
System of testing: E. coli PQ37
Concentration:
Metabolic activation: with
Result: positive
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(156)

Type: other: Umu Gene Expression Test
System of testing: S. typhimurium TA 1535/pSK1002
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(157) (158)

Type: other: Umu Gene Expression Test
System of testing: S. typhimurium TA 1535/pSK1002
Concentration:
Metabolic activation: with
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(159)

Type: other: Yeast Forward–Mutation Assay
System of testing: S. pombe P1
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(160)

Type: other: Yeast Reversion Assay
System of testing: S. cerevisiae XV185–14C
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(161)

Type: other: Zorotest
System of testing: E. coli EMT–1, EMT–2. EMT–3, EMT–4 under the control of lambda prophage repressors
Concentration:
Metabolic activation: with
Result: ambiguous
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(162)

Type: other: tRNA Acceptance Assay
System of testing: tRNA for L–methionine
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: Bayer AG Leverkusen
(163)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: mouse **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: up to 48 h
Doses: 12.5, 25, 50 mg/kg
Result:
Method: other: see remark
Year: **GLP:**
Test substance:
Remark: Mice were injected i.p. with the agent at 0 and 24 h. Bone marrow smears were made 30 to 48 h after dosing.
No. of animals: 8/group.
Result: The compound gave questionable results.
Source: Bayer AG Leverkusen

(164)

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain:
Route of admin.: i.p.
Exposure period: 30 h
Doses: 12.5, 25, 50 mg/kg
Result:
Method: other: see remark
Year: **GLP:**
Test substance:
Remark: No. of animals: 2 m, 2 f/group.
The substance was administered i.p. twice, 24 h apart. The animals werde killed 6 h after the second application
Result: No clastogenic activity could be detected.
Source: Bayer AG Leverkusen

(165)

Type: Micronucleus assay
Species: mouse **Sex:** no data
Strain:
Route of admin.: i.p.
Exposure period: 48, 72, 96 h or 30, 48, 72 h
Doses: 80 and 50 % of LD50 or 75 and 50 % of LD50
Result:
Method: other: see remarks
Year: **GLP:**
Test substance:
Remark: No. of animals: 5/test.
To improve the sensitivity of the assay, in the 1. phase, mice were injected i.p. with the agent at 0 and 24 h, and samples were taken at 48, 72 and 96 h. If there was a significant increase in the frequency of micronuclei at any sample time, then the treatment was repeated. If no increase in the micronucleus frequency was detected in phase 1 or the confirmation test, then a single treatment was given and samples were taken at 30, 48, and 72 h (phase 2).
Result: The response was negative for both phases, and therefore the compound was classified as non–clastogenic.

Source: Bayer AG Leverkusen
(166)

Type: Micronucleus assay
Species: mouse **Sex:** no data
Strain:
Route of admin.: oral unspecified
Exposure period: 24 h
Doses: MTD (dose not mentioned)
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: no data.
Weanling mice were treated by the maximum tolerated dose. Bone marrow smears were examined for micronuclei, and sections of bladder, colon, liver and lung were examined for isolated nuclear anomalies.
Result: No adverse effects could be detected.
Source: Bayer AG Leverkusen
(167)

Type: Micronucleus assay
Species: mouse **Sex:** female
Strain:
Route of admin.: i.p.
Exposure period: 5 d
Doses: up to 300 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 4/dose.
Result: No clastogenic activity could be detected.
Source: Bayer AG Leverkusen
(70)

Type: Micronucleus assay
Species: mouse **Sex:** no data
Strain:
Route of admin.: i.p.
Exposure period: no data
Doses: 25 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: No data
Result: A questionable result was obtained
Source: Bayer AG Leverkusen
(168)

Type: other: Cell Transformation
Species: mouse **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: 4 d
Doses: 25 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 6/group
Result: 1–NA was dissolved in 1 ml PBS containing 100 mg phorbol 12–myriate 13–acetate diester and administered i.p.. Macrophages were collected by repeated peritoneal lavage 4 days later and were cultivated. 5–6 days later normal and transformed cells could be distinguished. 1–NA gave a positive result in this assay. In addition, several immortal cell lines could be established from NMRI mice treated with 1–NA. Athymic nu/nu mice injected subcutaneously with these cells developed tumors.
Source: Bayer AG Leverkusen

(169)

Type: other: Chromosomal Damage (bone marrow)
Species: rat **Sex:** no data
Strain:
Route of admin.: other
Exposure period: no data
Doses: no data
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: no data.
Result: negative
Source: Bayer AG Leverkusen

(79) (170)

Type: other: DNA Adduct Formation
Species: dog **Sex:** male
Strain:
Route of admin.: oral unspecified
Exposure period: 2 d
Doses: 60 micromole/kg bw = ca. 8.64 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: no data.
Result: Adduct formation from 1–NA was not detected in urothelial DNA and only very low levels were found in hepatic DNA.
Source: Bayer AG Leverkusen

(171) (172)

Type: other: DNA Damage
Species: rat **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: 4 h
Doses: 400 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 6.
Result: No statistically significant DNA damage in liver cells, tested by alkaline elution assay, was observed.
Light microscopy of histological preparations revealed areas of necrosis (clearly evident but of limited size) in the livers of the rats.
Source: Bayer AG Leverkusen

(21)

Type: other: DNA Damage
Species: mouse **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: 4 h
Doses: 150 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: Unpurified 1–naphthylamine was used, containing about 10 % of 2–naphthylamine.
No. of animals: 12/group.
Result: Single–strand breaks could be detected in the livers and in the kidneys; but not in the lung.
Source: Bayer AG Leverkusen

(173)

Type: other: DNA Damage
Species: mouse **Sex:** no data
Strain:
Route of admin.: i.p.
Exposure period: 4 h
Doses: 75, 150 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 4/group
Result: Single–stranded DNA breaks in liver and kidneys.
Source: Bayer AG Leverkusen

(174)

Type: other: DNA Fragmentation
Species: rat **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: 4, 12, 24 h
Doses: 413 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: no data.
Result: Viscometrically–detected DNA damage in the livers of rats could not be observed.
Source: Bayer AG Leverkusen

(175)

Type: other: Host–Mediated Mutagenicity
Species: mouse **Sex:** male
Strain:
Route of admin.: i.m.
Exposure period: 4 h
Doses: 125 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 4–6/group.
Result: Assay with S. typhimurium TA 1530 and TA 1538 negative.
Source: Bayer AG Leverkusen

(176)

Type: other: Host–Mediated Mutagenicity
Species: mouse **Sex:** no data
Strain:
Route of admin.: oral unspecified
Exposure period: 4 h
Doses: 167 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Result: Assay with S. thyphimurium TA 1538: positive
Assay with S. cerevisiae D 3: negative
Source: Bayer AG Leverkusen

(176)

Type: other: Implant Test
Species: mouse **Sex:** male/female
Strain:
Route of admin.: s.c.
Exposure period: 90 d
Doses: 2,9 mg/animal
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 10/sex
Result: S.c. implantation in of Milliporefilter discs overlaid with a gelatinous suspension of the test compound. The tissue surrounding the implant showed no alterations.
Source: Bayer AG Leverkusen
(31) (32)

Type: other: Induction of Resistant Hepatocytes
Species: rat **Sex:** no data
Strain:
Route of admin.: other
Exposure period: 12 h
Doses: 400 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 10/group.
Result: 1–NA showed a significant difference only in the no. of gamma–glutamyl transferase–positive foci but not in the area and size.
Source: Bayer AG Leverkusen
(177)

Type: other: Promoting Activity Test
Species: rat **Sex:** male
Strain:
Route of admin.: gavage
Exposure period: 48 h
Doses: 15 to 30 % of LD50
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 6–9/group.
Result: 1–NA showed no promoting activity in rat adrenocortical epithelia.
Source: Bayer AG Leverkusen
(178)

Type: other: Promoting Activity Test
Species: hamster **Sex:** no data
Strain:
Route of admin.: gavage
Exposure period: 48 h
Doses: 15 to 30 % of LD50
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 6–9/group.
Result: 1–NA showed a promoting activity in hamster adrenocortical epithelia.
Source: Bayer AG Leverkusen

(178)

Type: other: Recessive Lethal Test
Species: Drosophila melanogaster **Sex:** no data
Strain:
Route of admin.: unspecified
Exposure period:
Doses: no data
Result:
Method:
Year: **GLP:**
Test substance:
Result: No induction of mutations could be observed.
Source: Bayer AG Leverkusen

(179)

Type: other: Recessive Lethal Test
Species: Drosophila melanogaster **Sex:** male
Strain:
Route of admin.: other
Exposure period: 48 h
Doses: 250, 850 ppm
Result:
Method:
Year: **GLP:**
Test substance:
Result: No indication of mutagenicity could be detected.
Source: Bayer AG Leverkusen

(180)

Type: other: Recessive Lethal Test
Species: Drosophila melanogaster **Sex:** male
Strain:
Route of admin.: other
Exposure period: 3 d
Doses: 0.1 %
Result:
Method:
Year: **GLP:**
Test substance:
Result: Delayed mortality of treated males was observed. No mutagenic activity could be detected.
Source: Bayer AG Leverkusen

(181)

Type: other: SCE Induction
Species: mouse **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: 24 h
Doses: 37.5, 75 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: no data.
Result: A significant and dose–dependent induction of SCE‘s in bone– marrow cells was observed.
Source: Bayer AG Leverkusen

(182)

Type: other: SCE Induction
Species: mouse **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: up to 54 h
Doses: 0.03, 0.08, 0.2, 0.7, 2.1, 6.2, 18.7, 56.0 mg/kg
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 2/group.
Result: No induction of SCE‘s in bone marrow or liver cells was observed.
Source: Bayer AG Leverkusen

(183)

Type: other: SCE Induction
Species: rabbit **Sex:**
Strain:
Route of admin.: gavage
Exposure period: no data
Doses: 5 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: no data
Result: No significant rise in the number of exchanges of sister chromatids was observed.
Source: Bayer AG Leverkusen

(184)

Type: other: SCE Induction
Species: mouse **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: no data
Doses: 1, 5, 10, 30, 60, 120 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: no data
Result: No effect of 1–NA was noted.
Source: Bayer AG Leverkusen

(185)

Type: other: Sebaceous Gland Test
Species: mouse **Sex:** male
Strain:
Route of admin.: dermal
Exposure period: 3 d
Doses: 6 x 0,4 mg/animal
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 10
Result: No significant depression of the ratio of sebaceous glands to hair follicles.
Source: Bayer AG Leverkusen

(32) (186)

Type: other: Sperm Abnormality Assay
Species: mouse **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: 5 d
Doses: up to 300 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 4/group.
Result: The mice were killed on the 35th. d after the last injection. 1–NA gave a positive increase in the frequency of sperm abnormalities.
Source: Bayer AG Leverkusen

(70)

Type: other: Sperm Abnormality Assay
Species: mouse **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: 5 d
Doses: 10, 25, 50, 100 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 5/dose.
Result: 1–NA gave a questionable result.
Source: Bayer AG Leverkusen

(187)

Type: other: Sperm Abnormality Assay
Species: mouse **Sex:** male
Strain:
Route of admin.: i.p.
Exposure period: 5 d
Doses: 25, 50, 100, 200, 400 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 4/dose.
Result: 1–NA gave a negative result.
Source: Bayer AG Leverkusen

(188) (189)

Type: other: Tetrazolium Reduction Test
Species: mouse **Sex:** male
Strain:
Route of admin.: dermal
Exposure period: 1 d
Doses: 1 mg/animal
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 10
Result: No indication of a positive response.
Source: Bayer AG Leverkusen

(31) (32)

Type: other: Thymidine Incorporation Inhibition
Species: mouse **Sex:** no data
Strain:
Route of admin.: gavage
Exposure period: 24 h
Doses: 130 mg/kg bw
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 3/group.
Result: 1–NA did not show a suppresive effect on the nuclear DNA synthesis in renal tubular or liver epithelium.
Source: Bayer AG Leverkusen

(190)

Type: other: Thymidine Incorporation Inhibition
Species: mouse **Sex:** no data
Strain:
Route of admin.: i.p.
Exposure period: 15 h
Doses: 15 to 30 % of LD50
Result:
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 3/group.
Result: 1–NA showed a suppressive effect in liver and kidney–epithelium.
Source: Bayer AG Leverkusen

(191)

5.7 Carcinogenicity

Species: rat **Sex:** male
Strain: Osborne–Mendel
Route of admin.: dermal
Exposure period: 52 w
Frequency of treatment: 2 d/w
Post. obs. period: 1 a
Doses: 1.5 mg/animal = ca. 4–15 mg/kg bw/d
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 6/group.
The animals were painted on the dorsal skin.
Result: No tumors developed on the treated skin or at other sites in any of the rats.
Source: Bayer AG Leverkusen

(192)

Species: rat **Sex:** male/female
Strain: Sprague–Dawley
Route of admin.: dermal
Exposure period: 52 w
Frequency of treatment: 2 d/w
Post. obs. period: 1 a
Doses: 1.5 mg/animal/d = ca. 4–15 mg/kg bw/d
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 6/sex/group.
The rats were painted on the dorsal skin. In addition the painted area was wounded once each week by 4 paralle cuts.
Result: None of the rats developed any tumors of the skin or any other site that could be observed on full postmortem examination.
Source: Bayer AG Leverkusen

(192)

Species: mouse **Sex:** male/female
Strain: no data
Route of admin.: drinking water
Exposure period: 84 w
Frequency of treatment: daily
Post. obs. period: none
Doses: 0.01 % = ca. 30 mg/kg bw/d
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 61/sex.
Result: The treatment did not induce tumors other than the liver. The incidence of hepatomas was in males 4/18, in the controls 4/24; in females the incidence was 5/43 compared to 0/36 in the controls. The yield of hepatomas and the latent period of their induction was not significantly different from that in animals kept without treatment.
Source: Bayer AG Leverkusen

(193) (194)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: i.p.
Exposure period: 90 d
Frequency of treatment: 2 d/w
Post. obs. period: up to 21 m
Doses: 50 mg/kg bw
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 12/group.
Result: The animals were examined at death or when tumors were palpable. No notable carcinogenic effects could be detected.
Source: Bayer AG Leverkusen

(26)

Species: rat **Sex:** female
Strain: Sprague–Dawley
Route of admin.: i.p.
Exposure period: 1 d
Frequency of treatment: –
Post. obs. period: 21 d
Doses: 500 micromol/kg = ca. 72 mg/kg bw
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 3–5/group.
Result: It was found that carcinogen–treatment induced the circulation of a 60–kd oncofetal protein in the plasma of rats. 1–NA did not induce the formation of the protein, whereas 2–NA did increase the relative plasma activity of this tumor marker.
Source: Bayer AG Leverkusen

(195)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: i.p.
Exposure period: 1 d
Frequency of treatment: –
Post. obs. period: no
Doses: 20 mg/kg bw
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 5/group.
Result: It appears that a relationship exists between the carcinogenicity of aromatic amines and their ability to induce hepatic P450 I activity. 1–NA and 2–NA had no effect on either total cytochrome P450 or microsomal protein levels. The O–deethyl– ation of ethoxyresorufin, however, was induced by both amines, with 2–NA being by far the more potent. Only 2–NA enhanced the dealkylation of pentoxyresorufin. Both amines enhanced the debenzylation of benzyloxyresorufin. Both amines also enhanced the transformation of the premutagen Glu–P–1 to mutagens. The poor mutagenicity of 1–NA reflects very low N–hydroxylation of this compound by hepatic microsomal preparations.
Source: Bayer AG Leverkusen

(196)

Species: mouse **Sex:** male/female
Strain: other: A/St
Route of admin.: i.p.
Exposure period: 8 w
Frequency of treatment: 3 d/w
Post. obs. period: 16 w
Doses: 12.5, 25, 50 mg/kg bw
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 10/sex/dose.
Result: No significant increase in surface lung tumors resulted from the injection of the compound.
Source: Bayer AG Leverkusen

(197)

Species: rabbit **Sex:** no data
Strain: no data
Route of admin.: inhalation
Exposure period: ca. 6–24 m
Frequency of treatment: daily
Post. obs. period: no
Doses: 100 g evaporated daily
Result:
Control Group: other: no data
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: probably 2; continous whole body exposure. No data about the purity of the compound (probably technical 1–NA) and about the actual concentration in the air.
Result: One animal died after 20 m of exposure. A benign polyp was found at bottom of the urinary bladder. The polyp was formed by a massing connective tissue, covered with several layers of irregular squamous epithelium. In addition there was a severe inflammation of the mucosa. The fate of possible other rabbits, exposed to 1–NA, cannot explicitly deduced from the text.
Source: Bayer AG Leverkusen

(198)

Species: dog **Sex:** no data
Strain: no data
Route of admin.: oral feed
Exposure period: 9 a
Frequency of treatment: 3 d/w
Post. obs. period: no data
Doses: 500 mg/animal/d = ca. 50 mg/kg bw/d
Result:
Control Group: no data specified
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 3.
The compound contained 3–5 % 2–naphthylamine.
Result: After 9 years 1 dog had a bladder papilloma. (No other informations).
Source: Bayer AG Leverkusen

(199)

Species: other: golden hamster **Sex:** male/female
Strain: other: Syrian
Route of admin.: oral feed
Exposure period: lifespan
Frequency of treatment: daily
Post. obs. period: none
Doses: 1000 ppm
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 30/sex/group.
Result: Administration of the compound failed to produce any significant carcinogenic effect.
Source: Bayer AG Leverkusen

(200)

Species: other: golden hamster **Sex:** male/female
Strain: other: Syrian
Route of admin.: oral feed
Exposure period: 70 w
Frequency of treatment: daily
Post. obs. period: no data
Doses: 10000 ppm
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 30/sex/group.
Result: No bladder or liver lesions have been found with the compound. (No other informations).
Source: Bayer AG Leverkusen

(201)

Species: mouse **Sex:** male
Strain: other: C57xIF
Route of admin.: oral unspecified
Exposure period: up to 6 w
Frequency of treatment: 6 d/w
Post. obs. period: none
Doses: 1 mg/animal/d = 50 mg/kg bw/d
Result:
Control Group: no
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 2–3/group
Result: 1–NA did not induce hyperplastic changes in the bladders of mice
Source: Bayer AG Leverkusen

(202)

Species: dog **Sex:** no data
Strain: no data
Route of admin.: oral unspecified
Exposure period: 4.5 a
Frequency of treatment: 5 d/w
Post. obs. period: none
Doses: 301 mg/animal/d = ca. 30 mg/kg bw/d
Result:
Control Group: other: no data
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 3.
The pure compound was tested.
Result: The compound was administered in gelatine capsules. No bladder tumors could be detected. (No other informations).
Source: Bayer AG Leverkusen

(203)

Species: dog **Sex:** no data
Strain: no data
Route of admin.: oral unspecified
Exposure period: 4.5 a
Frequency of treatment: 5 d/w
Post. obs. period: none
Doses: 330 mg/animal/d = ca. 33 mg/kg bw/d
Result:
Control Group: other: no data
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 2.
The technical product was tested.
Result: The compound was administered in gelatine capsules. No bladder tumors could be detected. (No other informations).
Source: Bayer AG Leverkusen

(203)

Species: dog **Sex:** male/female
Strain: Beagle
Route of admin.: oral unspecified
Exposure period: 9 a
Frequency of treatment: 5 d/w
Post. obs. period: none
Doses: 15 mg/kg bw/d
Result:
Control Group: no
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 3/sex.
The pure compound was tested.
The compound was administered in gelatine capsules.
Result: At autopsy, no tumors or other pathological changes were observed in the bladders of any of these animals. With the possible exception of the excessive accumulation of lipofuscin in the hepatocytes of these dogs, no test compound related pathological changes in other tissues of the body were observed.
Source: Bayer AG Leverkusen

(204)

Species: dog **Sex:** male/female
Strain: Beagle
Route of admin.: oral unspecified
Exposure period: up to 109 m
Frequency of treatment: 5 d/w
Post. obs. period: 19 m
Doses: 400 mg/animal/d = ca. 20 mg/kg bw/d
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 4/sex/group.
The compound was administered in gelatine capsules and contained 6% of 2–naphthylamine as contamination.
Result: 2/8 dogs developed early carcinomas of the bladder.
Histopathological examinations of the other organs revealed no compound–related changes.
Source: Bayer AG Leverkusen

(205)

Species: dog **Sex:** male/female
Strain: Beagle
Route of admin.: oral unspecified
Exposure period: up to 109 m
Frequency of treatment: 5 d/w
Post. obs. period: 19 m
Doses: 400 mg/animal/d = 20 mg/kg bw/d
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 4/sex/group.
The compound was administered in gelatine capsules and contained 0.5% of 2–naphthylamine as contamination.
Result: 2/8 dogs developed solitary haemangiomas arising in the submucosa and protruding into the bladder lumen.
Histopathological examinations of the other organs revealed no compound–related changes.
Source: Bayer AG Leverkusen

(205)

Species: dog **Sex:** male/female
Strain: Beagle
Route of admin.: oral unspecified
Exposure period: up to 109 m
Frequency of treatment: 5 d/w
Post. obs. period: 19 m
Doses: 400 mg/animal/d = ca. 20 mg/kg bw/d
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 4/sex/group.
The compound was adminestered in gelatine capsules and contained purified 1–naphthylamine.
Result: Histopathological examinations of the bladder and the other organs revealed no compound–related changes.
Source: Bayer AG Leverkusen

(205)

Species: dog **Sex:** no data
Strain: no data
Route of admin.: other
Exposure period: 81 m
Frequency of treatment: 5 d/w
Post. obs. period: none
Doses: 300-320 mg/animal/d = 30-32 mg/kg bw/d
Result:
Control Group: no
Method:
Year: **GLP:**
Test substance:
Remark: 2 dogs were exposed to technical 1-NA (containing 7-9% 2-NA) and 3 dogs werde exposed to pure 1-NA.
No. of animals: 2-3/group
Result: On the last cystoscopy report, one dog in each group had abnormal areas of coloring in the bladder mucosa. None of the animals in either group have shown evidence of tumor formation by urina lysis or cystoscopy. Biopsies on suspicious areas in thebladders were reported as lymphoid hyperplasia. These were unaccompanied by any changes in the bladder epithelium.
Source: Bayer AG Leverkusen

(206)

Species: mouse **Sex:** male/female
Strain: Swiss
Route of admin.: s.c.
Exposure period: 1.,3. and 5 d of life
Frequency of treatment:
Post. obs. period: 12 m
Doses: 0.1 mg/animal = ca. 5 mg/kg bw/d
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 38 m and 27 f.
Result: 5/35 male mice had tumors after 12 m when the animals were sacrificed. Findings included 3 pulmonary tumors, 1 hepatoma and 1 lymphosarcoma. In control mice only 1 lymphosarcoma was observed. One lung adenoma was found in the treated females, with no tumors in the female controls.
Source: Bayer AG Leverkusen

(207)

Species: mouse **Sex:** no data
Strain: Swiss
Route of admin.: s.c.
Exposure period: 1. d of life
Frequency of treatment:
Post. obs. period: 10 m
Doses: 0.03 mg/animal = ca. 1.5 mg/kg bw
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 68.
Result: This experiment resulted in the occurrence of 4 tumors in 65 treated mice (3 lung tumors and 1 hepatoma). No tumors were observed in the controls.
Source: Bayer AG Leverkusen

(207)

Species: mouse **Sex:** male/female
Strain: no data
Route of admin.: s.c.
Exposure period: 52 w
Frequency of treatment: 2 d/w
Post. obs. period: lifetime
Doses: 6 mg/mouse/w = ca. 50 mg/kg bw/d
Result:
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No. of animals: 30/sex/group.
Result: There was no evidence that the purified compound is carcino– genic either to the bladder or to any other organ.
Source: Bayer AG Leverkusen

(208)

5.8 Toxicity to Reproduction

Type: other
Species: mouse **Sex:** male
Strain: other: CBA x BALB
Route of admin.: i.p.
Exposure Period: 5 d
Frequency of treatment: daily
Duration of test:
Doses: 10, 20, 25, 40, 50, 60, 80, 100 mg/kg bw/d
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: post observation period: 5 weeks
No. of animals: 5/group
Result: No increases in abnormal sperm heads could be observed.
Source: Bayer AG Leverkusen

(209)

5.9 Developmental Toxicity/Teratogenicity

Species: other: cricket **Sex:** no data
Strain: other: Acheta domesticus
Route of admin.: other
Exposure period: 24 h
Frequency of treatment: –
Duration of test:
Doses: no data
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: post observation period: 5 days
Result: No gross morphological abnormalities after exposure to 1–NA could be demonstrated in the cricket embryo bioassay.
Source: Bayer AG Leverkusen

(210)

5.10 Other Relevant Information

Type: Metabolism
Remark: The urinary excretion of sulfate and glucuronide conjugates of metabolites ring–hydroxylated in the 2– and 4–position was demonstrated by paper chromatography. The species investigated included the dog, rat, mouse, hamster, rabbit, guinea–pig, and ferret.
Source: Bayer AG Leverkusen

(193)

Type: Metabolism
Remark: It was demonstrated that unconjugated N,1-naphthyl-hydroxylamine is a urinary metabolite of 1-NA in the beagle dog.
Source: Bayer AG Leverkusen
(211)

Type: Metabolism
Remark: The main urinary metabolites in female beagle dogs were 1-Amino- 4-naphthyl sulfate (52.6 %) and 1-Amino-2-naphthyl sulfate (25.4 %).
Source: Bayer AG Leverkusen
(212)

Type: Metabolism
Remark: Dogs given a single oral 70 mg/kg dose of 1-NA were found to excrete almost as much of N-oxidation products in the urine as dogs given the same dose of 2-NA. However, when the dose was reduced to 5 mg/kg, a dose at which 2-NA is carcinogenic and 1-NA is not, negligible quantities of N-oxidation products were found in dogs given 1-NA.
Source: Bayer AG Leverkusen
(213) (214)

Type: Metabolism
Remark: It was found that N-hydroxylation and subsequent N-glucuronidation of 1-NA and 2-NA is a significant, though relatively minor pathway (<2 %), in the rhesus monkey. The N-hydroxy-N- glucuronide of 2-NA was found to be excreted at a rate that was 6.8 times that of the 1-NA isomer. Furthermore, the unoxidized 1-NA is excreted at a level 10 times that of 2-NA, indicating that it may be a poor substrate for the oxidative metabolic enzymes of the monkey.
Source: Bayer AG Leverkusen
(215)

Type: Metabolism
Remark: After oral administration of 71.6 mg/kg bw to female beagle dogs, a blood concentration of about 0.015 mg/ml after 60-80 min. could be detected. The formation of ferri-hemoglobin was with 4-5 % after 2-3 h decreased, compared to an administration of 2-NA. Within 8 h, 25 mg unchanged 1-NA, and 0.5 mg of N- oxidationproducts were excreted in the urine.
Source: Bayer AG Leverkusen
(216)

Type: Metabolism
Remark: It was found that in dogs and a worker of the dyestuff industry, 1-NA is largely excreted unchanged.
Source: Bayer AG Leverkusen
(217)

Type: Metabolism
Remark: The feeding of 25 mg/kg to dogs for 2 weeks to 6 months resulted in no increase in the urinary excretion of their N–oxidized metabolites.
Source: Bayer AG Leverkusen
(218)

Type: Metabolism
Remark: 1–NA is also partly oxidized to alpha–amino–naphthol in dogs and excreted in conjugation with sulfuric and especially glucuronic acid.
Source: Bayer AG Leverkusen
(219)

Type: other
Remark: Creation Date Toxicology: 8/91
Source: Bayer AG Leverkusen

Type: other: In Vitro
Remark: In liver microsomes of rabbits, only traces of N–oxidation–products could be detected after treatment with 1–NA. This is in contrast to the treatment with 2–NA.
Source: Bayer AG Leverkusen
(216)

Type: other: In Vitro
Remark: By incubation of 1–NA with microsomes from dog liver, dog bladder, and bovine liver an N–oxidation by either HPLC or GLC analysis could not be demonstrated.
Source: Bayer AG Leverkusen
(220)

Type: other: In Vitro
Remark: The oxidation of 1–NA with purified porcine flavin–containing monooxygenase could be demonstrated, although the structure of the metabolite(s) was not investigated in detail.
Source: Bayer AG Leverkusen
(221)

Type: other: In Vitro
Remark: The metabolism of 1–NA with microsomes from rat, dog, and human liver was investigated. In all cases, 1–amino–2–naphthol was the only metabolite detected. The overall rates of metabolism were significantly lower than with 2–NA.
Source: Bayer AG Leverkusen
(222)

Type: other: In Vitro
Remark: Guinea–pig liver kynurenine formamidase can transfer an acyl– group to 1–NA. Formylation catalyzed by this enzyme may represent a detoxification mechanism of the organism.
Source: Bayer AG Leverkusen
(223)

Type: other: In Vitro
Remark: The amount of free radical formed from incubation of 1-NA with rat liver microsomes was much less than that from 2-NA. The radical structure could not be identified unambiguously. From the viewpoint of radical formation, the metabolic patterns of 2-NA and 1-NA are quite different and such different behavior might be correlated with distinct differences in their carcinogenicities.
Source: Bayer AG Leverkusen

(224)

Type: other: In Vitro
Remark: The metabolic N-oxidation of 1-NA has been investigated with intact dog bladder, whole intact bladder mucosa, and microsomes prepared from this tissue. Very low levels of metabolic N-oxidation could be detected with these tissues. The concentrations of N-oxidized metabolites observed in the urine of dogs exposed to 1-NA suggest that N-oxidation takes place predominantly in the liver of the dogs.
Source: Bayer AG Leverkusen

(225)

Type: other: In Vitro
Remark: The formation of N-glucuronides in rat and human liver microsomes was studied. 1-NA was conjugated about 10 times faster than 2-NA. In humans this difference was less marked between the two amines.
Source: Bayer AG Leverkusen

(226)

Type: other: In Vitro
Remark: A genetic difference in the capacity of human and rabbit liver to acetylate 1-NA, could be demonstrated.
Source: Bayer AG Leverkusen

(227)

Type: other: In Vitro
Remark: Rates of formation of N- and C-oxygenated products of 1-NA were measured with 10 individual forms of rat liver P-450. The major pathway of C-hydroxylation with 1-NA is the formation of 2-Hydroxy-1-amino-naphthalene. None of the P-450 enzymes catalyzed the N-hydroxylation of 1-NA.
Source: Bayer AG Leverkusen

(228)

Type: other: In Vitro
Remark: 1-NA accelerates anaerobic guinea-pig brain glycolysis in a calcium-free medium.
Source: Bayer AG Leverkusen

(229)

Type: other: In Vitro
Remark: 1-NA-inhibited the respiration and succinate-oxidizing activity in the ciliated protozoan Tetrahymena pyriformis.
Source: Bayer AG Leverkusen

(230)

Type: other: Methemoglobin Determination
Remark: Concentrations of methemoglobin in 4 dogs receiving a dose of 70 mg/kg bw, were essentially negligible.
Source: Bayer AG Leverkusen
(213) (214)

Type: other: Methemoglobin Determination
Remark: Dogs which had been fasted for 18 h were given 200 mg/kg bw 1–NA via stomach tube. A 25 % accumulation of MetHb was detected 6 h to 8 h after treatment.
Source: Bayer AG Leverkusen
(231)

Type: other: Methemoglobin Determination
Remark: A dose of 10 mg/kg bw of purified 1–NA (99 %) was administered via stomach tube to one cat. The compound induced a transient methemoglobin formation of ca. 10 %. The no. of Heinz bodies was not affected.
Source: Bayer AG Leverkusen
(232)

Type: other: Symptoms
Remark: A dog, treated s.c. with 800 mg 1–NA showed strangury and hematuria. The symptoms declined 4 days later. The same dog showed at cystoscopy purpura of the bladder epithelium with numerous pinheadsize subepidermal hemorrhages. Half a year later, at necropsy, the dog showed no macroscopical changes.
Source: Bayer AG Leverkusen
(233) (234)

5.11 Experience with Human Exposure

Remark: Metabolism:
Upon oral administration, 1–Na yielded a greater urinary quantity of the N–hydroxy metabolite than the strong carcinogen 2–NA in humans
Source: Bayer AG Leverkusen
(26) (235)

Remark: It has been suggested that the 2–NA impurity in technical 1–NA is the causative factor in bladder tumor production in humans.
Source: Bayer AG Leverkusen
(236)

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7.1 Risk Assessment

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