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[CAPROLACTUM](#)
CAS N°: 105-60-2

SIDS Initial Assessment Report

for

12th SIAM

(Paris, France, June 2001)

Chemical Name : ϵ -caprolactam
CAS No : 105-60-2
Sponsor Country : Germany

National SIDS Contact Point in Sponsor Country

Lead Organization:

Name of lead organization: BMU (Bundesministerium für Umwelt, Naturschutz
und Reaktorsicherheit)
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History: see next page

Comments:

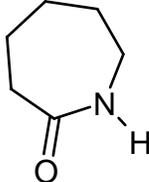
Date of Revision: 26 November 2001

OECD/ICCA - The BUA Peer Review Process

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4) not assignable)
- Review of validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)
- In case of data gaps, review of testing plan or rationale for not testing.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	105-60-2
Chemical Name	ε-caprolactam
Structural formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

The LD50 for the rat after oral application is 1475-1876 mg/kg bw. After inhalation of the substance as an aerosol by rats, the LC50 is 8.16 mg/l/4h. The LD50 for rats after dermal application is >2000 mg/kg bw. Main symptoms following exposure are clonic convulsions (oral), and irregular respiration (inhalation). Key effect following inhalation exposure to Caprolactam in humans and rats is irritation (skin, eyes, respiratory tract). Caprolactam was not sensitising in a guinea pig maximisation test and in a Buehler test with guinea pigs. The observed dermal effects in the study were regarded to be due to irritation. However, there are very few cases of sensitization in humans (see below),

Caprolactam given by feed (up to 1333 mg/kg bw) to rats in a 90-day study caused a species and sex-specific effect on the kidney of the male rat (hyaline-droplet-related nephropathy), which is supposed to be of no relevance for other species, including humans (NOEL 33 mg/kg bw). Furthermore there are no lesions in the kidney in two 2-year carcinogenicity bioassays.

A 13 week-inhalation study with caprolactam (aerosol, MMAD 3 μm) resulted in local nasoturbinal and laryngeal tissue changes and transient clinical signs in all treated rats. There is no NOEC from this study. These effects have been interpreted as an adaptive response by the authors. However, recovery from these effects was not complete after 4 weeks. Keratinization of the metaplastic epithelium in the larynx (reversible within 4 week recovery) was observed in the highest dose group indicating a NOAEC for local effects in the upper respiratory tract, of 70 mg/m³ (14 mg/kg bw./day[‡]). Systemic toxic effects also with respect to ophthalmology and neurobehaviour were not observed, NOAEC 243 mg/m³ (49 mg/kg bw./day).

Caprolactam showed neither mutagenic nor clastogenic potential with respect to most of the different genetic endpoints tested. Positive results in *in vitro* cytogenetic tests are observed only with high concentrations tested (> 10 mM). However, several tests *in vitro* and *in vivo* show induction of mitotic recombination. The relevance of this effect remains unclear, especially taking into account the negative results in rats and mice carcinogenicity bioassays.

Caprolactam was not carcinogenic in two 2 year oral studies in rats and mice when tested up to 7500 ppm and 15000 ppm by feed (750 and 2143 mg/kg bw/day.).

No adverse effect to reproductive organs was found in a three-generation feeding study with rats (feed: 1000-10 000 ppm=83-833 mg/kg bw; NOAEL parental: 417 mg/kg bw, NOAEL F1/F2/F3 generation: 83 mg/kg bw, NOAEL fertility: 833 mg/kg bw. Maternal as well as fetal effects are reduced body weight gain. Developmental studies performed in rats and rabbits with doses of caprolactam that were non-detrimental to the parental animals showed no evidence of a fetotoxic effect. Observed effect again was reduced maternal and fetal body weight gain. Teratogenicity from the gavage application of caprolactam was not observed in rats and rabbits (rats: NOAEL maternal toxicity: not established; NOAEL teratogenicity: 1000 mg/kg bw; NOAEL fetotoxicity 500 mg/kg bw; rabbit: NOAEL maternal toxicity: 50 mg/kg bw; NOAEL teratogenicity: 250 mg/kg bw; NOAEL fetotoxicity 50 mg/kg bw).

According to the data from rats and mice, Caprolactam appears to be absorbed rapidly. Excretion is also rapid and predominantly via the urine, mainly in metabolized form with only a small portion of unchanged substance.

In humans, irritation of the skin and the mucous membranes were reported. No signs of irritation was observed at 33 mg/m³ for Caprolactam vapour. The irritation threshold was reported to be at 56 mg/m³ and an irritation effect was noted at 61mg/m³ for vapour. There is no information on severity of irritating effects by dust compared to vapours, however, effects seem to be more severe in dry air. Caprolactam fumes at 68 mg/m³ are irritating to the skin .In some rare cases allergic contact dermatitis also occurs. Positive patch-test reactions were reported. Disturbance of the menstrual function and an increased number of toxicosis, premature delivery and post-natal hemorrhages were reported in female employees in the processing industry, where exposure to other compounds was also possible (no evaluation possible).

Environment

The distribution of the substance between the compartments air, biota, sediment, soil and water was calculated according to Mackay Level I. The main compartment is water 99,98%.

The low vapour pressure (0.13 Pa at 20 °C) and complete water solubility (4560 g/l at 20 °C) of caprolactam suggest that volatilization from water and soil surfaces would not be an important fate process. The substance has no considerable potential for bio- and geoaccumulation (log P_{OW} = 0.12, measured). It is readily biodegradable (OECD 301 C 82% after 14 days). The hydrolysis rate is extremely slow (t_{1/2} > 1 year). The photodegradation rate is fast under environmental conditions (50% after 4.9 hours).

The following aquatic effects are available:

Salmo gairdneri LC₅₀ (96 h) = >500<1000 mg/l

Daphnia magna EC₅₀ (48 h) > 500 mg/l; 2430 mg/l

Scenedesmus subspicatus EC₅₀ (72 h) = 130 mg/l; *Selenastrum capricornutum* 4550 mg/l

Pseudomonas putida EC₅₀ (17 h) = 4200 mg/l

From the effect value for the most sensitive species, *Scenedesmus subspicatus*, a PNECaqua of 130 µg/l was derived by applying an assessment factor of 1000. This factor is justified as only short-

term effect values are available. No data are available on terrestrial organisms.

Exposure

The production volume of this chemical in EU was 500,000 -1 000,000 t in 1999. More than 1 000 000 tonnes are produced in Asia and 500 000 – 1 000 000 tonnes in North America. The substance is used as an intermediate (non-disperse use) in chemical industry to produce polyamides. Currently 73% of the polyamide is being used for fibre-based applications (carpets and clothing), while the remainder 27% is used for the production of engineering plastics (gear wheels, drive systems, intermediates into Nylon-6). SIAM was informed that exposure to workers is adequately controlled in the industry of the Sponsor country (Germany) and in other countries (Japan and the USA).

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

FULL SIDS SUMMARY

CAS NO:105-60-2		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			69.2 °C
2.2	Boiling Point			270.8°C at 1013.25 hPa
2.3	Density			1.014 g/cm ³ at 80°C
2.4	Vapour Pressure		measured 79/831/EWG	0.13 Pa at 20°C
2.5	Partition Coefficient (Log Pow)		measured	0.12 at 25°C
			calculated	-0.19
2.6	Water Solubility			4560 g/l at 20°C
	pH			7-8.5 at 333 g/l and 20°C
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		calculated	t _{1/2} after 4.9 hours
3.1.2	Stability in Water		calculated	t _{1/2} > 1 year
3.2	Monitoring Data			no data
3.3	Transport and Distribution		calculated (Fugacity Level I type) acc. to Mackay	99.98 % in water
3.5	Biodegradation		OECD 301 C	82 % after 14 days
			DOC/CO ₂ combination test modified to OECD 301 A and B, industrial sludge	90-100 % DOC after 28 days 60-70 % CO ₂ after 28 days
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	<i>Salmo gairdneri</i>	comparable to OECD 203	LC ₅₀ (96 h) = 500-1000 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates	<i>Daphnia magna</i>	EEC-guideline 79/831/annex V, part C	EC ₅₀ (48 h) = > 500 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	<i>Scenedesmus subspicatus</i>	according to DIN 38412, part 9	EC ₅₀ (72 h) = 130 mg/l
4.4	Toxicity to bacteria	<i>Pseudomonas putida</i>	according to Bringmann-Kühn	EC ₅₀ (17 h) = 4200 mg/l
(4.6.3)	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			no data
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Directive 84/449/EEC	LD ₅₀ = 1475-1876 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	Directive 83/467/EEC	LC ₅₀ = 8.16 mg/l/4h
5.1.3	Acute Dermal Toxicity	Rat	Directive 84/449/EEC	LD ₅₀ > 2000 mg/kg
5.4	Repeated Dose Toxicity	Rat	90 day feed study	NOAEL 33 mg/kg
		Rat	13 week inhalation (EPA)	NOAEC 234 mg/m ³ (systemic effects) NOAEC 70 mg/m ³ (local effect, upper respiratory tract)
		Dog	13 week feed study	NOAEL males 250 mg/kg bw

CAS NO:105-60-2		SPECIES	PROTOCOL	RESULTS
				NOAEL females 125 mg/kg bw
5.5	Genetic Toxicity <i>In Vitro</i>			
A.	Bacterial Test (Gene mutation)	Salmonella typh.	According to Ames 1975	Negative with and without metabolic activation
B.	Non-Bacterial <i>In Vitro</i> Test (Chromosomal aberrations)	CHO cells	According to Galloway, 1985, cytogenetic study	Negative with and without metabolic activation
5.6	Genetic Toxicity <i>In Vivo</i>	Mouse	According to Schmid, 1975, micronucleus i.p.	Negative
		Mouse	Cytogenetic, gavage, EEC 79/831	Negative
		Mouse	Mouse spot test according to Fahrig, 1975	Induction of mitotic recombination, no induction of gene mutation.
5.8	Toxicity to Reproduction	Rat	Three generation study	NOAEL parental: 417 mg/kg, NOAEL F1/F2: 83 mg/kg NOAEL F3: 417 mg/kg NOAEL reprod. toxicity: 833 mg/kg
5.9	Developmental Toxicity/ Teratogenicity	Rat	Gavage, day 6-15	NOAEL maternal: <100 mg/kg NOAEL teratogen: 1000 mg/kg
		Rabbit	Gavage, day 6-28	NOAEL fetotoxicity: 500 mg/kg NOAEL maternal: 150 mg/kg NOAEL teratogen: 250 mg/kg NOAEL fetotoxicity: 50 mg/kg
Further Data	Corrosiveness/Irritation Skin	Human, rat	Human, 13 week study	Irritating
	Corrosiveness/Irritation Eye	Human, rat	Human, 13 week study	Irritating
	Sensitisation	Guinea pig	Maximisation test, Buehler test	Not sensitising
	Carcinogenicity	Rat	103 weeks, oral feed, up to 7500 ppm	Negative
		Mouse	103 weeks, oral feed, up to 15 000 ppm	Negative
5.11	Experience with Human Exposure	human		In humans irritation of the skin and the mucous membrans were reported. Caprolactam vapor is irritating at concentrations of 66 mg/m ³ , the irritation threshold is at 56 mg/m ³ and at 33 mg/m ³ no signs of irritation occur. Caprolactam dust at 84 mg/m ³ is irritating to the skin and at 61 mg/m ³ to the mucous membrans. In some rare cases allergic contact dermatitis, resp. positive patch-test reactions were reported. Disturbance of the menstrual function and an increased number of toxicosis, premature delivery and post-natal hemorrhages were reported in female employees in the caprone industry.

SIDS Initial Assessment Report

1. IDENTITY

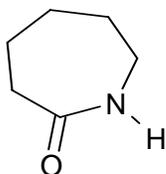
Chemical Name ε-caprolactam

Synonyms: 6-caprolactam
 2-Perhydroazepinone
 2-Oxohexamethylenimine
 2-Ketohexamethylenimine
 6-Hexanelactam
 Hexahydro-2-azepinone
 Aminocaproic lactam

CAS Number: 105-60-2

Empirical Formula: C₆ H₁₁ N O

Structure:



General Substance Information

Substance type: organic
Physical status: solid
Purity: 99.9% w/w

Physical and chemical properties

Caprolactam is a white solid at 20 °C. The solubility in water is 4560 g/l at 20°C (BASF AG, 1999). The vapor pressure is very low (0.13 Pa at 20°C) (BASF AG, 1992). The density of molten caprolactam is very close to water (1.014 g/cm³ at 80 °C) (BASF AG, 1999). The partition coefficient log P_{OW} is measured to 0.12 at 25°C (BASF AG, 1988c) and is calculated to -0.19 (Hansch, C. and Leo, A.J., 1979. Both values are in the same order. For the hazard assessment, the measured value for the log P_{OW} is preferred.

2. GENERAL INFORMATION ON EXPOSURE

Quantity produced: The production volume of caprolactam in EU was 500 000 – 1 000 000 tonnes in 1999. More than 1 000 000 tonnes are produced in Asia and 500 000 – 1 000 000 tonnes in North America.

The production volume is used as an intermediate (non-disperse use) in chemical industry to produce polyamides. Currently 73% of the polyamide is being used for fiber-based applications.

(carpets and clothing), while the remainder 27% is used for the production of engineering plastics (gear wheels, drive systems, connectors into polyamide). Various manufacturers do the processing to polyamides in-house, but also sell caprolactam on the merchant market.

The Swedish product registry shows that caprolactam is present in a small number of products adhesives/glues available to consumers. The concentration is below the limit of classification in the EU. Information from Danish product register show that the substance is present in a total number of 30 products in concentrations up to 100 %. Products types are described as intermediates and adhesives, binding agents.

2.1 Environmental Exposure and Fate

Releases into the environment may occur during production and processing of caprolactam.

According to the German Emission Register (year of reference: 2000) at BASF in Ludwigshafen during production and processing about 4.3 t/a of caprolactam were emitted into the atmosphere.

Measured data on emission into waste water treatment plant and into surface water at this site are not available.

Emission data from other production and processing sites are not available. The distribution modeling using Mackay, Level I indicates water to be the main compartment with 99.98% (BASF AG, 2001).

Hydrolysis is extremely slow ($t_{1/2} > 1$ year) (BASF AG, 2000). A soil adsorption coefficient (K_{OC}) of 12.1 was estimated for caprolactam based on a $\log P_{OW}$ of 0.12 according to the formula for nonhydrophobic chemicals proposed in the Technical Guidance Document for the European risk assessment procedure (BASF AG, 2001). This K_{OC} value suggests that this compound would be extremely mobile in soil and adsorption to suspended solids would not be important.

The Henry constant is calculated to $3.23 \cdot 10^{-6} \text{ Pa m}^3 \text{ mol}^{-1}$ (BASF, 2001). The low vapor pressure and complete water solubility of caprolactam suggest that volatilization from water and soil surfaces would not be an important fate process. Fast degradation can be expected according to calculated photodegradation (50% after 4.9 hours) (Atkinson, R., 1987). Due to the partition coefficient ($\log P_{OW}$ 0.12) an accumulation in organisms is not to be expected.

Caprolactam is readily biodegradable according to OECD 301 C with 82% after 14 days (Chemical Industry Ecology-Toxicology & Information Center, Japan 1992). MITI does not publish information about the 10 day window. This result is supplemented by another biodegradation test. It is a combination method modified according to OECD 301 A and B. The analysis parameters are the decrease of DOC and the evolution of CO_2 . Industrial activated sludge with a concentration of 150 mg/l dry matter was used as inoculum. The test concentration of caprolactam was 67 mg/l corresponding to 41.9 mg/l DOC. The degradation degree was 90-100 % DOC elimination and 60-70 % CO_2 evolution after 28 days (BASF AG, 1995).

2.2 Human Exposure

The results of BASF AG Ludwigshafen of workplace measurements (air exposure) are expressed as 95-percentile. The 95-percentile value was 1.1 mg/m^3 at the working place of production.

3. HUMAN HEALTH

3.1 Hazard Assessment Experience with Human Exposure

Minor complaints of sensory irritation and peeling and/or fissuring of the skin were reported in a group of eight workers exposed to caprolactam fume/dust levels of 68 mg/m^3 (range 22-168 mg/m^3) for 9 months to 13 years) (Kelman, 1986). At mean concentration of 61 mg/m^3 caprolactam vapor workmen in spinning rooms reported dry, splitting nose and lips, nose bleed and upper respiratory catarrh (Hohensee, 1951). In human volunteers exposed to different caprolactam vapor concentrations at 66 mg/m^3 burning nostrils and throat were reported, at 56 mg/m^3 transient burning nostrils and throat was still present in some of the subjects. In active and semi-active work areas no distress was noted at 33 mg/m^3 (Ferguson et al, 1973).

Caprolactam (5 %) produced no signs of irritation or indication of sensitization reactions when applied to the forearms of six, resp. five volunteers (Goldblatt et al, 1954).

In two of four cases with eczema on the legs after wearing nylon stockings a positive patch test (caprolactam 5 %) was reported (Jansson, 1959). Occupational contact dermatitis in a textile worker handling nylon fibers with a 18-month history of itchy, erythematous scaly eczema on the neck, chest and limbs was confirmed by patch testing (caprolactam 5 % aq.) (Aguirre et al, 1995).

Different types of dysmenorrhea in 300 female workers of chemical and spinning departments of caprone industry and an increased number of toxicosis, premature delivery and post-natal hemorrhages in 136 female employees in caprone production were reported. Caprolactam concentration exceeded 9 times the national threshold value of 10 mg/m^3 for nine years. The women were potential exposed not only to caprolactam but also to a mixture of diphenyl and diphenyl oxide (Martynova et al, 1972). Increased number of subjects with disturbance of the menstrual function was observed in 170 female caprolactam production employees. The capacity to conceive or number of abortions was not impaired. Besides caprolactam exposure to benzene, cyclohexane, cyclohexanone, cyclohexanone oxime and trichloroethylene was also possible. No workplace concentrations of caprolactam or other chemicals were available (Nadezhdina et al, 1969).

Conclusion: Caprolactam has irritant effects on the skin and the mucous membranes in humans. Considering the rarely reported cases potential of sensitization in man is regarded as neglectable. According to coexposures and/or missing data on exposure levels no evaluation of reports on disturbance of menstrual cycle and pregnancy of employees in the caprone industry is possible, especially because there is no confirmation of effects on reproduction by animal experiments.

3.2 Effects on Human Health

3.2.1 Acute Toxicity

After oral application the LD_{50} for rats is determined with 1475 mg/kg bw for female and with 1876 mg/kg bw for male animals; clonic convulsions were seen (Bayer AG 1987 a). The inhalation of an aerosol for 4 h resulted in rats in a LC_{50} -value of 8.16 mg/l (BASF 1985). The main symptoms during exposure were lid closure, piloerection and irregular respiration. The LD_{50} for dermal application is $>2000 \text{ mg/kg bw}$; no clinical symptoms were observed (Bayer AG 1987 b).

3.2.2 Corrosiveness and Irritation

No valid animal data are available. Experience with human exposure (sensory irritation at mean concentration of 68 mg/m³; Kelman 1986) and the results of 13-week inhalation study in rats (larynx: dose-related effects up to 243 mg/m³, effects at the nasoturbinal tissues at doses of 70 mg/m³ and 243 mg/m³; Huntington 1997; Reinhold et al. 1998) indicate an irritating effect to the skin, eyes and respiratory tract.

3.2.3 Sensitization

Caprolactam was tested according to EPA-guidelines in a guinea pig maximisation test (challenge: 75% caprolactam in water) and in a modified Buehler test (challenge: 25% caprolactam in water) and was considered to be not sensitizing. (Springborn Lab., 1991).

In the Buehler test a minimal dermal reaction (grades 0 to marginal) was observed in both test and negative control animals after the challenge, as well as after the rechallenge. Mean dermal scores were comparable between both groups. Ambiguous result: in test group 18/20 (24h) and 4/20 (48h) as well as in controls 8/10 (24h) and 2/10 (48h). In rechallenge also only ambiguous results were found 11/20 (24h) and 5/20 (48h) in test groups and in control 8/10 (24h) and 5/10 (48h). The skin effects observed in the control animals after the challenge are an indication of an irritation reaction to the test concentration used. The use of the data for determining skin sensitization potential is limited by the use of an irritating concentration for the challenge treatment. However, caprolactam was not considered to be a contact sensitizer under the test conditions chosen.

Following challenge with caprolactam in the maximisation test, dermal responses in the test group consisted of grade ± reactions (13/20) and grade 1 reactions (7/20). Slight edema were also observed at 7/20 test sites at the 24 hours interval. By 48 hours, a grade 1 reaction was noted in 1/20 test animals. Dermal responses in control group animals consisted of a grade 1 reaction (with slight edema) in 1/5 animals at 24 hours and of grade + to 0 reaction at all other control sites during the scoring intervals. The skin effects in the control group animals after challenge treatment are an indication of an irritation reaction to the test concentration used. In conclusion, the use of the data for determining based on the concurrent reaction in the control animals and the decrease in the reaction after 24 to 48 hours, caprolactam is not considered to be a contact sensitizer under the test conditions chosen.

3.2.4 Repeated Dose Toxicity

In a 13-week inhalation study performed according to an EPA guideline (10/ rats/sex and concentration), Sprague-Dawley rats were exposed to 24, 70 and 243 mg/m³ (corresponding to 5; 14 and 49 mg/kg bw resp.; rats with body weight of 300 g and inhalation volume 10 l/h) caprolactam as an aerosol for 6 hours/day, 5 days/week (whole body exposure). The particle size was on average of 2.9 µm. No compound-related deaths occurred.

There were no treatment-related responses observed in ophthalmic parameters, body weights, food consumption, neurobehavioral effects, organ weights, or macroscopic findings. Exposure resulted in transient clinical signs (secretory- nasal discharge- and respiratory-labored breathing), as well as respiratory tract effects (hypertrophy /hyperplasia of goblet cells in the nasal mucosa; intracytoplasmic eosinophilic material in the epithelium of the nasal mucosa and squamous/squamoid metaplasia/hyperplasia in the larynx mucosa) at all exposure levels, with incomplete recovery within the four weeks after exposure. There is no NOEC for this study. These effects have been interpreted as an adaptive response to inhaled foreign particulate material by the authors. Keratinisation of the metaplastic epithelium in the larynx (reversible within 4 week recovery) was observed in the highest dose group indicating a NOAEC for local effects in the upper

respiratory tract, of 70 mg/m³. Systemic toxic effects also with respect to ophthalmology and neurobehavior were not observed, NOAEC 243 mg/m³ (Reinhold et al., 1998).

No other valid inhalation studies are available or described in the literature.

10 rats per dose and gender were used in two 90-day oral feeding studies with caprolactam.

In one study using caprolactam 0.1, 0.3, 1.0, 2.0 % in feed (ca. 67, 200, 667, 1333 mg/kg bw) the following effects were seen in Wistar rats: in males reduced body weight compared to control and significant increase in relative organ weights in kidney (1 and 2%), thyroid and brain (2%) and liver (all doses). In females there were the following effects: reduced body weight compared to control and increased relative liver weight (1 and 2%). In males, histopathologically clear nephrotoxic effects were observed at 0.3 %. Slight renal effects were found at 0.1 %. In males hyaline droplets were observed dose-dependently in the 0.3 to 2.0 % dose group, and tubular nephrosis occurred to a higher degree and incidence in all treated male rats in comparison to the control. Due to the effects on the kidney the authors gave this study a NOEL slightly below 0.1 % (ca. 67 mg/kg bw), (TNO, 1970).

In the other study, 0.05, 0.1, 0.25, 0.5 and 1.0 % caprolactam in feed (ca. 33, 67, 167, 333, 667 mg/kg bw) were tested with Sprague-Dawley rats. No treatment-related effects were seen in hematological data, biochemical blood values and in urine composition. In the high dose group body weight were reduced compared to controls, furthermore the relative weights of kidneys and testes were significantly increased in males; the relative liver weights were increased in both sexes. Gross examination also revealed renal discolouration in males at 1.0 %. In the kidneys of all male dose groups, except for the 0.05 % group, a hyaline-droplet degeneration was observed microscopically.

This is a rather common observation in male rats and may either indicate a substance-related binding to alpha-2μ-globulin or an earlier manifestation of other kidney nephropathy in male rats. These findings are supposed to be of no relevance for other species including humans (Haschek and Rousseaux, 1996). Furthermore, the subsequent 2 year cancer bioassay with rats and mice did not reveal any type of carcinogenicity nor any impairment of kidneys (see 3.2.8). In any case, a clear NOEL of 0.05 % (ca. 33 mg/kg bw) was obtained (TNO, 1971).

In other NTP 13-week range-finding studies performed to set doses for chronic studies, the only finding was decreased body weights in the high dose groups of B6C3F1 mice and F344 rats. Since the body weight gain was reduced due to reduced food consumption, a palatability problem cannot be excluded. No compound-related histopathological effects were found in rats (625, 1250, 2500, 5000, 7500 ppm = ca. 41, 83, 167, 333, 500 mg/kg bw) or in mice (5000, 10000, 15000, 20000, 30000 ppm = ca. 715, 1430, 2143, 2857, 4286 mg/kg bw) treated with caprolactam in the feed (NOAEL rats 500 mg/kg bw; NOAEL mice 4286 mg/kg bw). No further information was given, due to the aim of the study (NTP report No. 214).

4 dogs per dose and gender were treated via feed with caprolactam (25, 125, 250 mg/kg bw) for 13 weeks. The only finding was decreased mean body weight in the high-dose females. This finding was not evident in the high-dose males or in the other dose groups. No treatment-related effects were noted in clinical chemistry, pathology, ophthalmology or organ weights (NOAEL males 250 mg/kg bw.; NOAEL females 125 mg/kg bw), (Hazleton, 1980).

Conclusion:

Caprolactam given by feed to rats only caused specific effects in the male rat kidney, which is supposed to have little or no relevance for other species, including humans.

The inhalation of caprolactam as an aerosol resulted in nasoturbinal and laryngeal tissue changes in all treated rats, NOAEC local 70 mg/m³. A NOAEC was considered to be 243 mg/m³ for the lower respiratory tract, systemic toxicity and neurotoxicity.

3.2.5 Genetic Toxicity

3.2.5.1 Genetic toxicity in vitro

Caprolactam was not mutagenic in vitro in the Ames test with and without metabolic activation (Green et al., 1979; Jung et al., 1992), the HPRT Test with V79 cells (Fox et al., 1985), the mouse lymphoma test (Myhr et al., 1985), a chromosomal aberration test with CHO cells (Gulati et al., 1989), or in the UDS test with primary rat hepatocytes (Probst et al., 1985).

As part of an interlaboratory survey, further in vitro tests were performed with caprolactam. All of these with the exception of three tests on human lymphocytes had negative results. In the three lymphocyte studies only high cytotoxic concentrations, which were much higher than the highest concentration recommended in the guideline (10 mM), caused chromosomal aberrations (Sheldon, 1989a, Kristiansen, 1989, Norppa, 1989)

3.2.5.2 Genetic toxicity in vivo

In mammals, neither chromosomal aberrations (tested at 1000 mg/kg bw) nor micronuclei (tested with up to 700 mg/kg bw) were induced by caprolactam in bone marrow cells of mice (Adler and Ingwersen, 1989, Sheldon, 1989b, Ishidate and Odagiri 1989). No induction of DNA strand breaks or unscheduled DNA synthesis was observed in hepatocytes of caprolactam-treated (750 mg/kg bw) rats (Bermudez et al., 1989). The results of a mouse spot test (treated with up to 500 mg/kg bw) were ambiguous and showed a slight increase in colored spots that were not dose-related, but the nature of these spots suggest that caprolactam may have induced these spots through the induction of mitotic recombination under the conditions of the assay due to high dose levels. (Fahrig, 1989; Fahrig and Neuhäuser-Klaus, 1989). The relevance of this effect remains unclear, especially taking into account the negative results in rats and mice carcinogenicity bioassays.

Conclusion:

Caprolactam showed neither mutagenic nor clastogenic potential with respect to most of the different genetic endpoints tested. Positive results in in vitro cytogenetic tests are observed only with high concentrations tested (> 10 mM). However, several tests in vitro and in vivo show induction of mitotic recombination. The relevance of this effect remains unclear, especially taking into account the negative results in rats and mice carcinogenicity bioassays.

3.2.6 Toxicity to reproduction

In a three-generation study F344 rats were continuously fed caprolactam at doses of 1000, 5000 and 10000 ppm (ca. 83, 417, 833 mg/kg bw) through three successive generations. No treatment-related clinical signs, changes in reproductive performance or gross-pathological findings were noted within the parental generations.

Compound-related histopathologic findings noted in the high-dose first parental (F0) animals consisted of a slight increase in the severity of spontaneous nephropathies, occasionally

accompanied by granular casts. The offspring data revealed no treatment-related effects with respect to gross appearance, gross pathology, survival, number of pups, percentage of male pups or kidney weight. The effects on mean body weight (lower mean body weight in the filial generation, female: 10% decrease in F1 and 7% in F2; male: to 16% decrease in F1 and to 18% in F2), mean food consumption (to 18% decrease in F2 and 21% in F3) and a slight increase in the severity of nephropathy in the high dose group, accompanied by the presence of granular casts in some animals, were considered to be related to the administration of caprolactam (Serota et al., 1988).

NOAEL parental:	417 mg/kg bw
NOAEL F1 / F2 / F3 generations :	83 mg/kg bw
NOAEL fertility:	833 mg/kg bw

Conclusion:

No adverse effect on reproductive organs or function was found in a 3-generation study with rats.

3.2.7 Developmental Toxicity / Teratogenicity

Twenty F344 rats/group were treated on day 6 through day 15 of gestation with 100, 500 and 1000 mg/kg/d bw by gavage, mother and fetuses were examined on day 21. The maternal survival rate was statistically lower in the high-dose group when compared with the control. Nine high-dose females were found dead during the treatment phase of this study. Clinical observations such as urine stains, rough hair coat, red discharge from the vagina, bloody crust on eyes, mouth and nose, thin and/or hunched appearance were observed in all treated groups. The mean body weight values of the high dose group on day 15 and 20 of gestation (10 % and 11% decrease) and the mean body weight changes of the mid- and high dose group for the days 6-11 and 6-15 were statistically significantly lower than the control values at these intervals. The mean food consumption was significantly lower in the mid- and high-dose groups. Therefore, a NOAEL for maternal toxicity could not be established. In these maternally toxic doses, a slight reduction in fetal body weight was also observed. The mean number of corpora lutea and implantations per group were not affected by treatment, but the mean implantation efficiencies were slightly reduced in high-dose group. The increase in resorptions was statistically significant in the high-dose group. There were no treatment-related statistically significant differences between treated and control groups in terms of the incidence of visceral abnormalities. Skeletal variants consisting mainly of incomplete ossification and additional rib elements in all dose and control group. No skeletal malformations were observed (Gad et al. 1984, 1987).

An analogous study in the same laboratory was performed with 25 New Zealand white rabbits/group. They were treated on days 6-28 of gestation with 50, 150 and 250 mg/kg bw by gavage, and fetuses were examined on day 29. In the 250 mg/kg bw group 4 rabbits died during the treatment period. There were no deaths in the other groups. In the high dose group the overall weight gain between day 6 and 29 of gestation was significantly decreased. For the corrected weight gain (weight gain day 6 to day 29 of gestation minus weight of gravid uterus), there was a significantly greater weight loss in the mid-dose group. The body weights in the 50 mg/kg/day dose group were unaffected. No effects on the reproduction parameters (i.e. number of corpora lutea, or sex ratio) were found. There were no treatment-related indications of embryo- or fetotoxicity (number of live and dead fetuses, resorptions, pre- or postimplantation losses), except decreased fetal weight (15% and 12%, resp.) at the maternally toxic dose levels of 150 and 250 mg/kg/bw. No signs of teratogenicity were observed at any dose level (Gad et al. 1984, 1987).

Rat:	NOAEL maternal toxicity:	not established
	NOAEL teratogenicity:	1000 mg/kg bw

	NOAEL fetotoxicity:	500 mg/kg bw
Rabbit:	NOAEL maternal toxicity:	50 mg/kg bw
	NOAEL teratogenicity:	250 mg/kg bw
	NOAEL fetotoxicity:	50 mg/kg bw

Conclusion:

No teratogenic effects from the oral application of caprolactam were observed in rats or rabbits. Fetotoxic effects were only observed in rats and rabbits at doses that also produced maternal toxicity.

3.2.8.1 Carcinogenicity

Caprolactam was tested in the NTP Carcinogenesis Testing Programm using rats and mice.

Fischer-344 rats, 50 males and 50 females per group, were fed a diet containing 3750 ppm (188-375 mg/kg bw) and 7500 ppm (375-750 mg/kg bw) caprolactam over 103 weeks. A dietary control group was also included.

Survival at the termination of the experiment was 32/50 (64%) of the control group, 33/50 (66%) of the low-dose group, and 37/50 (74%) of the high-dose group in the males. In the females, 40/50 (80%) of the controls, 42/50 (84%) of the low-dose group, and 38/50 (76%) of the high-dose group survived to the end of the study (week 105).

The various types of neoplasms occurring in dosed and control rats were comparable and did not appear to be related to caprolactam administration.

In all exposed groups, including the control, high rates of interstitial-cell tumors were observed in the testes (84% control, 86% low dose, 96% high dose). This is a very common tumor in old Fischer rats (up to 98% in historical data, Haseman et al., 1998). The relative risks of these tumors in the 3750 and 7500 ppm group (in relation to control) were recorded with 1.028 (upper limit 1.221, lower limit 0.859) and 1.147 (upper limit 1.241, lower limit 0.984); indicating that a constant risk of 1 is still within the confidence intervals. Furthermore, the latency period (time to first observed tumor) was not increased (79, 80, 83 week resp.). Therefore, there was no indication of a treatment-related effect. The number and type of all other tumors noted in the treated groups were comparable to those determined in the control group.

The large number of degenerative, proliferative, and inflammatory lesions encountered in dosed and control animals were of the type and frequency encountered in aging F344 rats, and none were believed to be related to treatment. No treatment-related non-neoplastic changes were observed at necropsy. The results of histopathologic examination indicated that caprolactam was not carcinogenic and did not show other chronic effects in F344 rats at doses up to 7500 ppm (Huff J., 1982; NTP report No. 214).

B6C3F1 mice, 50 males and 50 females per group, were fed with 15000 ppm (2143 mg/kg bw) and 7500 ppm (1072 mg/kg bw) caprolactam over 103 weeks. A dietary control group was also included.

Survival at the termination of the experiment was 40/50 (80%) of the control group, 48/50 (96%) of the low-dose group, and 43/50 (86%) of the high-dose group in the males. In the females, 38/50

(76%) of the controls, 41/50 (82%) of the low-dose group, and 46/50 (92%) of the high-dose group lived to the end of the study (week 105).

Various types of neoplasms occurred in both the dosed and the control mice, but no increased incidence of any type of neoplasms was seen in dosed mice. The observed neoplasms were typical of those seen in this strain of mouse. Degenerative changes were found in mice, but no increase in the severity or frequency of these lesions was observed in dosed versus control animals. No treatment-related non-neoplastic changes were observed at necropsy. The results of histopathologic examination indicated that caprolactam was not carcinogenic and did not show other chronic effects in B6C3F1 mice at doses up to 15000 ppm (Huff J.,1982, NTP report No. 214).

Conclusion:

Caprolactam is not carcinogenic in rats and mice and did not induce other toxic effects when tested up to 7500 ppm (rats) and 15000 ppm (mice) in the diet.

3.2.9 Toxicokinetics

According to the data from rats and mice, caprolactam appears to be absorbed rapidly. Excretion is also rapid and predominantly via the urine.

Caprolactam is excreted in the urine mainly in metabolized form with only a small portion of the dose being excreted unchanged (Unger,1981, Unger and Friedman, 1980).

4. HAZARDS TO THE ENVIRONMENT

The following ecotoxicity tests with aquatic organisms are available:

<i>Species</i>	<i>Method</i>	<i>Effect value</i>	<i>Reference</i>
<i>Salmo gairdneri</i>	static; comparable to OECD 203; nominal conc.	96h-LC ₅₀ > 500<1000 mg/l	BASF AG, 1987
<i>Daphnia magna</i>	EEC 79/831, annex V, part C; nominal conc..	48h-EC ₅₀ > 500 mg/l	BASF AG, 1988b
<i>Daphnia magna</i>	DIN 38412, part 11, nominal conc.	24h-EC ₅₀ = 4380 mg/l	Bringmann/Kühn, 1982
<i>Daphnia magna</i>	OECD 202, nominal conc.	48h-EC ₅₀ = 2430 mg/l	Murin et al., 1997
<i>Scenedesmus subspicatus</i>	DIN 38412, part 9; nominal conc..	72h-E _b C ₅₀ = 130 mg/l 72h-E _b C ₂₀ = 34 mg/l	BASF AG, 1988d
<i>Selenastrum capricornutum</i>	OECD 201, nominal conc.	72h-E _r C ₅₀ = 4550 mg/l 72h-NOEC = 1250 mg/l	Murin et al., 1997
<i>Pseudomonas putida</i>	according to Bringmann-Kühn; nominal conc.	17h-EC ₅₀ = 4200 mg/l	BASF AG, 1988a

Further test with fish and *Daphnia* are available that are either invalid or the validity cannot be checked. However, the results from these tests are not in contradiction to the effect values described above.

Based on acute toxicity data the most sensitive species is the green algae *Scenedesmus subspicatus*. From the EC₅₀ value of 130 mg/l, a PNEC_{aqua} of 130 µg/l can be derived by applying an assessment factor of 1000. This factor is justified as only short-term effect values are available.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

The production volume of caprolactam in EU was 500 000 – 1 000 000 tonnes in 1999. More than 1 000 000 tonnes are produced in Asia and 500 000 – 1 000 000 tonnes in North America.

The production volume is used as an intermediate (non-disperse use) in chemical industry to produce polyamides. Currently 73% of the polyamide is being used for fibre-based applications (carpets and clothing), while the remainder 27% is used for the production of engineering plastics (gear wheels, drive systems, intermediates into Nylon-6).

The distribution modeling using Mackay, Level I indicates water to be the main target compartment for caprolactam. The substance has no considerable potential for bio- and geoaccumulation (log P_{OW} = 0.12). It is classified as readily biodegradable. The hydrolysis is slow (t_{1/2} > 1 year) and the photodegradation is fast (t_{1/2} = 4.9 hours) under environmental conditions.

Based on acute toxicity data the most sensitive species is the green algae *Scenedesmus subspicatus*. From the EC₅₀ value of 130 mg/l, a PNEC_{aqua} of 130 µg/l can be derived by applying an assessment factor of 1000.

No data are available on terrestrial organisms.

LD₅₀ rat (oral) 1475-1876 mg/kg bw, LC₅₀ rat (inhalation, aerosol) 8.16 mg/l/4h, LD₅₀ rat (dermal) > 2000 mg/kg bw. Main symptoms following exposure are clonic convulsions (oral), and irregular respiration (inhalation).

Key effect following inhalation exposure to caprolactam in humans and rats is irritation (skin, eyes, respiratory tract).

Caprolactam was not sensitizing in a guinea pig maximization test and in a Buehler test with guinea pigs.

Caprolactam given by feed (up to 1333 mg/kg bw) to rats in a 90-day study caused a species- and sex-specific effect on the kidney of the male rat (hyaline-droplet-related nephropathy), which is supposed to be of no relevance for other species, including humans (NOEL 33 mg/kg bw). Furthermore there are no lesions in the kidney in two-year carcinogenic bioassays.

A 13 week-inhalation study with caprolactam (aerosol) resulted in local nasoturbinal and laryngeal tissue changes and transient clinical signs in all treated rats. A NOEC was not achieved for this study, since there were transient clinical signs (labored breathing, nasal discharge) as well as mild to moderate effects in nasoturbinal tissues /hypertrophy/hyperplasia of goblet cells in the respiratory mucosa and in the cytoplasmic eosinophilic material in epithelial cells of the olfactory mucosa) and in laryngeal tissues. These effects have been interpreted as an adaptive response by the authors. However, recovery from these effects was not complete after 4 weeks. Keratinization of metaplastic epithelium in the larynx (reversible within 4 week recovery) was observed in the

highest dose group indicating a NOAEC for local effects in the upper respiratory tract, of 70 mg/m³. Systemic toxic effects also with respect to ophthalmology and neurobehaviour were not observed, NOAEC 243 mg/m³.

Caprolactam showed neither mutagenic nor clastogenic potential with respect to most of the different genetic endpoints tested. Positive results in in vitro cytogenetic tests are observed only with high concentrations tested (> 10 mM). However, several tests in vitro and in vivo show induction of mitotic recombination. The relevance of this effect remains unclear, especially taking into account the negative results in rats and mice carcinogenicity bioassays.

No adverse effects on reproductive organs were found in a three-generation study with rats (NOAEL parental: 417 mg/kg bw ; NOAEL F1/F2/F3 generations: 83 mg/kg bw; NOAEL fertility: 833 mg/kg bw).

In developmental studies with rats and rabbits no evidence of fetotoxic effects was seen with doses non-detrimental to the parental animals. No teratogenicity from the oral application of caprolactam was observed in rats and rabbits (rat: NOAEL maternal toxicity: not established; NOAEL teratogenicity: 1000 mg/kg bw; NOAEL fetotoxicity 500 mg/kg bw; rabbit: NOAEL maternal toxicity: 50 mg/kg bw; NOAEL teratogenicity: 250 mg/kg bw; NOAEL fetotoxicity 50 mg/kg bw).

Caprolactam did not induced non-neoplastic nor carcinogenic effects in rats and mice when tested up to 7500 ppm (375 mg/kg bw/d) and 15000 ppm (750 mg/kg bw/d via feed, respectively, in 2 year studies.

According to the data from rats and mice, caprolactam appears to be absorbed rapidly. Excretion is also rapid and predominantly via the urine, mainly in metabolized form with only a small portion of unchanged substance.

In humans, irritation of the skin and the mucous membrans were reported.

No signs of irritation was observed at 33 mg/m³ for caprolactam vapor. The irritation threshold was found at 56 mg/m³ and an irritation effect was noted at 61 mg/m³.

Caprolactam fume/dust at 68 mg/m³ is irritating to the skin. In some rare cases allergic contact dermatitis, resp. positive patch-test reactions were reported. Disturbance of the menstrual function and an increased number of toxicosis, premature delivery and post-natal hemorrhages were reported in female employees in the processing industry, where exposure to other compounds was also possible (no evaluation possible).

5.2 Recommendations

There is no need for further work.

REFERENCES

- Adler, I.D. & Ingwersen, I., *Mutat. Res.* 224, 343-345 (1989)
- Agiurre A., et al., *Contact Dermatitis* 32, 174-175 (1995)
- Atkinson, R., *Inter. J. Chem. Kinet.* 19, page 799-828 (1987)
- BASF AG, Department of Toxicology, unpublished data (84/217), August 19, 1985
- BASF AG, Department of Toxikology, unpublished data (87/100), Sep. 8, 1987
- BASF AG, Department of Ecology, unpublished data (88/1282), Oct. 5, 1988 (1988a)
- BASF AG, Department of Ecology, unpublished data (88/1282), Oct. 6, 1988 (1988b)
- BASF AG, Department of Analytic, unpublished data (Report No 101025), Oct. 10, 1988 (1988c)
- BASF AG, Department of Ecology, unpublished data (88/1282), Dec. 16, 1988 (1988d)
- BASF AG, Department of Physical Chemistry, unpublished data (Report BRU 92.201), Jan. 7, 1992
- BASF AG, Department of Ecology, unpublished data (94/1252), Feb. 22, 1995
- BASF AG, Department of Ecology, unpublished calculations, March. 21., 2001
- BASF AG, Safety Data Sheet Caprolactam liquid, Dec. 17, 1999
- BASF AG, Department of Ecology, unpublished calculation, July 7, 2000
- Bayer AG, Institute for Toxicology, unpublished data (No. 15882) (1987a)
- Bayer AG, Institute for Toxicology, unpublished data (No. 15897) (1987b)
- Bermudez, E. et al., *Mutat. Res.* 224, 361-364 (1989)
- Bringmann,G., Kühn,R., *Zeitschrift für Wasser- und Abwasser-Forschung*, 15(1), 1-6 (1982)
- Chemical Industry Ecology-Toxicology & Information Center, *Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan*, 1992
- Fahrig, R., *Mutat. Res.* 224, 373-375 (1989)
- Fahrig R. and A. Neuhaeuser-Klaus: *Mutat. Res.* 224, 377-378 (1989)
- Ferguson W. S., Wheeler D. D., *Am. Ind. Hyg. Assoc. J.* 34, 384-389 (1973)
- Fox, M. & Delow, G.F., *Prog. Mutat. Res.* 5, 517-523 (1985)
- Gad S.C. et al.: *J Appl.Toxicol.* 7, 317-326 (1987)

- Gad, S.C. et al., Proc. Symp. Ind. Approach Chem. Risk Assess. Caprolactam Relat. Compd. Case Study, 164-189 (1984)
- Goldblatt M. W., et al., Br. J. Ind. Med. 11, 1-10 (1954)
- Green, E.J. et al., Environ. Mutagen. 1, 399-407 (1979)
- Gulati D.K. et al.: Env. Molec. Mutagen. 13, 133-193 (1989)
- Hansch, C. and Leo, A.J., Substituent Constants for Correlation for Analysis in Chemistry and Biology, Claremont CA, Pomona College (1979)
- Haschek W.M. and C.L.Rousseaux Ed., Fundamentals of Toxicologic Pathology, Academic Press(1996)
- Haseman J.k. et al. , Society of Toxicologic Pathologists 26, 428-441 (1998)
- Hazleton laboratories Project No.: 2008-107, unpublished data, October 3 (1980)
- Hohensee F., Faserforsch. Textiltech. 1, 299 (1951)
- Huff, J., Environ. Health Perspect. 45, 199-200 (1982)
- Untington Life Sciences Study No. 95-6095, IHF 3-95PA (1997)
- Ishidate, M. Jr. & Odagiri, Y., Mutat. Res. 224, 357-359 (1989)
- Jansson H., Zt. Haut. Geschlechtskr. 26, 37-39 (1959)
- Jung R. et al.: Mutat. Res. 278, 265-270 (1992)
- Kelman G. R., Human Toxicol. 5, 57-59 (1986)
- Kristiansen E. and D. Scott, Mutat. Res. 224, 329-332, (1989)
- Murin, M. et al., Chemosphere 34/1, 179-190 (1997)
- Myhr, B. et al., Prog. Mutat. Res. 5, 555-568 (1985)
- Norppa H. and H. Järventaus, Mutat. Res. 224, 333-337, (1989)
- NTP-Report NTP-80-26, NIH Publication No. 81-1770, (1982), PB82-190182; Technical report series No. 214.
- Palitti, F. et al., Prog. Mutat. Res. 5, 443-450 (1985)
- Probst, R.A.J. & Hill, L.E., Prog. Mutat. Res. 5, 381-386 (1985)
- Reinhold R.W. et al.: Toxicological Sciences 44, 197-205 (1998)
- Serota, D.G. et al., J. Appl. Toxicol. 8, 285-293 (1988)

Sheldon, T., *Mutat. Res.* 224, 325-327 (1989a)

Sheldon, T., *Mutat. Res.* 224, 351-355 (1989b)

Springborn Laboratories, Inc.: Life Sciences Division, SLS Study No. 3224.7, April 25 1991

TNO: Central Institute for Nutrition and Food Research, Report No. 3157, April 1970

TNO: Central Institute for Nutrition and Food Research, Report No. 3489, June 1971

Unger P.D. et al.: *Fd. Cosmet. Toxicol.* 19, 457-462 (1981)

Unger P.D. and Friedman M.A.: *J. Chromat.* 187, 429-435 (1980)